490. *Electrophilic Substitution. Part XI.* Nitration of Some Six-membered Nitrogen-heterocyclic Compounds in Sulphuric Acid.*

By M. J. S. Dewar and P. M. Maitlis.

The proportions of mononitro-derivatives formed from quinoline and *iso*quinoline in sulphuric acid have been determined. Quinoline gave at 0° 52·3% of 5- and 47·7% of 8-nitroquinoline; *iso*quinoline gave 5- and 8-nitro*iso*quinolines in the proportions: 90·4% 5-, 9·6% 8- at 0°; 84·8% 5- and 15·2% 8- at 100°. Both reactions take place readily under mild conditions. For *iso*quinoline a value for the parameter α has been derived from the partial rate factors and has been used, together with a value for β, for predictions of the reactivities of different positions in several six-membered heterocyclic systems, giving excellent agreement with experiment. Competitive nitrations have also been carried out with quinoline–*iso*quinoline and quinoline–acridine; their significance is discussed.

Previous papers [1] of this series have described electrophilic substitution of various aromatic hydrocarbons. The orientation and partial rate factors were shown to follow closely the pattern predicted [2] on the basis of a simplified molecular-orbital treatment. We have extended this investigation to some simple heterocyclic systems and now describe a study of the nitration of quinoline and *iso*quinoline in sulphuric acid.

This solvent was chosen to ensure that the reactions would involve simple electrophilic substitution. It was found that quinoline gives unexpected products in acetic anhydride or with nitrogen peroxide; we have examined [3] these reactions and given reasons for believing that they involve preliminary addition of the reagent to the 1 : 2-bond of quinoline with the formation of a reactive intermediate. Additions of this type would not be expected to occur in sulphuric acid.

Many workers have described the nitration of quinoline and *iso*quinoline. The conditions used for the former were usually drastic, involving nitric acid in oleum or in hot concentrated sulphuric acid.[4] The total yields of mononitroquinolines were around 80%, and consisted of the 5- and 8-isomers in roughly equal amounts. Nitration of *iso*quinoline has been less studied; Andersag [5] and Robinson [6] have shown it to produce both 5- and 8-nitro*iso*quinoline, but the latter was not isolated and the relative proportions of the isomers were not determined.

We have examined both these reactions in some detail, under conditions such that some of the base remained unchanged (in order to avoid dinitration and other side reactions). The mononitro-fractions were isolated by fractional basification and analysed spectrophotometrically. There was no evidence for the formation of any of the other mononitroquinolines in the nitration of quinoline; less than 1% of the 3-, 6-, or 7-nitroquinoline

* Part X, preceding paper.

[1] Dewar, *J.*, 1956, 3570, 3572, 3576, 3581.
[2] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3357.
[3] Dewar and Maitlis, *J.*, 1957, 944.
[4] Claus and Kramer, *Ber.*, 1885, **18**, 1243; Noelting and Trautmann, *Ber.*, 1890, **23**, 3655; Dufton, *J.*, 1892, **61**, 783; Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1940, **62**, 1640.
[5] Andersag, "Medicine in its Chemical Aspects," Rep. Medico-chem. Res. Lab. of the I.G. Farbenind. A.-G., 1934, **2**, 361.
[6] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1939.

would have been easily detected. Similarly, in the nitration product of *iso*quinoline, there were no anomalies in the spectra to indicate presence of other isomers.

Synthetic mononitroquinolines and 5-nitro*iso*quinoline, for use as spectroscopic standards, were available. Synthesis of 8-nitro*iso*quinoline has been reported by Ochiai *et al.*,[7] by nitration of *iso*quinoline *N*-oxide, separation of the two nitro-isomers, and removal of oxygen from the 8-nitro*iso*quinoline *N*-oxide. As we were unable to repeat their work, we developed an alternative procedure. We reduced 8-nitro- to 8-amino-*iso*quinoline, which had the melting point reported by Andersag.[5] The melting point of 8-nitro*iso*quinoline (72°) and its *N*-oxide (179—180°) quoted by Ochiai *et al.* are considerably lower than those found by us.; the Japanese workers were probably dealing with eutectic mixtures of the 5- and the 8-isomer. Further they failed to obtain 8-amino*iso*quinoline by reducing their 8-nitro*iso*quinoline.

We also separated the isomeric nitro*iso*quinolines by chromatography and, with sufficiently small quantities (*ca.* 50 mg.), this separation was readily visible under ultraviolet light in the dark.

Results

In the nitrations we were unable to account for more than about 90% of the starting material in terms of unchanged base and mononitro-derivatives. However, the proportions of isomers were not only independent of the initial concentration of nitric acid but remained unchanged when the mixture of mononitro-compounds produced was treated again with nitric acid in sulphuric acid. This is indicated in the Table, where in the column headed " 8-Isomer " the first two figures refer in each line to nitration with different amounts of nitric acid, and the third figure to a mixture from one of the preceding experiments after renitration.

Compound	Reaction temp.	8-Isomer (%) (± 1%)	Mean compn. of product : 5-isomer (%)	8-isomer (%)
Quinoline	0°	52·8, 51·8, 52·2	47·7 ± 1	52·3 ± 1
*iso*Quinoline	0	9·7, 9·2, 10·0	90·4 ± 1	9·6 ± 1
,, ...	100	15·1, 15·3, 15·1	84·8 ± 1	15·2 ± 1

Several attempts to follow the kinetics failed because the reactions were essentially complete in <1 min. at 0°. (Clearly the conditions of nitration used in the past for quinoline and *iso*quinoline have been unnecessarily violent.)

Competitive nitrations were also carried out between quinoline and *iso*quinoline, and between quinoline and acridine. The relative reactivities, evaluated by the method of Dewar, Mole, and Warford,[8] were : quinoline : *iso*quinoline = 1 : 24·5; quinoline : acridine = 1 : 190.

Discussion

As recently as 1950 Schofield [9] was able to state that the electrophilic substitution of heterocyclic compounds lacked a comprehensive explanation. Since then, however, considerable progress has been made, both on the experimental and on the theoretical side, and it now seems possible to begin to provide a satisfactory and comprehensive theory.

Most theoretical treatments of aromatic substitution are based on the Wheland model [10] of the transition state and in previous papers [1] of this series it has been shown that substitution in hydrocarbons can be well interpreted in such terms. In this approach it is necessary to know the relative π-electron energies of the parent aromatic compound and of the transition state; this energy difference can be estimated [2] by a simple molecular-orbital treatment. The object of the present paper is to extend this treatment to heterocyclic systems.

[7] Ochiai *et al.*, *J. Pharm. Soc. Japan*, 1945, **65**, 73; 1951, **71**, 1385; 1953, **73**, 660 (*Chem. Abs.*, 1951, **45**, 8526; 1952, **46**, 7101; 1954, **48**, 7014).
[8] Dewar, Mole, and Warford, *J.*, 1956, 3576.
[9] Schofield, *Quart. Rev.*, 1950, **4**, 382.
[10] Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.

The required equations have already been published.[11] The π-electron energy difference $\Delta E_\pi'$ for substitution in a heterocycle is given by :

$$\Delta E_\pi' = \Delta E_\pi - A\sum_i a_{oi}^2\alpha_i \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

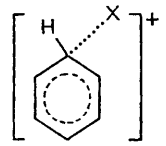
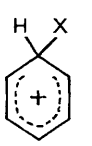
where ΔE_π is the corresponding energy difference for substitution at the corresponding position in the isoconjugate hydrocarbon, a_{oi} is the non-bonding molecular-orbital coefficient at atom i in the hydrocarbon transition state, α_i is the difference between the coulomb integral of atom i and that of carbon, and A has the value -1 for electrophilic, zero for radical, and $+1$ for nucleophilic substitution. The energy difference ΔE_π is given by :

$$\Delta E_\pi = 2\beta(a_{or} + a_{os}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where atoms r and s are those adjacent to the point of attack.

In applying equation (1) allowance must be made for the change in electronegativity of carbon atoms adjacent to heteroatoms, as the inductive effect operates along the intervening 4-bonds. It may be assumed [12] that if α is the coulomb term for a nitrogen atom, the coulomb terms of the adjacent carbon atoms are $1/3\alpha$, of the next adjacent atoms $1/9\alpha$, etc.; in practice only the nearest neighbours need be included.

In the simple Hückel treatment the appropriate value for the coulomb term (α) of nitrogen is found to lie between β and 2β (where β has its normal value of −20 kcal./mole). It was soon apparent that these values did not give agreement between the observed and the predicted values for substitutions. Further it has been shown earlier that β in

(I)  (II) 

equation (2) is not the normal carbon–carbon resonance integral; the transition state (I) does not have the structure (II) postulated by Wheland but a structure intermediate between (II) and the reactants. The quantity β in equation (2) is the difference between the carbon–carbon resonance integral in the parent hydrocarbon between the point of attack and the atoms r, s and the corresponding value in the transition state. Equation (2) can thus be rewritten as :

$$\Delta E_\pi = 2\beta_X'(a_{or} + a_{os}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where β_X' is the value that β will have for a substituting agent X. β_X' will vary according to the nature of X, being numerically smaller the more reactive the substituting agent. Its value in equation (3) for nitration in acetic anhydride has been found to be −6 kcal./mole.[1] For nitration with nitric acid in sulphuric acid, a more reactive agent, β_X' should be still smaller; we have assumed a value of −4 kcal./mole.

With the usual assumption that entropy effects can be neglected, it can be shown that, for a given reagent X, the velocity constant K_r of the reaction is given by :

$$\log K_r = A_X - (\Delta E_\pi)_i/\boldsymbol{R}T \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where A_X is a constant characteristic of X, and $(\Delta E_\pi)_i$ is the change in conjugation energy of the aromatic system when atom i is removed from it. In the case of the nitration of *iso*quinoline, the difference between the change in conjugation energies at the 8- and the 5-position ($\Delta E_8 - \Delta E_5 = \delta\Delta E_\pi$) is $(p_5/p_8)_T = \exp \delta\Delta E_\pi/\boldsymbol{R}T$, where p_5 and p_8 are the partial rate factors for 5- and 8-substitution respectively. Thus, if both reactions are

[11] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265, 275, 283.
[12] Dewar, *J.*, 1949, 463.

assumed complete, the experimental value for $\delta\Delta E_\pi$ can be obtained from a knowledge of the percentages of the isomers formed. Our results (9·6 ± 1% at 0°, and 15·2 ± 1% at 100°, of 8-nitro*iso*quinoline) give an average value of −1·27 ± 0·06 kcal./mole for $\delta\Delta E_\pi$. From calculations of the $\delta\Delta E_\pi$ values (see below), $\delta\Delta E_\pi$ can be shown to be $0{\cdot}032\alpha$. Thus $\alpha = -39{\cdot}7 \pm 2$ kcal./mole.

Such a value for α is not greater than the maximum value found appropriate in calculating ground-state properties of molecules by the Hückel method. The evidence therefore suggests that α has a value close to that found appropriate for calculating ground-state energies, etc., of heterocyclic compounds. This must be so if the theory is correct that the charge displacements in the transition state (I) are already close to those in the Wheland model (II); for if the charge displacements in (I) were less, α would have a numerically smaller value, just as β_X' in equation (3) is smaller numerically than the normal carbon–carbon resonance integral.

Naturally α has this value only in electrophilic substitutions where the nitrogen atom can certainly be assumed to be protonated. It has been shown by Brown [14] for free-radical, and by Chapman *et al.*[15] for electrophilic, substitution that α has values of approximately −10 and −25 kcal./mole respectively, suggesting that the ring-nitrogen atom has the greatest influence in determining substitution by electrophilic, and the least in determining substitution by free-radical, reagents, the order which would be expected.

We have adopted a value for α of −40 kcal./mole and for β_X' of −4 kcal./mole in the following calculations. Using these values and making the usual assumption that entropy effects can be neglected, we obtain remarkable agreement between predictions and experimental results. There are only two cases where the theory fails and these can be explained.

First, when the position being considered is *ortho* to the ring-nitrogen atom (as, for instance, the 8-position in quinoline and the 1-position in acridine). There are two reasons why this might be. One of the carbon atoms attached to this atom is adjacent to the nitrogen atom, therefore the electron density there and thus the coefficient will be higher than in the isoconjugate homocycle, making ΔE_π proportionately greater. A similar consideration applies to positions in the hetero-ring, but electrophilic substitution never occurs there. A second reason is that, under the conditions considered, the ring-nitrogen atom will almost invariably be protonated. Thus in attack at, say, the 8-position in quinoline, the NO_2^+ ion will approach close to a positively charged site and will be strongly hindered from substituting. Both these effects will oppose substitution *ortho* to nitrogen, and the proportion of this type of isomer will be less than expected.

The second case where the theory breaks down is for positions analogous to the 4-phenanthryl positions. It has been shown [1] that these positions are not as reactive in the hydrocarbon series as predicted, and steric hindrance in the formation of the transition state explains this for carbocyclic and heterocyclic compounds.

The results for a series of calculations on some six-membered heterocycles are listed below; the relative reactivities at different positions as calculated are compared with the experimental data. Values in parentheses are for positions where accurate value of the reactivity cannot be estimated for the reasons set out above.

$\Delta E_2 \ldots \Delta E_{10}$ refer to the values of ΔE_π for substitution at positions 2 . . . 10 in a given molecule, and are given in kcal./mole.

(1) *Pyridine.*

$\Delta E_2 = \Delta E_4 = 2{\cdot}31\beta + 0{\cdot}333\alpha = -22{\cdot}6$. $\Delta E_3 = 2{\cdot}31\beta + 0{\cdot}222\alpha = -18{\cdot}1$.

Pyridine is nitrated, with great difficulty,[16] at the 3-position, as predicted.

[13] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87; Dewar, *J.*, 1950, 2329; D. A. Brown and Dewar, *J.*, 1953, 2406; R. D. Brown, *Quart. Rev.*, 1952, **6**, 63.

[14] R. D. Brown, *J.*, 1956, 272.

[15] Chapman and Russel-Hill, *J.*, 1956, 1563; *Chem. and Ind.*, 1954, 281, 1298; see also Chapman, *Chem. Soc. Special Publn. No.* 3, 1955, p. 155.

[16] Den Hertog and Overhoff, *Rec. Trav. chim.*, 1930, **49**, 552.

(2) *Quinoline.*

$\Delta E_2 = 2{\cdot}12\beta + 0{\cdot}500\alpha = -28{\cdot}5.$ $\Delta E_6 = 2{\cdot}12\beta + 0{\cdot}083\alpha = -11{\cdot}8.$
$\Delta E_3 = 2{\cdot}12\beta + 0{\cdot}083\alpha = -11{\cdot}8.$ $\Delta E_7 = 2{\cdot}12\beta + 0{\cdot}125\alpha = -13{\cdot}5.$
$\Delta E_4 = 1{\cdot}81\beta + 0{\cdot}364\alpha = -21{\cdot}8.$ $\Delta E_8 = 1{\cdot}81\beta + 0{\cdot}059\alpha = -\ 9{\cdot}6.$
$\Delta E_5 = 1{\cdot}81\beta + 0{\cdot}091\alpha = -10{\cdot}9.$

The expected order of reactivity is (8) > 5 > 6 = 3 > 7 ⩾ 4 ⩾ (2). Experimentally we found roughly equal amounts of 5- and 8-nitroquinoline.

(3) iso*Quinoline.*

$\Delta E_1 = 1{\cdot}81\beta + 0{\cdot}364\alpha = -21{\cdot}8.$ $\Delta E_6 = 2{\cdot}12\beta + 0{\cdot}125\alpha = -13{\cdot}5.$
$\Delta E_3 = 2{\cdot}12\beta + 0{\cdot}125\alpha = -13{\cdot}5.$ $\Delta E_7 = 2{\cdot}12\beta + 0{\cdot}083\alpha = -11{\cdot}8.$
$\Delta E_4 = 1{\cdot}81\beta + 0{\cdot}243\alpha = -13{\cdot}0.$ $\Delta E_8 = 1{\cdot}81\beta + 0{\cdot}091\alpha = -10{\cdot}9.$
$\Delta E_5 = 1{\cdot}81\beta + 0{\cdot}059\alpha = -\ 9{\cdot}6.$

The expected order of reactivity is 5 > 8 > 7 > 4 > 6 = (3) ⩾ (1). In practice 9·6% of 8- and 90·4% of 5-nitro*iso*quinoline are formed at 0°.

(4) *Quinoxaline.*

$\Delta E_2 = \Delta E_3 = 2{\cdot}12\beta + 0{\cdot}583\alpha = -31{\cdot}8.$ $\Delta E_6 = \Delta E_7 = 2{\cdot}12\beta + 0{\cdot}208\alpha = -16{\cdot}8.$
$\Delta E_5 = \Delta E_8 = 1{\cdot}81\beta + 0{\cdot}151\alpha = -13{\cdot}3.$

The expected order of reactivity is (5) > 6 ⩾ (2). 5-Nitroquinoxaline was found as the sole monosubstituted derivative.[17]

(5) *Quinazoline.*

$\Delta E_2 = 2{\cdot}12\beta + 0{\cdot}625\alpha = -33{\cdot}5.$ $\Delta E_6 = 2{\cdot}12\beta + 0{\cdot}125\alpha = -13{\cdot}5.$
$\Delta E_4 = 1{\cdot}81\beta + 0{\cdot}728\alpha = -36{\cdot}8.$ $\Delta E_7 = 2{\cdot}12\beta + 0{\cdot}250\alpha = -18{\cdot}5.$
$\Delta E_5 = 1{\cdot}81\beta + 0{\cdot}182\alpha = -14{\cdot}5.$ $\Delta E_8 = 1{\cdot}81\beta + 0{\cdot}091\alpha = -10{\cdot}9.$

The expected order of reactivity is (8) > 6 > 5 > 7 ⩾ (4) > (2). Elderfield *et al.*[18] and Schofield and Swain [19] report formation of 6-nitroquinazoline (56%). No other isomers have been reported.

(6) *Cinnoline.*

$\Delta E_3 = 2{\cdot}12\beta + 0{\cdot}208\alpha = -16{\cdot}8.$ $\Delta E_5 = \Delta E_8 = 1{\cdot}81\beta + 0{\cdot}121\alpha = -\ 12{\cdot}1.$
$\Delta E_4 = 1{\cdot}81\beta + 0{\cdot}606\alpha = -31{\cdot}5.$ $\Delta E_6 = \Delta E_7 = 2{\cdot}12\beta + 0{\cdot}166\alpha = -\ 15{\cdot}1.$

The expected order of reactivity is 5 = (8) > 6 = 7 > (3) ⩾ 4. Morley [20] has reported 5-nitrocinnoline (33%) and 8-nitrocinnoline (28%) as the sole nitration products.

(7) *Acridine* (numbering recommended by Albert, " Heterocyclic Compounds," Vol. 4, Wiley, New York, 1952).

$\Delta E_1 = 1{\cdot}57\beta + 0{\cdot}026\alpha = -\ 7{\cdot}3.$ $\Delta E_4 = 1{\cdot}57\beta + 0{\cdot}154\alpha = -12{\cdot}4.$
$\Delta E_2 = 1{\cdot}89\beta + 0{\cdot}222\alpha = -16{\cdot}4.$ $\Delta E_5 = 1{\cdot}28\beta + 0{\cdot}400\alpha = -21{\cdot}1.$
$\Delta E_3 = 1{\cdot}89\beta + 0{\cdot}037\alpha = -\ 9{\cdot}0.$

The expected order of reactivity is (1) > 3 > 4 > 2 ⩾ 5. Lehmstedt [21] found 3 > 1 > 4. At 50° the ratio of the isomers 3 : 4 is calculated to be 42 : 1. Lehmstedt found it to be 25 : 1.

(8) *Phenanthridine.*

$\Delta E_1 = 1{\cdot}86\beta + 0{\cdot}092\alpha = -11{\cdot}1.$ $\Delta E_6 = 2{\cdot}04\beta + 0{\cdot}167\alpha = -14{\cdot}8.$
$\Delta E_2 = 2{\cdot}18\beta + 0{\cdot}048\alpha = -10{\cdot}6.$ $\Delta E_7 = 2{\cdot}18\beta + 0{\cdot}032\alpha = -10{\cdot}0.$
$\Delta E_3 = 2{\cdot}04\beta + 0{\cdot}111\alpha = -12{\cdot}6.$ $\Delta E_8 = 1{\cdot}86\beta + 0{\cdot}138\alpha = -13{\cdot}0.$
$\Delta E_4 = 1{\cdot}96\beta + 0{\cdot}039\alpha = -\ 9{\cdot}4.$ $\Delta E_9 = 1{\cdot}80\beta + 0{\cdot}516\alpha = -27{\cdot}8.$
$\Delta E_5 = 1{\cdot}96\beta + 0{\cdot}026\alpha = -\ 8{\cdot}9.$

[17] Dewar and Maitlis, preceding paper.
[18] Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 418.
[19] Schofield and Swain, *J.*, 1949, 1367.
[20] Morley, *J.*, 1951, 1972; cf. Alford and Schofield, *J.*, 1953, 611.
[21] Lehmstedt, *Ber.*, 1938, **71**, 808.

The expected order of reactivity is (5) > (4) > 7 > (1) > 3 > 8 > 6 ⩾ (9). The calculated percentages of isomers formed at 100° are: 8, 0·2%; 3, 0·3%; 1, 2·6%; 2, 5·2%; 7, 8·4%; 4, 26·8%; 5, 53·1%. Caldwell and Walls [22] found: 3, 3% 1, 1%; 2, 6%; 7, 11%; 4, 26%; 5, 21%.

(9) *Benzo*[f]*quinoline* (Ring Index numbering).

$\Delta E_1 = 1{\cdot}86\beta + 0{\cdot}310\alpha = -19{\cdot}8$. $\Delta E_7 = 1{\cdot}86\beta + 0{\cdot}034\alpha = -8{\cdot}8$.
$\Delta E_2 = 2{\cdot}12\beta + 0{\cdot}127\alpha = -13{\cdot}6$. $\Delta E_8 = 2{\cdot}18\beta + 0{\cdot}032\alpha = -10{\cdot}0$.
$\Delta E_3 = 2{\cdot}04\beta + 0{\cdot}375\alpha = -23{\cdot}2$. $\Delta E_9 = 2{\cdot}04\beta + 0{\cdot}042\alpha = -9{\cdot}8$.
$\Delta E_5 = 1{\cdot}80\beta + 0{\cdot}022\alpha = -8{\cdot}1$. $\Delta E_{10} = 1{\cdot}96\beta + 0{\cdot}026\alpha = -8{\cdot}9$.
$\Delta E_6 = 1{\cdot}80\beta + 0{\cdot}129\alpha = -12{\cdot}4$.

The expected order of reactivity is (5) > 7 > (10) > 9 > 8 > 6 > 2 ⩾ (1) ⩾ (3). The order of reactivity found was 7 > 10 > 9. The calculated ratio of isomers, 7 : 9 at 0° is 6·7 : 1. Ochiai *et al.*[23] found it to be 5·7 : 1; Boehm [24] found it as 4·8 : 1.

(10) *Phenazine.*

$\Delta E_1 = 1{\cdot}57\beta + 0{\cdot}180\alpha = -13{\cdot}5$. $\Delta E_2 = 1{\cdot}89\beta + 0{\cdot}259\alpha = -17{\cdot}9$.

The 1- would be expected to be formed in preference to the 2-isomer. Maffei and Aymon [25] reported finding the 1-isomer as the sole mono-substituted product.

(11) *Benzo*[c]*cinnoline* (Ring Index numbering).

$\Delta E_1 = 1{\cdot}96\beta + 0{\cdot}051\alpha = -10{\cdot}0$. $\Delta E_3 = 2{\cdot}18\beta + 0{\cdot}063\alpha = -11{\cdot}3$.
$\Delta E_2 = 2{\cdot}04\beta + 0{\cdot}222\alpha = -17{\cdot}0$. $\Delta E_4 = 1{\cdot}86\beta + 0{\cdot}184\alpha = -14{\cdot}8$.

The expected order of reactivity is (1) > 3 > (4) > 2. Smith and Ruby [26] found 1-nitrobenzo[*c*]cinnoline (57%) together with another substance which they considered to be the 3-isomer (12%).

Except in this paper, no attempt has been made to compare the relative reactivities of two heterocycles. From our results the ratio of the partial rate factors $K_{5\text{-nitro}iso\text{quinoline}} : K_{5\text{-nitroquinoline}}$ was calculated [8] to be 46·4 : 1. From the above calculations $\Delta E_{\pi(5\text{-nitroquinoline})} - \Delta E_{\pi(5\text{-nitro}iso\text{quinoline})}$ is found to be −1·3 kcal./mole. This gives a theoretical value for the ratio of these partial rate factors of 10·5 : 1.

An attempt was also made to see whether the allowance to be made for positions *ortho* to the nitrogen atom was constant, by comparing the reactivities of the 8-position in quinoline with those for the 1-position in acridine. Using the figures obtained by Lehmstedt [21] for the ratios of mononitroacridines formed in nitration, we arrived at a value of 27·5 : 1 for the ratio of the partial rate factors, 8-nitroquinoline : 1-nitroacridine. The calculated value is 79 : 1.

In both these cases, having regard to the difficulty of obtaining accurate experimental data, it must be concluded that the correspondence between the experimental facts and theory is of the correct order.

Experimental

Microanalyses were by the Microanalytical Laboratory, Imperial College of Science and Technology, London.

Materials.—*iso*Quinoline (from B.D.H.) was recrystallised. Commercial quinoline of " puriss." grade was used for some experiments; this contained 5·9% of *iso*quinoline, estimated as previously described.[27] Allowance could be made for this impurity since nitro*iso*quinolines can easily be separated from nitroquinolines by chromatography. In the quinoline–acridine

[22] Caldwell and Walls, *J.*, 1952, 2156.
[23] Ochiai and Tamura, *J. Pharm. Soc. Japan*, 1952, **72**, 985 (*Chem. Abs.* 1953, **47**, 12385).
[24] Boehm, *Roczniki Chem.*, 1950, **24**, 128.
[25] Maffei and Aymon, *Gazzetta*, 1954, **84**, 667.
[26] Smith and Ruby, *J. Amer. Chem. Soc.*, 1954, **76**, 5807.
[27] Maitlis, *Analyst*, 1957, **82**, 135.

competitive nitration, synthetic quinoline was used. The nitric acid was commercial fuming nitric acid (*d* 1·5; HNO_3 97%); sulphuric acid (*d* 1·84) was used as a medium for all nitrations. Solvents for chromatography were distilled before use. Light petroleum was of b. p. 40—60° unless otherwise stated.

6- and 8-Nitroquinoline were available commercially; the 5- and the 7-isomer were prepared by Bradford, Elliot, and Rowe's method.[28] 5-Nitro*iso*quinoline (m. p. 110·5—111·5°) was obtained by repeated recrystallisation (from aqueous alcohol) of the nitration product from *iso*quinoline. All the isomers were crystallised to constant m. p. and vacuum-sublimed before use. Spectra were measured on a Unicam S.P.500 spectrophotometer; *cyclo*hexane (spectroscopically pure) was used as solvent.

8-*Nitro*iso*quinoline*.—Nitric acid (6·2 ml.) was added to a solution of *iso*quinoline *N*-oxide [7] (18 g.) in sulphuric acid (80 ml.) and the mixture heated for 1 hr. at 95°, cooled, and poured on ice. The nitro*iso*quinoline *N*-oxides were isolated with chloroform and recrystallised from acetone, to give 5-nitro*iso*quinoline *N*-oxide (13 g., 64%), which after recrystallisation from nitromethane had m. p. 220—221° (lit., 220°). The mother-liquors, on evaporation, left a black tar, which was chromatographed on alumina to give fractions (*a*) *iso*quinoline *N*-oxide (2·2 g.) and (*b*) a yellow solid (2·7 g.) which on fractional crystallisation from acetone gave 8-nitro*iso*quinoline *N*-oxide (1·4 g., 7%), m. p. 188—189° (Found: C, 57·1; H, 3·2; N, 14·9. Calc. for $C_9H_6O_3N_2$: C, 56·8; H, 3·2; N, 14·7%). A solution of the *N*-oxide (0·5 g.) in phosphorus trichloride (7 ml.) was boiled under reflux for 30 min.; water was then added and the 8-nitro*iso*quinoline isolated with chloroform, chromatographed, and crystallised from ether–light petroleum to m. p. 87—87·5° (yield 65%) (Found: C, 61·9; H, 3·3; N, 15·8. Calc. for $C_9H_6O_2N_2$: C, 62·1; H, 3·4; N, 16·1%).

Reduction of the nitro-compound with hydrazine hydrate and palladized charcoal (cf. Dewar and Mole [29]) gave 8-amino*iso*quinoline (60%), yellow needles (from light petroleum), m. p. 170—171° (lit.,[5] 171°). 5-Nitro*iso*quinoline was prepared from the *N*-oxide in an analogous manner in 52% yield.

Nitrations of Quinoline and iso*Quinoline*.—The reactions were carried out in sulphuric acid, a solution of nitric acid being added gradually to one of the base. After 30 min. the solutions were poured on ice. The mononitro-fraction was separated by partial basification (at pH 2·1 for quinoline; at pH 2·5 for *iso*quinoline) from unchanged base and analysed spectroscopically. The results were evaluated by Dewar and Urch's method,[30] which is highly accurate for two-component mixtures (in this case better than ±1%). In the quinoline series, both the 5- and the 8-nitroquinoline have peaks around 300 mμ and troughs at about 250 mμ, whereas the 3-, 6-, and 7-isomer have considerable peaks at 250 mμ; this would make it possible to detect less than 1% of any of these isomers. Further no anomalies could be found in the spectra of any of the mixtures such as would be caused by the presence of a third isomer. The peaks of the spectra are given (log ε values in parentheses):

Quinoline	Max.
3-Nitro ...	252 mμ (4·58), 298 mμ (4·14)
5-Nitro ...	305 mμ (3·80)
6-Nitro ...	249 mμ (4·40), 257 mμ (4·34), 286 mμ (3·98)
7-Nitro ...	249 mμ (4·35), 257 mμ (4·28), 286 mμ (3·96)
8-Nitro ...	275 mμ (3·74), 301 mμ (3·54), 315 mμ (3·52)

*iso*Quinoline	Max.
5-Nitro- ...	235 mμ (4·12), 333 mμ (3·70)
8-Nitro ...	235 mμ (4·17), 292 mμ (3·56), 328 mμ (3·54)

Check experiments were also carried out in which the mixtures of nitro-compounds were re-treated with the nitration mixture; in each case at least 95% of the material was recovered. The nitration data are summarised in the following Table (Q = quinoline; I = *iso*quinoline).

Summary of nitration experiments.

Base	Temp.	Base (g.)	Solution (ml.)	10% HNO_3 (ml.)	Base recovered (mol. %)	Nitro-isomers isolated (mol. %)
Q	0°	1·738	20	2·0	69	24
Q	0	1·738	20	4·0	44	46
I	0	5·120	30	7·0	45	38
I	0	5·120	30	15·0	2	80
I	100	5·120	30	7·0	52	36
I	100	5·120	30	15·0	15	75

[28] Bradford, Elliot, and Rowe, *J.*, 1947, 442.
[29] Dewar and Mole, *J.*, 1956, 2556.
[30] Dewar and Urch, *J.*, 1957, 345.

Competitive Nitration of Quinoline and iso*Quinoline.*—A mixture of *iso*quinoline (4·452 g.) and quinoline (8·500 g.) (both corr. for the presence of 5·9% of *iso*quinoline in the quinoline) was dissolved in sulphuric acid and the volume made up to 90 ml. (*A*). A solution of nitric acid in sulphuric acid (10% v/v/; 2·7 ml.) was added to solution (*A*) (30 ml.), and the mixture was kept at 0° with stirring for 30 min., then worked up in the usual way, partial basification being carried out at pH 2·5. The solid residue of mixed nitroquinolines and nitro*iso*quinolines was chromatographed. A second parallel nitration was carried out. Results were :

(*a*) nitroquinolines 0·092 g.; nitro*iso*quinolines 0·904 g.

(*b*) nitroquinolines 0·088 g.; nitro*iso*quinolines 0·884 g.

Competitive Nitration of Quinoline and Acridine.—A mixture of pure synthetic quinoline (7·042 g.) and acridine (1·176 g.) was dissolved in concentrated sulphuric acid (15 ml.); to this was added nitric acid in sulphuric acid (10% v/v; 2·0 ml.) with stirring at 0°. The whole was left at this temperature for 30 min., then poured on ice. By the usual procedure of partial basification a solid fraction was obtained not containing any quinoline. This was chromatographed in benzene–light petroleum (1 : 1) on alumina. The material soon separated into two bands, the first fluorescent, but with a small dark patch in it visible under ultraviolet light (acridine, 0·755 g., containing a small amount of nitroquinolines). It was not possible to separate the mixture of nitroquinoline and acridine, and it was therefore hoped that it would be possible to analyse the mixture microanalytically, since the percentages of carbon in the two constituents were so different. Unfortunately the results were not very consistent and an average value (C, 84·2%) had to be used, corresponding to 11·8% of nitroquinolines (0·033 g.) in the mixture.

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QUEEN MARY COLLEGE, UNIVERSITY OF LONDON, E.1. [*Received, January 1st,* 1957.]