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Electrophilic Substitution in the Series of Six-membered Nitrogen-containing Heteroaromatic Compounds and Their *N*-Oxides

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This review deals with the present state of the problem of electrophilic substitution in the series of six-membered nitrogen-containing heterocycles using as an example simple derivatives of neutral monoazines and diazines, their *N*-oxides, and certain condensed structures containing not more than 2 nitrogen atoms in one ring. Much attention has been devoted to problems of the comparison of the reactivities of heteroaromatic compounds with the results of theoretical calculations by the molecular orbital method and also the application of kinetic methods to the determination of the nature of the reactants. The bibliography includes 199 references.

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1. INTRODUCTION

The extensive data on the reactivities of various nitrogen-containing heterocycles have been comprehensively described in the literature. The problems of the chemistry and in particular the electrophilic substitution of heterocyclic compounds which are extremely important both theoretically and in practice, such as mono- and diazines (pyridine, pyrazine, pyrimidine, etc.), their benzo-derivatives (quinoline, quinoxaline, etc.), and also more complex condensed structures, containing together with nitrogen atoms also other heteroatoms (phenoxazine, phenothiazine, and others), have been discussed in detail in reviews edited by Elderfield[1], Weissberger[2], and Katritzky[3] and in a number of monographs[4-6].

Studies by Soviet scientists have made a valuable contribution to the development of the chemistry of nitrogen-containing heterocyclic compounds. In this connection, mention should be made of the work of Yur'ev[7,8], Rubtsov[9], Nesmeyanov and Kochetkov[10,11], Postovskii[12], and many others[13,14]. In recent years, considerable advances, associated primarily with the study of the mechanism of heteroaromatic substitution, have been made in research on the reactivities of nitrogen-containing heterocyclic compounds. These advances have been reviewed recently by Katritzky[15] and Ridd[16,17] and also in monographs by Schofield[18] and Palmer[19] based on data from both experimental and theoretical studies of the mechanisms of these reactions.

In the present review an attempt is made to examine in detail the results of investigations of electrophilic substitution in the series of six-membered aromatic nitrogen-containing heterocycles from the standpoint of modern concepts of reaction mechanisms and also to compare these results with the calculated indices of the reactivity of the compounds. Neutral model systems are chosen for dis-

cussion: pyridine and also pyridazine, pyrimidine, and pyrazine (i.e. heterocycles containing not more than two nitrogen atoms in the ring) and some of their condensed systems and *N*-oxides.

The electrophilic substitution reaction in the series of nitrogen-containing six-membered heteroaromatic compounds takes place under much more severe conditions than those involving the corresponding hydrocarbons, i.e. the replacement of a =CH group by the more electronegative nitrogen atoms leads to a decrease of reactivity in both the heterocyclic and the fused aromatic ring. Thus the ring nitrogen atom plays the role of an electron-accepting *meta*-directing substituent.

On the whole, electrophilic substitution in the heterocyclic series has much in common with substitution in the series of aromatic-hydrocarbons. The directive influence of substituents on electrophilic attack in the series of six-membered nitrogen-containing heteroaromatic compounds is qualitatively the same as for aromatic hydrocarbons. Thus powerful electron-accepting groups (NO_2, SO_3H, COOH) hinder electrophilic substitution of pyridine derivatives, while powerful electron-donating groups (OH, NH_2, OR, NR_2) greatly facilitate such reactions.

Quantitatively the effect of substituents is different for heterocyclic and aromatic systems. For example, comparison of the rates of nitration of chloro- and methoxypyridines and the corresponding substituted benzene derivatives shows that the same substituents exhibit greater conjugative effects in pyridine than in benzene[15].

The principal characteristic of electrophilic substitution reactions in the heteroaromatic series is that the attack by electrophilic agents may be directed to the nitrogen atom, by virtue of its *p*-electron pair (an analogous situation is encountered in the series of amino-derivatives of aromatic compounds). The ease of this reaction depends on the electron density at the nitrogen atom and also on steric factors.

As a result of electrophilic attack, the nitrogen atom acquires a positive charge, which strongly deactivates the carbon atoms in the ring. Calculation of the partial rate factors for the nitration and hydrogen isotope exchange reactions of substituted pyridine derivatives in neutral and protonated forms shows that the replacement of a =CH group in benzene by the $=\overset{+}{N}H-$ group deactivates the ring in the *meta*-position much more than the replacement by =N– (the rate constants for these reactions in the case of the protonated and neutral forms are reduced relative to the rate constants for the reactions of benzene by a factor of 10^{12}–10^{18} and 10^{6}–10^{7} respectively)[20,21].

The effect of the nitrogen atom and the $=\overset{+}{N}H-$ group in pyridine on the reactivity of the ring carbon atoms can also be estimated quantitatively with the aid of Hammett's σ constants, with =N– and $=\overset{+}{N}H-$ regarded as ring substituents introduced into the benzene molecule[22].

	α	β	γ
$\sigma_{=N-}$	0.8	0.6	0.9
$\sigma_{=\overset{+}{N}H-}$	—	2.1	2.3

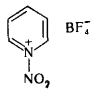
The constants quoted are smallest for the β-position, which is consistent with the *meta*-directing effect of the substituting groups in electrophilic substitution reactions. Moreover, all the $\sigma_{=N-}$ are smaller than $\sigma_{=\overset{+}{N}H-}$, which is evidence of the greater reactivity of the neutral pyridine molecule compared with its cations. This is consistent with the conclusion based on the calculation of the partial rate factors for substitution in the pyridine series.

Experimental studies of the mechanism of electrophilic substitution in the heteroaromatic series permits solution of the problem of the nature of the reactive species—whether it is the free base or the species resulting from preliminary addition of a proton or the attacking agent to the nitrogen atom. These processes are frequently reversible and therefore even in weakly acid solutions there is a low equilibrium concentration of the free base. Furthermore, the predominant species present in solution is not always active, so that the nature of the reactive form of the compound may be established only by kinetic methods.

Since the mode of electrophilic substitution reactions in heterocyclic compounds, as well as in aromatic compounds, is determined by the state of the electron cloud in the molecule, the application of the molecular orbital theory permits the prediction of the preferred location of the substituent. For this purpose, one uses as the indices of reactivity the π-electron density, boundary π-electron density, localisation energy, etc.

2. SUBSTITUTION IN THE PYRIDINE SERIES

Electrophilic attack on unsubstituted pyridine is directed to the carbon atom in the 3-position. Pyridine is nitrated under very severe conditions—in oleum at 300°C—with a low yield (4.5%).[23] The kinetics of this process cannot be studied, since it has still not been established whether the result of this type of nitration is a consequence of the low reactivity of the positively charged pyridinium ion or whether the reaction involves the very small amount of the free base in the highly acid medium. The nitration of pyridine in a homogeneous aprotic medium at 30°C, using a solution of nitronium tetrafluoroborate (NO_2BF_4) in sulpholane (tetrahydrothiophen 1,1-dioxide), results in the formation of an *N*-nitropyridinium ion, as shown by ultraviolet and NMR spectroscopy[24]:



The sulphonation of pyridine also takes place in the 3-position under severe conditions (H_2SO_4–SO_3, 350°C).[25] Many electrophilic substitution reactions of pyridine derivatives are catalysed by salts of di- and ter-valent metals [$Hg(CH_3COO)_2$, $AlCl_3$, etc.], which can probably be accounted for by partial transfer of electron density from the coordinated metal atom to the nitrogen atom. This tends to decrease the formal positive charge of the nitrogen atom and consequently of the ring as a whole[26]. The use of optimum conditions for the sulphonation of pyridine—heating for 24 h in 20% oleum at 220–230°C in the presence of catalytic amounts of mercury(II) sulphate—leads to the formation of pyridine-3-sulphonic acid in 71% yield[27].

Gas-phase halogenation of pyridine at 300°C leads to the formation of 3-mono- and 3,5-di-halogeno-derivatives, while at 500°C 2-mono- and 2,6-di-halogeno-substituted compounds are formed[28]; probably in the latter case the reaction takes place not by an electrophilic but by a radical mechanism. Recently a method was described for the direct halogenation of pyridine in sulphuryl chloride or phosphorus oxychloride[29]. Thus bromination in the presence of one equivalent of sulphuryl chloride at 160–170°C gives a 45% yield of 3,5-dibromopyridine, while in phosphorus oxychloride the yield is about 20%. It is interesting to note that sulphuryl chloride is itself an electrophilic agent as a result of ionisation of the type $\overset{\delta+}{Cl}-\overset{\delta-}{SO_2Cl}$.[30]

Pyridine readily combines with mercury(II) acetate at 155°C, giving a 35% yield of 3-pyridylmercury acetate[31].

According to the LCAO-MO calculation[32,33], the electron densities q_r at the C_3 atom of pyridine and its cation is greater and the localisation energy for electrophilic substitution A_e smaller than the corresponding values for C_2 and C_4 (Table 1). Consequently electrophilic substitution of pyridine, both as a neutral molecule and in the protonated form, should be directed to the 3-position, in agreement with experiment.

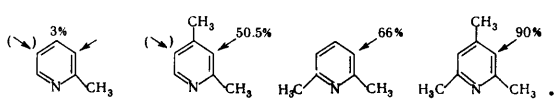
Table 1. Indices of the reactivity of pyridine[32,33].

Structure	q_r, charge units	A_e (−β)	position of carbon atoms	A_e (−β)	q_r, charge units	Structure
	0.923 1.004 0.950	2.672 2.538 2.701	2- 3- 4-	2.709 2.560 3.071	0.759 1.012 0.835	

Note. This and other Tables present the results obtained by the simple Hückel method without taking into account adjacent orbital overlap, using the parameters $h = 0.5$ and $h' = 0$ for the tertiary nitrogen atom and $h = 2$ and $h' = 0.2$ for the secondary nitrogen atom[34]. It should be noted that the predicted positions of highest reactivity for a given heterocyclic compound obtained by this method and also by the more accurate self-consistent field calculations agree[33].

On the other hand, the correlation between the calculated data and the observed relative reactivities in the series benzene–pyridine–pyridinium cation is unsatisfactory. While the capacity for electrophilic substitution decreases on going from benzene to pyridine, the electron density at the C_3 carbon atom of pyridine is higher than for benzene ($q_r = 1$) and the localisation energy for the pyridine C_3 atom is lower than for benzene ($A_e = 2.540$); moreover, the electron density at the carbon atom in the 3-position increases on transition from pyridine to its cation.

Depending on the position of the activating group, substituted pyridine derivatives can undergo electrophilic attack in the $\alpha\alpha'$- or $\beta\beta'$-positions. The nitration of alkylpyridines takes place more readily than that of unsubstituted pyridine. Thus 2-mono-, 2,4-, and 2,6-di- and 2,4,6-tri-methylpyridines interact with potassium nitrate or nitric acid in sulphuric acid at 100–160°C with formation of 3-mononitro-derivatives (in the case of 2-picoline and 2,4-lutidine, as a result of the concerted directing effects of the CH_3 groups and the nitrogen atom, an equimolar mixture of 3- and 5-mono-nitrocompounds is obtained), the yield in these reactions increasing with the number of methyl groups in the pyridine molecule[35–37]:

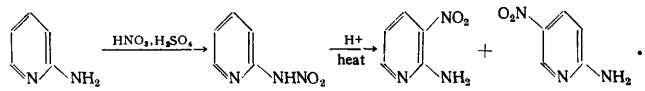


Nitration of the cation of 1,2,4,6-tetramethylpyridine in the 3-position takes place under the same conditions as the nitration of 2,4,6-trimethylpyridine and therefore the latter compound reacts in the protonated form[38]. This conclusion has also been confirmed by kinetic investigations.

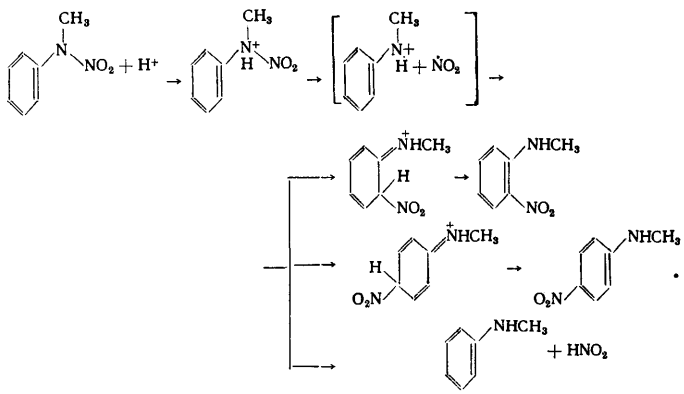
Katritzky and coworkers[21] established that the variation of the nitration rate constant with the acidity of the medium is similar for collidine and its *N*-methyl cation; the maximum possible rate constant for the reaction with participation of the free base, calculated on the basis of the transition state theory (2.26×10^9 litre mole^{-1} s^{-1}), is much less than the experimental rate constant (1.6×10^{11} litre mole^{-1} s^{-1}); finally, the entropy of activation for this reaction is −26.7 e.u. The theoretical entropy of activation should be higher for a reaction between two charged species (about −20 e.u.) than between a neutral molecule and a monocation[39]. All these data show that 2,4,6-trimethylpyridine enters into the nitration reaction in the protonated form.

Nitration of 3-bromopyridine as well as nitration of unsubstituted pyridine takes place under very severe conditions—with potassium nitrate in 10% oleum at 270°C in the presence of iron as a catalyst—and leads to the formation of 3-bromo-5-nitropyridine in 7% yield[40]. Thus the *ortho–para*-directing effect of the halogen atom in the pyridine series is less than the *meta*-directing effect of the ring nitrogen (or the $=\overset{+}{N}H$ group).

The presence in pyridine of the powerful electron-donating amino-group greatly facilitates electrophilic attack on the ring of the molecule. Nitration of 2-aminopyridine with nitric acid and sulphuric acid takes place in two stages: at 20°C and below 2-aminonitropyridine is formed initially and then at 40°C it undergoes endothermic rearrangement to a mixture of 2-amino-3-nitro- and 2-amino-5-nitropyridines in proportions of 1 : 8[41,42]:

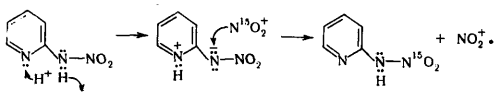


The preferential substitution in the *para*-position relative to the amino-group in this reaction is evidence of an intermolecular or a partially intermolecular nature of the rearrangement. On the basis of a spectrophotometric determination of the amount of nitrous acid formed in the rearrangement of *N*-methyl-*N*-nitroaniline, it has been suggested[43] that the acid-catalysed rearrangement of the nitroamines takes place with dissociation of the N–NO_2 bond and the intermediate formation of two free radicals and therefore further reaction takes place not by an electrophilic but by a radical mechanism:



On the other hand, there are data supporting an intramolecular mechanism of the rearrangement. In a study of the rearrangement of α-nitroaminopyridine in sulphuric acid in the presence of sodium nitrate containing nitrogen-15, it was found that the labelled nitrogen enters into

α-amino-β-nitro- and α-amino-β'-nitro-pyridines in a smaller amount than that remaining in the nitrate. The exchange of nitro-groups under these conditions probably involves a mechanism with electrophilic substitution at the amino-nitrogen, where a negative charge appears in consequence of the removal of a proton under the influence of two strongly electron-accepting groups[44]:



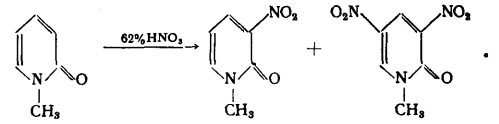
4-Aminopyridine is nitrated in the 3-position; the reaction also proceeds via a stage with rearrangement of the *N*-nitroamine but at a higher temperature (160°C). It is interesting to note that 3-nitroaminopyridine does not rearrange to the aminonitro-compound, while 3-(*N*-methyl-*N*-nitroamino)pyridine is readily converted into 3-methylamino-2-nitropyridine[45].

Table 2. Nitration of alkoxy- and hydroxy-pyridines with nitric acid.

R	R'	Reaction conditions: medium	Reaction conditions: temp., °C	Position of entry of NO_2 group	Yield, %	Refs.
2-CH_3O (C_2H_5O)	H	H_2SO_4	100	5-	—	46, 47
3-CH_3O (C_2H_5O)	H	H_2SO_4	60—80	2-	44.5 (80)	48, 49
3-CH_3O	H	H_2SO_4	120	2,6-	—	50
3-C_2H_5O	2-Br	H_2SO_4	55	6-	75	49
2-OH	H	H_2SO_4	0	3-; 3,5-	—	51
2-OH	6-CH_3	CH_3COOH	100	3-	—	52
2-OH	3-NO_2	H_2SO_4	80	5-	50.5	53
2-OH	5-NO_2 (COOH)	HNO_3(*d* 1.52),	50—80	3-	38 (46.5)	51
3-OH	H	H_2SO_4	0	2-	—	54
3-OH	2-NO_2	CH_3COOH	30	6-	68	55
3-OH	2-CH_3 (Cl)	H_2SO_4	0—5	4-; 6-	26.6	56
3-OH	2-CH_3	H_2SO_4	20	4,6-	52	57
3-OH	2,6-$(CH_3)_2$	H_2SO_4	20	4-	80	57
4-OH	H	H_2SO_4	100	3-	31	58
4-OH	2-OH 2-Cl	HNO_3(*d* 1,4),	100	3-	87	59
4-OH	3-CH_2CH_2Cl 6-OH	HNO_3(33%)	20	5-	48	60

For alkoxy- and hydroxy-pyridines, as for aminopyridines, the mode of the electrophilic substitution reaction is determined by the *ortho–para*-directing effect of the substituents present in the molecule. Table 2 presents data on the nitration of various alkoxy- and hydroxypyridines.

It is striking that in the nitration of 2-alkoxypyridines *para*-substitution takes place, while in the analogous reaction of 2-hydroxypyridines *ortho*-substitution is preferred. This difference in the mode of the nitration reactions of alkoxy- and hydroxy-derivatives of pyridine may be attributed to the tautomeric equilibrium of the hydroxy-compounds. Since 2-hydroxypyridine is present in solutions mainly in the oxo-form[61], it may also participate in the reaction in this form. This conclusion is confirmed by the preferred *ortho*-substitution in *N*-methyl-2-pyridone, which has a fixed lactam structure[51]:



Moreover, it has been established by kinetic methods that 4-hydroxypyridine, which like 2-hydroxypyridine is present in solutions in the pyridone form[61], enters into hydrogen isotope exchange in an acid medium in the oxo-form[62].

Another explanation of the *ortho*-nitration of 2-hydroxypyridine, namely that the substance reacts in the hydroxy-form and in the transition complex the NO_2 and OH groups are coordinated[63], appears to be unlikely.

The possibility in principle of the nitration of substituted pyridine in the γ-position relative to the heteroatom when the α-position is blocked was recently demonstrated by Dyumaev and coworkers[57] for 2-mono- and 2,6-di-alkyl-3-hydroxypyridines and then independently by De Selms[58] for 3-hydroxy-2-methylpyridine and 2-chloro-3-hydroxypyridine.

A systematic study of the kinetics of the nitration of a number of substituted pyridines in sulphuric acid enabled Katritzky and coworkers[64] to establish the following facts. In the nitration of more basic pyridines ($pK_a > +1$) containing electron-donating groups, the compounds react in the protonated form. Weakly basic pyridines ($pK_a < -2.5$) are nitrated as free bases. The behaviour of compounds with intermediate pK_a values has not as yet been investigated. The ring position occupied by nitro-groups is consistent with the general dependence on the type of substituents in the molecule.

Thus 2,6-dichloropyridine ($pK_a = -2.86$) is smoothly nitrated in the 3-position at 100°C.[21] At first sight this result is unexpected, since the chlorine atom in the benzene ring has a deactivating effect, but in the case of 2,6-dichloropyridine the reaction takes place via the free base, which is more reactive than the corresponding pyridinium cation[21]. In the case of 2,6- and 3,5-dimethoxypyridines, which are nitrated in the protonated form ($pK_a = 1.60$ and 4.44 respectively), the introduction of the first nitro-group reduces the basicity of substituted pyridines to such an extent that the mononitro-compounds formed ($pK_a = -3.86$ and -2.52) react further as free bases[21,64]:

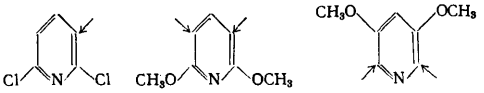


Table 3. Activation parameters for the nitration of substituted pyridine derivatives[21,64].

Substituted pyridine	H_0	E_a, kcal mole^{-1}	$\Delta S^{\neq}$, e.u.
2,6-Dichloro-	—8.15	27.1	+13.1
2,6-Dimethoxy	—8.99	13.1	—18.2
2,6-Dimethoxy-3-nitro-	—8.89	19.7	+12.4
3,5-Dimethoxy-	—9.00	12.5	—20.0
3,5-Dimethoxy-3-nitro-	—8.97	22.7	+15.9

The conclusions concerning the form in which chloro- and methoxy-pyridines are nitrated were based on a study of the kinetics of the processes, and in particular on the estimation of the activation parameters of these reactions (Table 3).

It follows from the data in Table 3 that all the above compounds may be divided into two groups with $\Delta S^{\neq}$ from +12 to +16 e.u. and from −18 to −20 e.u. This difference in activation entropy is evidence that they react by different mechanisms[39], namely that the compounds of the first group react as free bases and those of the second group in the protonated form.

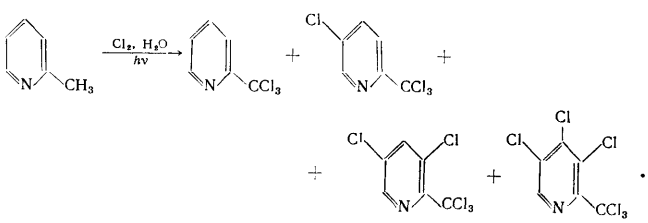
Comparison of the dependence of the nitration rate constants of substituted pyridines on the acidity of the medium with the theoretical dependence calculated for each of the possible reacting species on the basis that substituted pyridines are Hammett bases leads to the same conclusion [65].

The determination by kinetic methods of the form in which unsubstituted pyridine is nitrated is impossible. Most probably the reaction takes place as for methylpyridines, with participation of the pyridinium cation, since the pyridine nitrogen is fairly basic (for pyridine, pK_a = 5.23). [64]

A kinetic study of the mechanism of electrophilic substitution in the series of substituted pyridines has also been made in acid-catalysed hydrogen isotope exchange.

On heating, the tritilation of 2,6-lutidine and 2,4,6-collidine in a sulphuric acid–trityl ether mixture takes place in the 3- and 5-positions [20]. The study of the kinetics of these reactions showed that the protonated species are subjected to electrophilic attack; the reaction was shown to be pseudomonomolecular and to have an AS_E2 mechanism [20].

The halogenation of alkylpyridines as well as their nitration takes place under milder conditions than the halogenation of unsubstituted pyridine. Thus 2- and 4-picolines are readily brominated in the 3- and 5-positions at 80°C in the presence of aluminium chloride [26]. The chlorination of 2-picoline with chlorine water in the light involves homolytic substitution of the side chain and subsequent electrophilic substitution of the ring; under the same conditions, 3- and 4-picolines do not react [66]:



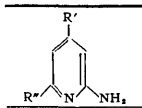
Bromination of monohalogenopyridines as well as their nitration requires more severe conditions. 2-Bromopyridine reacts with bromine in the gas phase at 300°C in the presence of an iron salt with formation of a mixture of 2,5-dibromo- and 2,3,5-tribromo-derivatives [28].

Halogenation of 2-aminopyridines takes place readily under mild conditions in the 5-position with formation of aminomonohalogenopyridines. Halogenation under severe conditions leads to 3,5-dihalogeno-derivatives. Thus *para*-substitution relative to the amino-group is preferred for 2-aminopyridines both in halogenation and in nitration (Table 4). 4-Aminopyridines are also halogenated in the 3- and 5-positions [68] and 3-aminopyridines in the 2- and 6-positions [69].

Halogenation of hydroxypyridines takes place under mild conditions. 2- and 4-Hydroxypyridines are readily brominated with bromine water, forming 3,5-dibromo-derivatives [70]. Bromination of 2,4-dihydroxypyridines under the same conditions leads only to the 3-monobromo-substituted compound. Analogous results were obtained in a study of the bromination of 2-ethoxy-4-pyridone and 4-ethoxy-2-pyridone—in these compounds the carbon atom between the carbonyl and ether groups is most reactive [71]. On the other hand, 2,4-diethoxypyridine is brominated in the 5-position, which may be associated with the steric screening of the carbon atom in the 3-position by the two ethoxy-groups [71].

In contrast to nitration, bromination of 3-hydroxypyridine takes place readily in aqueous solution at 20°C in the 2-, 4-, and 6-positions with formation of a tribromo-derivative (yield 50%). [72]

Table 4. Bromination of 2-aminopyridines with free bromine [67].



R′	R″	Reaction conditions: medium	Reaction conditions: temp., °C	Position of entry of bromide
CH_3	H	—		5-
H	CH_3	20 % H_2SO_4	0	5-
H	CH_3	20 % H_2SO_4	35	3,5-
CH_3	CH_3	—		5-
Br	H	CH_3COOH	0	5-
Br	H	CH_3COOH	20	3,5-
H	Br	CH_3COOH	0	5-; 3,5-
Br	Br	CH_3COOH	0	5-; 3,5-
C_2H_5	H	H_2SO_4	100	3,5-

Sulphonation of alkylpyridines takes place under the same conditions (20% oleum, 220°C, $HgSO_4$ catalyst) as that of unsubstituted pyridine but with a lower yield (for example, the yields of monosulphonic acids for 2-, 3-, and 4-picolines are 60, 23, and 40% respectively [27]), owing to a side reaction involving the oxidation of the alkyl groups in concentrated sulphuric acid. The position of the sulpho-group is determined by the *meta*-directing effect of the ring nitrogen atom, since only the 5-sulphonic acid is obtained from 3-picoline on sulphonation. In contrast to nitration, sulphonation of 2-picoline also takes place only in the 5-position. In all probability, under the above sulphonation conditions, picoline reacts in the protonated form. If one excludes the possibility of protonation, then substitution of the hydrogen atom takes place under much milder conditions. Thus 2,6-di-t-butylpyridine with a sterically screened nitrogen atom is readily sulphonated with sulphur trioxide in the 3-position at −10°C. [73]

In the sulphonation of aminopyridines substituted in different positions the location of the sulpho-groups is the same as in halogenation, but only monosulphonic acids are formed [74].

3. SUBSTITUTION IN THE DIAZINE SERIES

Diazines are more inert in electrophilic substitution reactions than monoazines let alone benzene. In the pyrimidine molecule the 5-position is most aromatic, which is consistent with the calculations of electron densities q_r and localisation energy A_e for this compound in both neutral and protonated form. In pyrazine and pyridazine molecules, where the nitrogen atoms are in the *para*- and *ortho*-positions relative to one another, the electronegative effects of both are not concerted and their resultant effect is much weakened. According to calculations, the electron charge q_r at any carbon atom in pyrazine and pyridazine, in both the neutral molecule and the cation, is higher than in the 2- and 4-positions but lower than in the 5-position of pyrimidine (Table 5).

The reactivity of unsubstituted pyrimidine is extremely low; for successful nitration, nitrosation, and sulphonation, the pyrimidine molecule must contain at least two activating electron-donating groups[77]. Thus 2- or 4-hydroxypyridine is not nitrated. 2,4-Dihydroxypyrimidine (uracil) is nitrated in boiling fuming nitric acid in the 5-position[78]. 4,6-Dihydroxypyrimidine and its derivatives are also nitrated in the 5-position but under milder conditions—in acetic acid at 20°C. This difference may be associated with the state of tautomeric equilibrium involving these dihydroxypyrimidines—it has been established by numerous spectroscopic studies that, while 2,4-dihydroxypyrimidine exists preferentially in the diketo-form, 4,6-dihydroxypyrimidine has one phenolic and one oxo-group[79]:

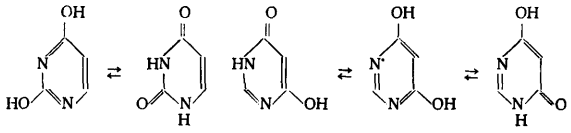


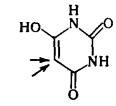
Table 5. Indices of the reactivities of pyrimidine, pyrazine, and pyridazine[32,33,75,76].

Neutral form	q_r, charge units	A_e (−β)	Position of carbon atom	A_e (−β)	q_r, charge units	Protonated form
	0.845 0.874 1.009	2.865 2.691 2.539	2- 4- 5-	3.456 3.146 2.579	0.467 0.632 1.029	
	0.926	2.664	2-	2.667	0.735	
	0.970 0.982	—	3- 4-	—	0.866 0.922	

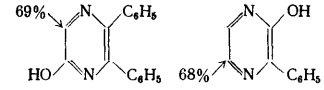
When the pyrimidine molecule contains together with the hydroxy-group also an amino- or alkylamino-group, nitration takes place in the 5-position at 50–60°C (nitric acid in sulphuric acid)[80,81].

For successful halogenation of pyrimidine derivatives, it is sufficient if one hydroxy or amino-group or two alkoxy-groups are present in the 2-, 4-, or 6-positions[82]. Halogenation takes place readily in the 5-position on heating with halogenosuccinimide in acetic acid or chloroform[82].

The halogenation of 2,4-dihydroxypyrimidine (uracil) and 2,4,6-dihydroxypyrimidine (barbituric acid) takes place in a more complex manner. On halogenation, barbituric acid gives rise initially to 5-mono- and then 5,5-di-halogeno-substituted compounds. The mechanism of this reaction has not been completely elucidated—it may involve the addition of HOHal to the double bond between the C_4 and C_5 atoms with subsequent dehydration[77]. Uracil usually yields monohalogeno-derivatives, but bromination in an aqueous medium yields 5,5-dibromo-2,4,6-trihydroxy-4,5-dihydropyrimidine[83], i.e. initially there is substitution in the 5-position accompanied by 4,5-addition[84]. This reaction differs fundamentally from the halogenation of barbituric acid:

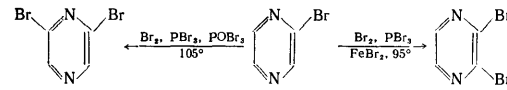


Electrophilic substitution in the pyrazine series, as in the pyrimidine series, usually requires the presence in the molecule of activating hydroxy- or amino-groups[85]. Thus arylpyrazines are nitrated in the benzene ring while the nitration of 2-hydroxy-5,6-diphenylpyrazine with fuming nitric acid in acetic acid at 25°C takes place in high yield in the 3-position of the pyrazine ring[86]. 2-Hydroxy-3-phenylpyrazine is nitrated under the same conditions in the *para*-position relative to the hydroxy-group[87]:



The halogenation of pyrazine can take place also in the absence of activating groups in the molecule, but under very severe conditions—in the vapour phase at 400°C.[88] Bromopyrazine is obtained also when pyrazine hydrobromide is treated with bromine in an inert solvent: the reaction results initially in the formation of a perbromide, which on heating to 200–250°C rearranges to 2-bromopyrazine[89].

Depending on the reaction conditions, the bromination of monobromopyrazine takes place in different positions in the molecule and leads to 2,3-[90] or 2,6-dibromo-derivatives[91]:



The mode of halogenation of hydroxypyrazines is determined by the *ortho–para*-directing effect of the hydroxy-group. Thus 2-hydroxy-3-methylpyrazine is brominated with bromine in chloroform in the 5-position (yield 20%); under the same conditions, 2-hydroxy-5,6-dimethylpyrazine gives the 3-bromo-derivatives (yield 61%), while 2-hydroxy-3,5-dimethylpyrazine is not brominated at all[87].

Substitution in the pyridazine series has been inadequately investigated. The pyridazine ring is very resistant to electrophilic substitution reactions. Powerful nitrating agents either have no effect at all on pyridazine or cause it to char[92]. 3-Pyridazinone also does not change under the action of the nitrating mixture, probably because of the low reactivity of the cation formed[93]. The introduction of a nitro-group into the pyridazine molecule takes place successfully only when amino-derivatives are employed and involves the rearrangement of the corresponding nitroamines. Thus nitration of 4-amino-3-methoxy-6-methylpyridazine with potassium nitrate in sulphuric acid at 20°C takes place in the 5-position[93], while 3,5-diaminopyridazine is nitrated in the 4-position[94].

Chlorination of 6-methyl-2-phenyl-3-pyridazinone with phosphorus pentachloride at 160°C leads mainly to the 4-chloro-derivative[95], while 3,6-dichloropyridazine forms with phosphorus pentachloride the 3,4,5,6-tetrachloro-derivative[96]. Under these conditions, 2,6-dimethyl-3-pyridazinone is not chlorinated and on reaction with chlorine at 100°C is substituted in the 5-position[97].

4. SUBSTITUTION IN THE BENZOMONOAZINE (QUINOLINE, ISOQUINOLINE, ACRIDINE) SERIES

In heteroatomic compounds containing a condensed benzene ring electrophilic substitution may take place both in the benzene and in the heterocyclic ring, depending on the reaction conditions.

In sulphuric acid quinoline is substituted in the 5- and 8-position. Nitration of quinoline with fuming nitric acid in concentrated sulphuric acid at 0°C yields a mixture of almost equal amounts of the 5- and 8-mononitro-derivatives[98].

Quinoline is nitrated faster than pyridine because of the presence of the condensed benzene ring; the rate of this process can be readily measured. The considerable rate of reaction (higher by a factor of 10^2 than expected for a diffusion-dependent process with participation of the free base) and the variation of the reaction rate constant with the acidity of the medium in the range 85–98% sulphuric acid are evidence that the nitronium cation reacts with the protonated species—the quinolinium cation[99]. The participation of quinoline in the nitration reaction as a protonated species is consistent also with the calculated entropy of activation for this reaction (−9.3 e.u; see p. 629) and is confirmed by a comparison of the rates of nitration of quinoline and the methylquinolinium ion[100].

Table 6. Indices of the reactivity of quinoline[98,101,102].

Neutral form	q_r, charge units	A_e* (−β)	Position of carbon atom	A_e** (−β)	q_r, charge units	Protonated form
	0.896	2.725	2-	4.75	0.690	
	1.008	2.487	3-	1.97	1.267	
	0.932	2.500	4-	3.63	0.787	
	0.988	2.350	5-	1.82	0.967	
	1.003	2.475	6-	1.97	1.078	
	0.984	2.544	7-	2.26	0.950	
	1.012	2.306	8-	1.60	1.346	

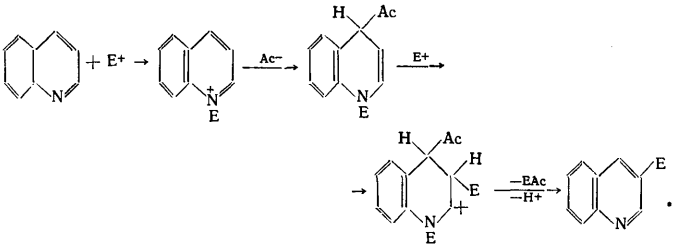
* Data presented in a graphical form.

** The energy data (in kcal mole^{-1}) have been expressed in units of $-\beta$, assuming that β = 6 kcal mole^{-1}.

It is noteworthy that the location of electrophilic substituents in the quinolinium cation is in good agreement with the calculated localisation energies for electrophilic substitution (A_e is a minimum for the 5- and 8-positions) but is in much worse agreement with the distribution of electron densities in this system (Table 6).

Calculation of the partial rates of nitration of quinoline and naphthalene in an acid medium shows that the 5- and 8-positions of the quinolinium ion are deactivated compared with the 1-position of naphthalene by a factor of 10^{10}. This result differs from the data obtained by the calculation of the localisation energy, which shows that the 5- and 8-positions of the quinolinium ion are less reactive than the 1-position of naphthalene by a factor of 5 and 100 respectively[99]. Probably the methods employed to calculate the localisation energy to a large extent underestimate the effects of the heteroatom of the aromatic system.

In the nitration of quinoline with nitric acid in acetic anhydride a low yield (about 6%) is obtained of 3-nitroquinoline and traces (0.7%) of the 6- and 8-isomers[103]. Probably under these conditions the non-protonated form mainly reacts; then the distribution of π-electron densities in the neutral quinoline molecule correctly indicates the location of the substituent in the 3-, 6-, and 8-positions but is inconsistent with the relative amounts of the isomers (3 > 6 and 8). This finding can be readily explained if one assumes that the reaction involves an addition–elimination mechanism, i.e. initially there is 1,2- or 1,4-addition of a weak nucleophilic agent (acetyl anion) and then substitution in the dihydroquinoline system[103]. Since this system does not have a positive charge, one may expect on substitution a correlation between the reactivity and the distribution of π-electron density. Calculations for 1,2-dihydroquinoline yields the following sequence of the decrease of π-electron density: 8 > 6 > 3, and for 1,4-dihydroquinoline: 3 > 6 > 8.[101] Thus the proposed mechanism for electrophilic substitution in the neutral quinoline molecule involves a preliminary 1,4-addition stage:



In the halogenation of quinoline the location of the substituent depends on the acidity of the medium, as happens in the nitration reaction. Thus, in the bromination of quinoline in sulphuric acid substitution takes place in the 5- and 8-positions[104] and in acetic acid in the 3-, 6-, and 8-positions[105]. Hence by varying the experimental conditions for the electrophilic substitution reaction, it is possible to obtain a number of quinoline derivatives differing in the positions of the substituents (Table 7).

Table 7. Bromination of quinoline[106].

Position of substituent	Yield, %	Reaction conditions
2-Bromo-	(50—60)	Br_2, 500°C, vapour phase
3-Bromo- 6-Bromo-	(91) (~2)	Br_2, CCl_4, pyridine, heat
4-Bromo-		neat treatment of 3-bromoquinoline hydrobromide, 300°C
5-Bromo- 8-Bromo-	(28) (29)	Br_2, Ag_2SO_4, H_2SO_4
1,1-Dibromo-	(~100)	Br_2, CCl_4, in the cold
3,6-Dibromo- 3,6,8-Tribromo-	(35)	Br_2, glacial CH_3COOH
5,8-Dibromo 5,6,8-Tribromo-	(43)	$2Br_2$, Ag_2SO_4, H_2SO_4 $3Br_2$, Ag_2SO_4, H_2SO_4

Depending on temperature, the sulphonation of quinoline (200–300°C) yields quinoline-5-, quinoline-6-, quinoline-7-, and quinoline-8-sulphonic acids or their mixture[107], the formation of these derivatives being probably determined by the stability of the quinolinium ion.

Quinoline substituted in the benzene ring usually directs electrophilic agents to the 5- or 8-position in an acid medium regardless of the nature of the substituent already present. Thus, electrophilic substitution of 8-hydroxyquinoline—halogenation, sulphonation, nitrosation, and mercuration—takes place preferentially in the 5-position, while under more severe conditions 5,7-disubstitution takes place. It is interesting that in the direct nitration

of 8-hydroxyquinoline with 37% nitric acid in sulphuric acid at 20°C it is impossible to isolate the mononitro-compound, only 8-hydroxy-5,7-dinitroquinoline being obtained in 57% yield[108].

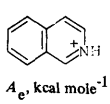
The presence of substituents in the pyridine ring of quinoline can alter significantly the position of the reaction centre relative to unsubstituted quinoline. Thus 4-hydroxyquinoline is nitrated in sulphuric acid as the protonated species, largely with formation of the 6-nitro-derivative[109].

Electrophilic substitution in two different positions has been observed for isoquinoline, as for quinoline. Nitration of isoquinoline by fuming nitric acid in concentrated sulphuric acid at 0°C gives a mixture of 5- and 8-mononitroisoquinolines, the 5-nitro-isomer predominating considerably (90.4%)[98], while under more severe conditions only the 5,7-dinitro-compound is formed. In the study of the kinetics of the nitration of isoquinoline it has been established that the reaction takes place with participation of the protonated form of isoquinoline, as in the nitration of quinoline. The simultaneous nitration of a quinoline–isoquinoline mixture shows that the ratio of the reactivities of these compounds is 1 : 24.5. [98]

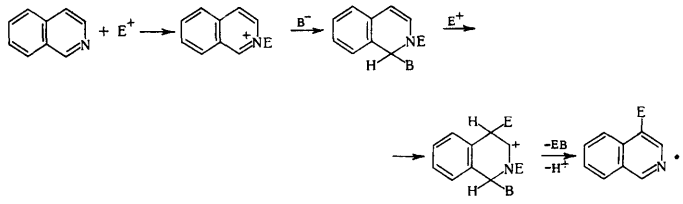
The fact that the reactivity of isoquinoline in electrophilic substitution reactions is higher than that of quinoline follows also from a comparison of the conditions for the sulphonation of these compounds. Isoquinoline is sulphonated under milder conditions (40% oleum, 180–200°C) than quinoline, and only isoquinoline-5-sulphonic acid is formed[110].

The location of the nitro- and sulpho-groups in the 5-position in the nitration and sulphonation of isoquinoline in a strong acid is in good agreement with the calculated localisation energies A_e for electrophilic substitution (Table 8).

Table 8. Indices of the reactivity of isoquinoline[98,111].

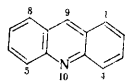
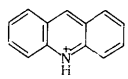
Position	 q_r, charge units	 A_e, kcal mole^{-1}
1-	0.844	—21.8
3-	0.943	—13.5
4-	0.973	—13.0
5-	1.001	—9.5
6-	0.968	—13.5
7-	0.992	—11.8
8-	0.971	—10.9

The mercuration of isoquinoline with mercury(II) acetate at 150–160°C takes place smoothly in the 4-position[112]; bromination takes place in the same position when isoquinolinium perbromide or its salts are heated[113]. Substitution in the 4-position is inconsistent with the distribution of electron densities q_r in the neutral isoquinoline molecule—calculation shows that the electron densities decrease in the sequence 5 > 7 > 4 ≃ 8 (Table 8). The experimentally observed mode of reaction can be accounted for by a 1,2-addition mechanism:



Calculation of the distribution of π-electron density in the 1,2-dihydrocation yields a higher value for the 4-position[34].

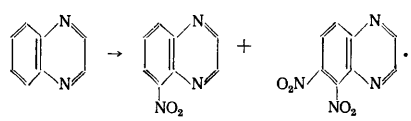
Table 9. Indices of the reactivity of acridine[98,115].

Position	 q_r, charge units	 A_e, kcal mole^{-1}
1-	0.984	—12.4
2-	1.005	—9.0
3-	0.979	—16.4
4-	1.016	—7.3
9-	0.915	—21.1

Substitution in the acridine series has been investigated in less detail. Nitration of acridine in sulphuric acid gives a mixture of 13% of the 4- and 68% of the 2-mononitro-derivative and a certain amount of 1- (3%) and 3-isomers (< 1%)[114]. This ratio of the 2- and 4-substituted compounds is unexpected, since it is inconsistent either with the distribution of π-electron density or with the localisation energies (Table 9). The reaction probably proceeds via the protonated form of the acridine molecule[98]. Evidently the above calculations fail to take adequate account of the inductive effect of the nitrogen atom in the α-position of the acridine molecule.

5. SUBSTITUTION IN THE BENZODIAZINE (QUINOXALINE, PHENAZINE, CINNOLINE, QUINAZOLINE) SERIES

Quinoxaline is resistant to nitration under mild conditions; when it is treated with fuming nitric acid in oleum at 90°C for 24 h, 1.5% of 5-mononitroquinoxaline and 24% of 5,6-dinitroquinoxaline are obtained[116]. The location of the electrophilic agent in the 5-position agrees well with calculated data (Table 10). It is interesting to note that the second nitro-group enters the *ortho*-position and not the *meta*-position relative to the first:



The presence of polar substituents in both the pyrazine and the benzene ring of quinoxaline favours electrophilic substitution. Nitration of 6-methoxyquinoxaline with potassium nitrate in sulphuric acid at 0°C takes place

readily in the 5-position; 5-methoxyquinoxaline yields on nitration the 6,8-dinitro-derivative, and it is impossible to isolate the mononitro-compound[117].

The location of the substituent in the nitration of 2-hydroxyquinoxaline, which is a very weak base ($pK_a = 1.37$), depends on the acidity of the medium; in acetic acid the 7-nitro-derivative is obtained[117], while in sulphuric acid the product is the 6-isomer[118]. Possibly the neutral molecule is nitrated in acetic acid and the monocation in sulphuric acid:

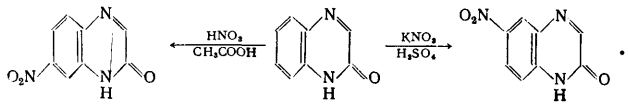
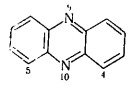


Table 10. Indices of the reactivities of quinoxaline and phenazine[98,102,111].

Structure	Neutral form q_r, charge units	Dication A_e, kcal mole^{-1}	Position of carbon atom	Dication A_e, kcal mole^{-1}	Neutral form q_r, charge units	Structure
	0.902 1.002 0.987	—31.8 —13.3 —16.8	1- 2- 5- 6-	—13.5 —17.9	0.991 0.955	

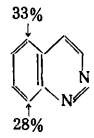
Substitution in the 6-position is observed also when quinoxaline-2,3-dione is treated with potassium nitrate in sulphuric acid; in the presence of an excess of the nitrate, the 6,7-dinitro-derivative is formed[119]. When quinoxaline is refluxed in aqueous nitric acid, the product is 6-nitroquinoxaline-2,3-dione, probably in consequence of the oxidation of quinoxaline and subsequent nitration of quinoxaline-2,3-dione[120].

Like quinoxaline, phenazine (Table 10) reacts with electrophilic agents only under very severe conditions. The α-carbon atoms are reactive in this case, in full agreement with calculation. Probably both quinoxaline and phenazine interact in the protonated form with electrophilic agents in an acid medium.

The nitration of phenazine with a mixture of nitric acid ($d = 1.42$) and sulphuric acid at 130°C gives 1-nitrophenazine in 1.5% yield. It is striking that in the nitration of phenazine under conditions corresponding to the synthesis of dinitro-derivatives, the nitro-groups enter into different benzene rings. Thus in the reaction with sulphuric acid with a tenfold excess of nitric acid ($d = 1.48$) at 70°C, a mixture of 1,5- and 1,8-dinitrophenazines is formed in 80% yield[121].

When phenazine derivatives with electron-donating substituents in the β-position are nitrated, the nitro-group enters the α-position adjacent to the substituent already present; in the nitration of substituted phenazines with electron-donating substituents in the α-position, the nitro-group enters the *para*-position relative to the substituent already present, with formation of 1,4-substituted phenazine derivatives[121].

Substitution reactions in the cinnoline and quinazoline series have been investigated much less than in the quinoxaline series and in the phthalazine series they are altogether unknown. Nitration of cinnoline with fuming nitric acid in concentrated sulphuric acid between −5° and 20°C yields a mixture of almost equal amounts of the 5- and 8-nitrocinnolines:



Under the same conditions, 4-methylcinnoline gives only the 8-nitro-derivative in 49% yield[122].

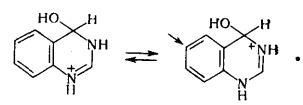
By comparing the rates of nitration of the 2-methylcinnolinium, 2-methylisoquinolinium, and isoquinolinium cations, it has been shown that in 76–83% sulphuric acid cinnoline is nitrated as the cation[123]. It is known that the cinnolinium monocation is formed with the positive charge in the 2-position[124]. The non-protonated nitrogen atom (N_1) deactivates the system of the cinnolinium cation to a greater extent than that of the isoquinolinium cation by a factor of 2×10^2 and the carbon atom in the 5-position is deactivated more than in the 8-position[123]. This leads to an increase in the amount of the 8-nitro-isomer in the nitration of cinnoline compared with the amount of the nitro-derivative formed in the nitration of isoquinoline.

The location of nitro-groups in the nitration of cinnoline agrees well with the distribution of π-electron density in the neutral molecule of this compound and the localisation energy of its cation (Table 11).

Table 11. Indices of the reactivities of cinnoline and quinazoline[98,102].

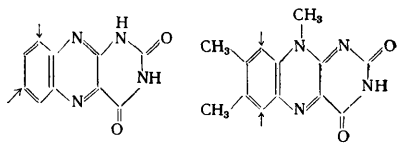
Structure	Neutral form q_r, charge units	Dication A_e, kcal mole^{-1}	Position of carbon atom	Dication A_e, kcal mole^{-1}	Neutral form q_r, charge units	Structure
	0.950 0.938 0.991 0.987 0.983 0.998	—16.8 —31.5 —12.1 —15.1 —15.1 —12.1	2- 3- 4- 5- 6- 7- 8-	—33.5 —36.8 —14.5 —13.5 —18.5 —10.9	0.841 0.830 0.973 1.003 0.969 1.016	

In contrast to the nitration of quinoline and isoquinoline, quinazoline is nitrated in an acid medium in the 6-position[125], which agrees poorly with theoretical calculations (Table 11). However, in a study of ultraviolet spectra of quinazoline solutions in sulphuric acid it has been established that the quinazolinium cation readily undergoes covalent hydration[126] and consequently electrophilic substitution in the hydrated cation takes place in the *para*-position relative to the NH group:



It is noteworthy that, among more complex condensed structures, compounds of the alloxazine and isoalloxazine series readily enter into electrophilic substitution reactions. Unsubstituted alloxazine is nitrated in a mixture of fuming nitric and concentrated sulphuric acid at 20°C with formation of the 6- and 8-mononitro-derivatives in proportions of 2:3, while in the nitration in oleum at 70°C 6,8-dinitroalloxazine is obtained[127]. This mode of the alloxazine nitration reaction corresponds to the distribution of π-electron density in the neutral alloxazine molecule[128]: there

are no calculated data available in the literature for protonated structures of this series.



6,7-Dimethyl-substituted alloxazines and isoalloxazines are nitrated in the 5- and 8-positions under mild conditions[129].

6. ELECTROPHILIC SUBSTITUTION OF HETEROAROMATIC *N*-OXIDES

Substitution reactions in the series of *N*-oxides of nitrogen-containing heterocyclic bases, which are unusually reactive, are of particular interest. Linton[130], Jaffé[131], and Katritzky et al.[132] demonstrated the presence in heterocyclic *N*-oxides of two opposed electronic effects due to the electron-accepting properties of the positively charged nitrogen atom on the one hand and the conjugation of the free electron pair of the oxygen atom in the N→O group with the π-electrons of the ring on the other. By virtue of the dual effect of the *N*-oxide group on the electronic structure of the heteroaromatic ring, electrophilic and nucleophilic substitution in this series may involve the same position in the molecule[133,134].

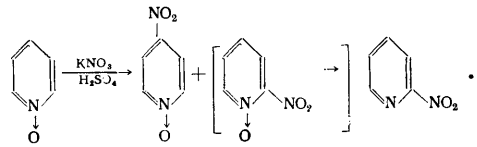
At the instant of the electrophilic substitution reaction, the *N*-oxide group in the neutral molecule is readily polarised and exhibits at the same time electron-donating properties and a *para*-orienting effect. An electrophilic agent may attack the ring of the *N*-oxide in the α- or γ-position, where, by virtue of the positive effect of conjugation, an enhanced electron density is created. However, the reaction in the γ-position should take place particularly readily, since the effect of conjugation in the α-position is partially compensated by the opposed inductive effect of the neighbouring nitrogen atom:



The presence of the N→O group in the molecule not only alters the mode of substitution in the initial heterocycle but also facilitates electrophilic substitution.

Tupitsyn and coworkers[135] investigated the kinetics of base-catalysed deuterium exchange involving methyl groups in isomeric picolines, quinaldines and their *N*-oxides, reactions which simulate electrophilic substitution in a side-chain of heterocycles, and showed that the *N*-oxides undergo exchange much faster than the non-oxidised bases. The authors discovered the main features of the mechanism of the transmission of the electronic effects of the heteroatoms on the reaction centre[136,137]. Similarly reactions involving substitution of the ring hydrogen atoms are faster with the *N*-oxides than with the initial heterocycles.

Indeed, in contrast to the nitration of pyridine, the nitration of pyridine *N*-oxide with potassium nitrate in sulphuric acid at 100°C takes place in the 4-position in 94% yield[138]. It is noteworthy that this involves the formation also of a small amount (1.5–4%) of 2-nitropyridine, probably in consequence of the reduction of its *N*-oxide[139]:

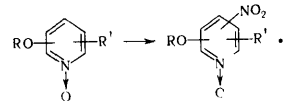


The *N*-oxides of alkyl- and halogeno-substituted pyridines are smoothly nitrated in the 4-position. Thus the *N*-oxides of 2-mono- and 2,6-di-methyl-[138], chloro[140,141], and bromo-pyridines[142,143] are nitrated with nitric acid in sulphuric acid at 90–100°C with formation of 4-nitro-derivatives as the sole reaction products. The same mode of substitution is noted also in the nitration of the *N*-oxides of 3-alkyl-, 3,5- or 2,5-dialkyl-[144–146], or 3-halogeno-pyridines[147,148] under identical conditions. Thus the strong *para*-directing effect of the *N*-oxide group is shown in these reactions.

The *N*-oxides of 2,4-lutidine and 2,4,6-collidine, where the 4-position is blocked by an alkyl group, are resistant to nitration under similar conditions[149].

It is interesting to note that, in the presence of the bulky t-butyl group in the 3-position of pyridine *N*-oxide, nitration takes place not in the γ-position but in the α-position and subsequent reduction leads to 3-t-butyl-2-nitro- or 3-t-butyl-6-nitro-pyridines; the isopropyl group does not show this type of effect[150].

Table 12. Nitration of the *N*-oxides of alkoxy- and hydroxy-pyridines with nitric acid



OR	R′	Reaction conditions: medium	Reaction conditions: temp., °C	Position of entry of NO_2 group	Yield, %	Refs.
2-OC_2H_5	H	H_2SO_4	85	4-	10—15	142
(OCH_3)	H	H_2SO_4	75	4-	55—60	151
3-OC_2H_5	H	H_2SO_4	85	4-	70—80	142
(OCH_3)	H	H_2SO_4	75	4-	70—75	151
3-OH	H	H_2SO_4	0—15	2-	60.5	152
2-OH	H	CH_3COOH	0	5-	67	153
2-OH	H	CH_3COOH	40	3,5-	—	154
4-OH	H	CH_3COOH	90—100	3,5-	80	155
4-OH	2-CH_3	CH_3COOH	65—75	3,5-	15	156
4-OH	3- or 5-NO_2	CH_3COOH	65—75	3,5-	—	156
3-OC_2H_5	5-OC_2H_5	H_2SO_4	0	2-	100	157
3-OC_2H_5	5-OC_2H_5	H_2SO_4	85	2,6-	90—95*	157
3-OCH_3	5-Br	H_2SO_4	30—35	2-	80	158
3-OCH_3	5-OCH_3	H_2SO_4	0°	2-	—	158

* With simultaneous de-oxidation of the *N*-oxide.

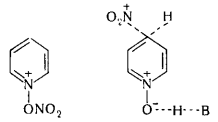
In electrophilic substitution reactions in the series of pyridine *N*-oxides the directing effect of the N→O group is greater than that of the alkoxy-group but smaller than the effect of the hydroxy-group. This is consistent with substitution in the 4-position in the *N*-oxides of alkoxy-pyridines and in the 2- or 3- and 5-positions of the *N*-oxides of hydroxy-derivatives of pyridine (Table 12).

It is striking that in the presence of two alkoxy-groups in the 3- and 5-positions, substitution takes place at the C_2 and C_6 carbon atoms[157,158], the authors explaining this

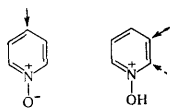
effect by the steric hindrance arising when the substitution reaction involves the 4-position. However, subsequently, using kinetic methods, it was shown that the difference in the location of the nitro-group in the *N*-oxides of 2- [2-6? (Ed. of Translation)] and 3,5-dialkoxypyridines is due to the fact that they undergo nitration in different forms[159].

It should, however, be noted that the mechanism of electrophilic substitution reactions in the series of pyridine *N*-oxides cannot be regarded as finally elucidated. The conclusions drawn from the study of the kinetics of the reactions may be contradictory when they are based on different kinetic criteria for the determination of the nature of the reactant. Thus Schofield and coworkers[160] showed that the *N*-methoxypyridinium cation does not react with nitric acid in 88% sulphuric acid at 95–125°C, i.e. under conditions where the *N*-oxide of pyridine is readily substituted in the γ-position. Probably the neutral molecule of the *N*-oxide participates in the latter reaction.

Subsequently, on the basis of a study of the dependence of the rate constant for the nitration of the *N*-oxide of 2,6-dimethylpyridine in the 4-position on the acidity of the medium, it was shown that the *N*-oxide of 2,6-lutidine is also nitrated as the neutral molecule[161]. The following activation parameters are quoted for these reactions: $E = 23.9$ kcal mole^{-1} and $\lg A = 10.7$ at 25°C in 81.4% sulphuric acid[161]. However, subsequently the same authors' calculations showed that the theoretical value is $\lg A = 4$ for this process and is even smaller when the *N*-oxide reacts in the protonated form[162]. Therefore it is possible that the reaction takes place either with formation of a pre-equilibrium *O*-nitro-complex, which then slowly rearranges to the 4-nitro-compound, or the nitronium cation is bound to the C_4 carbon atom of the pyridine ring and the proton is removed synchronously from the *N*-oxide group[162]:



On the other hand, in a study of the kinetics of the nitration of a number of substituted *N*-oxides of pyridine, Katritzky and coworkers[159] concluded that in the case of substitution in the 4-position *N*-oxides react as the free bases and in the case of 2- or 3-substitution as the protonated species:



The conclusion that in the nitration in the 4-position the *N*-oxides of substituted pyridines react as the free bases is confirmed also by the finding that the entropy of activation for these compounds (Table 13) is much lower than −20 e.u., i.e. the theoretical entropy of activation for the reaction of two charged species[39]. The estimation of the absolute reaction rates leads to the same conclusion: the experimental rate of nitration of the above *N*-oxides (10^{-1}–10^{-5} litre mole s^{-1}) is much lower than the limiting rate of the diffusion process with participation of the free bases (8.5×10^8 litre mole s^{-1}).

The kinetics of the nitration of the *N*-oxides of substituted pyridines in the β-position have been investigated for the *N*-oxides of 2,4,6-trimethoxy-, 2,6-dimethoxy-, and 4-methoxy-2,6-dimethylpyridines and the kinetics of α-nitration have been studied for the *N*-oxides of 3,5-dimethoxy- and 3,5-dimethoxy-2-nitropyridines[159].

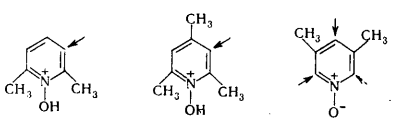
Examination of the dependence of the rate constants for α- and β-nitration on the acidity of the medium established that in all the examples quoted *N*-oxides react in the protonated form. For substitution in the α-position, this is also confirmed by a comparison of the rates of nitration of the *N*-oxides of 3,5-dimethoxypyridine and the 1,3,5-trimethoxypyridinium cation (this method has not been used for β-substitution).

The activation parameters have been determined for the nitration of substituted pyridine *N*-oxides in the α- or β-positions, as for γ-nitration (see above) (Table 13). The entropies of activation in the β-position ($\Delta S^{\neq}$ between −17 and −26 e.u.) agree well with the expected value of $\Delta S^{\neq}$ for a reaction with participation of the protonated form of the *N*-oxide. However, the entropy of activation for α-nitration (−12.3 e.u.) is lower than the expected value (−20 e.u.)[39].

Table 13. Activation parameters for the nitration of substituted pyridine *N*-oxides[159].

Position of substituent	Position of entry of NO_2 group	H_2SO_4, %	E_a, kcal mole^{-1}	$\lg A$	$\Delta S^{\neq}$
—	4-	87.9	23.5		
3,5-$(CH_3)_2$	4-	91.8	25.3	19.0	+26.3
2,6-Cl_2	4-	82.4	26.9	13.5	+1.5
3,5-Cl_2	4-	90.0	27.8	14.0	+15.1
2,4,6-$(OCH_3)_3$	3-	81.0	16.9	9.5	−17.2
2,6-$(OCH_3)_2$	3-	84.8	14.5	6.9	−26.1
2,6-$(CH_3)_2$-4-OCH_3	3-	90.3	16.6	9.1	−18.5
3,5-$(OCH_3)_2$	2-	82.3	20.3	10.5	−12.3
3,5-$(OCH_3)_2$-2-NO_2	6-	82.0	23.8	10.4	−13.0
1,3,5-Trimethoxypyridinium perchlorate	2-	82.3	14.5	6.9	−29.0

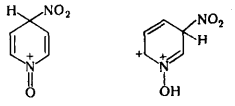
Conclusions analogous to those obtained as a result of the study of the kinetics of the nitration of substituted pyridine *N*-oxides were arrived at also in a study of the kinetics of acid-catalysed isotope exchange of hydrogen involving the same compounds. Katritzky and coworkers[163] established that the deuteration of 2,6-lutidine and 2,4,6-collidine *N*-oxides at 200–250°C and an acidity $H_0 = 8.7$ takes place in the 3-position in the protonated form, while the exchange of hydrogen in the *N*-oxide of 3,5-dimethylpyridine is observed in the 2-, 4-, and 6-positions with participation of the free base:



Under the same conditions, the rate of exchange of hydrogen in the β-position of pyridine *N*-oxide is only one-quarter of the rate of exchange in unoxidised pyridine, i.e. the N–OH group has a more deactivating effect than NH, in consequence of the negative inductive effect of the OH groups[164].

Comparison of the nitration and hydrogen isotope exchange reactions of the *N*-oxides of substituted pyridines reveals an interesting feature: the nitration takes place preferentially in the 4-position in the free base of the *N*-oxide, while the slower and consequently more selective

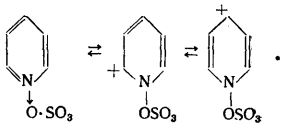
hydrogen exchange reaction involves the 3-position of the cation of the *N*-oxide, which is present in excess but is less reactive (for example, in the case of the *N*-oxide of 2,6-lutidine). This result is unexpected because of the high reactivity of the nitronium cation. The proposed explanation of this difference in the location of electrophilic agents is associated with the difference in the stabilities of the transition states in 4- and 3-nitration; possibly the electron-accepting effect of the NO_2 group in the case of β-substitution leads to a marked destabilisation of the doubly charged intermediate structure[163]:



Nevertheless sulphonation of *N*-oxides takes place preferentially in the 3-position, which makes this explanation less convincing, since the sulpho-group is also a powerful electron acceptor.

The appreciable conjugation effect of the N→O group in the nitration of pyridine *N*-oxide becomes very slight in the sulphonation reaction. Pyridine *N*-oxide is sulphonated under severe conditions (in 20% oleum at 220°C in the presence of mercuric sulphate) with formation of the 3-sulphonic acid (yield 67%).[165] Probably the *N*-hydroxypyridinium cation is sulphonated; substitution in the 3-position of the cations is in good agreement with the calculated localisation energies for electrophilic substitution (the values of A_e for the 2-, 3-, and 4-positions are respectively 2.70, 2.58, and 2.67 – β units)[166].

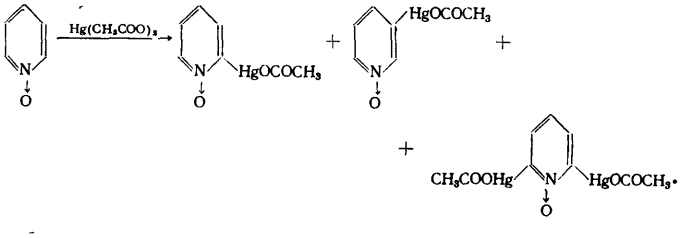
den Hertog et al.[167] showed that the bromination of pyridine *N*-oxide also takes place under severe conditions: with an excess of bromine in 90% sulphuric acid with heating to 200°C in the presence of catalytic amounts of silver sulphate—and leads to the formation of 2- and 4-monobromo-derivatives in proportions of 1 : 2 with an overall yield of about 10%. Bromination in 65% oleum at 120°C gives only the 3-bromo-compound and it is possible that an adduct of sulphur trioxide and pyridine *N*-oxide reacts[168]:



Nor can one exclude the possibility that in this case the reaction involves the protonated form of the *N*-oxide.

When the pyridine ring contains powerful electron-donating groups, the mode of halogenation of the *N*-oxide is determined by the conjugation effects of these groups and substitution takes place under milder conditions. Bromination of 2-hydroxypyridine *N*-oxide with bromine in acetic acid takes place in the 3-position[169], while iodination of 3-hydroxypyridine *N*-oxide gives the 4,6-di-iodo-derivative[170].

The mercuration of pyridine *N*-oxide with mercury(II) acetate in acetic acid at 100°C gives a mixture of 2-, 2,6-, and 3-substituted compounds in proportions of 8 : 1 : 2[171]:



The predominance of the α- and not the γ-derivative in this reaction may be attributed to a difference in the mechanism of the nitration and mercuration of *N*-oxides.

Mercuration with mercury(II) sulphate in sulphuric acid at 170°C yields only the 3-, and 2-monomercuri-derivatives in proportions of 2 : 1.[171] The higher amount of the β-isomer is probably associated with the protonation of the *N*-oxide.

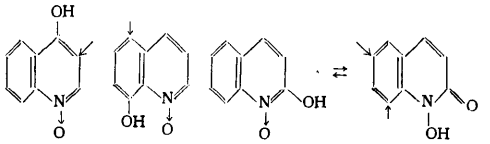
Quinoline *N*-oxide undergoes electrophilic substitution more readily than pyridine *N*-oxide. In the nitration of quinoline *N*-oxide in sulphuric acid, Ochiai[172] observed an interesting temperature variation: at 10°C a mixture of the 5- and 8-isomers is formed but on raising the temperature the formation of 4-nitroquinoline *N*-oxide becomes appreciable and this nitro-derivative constitutes the main reaction product at 70°C. Above 100°C reduction begins, and the amount of the 4-nitro-compound falls.

Later it was found for the *N*-oxides of 6-substituted quinoline derivatives that the directing effect of the N→O group in the nitration reaction depends to an even greater extent on the concentration of sulphuric acid than on temperature[173]. At the same temperature the amount of the 4-nitro-derivative diminishes and that of the 5- and 8-nitro-derivatives increases with the acidity of the medium. The use of the usual kinetic criteria enabled Schofield and coworkers[162] to establish that the 1-hydroxyquinolinium cation undergoes 5- and 8-nitration and the free base of quinoline *N*-oxide undergoes 4-nitration.

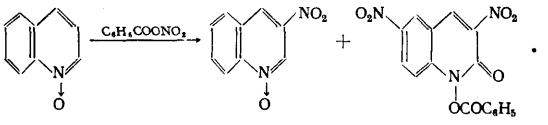
It is striking that the rate constant for the nitration of the 1-hydroxyquinolinium cation is lower than that for the quinolinium cation (0.78×10^4 and 1.67×10^4 litre mole^{-1} s^{-1} respectively[162]); consequently in the protonated form the *N*-oxide group plays the role of a deactivating electron-accepting substituent. The same effect is shown also in the electrophilic deuteration of quinoline and quinoline *N*-oxide in an acid medium, where both compounds react in the protonated form. Substitution involves the same positions (the 3-position in the benzene ring) but in the case of the *N*-oxide the yield of the reaction is lower[174].

In the series of quinoline *N*-oxide derivatives the usual direction to the *para*-position relative to the N→O group occurs when methyl[175] and halogeno-derivatives[176] are nitrated in concentrated sulphuric acid at 40–70°C. At the same time the alkoxy-group, in contrast to alkoxypyridine *N*-oxides, is a more powerful directing agent in this series than the N→O group[177].

Hydroxyquinoline *N*-oxides are nitrated in the *ortho*- and *para*-positions relative to the hydroxy-group under milder conditions—with nitric acid in glacial acetic acid[178–180]:

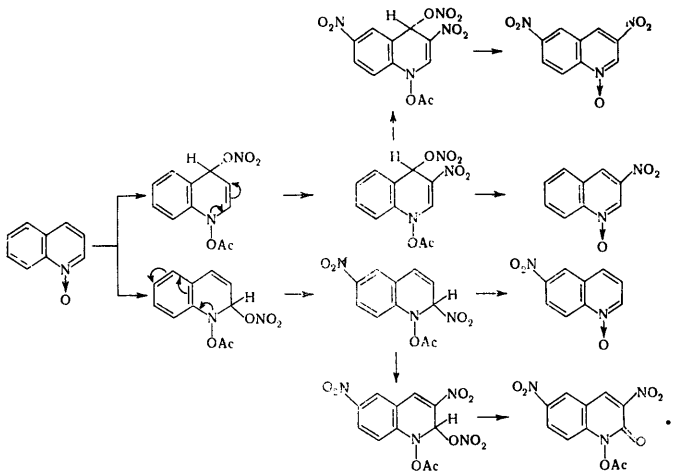


In the nitration of quinoline *N*-oxide with benzoyl nitrate in a neutral medium (in chloroform or dioxan) at 20°C, the *N*-oxide of 3-nitro-quinoline is formed in 40% yield together with some *N*-benzoyloxy-3,6-dinitro-2-oxoquinoline[181]:

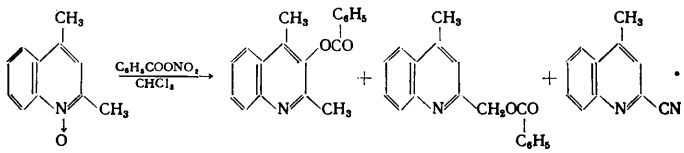


The use of a mixture of acetyl chloride with silver or potassium nitrate as a nitrating agent avoids the formation of 2-hydroxyquinoline and leads to the synthesis of 3- and 6-mono- and 3,6-di-nitro-compounds in yields of 32, 1.4, and 100% respectively[181].

Ochiai and Kaneko[181] suggested that in nitration with acyl nitrates in a neutral medium the reaction does not involve a simple electrophilic substitution mechanism but includes a stage with addition and subsequent elimination:

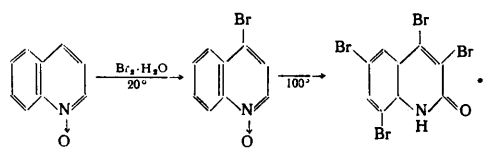


One may adduce in favour of this hypothesis data showing that 2- and (or) 4-substituted quinoline *N*-oxides do not give rise to nitration products on treatment with acyl nitrates, as shown for 2,4-dimethylquinoline *N*-oxide[182]:



Moreover, Ochiai and Ohta[183] showed that the *N*-methoxyquinolinium cation and also the adduct of quinoline *N*-oxide and boron trifluoride are nitrated with potassium nitrate in dimethyl sulphoxide at 140°C in the 3-position, which is likewise evidence of the validity of the above mechanism.

Hamana and Jamazaki[184] observed that, when quinoline *N*-oxide is brominated in a neutral medium, substitution also takes place in the 3-position: on refluxing quinoline *N*-oxide with bromine and chloroform in acetic anhydride, 3,6-dibromoquinoline *N*-oxide is formed in 60% yield (under the same conditions, pyridine *N*-oxide gives a 35% yield of the 3,5-dibromo-derivative). When quinoline *N*-oxide is brominated with bromine water at 20°C, initially normal substitution takes place in the *para*-position relative to the N→O group, but on heating to 100°C the *N*-oxide of 4-bromoquinoline formed may undergo further reaction, resulting in the formation of 3,4,6,8-tetrabromo-2-oxoquinoline[185]:

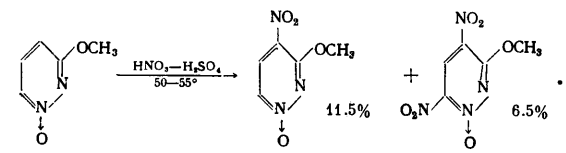


Electrophilic substitution of acridine *N*-oxide—nitration in sulphuric acid at 0°C and also bromination in glacial acetic acid at 100°C—takes place in the *para*-position relative to the N→O group and leads to the formation of 9-substituted acridine *N*-oxides[186].

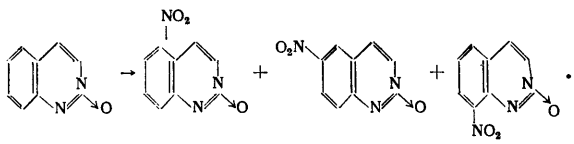
In isoquinoline *N*-oxide, where the *para*-position relative to the N→O group is occupied, the polar directing effect of the *N*-oxide group is not shown and, as in the case of isoquinoline, nitration takes place only in the 5-position (95%) and to a much lesser extent in the 8-position (1.5%)[187]. The study of the dependence of the rate of nitration of isoquinoline *N*-oxide and the *N*-methoxyisoquinolinium ion on the acidity of the medium by Schofield and coworkers[160] established that isoquinoline *N*-oxide reacts in the protonated form.

In the series of diazine *N*-oxides electrophilic substitution reactions have been studied only for the *N*-oxides of pyridazines, phthalazines, and cinnolines. While unsubstituted pyridazine is resistant to nitration under fairly severe conditions[92], the 1-*N*-oxide of pyridazine is nitrated in the *para*-position relative to the N→O group in a mixture of nitric and sulphuric acid at 130–140°C with a yield of 22%;[188] the same location of the new substituent is observed for the *N*-oxides of methylpyridazines[189].

In consequence of the competing directing effects of the substituents, nitration of 3-methoxypyridazine *N*-oxide results in the formation only of a mixture of 4-mono- and 4,6-dinitro-derivatives[190]:



When cinnoline 2-*N*-oxide is heated in a mixture of nitric and sulphuric acids at 90°C, 5-, 6-, and 8-mononitro-derivatives are formed in yields of 3, 15 and 23% respectively together with the unreacted initial *N*-oxide[193]:



The authors believe that these proportions of the isomers can be accounted for by the fact that the directing effect of the 2-N→O group favours substitution in the 6- and 8-positions, while the effect of the cinnoline ring favours 5- and 8-substitution, so that both effects reinforce one another in the 8-position. However, this explanation cannot be regarded as satisfactory, since isoquinoline *N*-oxide is substituted only in the 5-position[187]. The study of the kinetics of the nitration of cinnoline 2-*N*-oxide in 64.4–90.0% sulphuric acid suggests that 5- and 8-nitro-derivatives are formed entirely or largely in the nitration of the cation, while 6-substitution takes place in the free base of cinnoline 2-*N*-oxide[162].

Nitration of cinnoline 1-*N*-oxide with a mixture of nitric and sulphuric acids leads only to the 4-substituted compound[194], i.e. in this case the usual *para*-directing effect of the N→O group is shown.

Quinoxaline *N*-oxide is resistant to nitration with fuming nitric acid in concentrated sulphuric acid even at 100°C[117].

Phenazine 10-*N*-oxide behaves differently—it is readily nitrated even at 0°C with formation largely of 3- and small amounts of 1-nitro-compounds[191]; when the reaction is

carried out at 100°C, the 10-*N*-oxides of 3,6- and 1,6-dinitrophenazines are formed[192]:

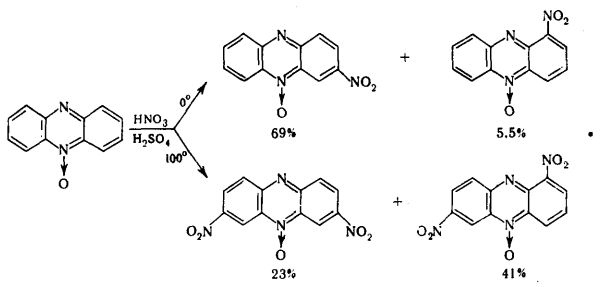


Table 14. Indices of the reactivities of pyridine and pyridazine *N*-oxides[131,166,195].

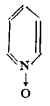
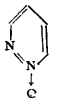
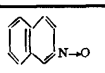
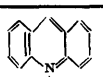
Structure	q_r, charge units	$A_e(-\beta)$	Position of carbon atom	q_r, charge units	Structure
	0.976 1.003 0.994	2.36 2.58 2.44	2- 3- 4- 5- 6-	0.922 1.001 0.955 0.978	

Table 15. Indices of the reactivities of quinoline, isoquinoline, and acridine *N*-oxides[196-199].

Position of carbon atom				
	q_r, charge units	A_e (−β)	q_r, charge units	q_r, charge units
1-	—	—	1.184	0.992
2-	0.975	2.30	—	0.959
3-	1.003	2.50	1.139	0.984
4-	0.994	2.21	0.896	1.012
5-	1.000	2.29	0.968	—
6-	1.000	2.48	0.990	—
7-	0.998	2.45	0.958	—
8-	1.004	2.32	1.022	—
9-				1.004

Note. The application of computational methods to the *N*-oxides requires the introduction of additional parameters for the Coulombic integral of the oxygen atom and the resonance integral of the N–O bond; usually the required values are found to be within the ranges $\alpha_{O^-} + (0.8 - 1.2)\beta$ and $\beta_{N^+-O^-} = (0.5 - 1)\beta$.

According to preliminary kinetic data, the monocation of the *N*-oxide formed by the addition of a proton to the unoxidised nitrogen atom is nitrated[15].

In the series of phenazine *N*-oxides the N→O group is a more powerful directing agent than halogens but weaker than alkoxy-groups and therefore the nitration of the 10-*N*-oxides of 1-, 2-, and 3-chlorophenazines takes place in the 6-position[193] and the nitration of the 10-*N*-oxide of 1-methoxyphenazine involves the *para*-position relative to the methoxy-group[121].

It is at present impossible to make a far-reaching analysis of the correlation between the experimental reactivities of the *N*-oxides of heteroaromatic compounds in electrophilic substitution reactions and the theoretical values obtained by the LCAO-MO method, because of the limited amount of calculated data. In particular, a calculation for the cationic form of the *N*-oxides has been made only in the case of pyridine *N*-oxide[166]. Tables 14 and 15 list the indices of the reactivities of certain *N*-oxides calculated by the simple LCAO-MO method. Comparison of these values with the experimental data shows that more successful correlations with the reactivities of the *N*-oxides are observed by considering the localisation energies A_e rather than the distribution of electron density q_r.

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