Russian Chemical Reviews

Uspekhi Khimii

November 1961

AROMATIC HETEROCYCLIC *N*-OXIDES

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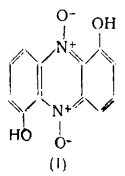
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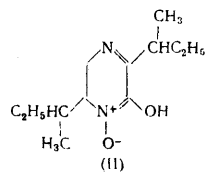
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INTRODUCTION

Heterocyclic *N*-oxides, a class of bipolar ammonium compounds, have been known for a relatively long time. In 1881, in their study of the reduction of the ethyl ester of *o*-nitrocinnamic acid, Friedländer and Ostermaier [1] isolated "oxycarbostyril", of empirical formula $C_9H_9NO_2$. It was not until 1914 that Friedländer established that this compound was carbostyril *N*-oxide [2], the first aromatic heterocyclic *N*-oxide to be synthesised. By the subsequent work of Meisenheimer [3,4] the heterocyclic *N*-oxides became easily obtainable. The interest in the chemistry of these compounds was later revived in an effort to find a method for introducing a substituent into a nitrogen-containing ring. One of such methods was the Chichibabin reaction, another involved quaternary ammonium salts, *e.g.* pyridinium salts. Methods employing *N*-oxides as starting material gave even better results [5]. The interest in heterocyclic *N*-oxides can also be accounted for by the discovery of such structures in certain biologically active natural products. For instance, the antibiotic iodinin [6] was shown by Kiprianov and his collaborators [7,8] to be 1,6-dihydroxyphenazine *N*,*N*-dioxide (I). Aspergillic acid, also an antibiotic, is a substitued pyrazine *N*-oxide (II). [9]



(I)



(II)

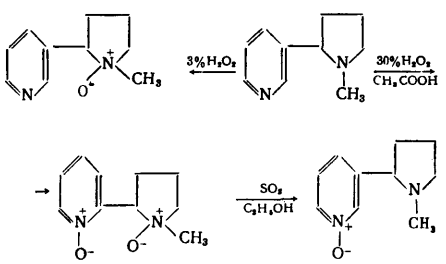
The chemistry of *N*-oxides has been the subject of several reviews. One of these reviews is devoted solely to the work of Japanese research workers [10]. Some have been published in journals that are not readily available [11,12], and others are only partly devoted to aromatic heterocyclic *N*-oxides [13,14]. The review by Katritzky [15], published in 1956, seems to be the best so far, but its author has himself, in the meantime, published over ten communications on the chemistry of *N*-oxides. Although a great deal of work has been done on this subject by Soviet workers, it has so far not been reviewed in Soviet literature. Hence the present review, in which are collected all the references which appeared through 1960. We shall only discuss the properties of the *N*-oxides of aromatic heterocyclic compounds, and not those of aliphatic amines, which have been treated in detail elsewhere [13].

I. METHODS OF PREPARATION OF AROMATIC HETEROCYCLIC *N*-OXIDES

1. Oxidation of Aromatic Heterocyclic Compounds

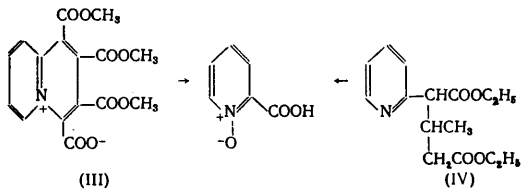
Oxidation of aromatic heterocyclic compounds is the most general method for the preparation of the *N*-oxides derived from them. Aliphatic amines are readily oxidised to *N*-oxides by hydrogen peroxide in neutral solution. Aromatic heterocyclic compounds, on the other hand, can only be oxidised in acid media, using peracids as oxidising agents. Meisenheimer first used a benzene solution of perbenzoic acid[3]. Monopernaphthoic[16,17], performic, and peracetic[18] acids have also been used.

The Japanese work showed that peracetic acid can successfully be replaced by a mixture of hydrogen peroxide and an organic acid, acetic acid being the best[10]. *N*-oxides are also prepared by using inorganic acids, *e.g.* sulphuric or phosphoric, but in that case the yields of the reaction products are very low[18]. However, addition of 0.3% sulphuric acid and 0.1% sodium phosphate to the reaction mixture has a favourable effect[19]. The oxidation of heterocyclic rings containing nitrogen with hydrogen peroxide in glacial acetic acid is described in textbooks[20] and can be used to prepare the *N*-oxides of numerous heterocyclic compounds, including various natural products[13]. The oxidation of natural products such as nicotine, which contain two nitrogen atoms, one in an aromatic, and another in a non-aromatic ring, is particularly interesting. Nicotine forms two monoxides and one dioxide. As shown by Gol'dfarb and Zvorykina[21], and somewhat later by Taylor and Boyer[22], individual nicotine *N*-oxides are best prepared by utilising the different ease of oxidation of aliphatic tertiary amines and heterocyclic nitrogen-containing rings and the different ease of reduction of the isomeric *N*-oxides:



All the *N*-methylanabasine *N*-oxides and aminonicotine *N*-oxides were prepared similarly[23,24].

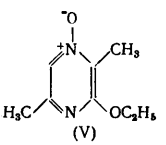
In spite of its universality, the direct oxidation of aromatic heterocyclic compounds containing nitrogen in the ring is occasionally complicated by side-reactions. Firstly, the formation of *N*-oxides may be accompanied by other oxidations. It was recently shown, for instance, that on oxidation, quinaldine and lepidine yield, in addition to *N*-oxides, products of oxidation at carbon atoms, namely 3-hydroxyquinaldine[25] and 3-hydroxy-4-methylcarbostyril[26] respectively. Similarly, the oxidation of quinoxaline and its derivatives yields large amounts of the 2,3-dihydroxy derivatives of quinoxaline[18]. If the compound undergoing oxidation contains readily oxidisable groups, the *N*-oxides of the oxidised compounds are formed. The oxidation of pyridine-2-aldehyde yields the *N*-oxide of picolinic acid[27], while that of the esters of 2- and 4-pyridylacetic acids yields 2- and 4-pyridine carboxylic acid *N*-oxides[28,29]. It should be noted that the oxidation of 3-pyridylacetic acid proceeds normally[29]. The increased mobility of hydrogen atoms in α- and γ-methylenic groups, discussed below, is clearly responsible for this difference in behaviour. The formation of *N*-oxides is sometimes preceded by oxidative degradation; picolinic acid *N*-oxide is obtained[28,30] by oxidation of compounds (III) and (IV).



(III) (IV)

Some readily oxidisable groups need to be protected before the oxidation is undertaken. For instance, 2-aminopyridine should first be acylated and then oxidised. 2-Aminopyridine *N*-oxide is obtained on saponification[31,32].

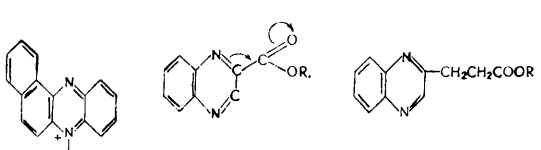
Low yields of *N*-oxides and even the complete failure of the oxidation can sometimes result from steric hindrance. This was the case in the oxidation of α- and especially di-α-substituted derivatives. For instance, 2,6-diphenylpyridine *N*-oxide can only be obtained in very low yields[33]. Although pyrazine yields its *N,N'*-dioxide on oxidation 2,5-dimethylpyrazine yields, owing to steric hindrance, a mixture of dioxide and monoxide, while 2,5-dimethyl-3-ethoxypyrazine forms the monoxide (V) only[34,35].



(V)

Steric hindrance increases with the size of the substituents. While 2,3-dimethylquinoxaline can be oxidised to the dioxide, its 2-methyl-3-isopropyl analogue only forms the monoxide, and 2,3-diisopropylquinoxaline is unable to form an *N*-oxide[36].

Certain substituents in the peri-position can also cause steric hindrance. 8-Nitroquinoline[37], certain 8-alkoxyquinolines[38], and 2-(4'-methoxyphenyl)- and 2-(4'-chlorophenyl)-8-methylquinolines[39,40] could not be oxidised, while the corresponding 6- and 7-substituted derivatives formed *N*-oxides. Quinoxalines which are 5- and 3-substituted and 1-carboxyphenazine only formed the monoxides[18,41], 5,8-dichloroquinoxaline[18] resisted oxidation, and 1,2-benzophenazine and its derivatives readily formed monoxides (VI) but could be oxidised to dioxides only with difficulty[42,43].

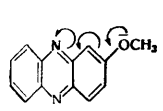


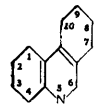
(VI) (VII) (VIII)

The introduction of a substituent in the nucleus affects the course of oxidation if it causes a change in the electron density of the electron pair carried by the nitrogen atom. Electron-accepting substituents, conjugated with nitrogen, lower the electron density and thereby render oxidation more difficult. The stability to oxidation of the derivatives of β-quinoxalinecarboxylic acid (VII) can easily be explained by the drift of the electrons towards the carboxyl group[44,45].

This view is supported because β-quinoxalinepropionic acid (VIII), in which such conjugation is out of the question, undergoes oxidation more readily[46]. The electron density at the nitrogen atom is lowered also by the presence of a nitro- or a cyano-group at position 6 of the quinoxaline 2,6-Pyridine and 2,5-pyridinedicarboxylic acids are so stable to oxidation that they are employed to stabilise peracids. oxidation that they are employed to stabilise peracids. Conversion of acids to their sodium salts lowers the electron-accepting power of the carboxyl group, and the corresponding *N*-oxides can be obtained in 75-80% yield[47].

Electron-donating substituents, on the contrary, increase the electron density at the nitrogen atom, and facilitate the oxidation. The predominant formation of 10-oxide in the oxidation of 2-methoxyphenazine (IX) is caused by the increased electron density at nitrogen atom 10.


(IX)

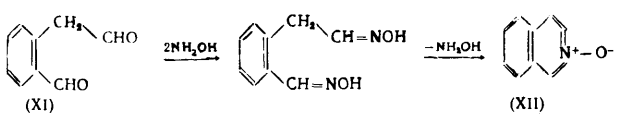

(X)

In the oxidation of 2-methyl- and 2-chloro-phenazine, 5- and 10-oxides are formed in equal amounts, while 1-chloro-phenazine yields entirely the 5-*N*-oxide, owing to steric hindrance[48].

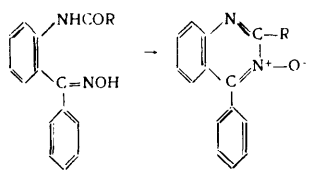
Both steric and electronic influences are observed in complex condensed systems containing several substituents. Phenanthridine (X) readily forms the *N*-oxide, as do its 6-methyl- and 6-ethyl-derivatives. The oxidation of 6-phenyl-and 6-nitro-phenthridine is more difficult, and 3,8-dinitro-6-phenylphenanthridine *N*-oxide could not be obtained[49]. It may also be noted that while pyrazine forms a dioxide, pyridazine and pyrimidine can only be oxidised to monoxides[50,51,52]. Purines, consisting of a condensed pyrimidine and iminazole ring, are oxidised by peracetic acid to monoxides derived from the pyrimidine ring[53,54].

2. Cyclisation of Hydroxylamine Derivatives

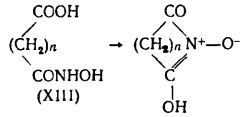
The dioximes of 1,5-dicarbonyl compounds can undergo cyclisation with elimination of one molecule of hydroxylamine, to form *N*-oxides. Glutaconic and homophthalic (XI) aldehydes react in this way with hydroxylamine forming pyridine[55] and isoquinoline *N*-oxides (XII)[56].


(XI) (XII)

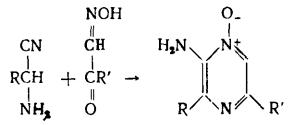
By dehydration of *o*-acylaminobenzophenone oxime the substituted quinazoline 3-oxide is obtained[57].



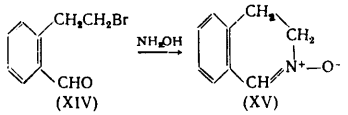
Other hydroxylamine derivatives, for instance those of type (XIII),[58] where n = 2,3, can similarly undergo ring-closure.


(XIII)

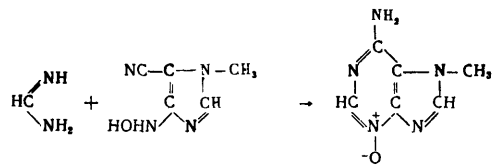
In a number of cases the intermediate oxime could not be isolated[59]. The monoximes of α,β-dicarbonyl compounds, themselves incapable of cyclisation, can be condensed with aminonitriles to form 2-aminopyrazine *N*-oxides[60]:



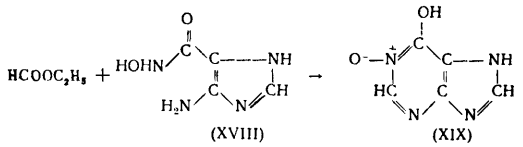
It is noteworthy[61] that the reaction of hydroxylamine with *o*-2-bromoethylbenzaldehyde (XIV) yields dihydroisoquinoline *N*-oxide (XV), resulting from intramolecular alkylation of the intermediate oxime[61].


(XIV) (XV)

The individual *N*-oxides of heterocyclic compounds containing several nitrogen atoms in the ring, in particular, purine *N*-oxides, have been obtained by transformations of the hydroxylamine derivatives. The reaction of 1-methyl--4-hydroxylamino-5-cyanoimidazole (XVI) with formamidine acetate yields 92% of 7-methyladenine 3-oxide (XVII)[62].


(XVI) (XVII)

Purine 1-oxides can also be obtained by other methods. The reaction of 4-aminoimidazole-5-hydroxamic acid (XVIII) with ethyl formate results in hypoxanthine 1-oxide (XIX).[63]


(XVIII) (XIX)

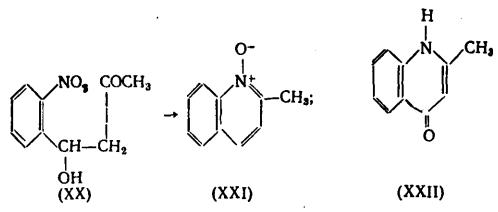
1-Oxides of 2-azapurines are formed from compounds of type (XVIII) on treatment with nitrous acid[64].

3. Reductive Cyclisation of Nitro-Compounds

As already mentioned, certain hydroxylamine derivatives form *N*-oxides readily even though the intermediate oxime cannot be isolated. For instance, the hydroxylamine derivatives formed in the reduction of aromatic

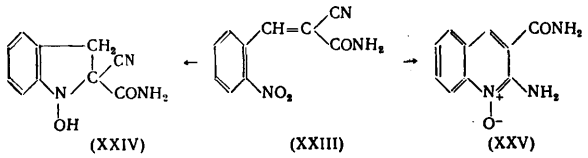
nitro-compounds containing various carbonyl functions in the *ortho*-position undergo ring closure forming aromatic heterocyclic *N*-oxides. This was in fact the first reaction to be discovered for the preparation of aromatic heterocyclic *N*-oxides.

Heller and his collaborators [65,66], who made a study of reductive cyclisation, incorrectly considered the reduction of methyl 2-hydroxy-2-(*o*-nitrophenyl)ethyl ketone (XX) to yield the carbonyl compound (XXII), whereas in fact the product obtained was quinaldine *N*-oxide (XXI).



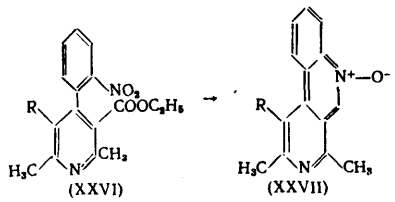
(XX) (XXI) (XXII)

The products of the reduction of *o*-nitrobenzylidenemalonic acid derivatives (XXIII) were similarly taken for dihydroindole derivatives (XXIV). [66] Later work by other authors showed that this reductive cyclisation yields quinoline *N*-oxides (XXV): [67]



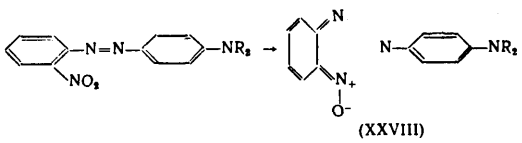
(XXIV) (XXIII) (XXV)

This reductive cyclisation can also be used for the synthesis of other types of oxides. For example, 2,6-dimethyl-3-ethoxycarbonyl-4-*o*-nitrophenylpyridine (XXVI) and its derivatives yield on reduction diazaphenanthrene 9-oxides (XXVII). [68]



(XXVI) (XXVII)

The *N*-oxides of compounds containing two [69] or three [70] nitrogen atoms in the ring can similarly be obtained, *e.g.* the substituted benzotriazole *N*-oxides (XXVIII).



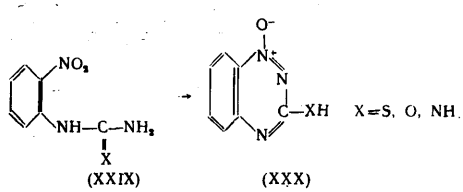
(XXVIII)

Ammonium sulphide [1], zinc in acetic [65,71] or hydrochloric [72] acids, and hydrazine [70] are the usual reducing agents in this reaction. Catalytic reduction on palladium has also been described [73]. The intermediate hydroxylamines have been isolated in certain cases [72].

4. Cyclisation of Nitro-Compounds

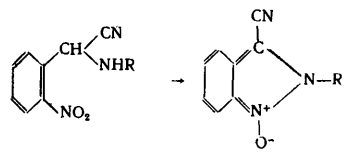
The reaction of aromatic nitro-compounds with aromatic amines in the presence of strong alkali (the Wohl–Aue reaction) yields, among other products, the *N*-oxides of the phenazine series [74]. When the Wohl–Aue reaction is carried out at 120°–125° the main product is the appropriate phenazine *N*-oxide. At higher temperatures (140°–160°) phenazine is the main product [75]. The *N*-oxide group is formed with partial reduction of the nitro-group [76]. Recent work on the structure of iodinin has aroused great interest in *N*-oxides of the phenazine series, and the Wohl–Aue reaction and its mechanism have been studied in great detail by Soviet workers [75,77–80].

If the nitro- and the amino-groups are present in the same molecule, intramolecular cyclisation can result from the transfer of the unshared electron pair of the amino-group to the nitro-group. For instance, the cyclisation of the *o*-nitrophenyl derivatives of urea, thiourea, and guanidine (XXIX) yields benzotriazine *N*-oxides (XXX): [81–83]

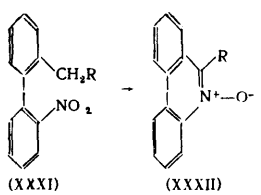


(XXIX) (XXX)

The ring closure in α-amino-*o*-nitrophenylacetonitriles [84] occurs similarly:



The formation of derivatives of phenanthridine *N*-oxides (XXXII) by the cyclisation of 2-alkyl-2′-nitrobiphenyl (XXXI) [85,86] is somewhat different in character. This cyclisation is only possible if the substituent R is a cyano-, carbamido-, or methoxycarbonyl-group; in other words, if the substituent increases the mobility of the hydrogen atom in the adjacent methylene group. If this is not the case (R = H, OH, Br), an *N*-oxide is not formed. The reason why a carbonyl group does not allow the reaction is not understood.

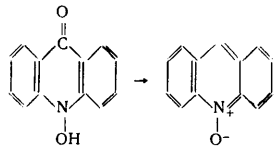


(XXXI) (XXXII)

5. Other Methods of Preparation of *N*-Oxides

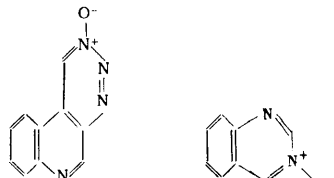
Certain particular cases of the formation of various aromatic heterocyclic *N*-oxides by routes other than the above have been reported in the literature. For instance,

acridine *N*-oxide (XXXIV) has been prepared by reduction of *N*-hydroxyacridone (XXXIII) with sodium amalgam[87].



(XXXIII) (XXXIV)

Pyrylium salts react with hydroxylamine forming *N*-oxides[61]. On treatment with nitrous acid, 3-aminolepidine forms 1,2,3,9-tetraazaphenanthrene 3-oxide (XXXV)[88]. Finally, by reaction with hydroxylamine, quinazoline forms a monoxide (XXXVI)[89].



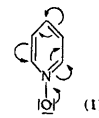
(XXXV) (XXXVI)

II. SOME PHYSICAL PROPERTIES OF AROMATIC HETEROCYCLIC *N*-OXIDES

The presence of a positively charged ammonium nitrogen considerably changes the properties of aromatic rings containing nitrogen. The *N*-oxides are solid, salt-like compounds, soluble in water. Nevertheless, the salt-like character of aromatic heterocyclic *N*-oxides is considerably less pronounced than that of the *N*-oxides derived from aliphatic amines. The melting and boiling points of *N*-oxides are lower in the heterocyclic than in the aliphatic series. Besides, the former are more soluble in organic solvents. Their infra-red spectra are also different. The N^+-O^- bond in the aliphatic series is characterised[90] by the frequency 950–970 cm^{-1}, while the *N*-oxides of aromatic heterocyclic compounds absorb intensely[51,91,92] in the 1240–1290 cm^{-1} region.

The difference between aromatic and heterocyclic *N*-oxides is especially pronounced in their dipole moments (Table 1).

The small differences in dipole moments between aromatic rings containing nitrogen and their corresponding *N*-oxides are worthy of note since such differences are considerably greater in the aliphatic series. The anionic centre, *i.e.* the negatively charged oxygen, is undoubtedly conjugated with the aromatic ring. Linton[93] pointed out that the conjugation in the molecule of pyridine oxide must involve the following scheme:



(I)

The low dipole moment of pyridine *N*-oxides is due to conjugation. The shift of electrons from the oxygen atom to the ring balances the dipole moment of the *N*-oxide group. The conjugation is even higher in condensed aromatic heterocyclic compounds, and as a result, the polarity of the N^+-O^- bond is lowered. This is clear from the work of Pushkareva *et al.*[94,95] who compared the polarity of the N^+-O^- bonds in the *N*-oxides of pyridine, quinoline, acridine, quinoxaline, and phenazine (see Table 1). The polarity of the N^+-O^- bond is inversely proportional to conjugation.

TABLE 1. Dipole moments of amines and their *N*-oxides[93–95].

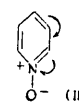
Compound	Dipole moment		Bond polarity	Compound	Dipole moment		Bond polarity
	amine	*N*-oxide			amine	*N*-oxide	
Trimethylamine	0.65	5.02	3.3	Acridine	1.96(1.84)	4.08	2.02(2.62)
Pyridine	2.22	4.24	3.01	Quinoxaline	1.92	2.53*	1.86
Quinoline	2.15	4.00	2.80	Phenazine	0.0	1.76*	1.76

* Dipole moments of monoxides.

TABLE 2. Dipole moments of 4-substituted pyridines and their *N*-oxides.

Substituent	Dipole moment	
	pyridine	pyridine *N*-oxide
—H	2.22	4.24
$-CH_3$	2.61	4.74
$-OCH_3$	2.96	5.08
$-N(CH_3)_2$	4.31	6.78

In addition to the above-mentioned conjugation (I) in the molecule of pyridine *N*-oxide, there also occurs a shift of electrons in the opposite direction.



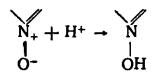
(II)

Katritzky and his coworkers[96] established the presence of this shift by comparing the dipole moments of a number of γ-substituted pyridines and their *N*-oxides. They found that by introducing electron-donating substituents into γ-position the dipole moment is increased, and more so in *N*-oxides than in unoxidised pyridines. This is clear from Table 2. The competition between the two types of conjugation can induce either a surplus or a deficiency of electrons at position 4 of the reacting molecule[96,97]. This is confirmed by the chemical behaviour of *N*-oxides, which we discuss below.

III. CHEMICAL PROPERTIES OF AROMATIC HETEROCYCLIC *N*-OXIDES

1. Reactions of the *N*-Oxide Group

Addition of a proton.



The basic properties of *N*-oxides are chiefly due to the negative charge on the oxygen atom. It is clear from Table 3 that the basicity of an *N*-oxide is lower than that of the corresponding amines.

The *N*-oxides of aromatic heterocyclic compounds form stable salts only with strong inorganic acids, and with picric and picrolonic acids[29]. Certain *N*-oxides do not form picrates[100]. The basicities of a number of substituted *N*-oxides are well represented[98] by the Hammett equation with $\rho = 2.09$.

Reduction. In contrast to aliphatic *N*-oxides, pyridine *N*-oxide, and its derivatives can be reduced only with difficulty. This is due to the decrease in the negative charge on the oxygen atom resulting from conjugation of the *N*-oxide group with the ring. The reduction potentials of various heterocyclic *N*-oxides vary, as can be seen from Table 4. Clearly, increased condensation of aromatic nuclei, and electron-accepting substituents, facilitate reduction. Nuclear electron-donating substituents, on the contrary, inhibit reduction. Pushkareva and Nechaeva[102] showed that the reduction potentials of *N*-oxides vary in the same sense as the dipole moments: the lower the dipole moment, the more easily is a compound reduced.

TABLE 3. Basicity of certain aromatic heterocyclic compounds and their *N*-oxides[98,99].

Compound	Basicity (pK_a)	
	parent base	*N*-oxide
Pyridine	5.29	0.79
Quinoline	4.94	0.70
Isoquinoline	5.4	1.1

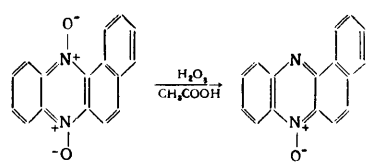
TABLE 4. Reduction potentials of *N*-oxides.

N-Oxide	Reduction potential		*N*-Oxide	Reduction potential	
	pH 3.5 (ref. 10)	pH 7.0 (ref. 101)		pH 3.5 (ref. 10)	pH 7.0 (ref. 101)
Trimethylamine	−0.4562	—	Quinoline	−1.0692	−1.164
Dimethylaniline	−0.7047	−1.018	Acridine	—	−0.854
Pyridine	−1.2786	−1.364	Quinoxaline*	—	−0.650
2,4,6-Collidine	−1.3924	—	Phenazine*	—	−0.218
4-Phenoxypyridine	−1.2820	—			

* Reduction potentials of monoxides.

Inspection of the reduction potentials shows that reducing agents such as sulphur dioxide and potassium iodide will not reduce pyridine *N*-oxide, but will reduce quinoline *N*-oxide[44]. In a number of cases iron in acid media[103,104], and sodium[104] or sulphide[105] in liquid ammonia were found to be satisfactory reducing agents. *N*-Oxides not containing reducible groups can satisfactorily be hydrogenated with palladium in alcoholic solution[107]. The reaction proceeds at normal pressure and room temperature. Reductions with Raney-nickel, on the other hand, require increased pressure. Since weaker reducing agents have, as a rule, no effect on the *N*-oxide group, they can be used for the selective reduction of reducible groups bound to the nucleus, for instance the nitro-group. The selective reduction of an *N*-oxide group can be carried out with any oxygen acceptor, most often with phosphorus trichloride[10]. This reaction proceeds under mild conditions, merely by heating the *N*-oxide and phosphorus trichloride in chloroform or ethyl acetate[109]. Quinoline *N*-oxide is somewhat harder to reduce than pyridine *N*-oxide, but the yield may be increased by using phosphorus tribromide instead of trichloride. Derivatives containing halogen in the nucleus, or in which radicals attached to the ring (*e.g.* the nitro-group) have been replaced by halogen, are obtained as by-products in the reaction of *N*-oxides with phosphorus trichloride. For instance, the reduction of 4-nitropyridine *N*-oxide with phosphorus trichloride yields 4-chloropyridine besides 4-nitropyridine[109], while the reduction of 4-nitroquinoline *N*-oxide with phosphorus tribromide yields 2-bromo-4-nitroquinoline as a by-product[110]. Triphenyl phosphite can also serve as oxygen acceptor, but compared to phosphorus halides, it requires more vigorous reaction conditions[111-113].

A rather unusual method for reducing *N*-oxides consists in prolonged heating in acid solution in the presence of oxidising agents. Heating a substituted quinoline *N*-oxide in sulphuric acid in the presence of chromic oxide results in the reduction of the *N*-oxide group[66]. Even more unusual is the behaviour of benzophenazine *N,N'*-dioxide (I). On being heated in acetic acid in the presence of hydrogen peroxide, namely under the conditions normally used to prepare *N*-oxides, this compound undergoes reduction to the monoxide[43].



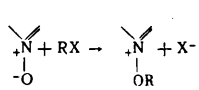
(I) (II)

The re-oxidation of the monoxide (II) is prevented by steric hindrance.

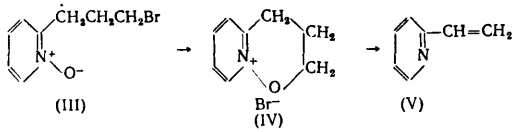
The oxidising properties of *N*-oxides are used for their detection. On heating *N*-oxides with dimethylaniline the solution becomes intensely coloured owing to the formation of crystal violet[114].

Heterocyclic *N*-oxides can be determined quantitatively by titanometric titration[115].

Alkylation.

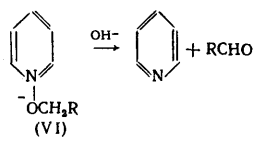


N-oxides react with alkylating agents, especially in polar solvents such as acetonitrile or nitrobenzene, yielding *O*-alkyl derivatives which are effectively quaternary salts with a discrete anion. If, however, the compound contains an amine nitrogen in addition to an *N*-oxide group (*e.g.* the monoxides of quinoxaline and phenazine), *N*-alkyl derivatives are formed instead[115,117]. The internal alkylation of α-(3-bromopropyl)pyridine *N*-oxide (III), which results[118] in the formation of a bicyclic quaternary salt (IV), is noteworthy:



(III) (IV) (V)

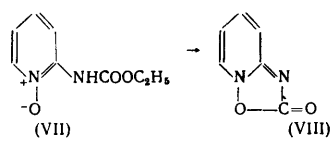
In common with aliphatic alkoxyalkyl ammonium salts, heterocyclic ammonium salts containing an alkoxy radical (VI) are decomposed by alkali forming an aldehyde and a reduced base:



(VI)

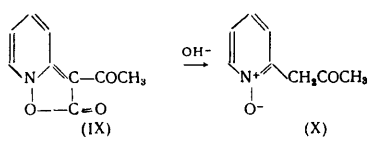
This reaction can be used for the preparation of aldehydes from alkyl halides. Substituted benzaldehydes were thus obtained in 90% yield from substituted benzyl chlorides[119]. The decomposition of the cyclic quaternary compound (IV) similarly yields vinylpyridine (V) and formaldehyde.

Intramolecular acylation. 2-Ethoxy-carbonylaminopyridine *N*-oxide (VII) splits off a molecule of alcohol when heated to 140° and undergoes ring closure[120,121] forming pyridino(1′:2′–2:3)-1-oxo-2,4-diazol-5-one (VIII).



(VII) (VIII)

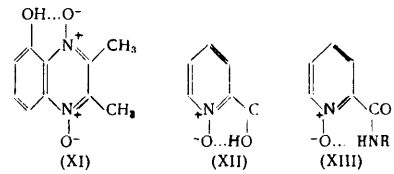
Compounds of this type are also formed in the reaction of 2-bromopyridine *N*-oxide with sodioacetoacetic ester. 2-Pyridineacetoacetic ester *N*-oxide, initially formed, is unstable and undergoes cyclisation[122] to 4-acetylpyridino-(1′:2′–2:3)isoxazol-5-one (IX).



(IX) (X)

Both these bicylic compounds are unstable and undergo decarboxylation under the action of alkali, the compound (IX) yielding 2-acetonylpyridine *N*-oxide (X).

Formation of an intramolecular hydrogen bond. The *N*-oxide oxygen atom has a tendency to form an intramolecular hydrogen bond. Such a bond exists in 5-hydroxy-2,3-dimethylquinoxaline 1,4-oxide (XI), as shown by the relative solubilities in organic solvents of this dioxide and of its 6-hydroxy isomer[19]. The refractoriness of certain *N*-oxides (XII) towards reduction has been ascribed to the presence of hydrogen bonds, which was demonstrated by the preparation of chelate compounds with copper[123,124]. Moreover, the hydrogen bond in the derivatives of picolinamide *N*-oxide (XIII) was detected spectroscopically[125].



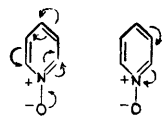
(XI) (XII) (XIII)

In addition to the foregoing reactions, the *N*-oxide oxygen atom is capable of reacting with various nucleophilic reagents, *e.g.* acid anhydrides. The resulting compounds are unstable and undergo rearrangement into compounds substituted in the nucleus. We shall discuss this type of reaction in the following section.

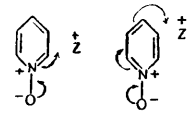
2. Substitutions in Aromatic Heterocyclic Compounds

By virtue of the electron-accepting property of the nitrogen atom, heterocyclic compounds containing nitrogen in the ring are very reluctant to undergo electrophilic substitution reactions.

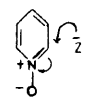
If electrophilic substitution does occur, the substituent is directed to the β-position, which has the greatest electron density (as compared with the α- and γ-positions). Reaction with nucleophilic reagents is somewhat easier, when the substituent is directed to position 2 (more rarely, 4). The conversion of a heterocyclic amine (for instance, pyridine) into its *N*-oxide is accompanied by appreciable changes in electronic structure. It has already been pointed out that two types of conjugation are possible in the molecule of an *N*-oxide. The *N*-oxide group can act as an electron-donating as well as an electron-accepting group:



The electrophilic reagent Z^+ can easily attack the nucleus at the α- or γ-positions, where the electron density is higher owing to the positive tautomeric effect. Substitution in the γ-position should proceed especially readily, as the conjugation effect at the α-position is partly compensated by the oppositely directed inductive effect of the adjacent nitrogen atom.



On the other hand, because of the electron withdrawing effect, a nucleophilic reagent is also capable of attacking the nucleus of an *N*-oxide:



The nucleophilic substitution occurs primarily in the α-position, where the tautomeric and the inductive effect are superposed. The nucleophilic reagent can also attack the oxygen atom first, the resulting compound subsequently undergoing rearrangement to form a product substituted in the ring.

These general theoretical considerations, applied to the *N*-oxide of the simplest heterocyclic compound, namely pyridine, have been confirmed by quantum-mechanical calculations. The localisation energies in different positions of the molecule of pyridine and its *N*-oxide, calculated by Jaffe[126], are collected in Table 5†. The energies of localisation were computed by a theoretical treatment of the basicity constants of various derivatives of pyridine and its *N*-oxide.

It follows from Table 5 that both nucleophilic and electrophilic substitution should proceed more readily in the molecule of the *N*-oxide than in the parent base. Position 2 is the most reactive in nucleophilic substitutions, and position 3 in electrophilic substitutions, in the molecule of pyridine, whereas in the *N*-oxides position 4 is the most reactive in both cases.

TABLE 5. Charge localisation energies in pyridine and its *N*-oxide.

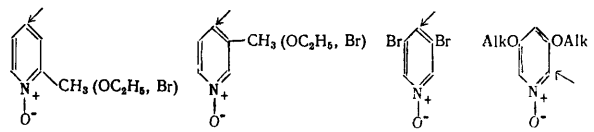
Compound	Position	Localisation energy, kcal/mole	
		electrophilic substitution	nucleophilic substitution
Pyridine	2	2.712	2.312
	3	2.487	2.378
	4	2.637	2.228
Pyridine *N*-oxide	2	2.634	2.689
	3	3.218	2.357
	4	2.474	1.714

Substitution in aromatic heterocyclic *N*-oxides, mainly in pyridine *N*-oxide, are considered below. Although the general picture of chemical properties may be somewhat changed when the derivatives of pyridine, or the condensed systems, are considered, the general assumptions remain unaltered.

Nitration. *N*-Oxides undergo nitration readily; the details of procedure can now be found in "Organic Syntheses"[127]. The main product of the nitration of pyridine *N*-oxide is 4-nitropyridine *N*-oxide; 2-nitro-pyridine is formed as a by-product, in amounts from 0.4 to 7.6%, depending on the reaction temperature. 2-Nitropyridine *N*-oxide can be obtained by the oxidation of the amino-group in 2-aminopyridine *N*-oxide with hydrogen peroxide in 30% oleum[128]. 3-Nitropyridine *N*-oxide can likewise be obtained by the oxidation of 3-aminopyridine with peracetic acid[129].

The nitration of quinoline *N*-oxide also yields predominantly the 4-isomer, but simultaneous nitration of the benzene ring gives the 5- and 8-nitro-derivatives in amounts depending on the reaction temperature[10,130]. In contrast to pyridine *N*-oxide, no 2-isomer is formed in the nitration of quinoline *N*-oxide. According to Ochiai[131,132] the nitration of quinoline and quinaldine *N*-oxides with benzoyl nitrate in aprotic solvents (chloroform, dioxane) yields mainly the 3-nitro derivatives.

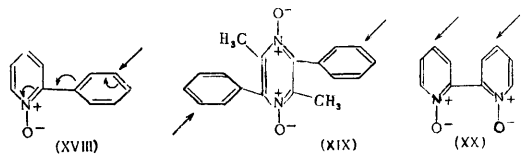
The *N*-oxide group has a strong *ortho-para*-directing effect. Hertog and his collaborators[133-137] showed that the nitration of 2-picoline, 2-ethoxypyridine, and 2-bromopyridine *N*-oxides yields 4-nitro-derivatives (XIV). The directing effect of the *N*-oxide group must therefore be stronger than that of the methyl or ethoxy group, or bromine. This has been confirmed[138] by the nitration of the approprate 3-substituted derivatives (XV).



(XIV) (XV) (XVI) (XVII)

3,5-Dibromopyridine *N*-oxide also undergoes nitration in position 4 (XVI). However, 3,5-dialkoxypyridine *N*-oxide yields the 2-isomer (XVII), probably owing to steric hindrance. The directive effect of the hydroxyl group is greater than that of the *N*-oxide group, and 2-hydroxypyridine *N*-oxide, for instance, yields the 5-nitro-derivative.

In the nitration of 2- or 4-substituted phenylpyridine *N*-oxides (XVIII), the nitro-group takes up the *meta*-position in the phenyl radical[139].



(XVIII) (XIX) (XX)

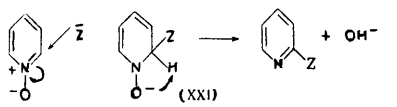
Meta-substitution is caused by the withdrawal of electrons from the phenyl radical towards the *N*-oxide group. In this case the *N*-oxide group, or rather the pyridyl-*N*-oxide radical, is a *meta*-directing substituent, whose electron-accepting properties are weaker than those of a positively charged pyridinium group[140]. The nitration of 2,5-dimethyl-3,6-diphenylpyrazine 1,4-dioxide (XIX) proceeds likewise[141]. The nitration of 2,2'-bipyridyl 1,1'-dioxide (XX) yields the 4,4'-dinitro derivative[142].

It has been shown that 2- and 4-phenylpyridine *N*-oxides undergo nitration not in the form of salts, but in the form of bases[139,140].

Other electrophilic substitutions. Attempts to halogenate or sulphonate pyridine *N*-oxide were unsuccessful[143]. The *N*-oxides of pyridine derivatives containing electron-donating groups, however, are capable of being halogenated. 2-Hydroxypyridine and 4-hydroxypyridine *N*-oxides undergo bromination forming 3,5-dibromo derivatives[137,144]. The iodination of these compounds proceeds similarly[144]. 4-Bromoquinoline *N*-oxide was also obtained, although in small yield, by direct bromination[145]. Acridine *N*-oxide is brominated[146] in position 9. According to some Japanese workers[147] the mercuration of pyridine and quinoline *N*-oxides yields the 4-mercuri-derivatives. Ammers and Hertog, however, who made a detailed study of this reaction, report[148] that the mercuration of pyridine *N*-oxide gives 2- and 2,6-derivatives.

† The localisation energy is the energy required for the localisation of a charge at any position in the molecule. In the opinion of several authors, this energy represents a considerable part of the activation energy.

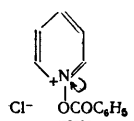
Action of organomagnesium compounds. In the reaction of aromatic heterocyclic compounds with strong nucleophilic agents the substituent takes up the α-position in the ring. Aromatic heterocyclic *N*-oxides also react with nucleophilic reagents, forming α-substituted derivatives. This latter reaction seems to proceed *via* an intermediate formation of compound (XXI).



(XXI)

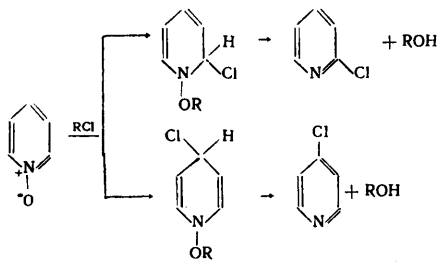
The Grignard reagents belong to this group of nucleophilic reagents. The reaction of phenylmagnesium bromide with pyridine *N*-oxide proceeds vigorously and yields 2-phenylpyridine and 2,6-diphenylpyridine [149]. The *N*-oxides of quinoline and its derivatives similarly yield α-phenyl quinolines [150]. The substituent was never found in the γ-position.

Owing to the positive charge carried by the nitrogen atom, aromatic heterocyclic *N*-oxides react more readily than the unoxidised bases with organomagnesium compounds. The decreased electron density of the *N*-oxide oxygen atom favours nucleophilic substitution in α-position. Therefore, if benzoyloxypyridinium ion (XXII) is reacted with phenylmagnesium bromide instead of pyridine *N*-oxide, the yield is greatly increased [151]. We shall see that the benzoyloxypyridinium ion can take part in other nucleophilic substitutions.



(XXII)

Reactions with sulphuryl chloride and phosphorus oxychloride. Although the direct chlorination of *N*-oxides does not yield satisfactory results, the reaction with sulphuryl chloride or phosphorus oxychloride gives the chloro-derivatives in good yields. For instance, pyridine and quinoline *N*-oxides react with sulphuryl chloride forming 2- and 4-chloro-derivatives [16,152]. Similarly results are obtained by the use of phosphorus oxychloride [153] and phosphorus pentachloride [154] It may be noted that the α- and γ-isomers are formed in almost equal amounts, in sharp contrast with reactions involving Grignard reagents, where there is selective α-substitution. For example, the reaction of pyridine *N*-oxide with sulphuryl chloride yields 2- and 4-chloropyridines in the ratio 57 : 43, and quinoline *N*-oxide yields the 2- and 4-isomers in the ratio 38 : 62. The chlorination mechanism seems to be the following [151]:

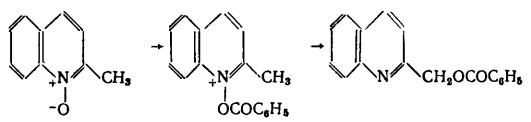


where R = $POCl_2$, PCl_4, SO_2Cl.

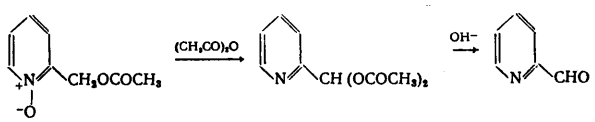
The substituents already present in the nucleus can modify the main course of the reaction and favour the formation of 4-isomers [155], as well as of polychloro-derivatives. Magidson and Rubtsov [156] showed that 6-methoxyquinoline *N*-oxide reacts with sulphuryl chloride forming di- and tri-chloro-derivatives of 6-methoxyquinoline.

The above reaction mechanism does not cover all cases of the reaction of *N*-oxides with inorganic acid halides. Cases are known in which the chlorination is not accompanied by reduction. 3,5-Diethoxypyridine *N*-oxide reacts with sulphuryl chloride forming a mixture of the *N*-oxides of 2,6-dichloro- and 2,4,6-trichloro-3,5-diethoxypyridine [157]. Nor does the above mechanism account for the formation of β-chloro-derivatives in the reaction of 5-nitroquinoline *N*-oxide with phosphorus oxychloride [37]. The chlorination of picoline *N*-oxides yielding products containing halogen in the side-chain also remains unexplained [158].

Action of organic acid anhydrides. The benzoyloxypyridinium ion has already been shown to be unstable, readily releasing the $PhCOO^-$ group which is capable of substituting hydrogen in the nucleus of the heterocyclic compound. Henze [159] studied the benzoylation of *N*-oxides (quinaldine *N*-oxide in particular), but was unable to identify the resulting 2-benzoyloxymethylquinoline [160].

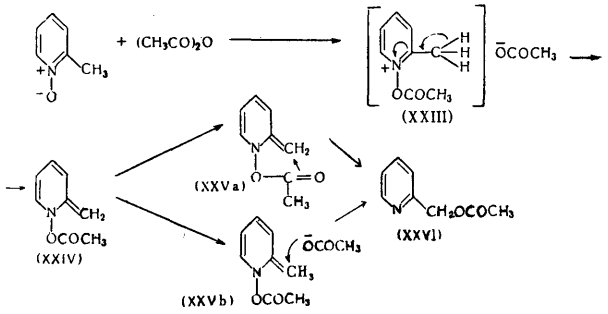


It was later shown that aromatic heterocyclic *N*-oxides react with acetic anhydride to form the esters of C-hydroxy compounds. Thus pyridine *N*-oxide gave 2-acetoxypyridine [10]. Pyridine *N*-oxide, like other heterocyclic *N*-oxides containing alkyl substituents in position 2 or 4, undergoes acetyloxylation in the alkyl group [161,162]. The anhydrides of other acids, benzoic [163] and acid chlorides, *e.g.* *p*-toluenesulphonyl chloride [164], act similarly. The *N*-oxides of the pyridine, quinoline, isoquinoline [165], pyrimidine [166], benzimidazole [167], and other series all react with acid anhydrides. This reaction is widely used in the chemistry of heterocyclic compounds for the synthesis of alcohols [17,166-170], and carbonyl compounds [171,172]. In the latter case *N*-oxides of 2- (or 4-) pyridylalkanoles or their esters are treated with acetic anhydride:



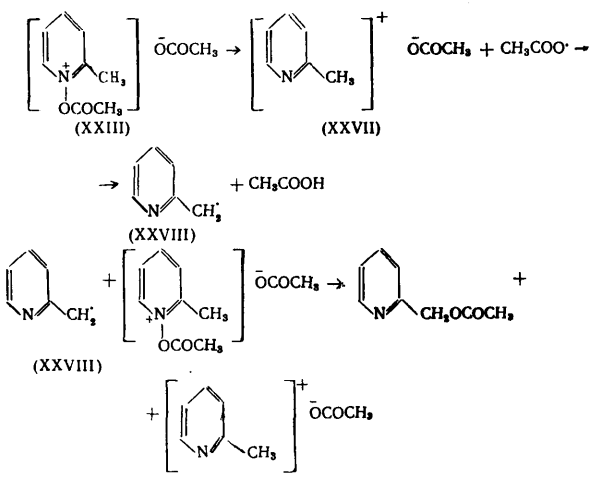
It has recently been shown that the reaction proceeds more vigorously and the resulting ester is easier to saponify if the acetic anhydride is replaced [173]. Several mechanisms have been suggested for the reaction of *N*-oxides with acid anhydrides. We shall discuss them below, using as an example the reaction of α-picoline *N*-oxide with acetic anhydride. The first stage of the reaction consists in the formation of *N*-acetoxy-2-methylpyridinium acetate

(XXIII). In the opinion of the supporters of the ionic reaction mechanism, (XXIII) spontaneously loses a proton forming the anhydronium base (XXIV), which subsequently either undergoes intramolecular rearrangement



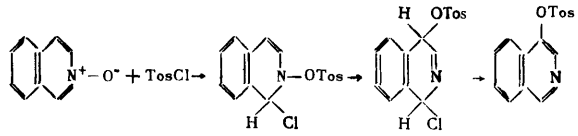
(*via* the intermediate compound XXVa), or is attacked by the acetate ion on the carbon of the methylene group (forming intermediate compound XXVb). In either case the final reaction product is 2-acetoxymethylpyridine (XXVI).

According to the radical mechanism, *N*-acetoxy-2-methylpyridinium acetate (XXIII) is also formed, homolytic decomposition of the N^+-O^- linkage then yields an acetoxy radical and the ion radical (XXVII). (XXVII) loses a proton yielding the 2-picolyl radical (XXVIII) which, by reacting with the *N*-acetoxy-2-methylpyridinium ion, forms the final product and regenerates the radical (XXVII):



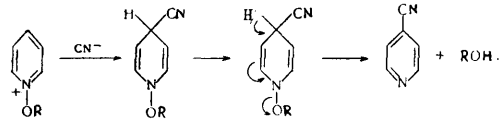
A great many facts speak in favour of the radical mechanism. The reaction has an induction period which is followed by vigorous evolution of heat. Boekelheide [174] demonstrated the formation of free radicals in the course of the reaction by introducing styrene into the reaction mixture and isolating its polymerisation product. It was subsequently shown, however, that the presence of free radicals cannot be taken as direct evidence in favour of the free-radical mechanism [175,176]. The addition of inhibitors of free-radical processes into the reaction mixture stopped the polymerisation of styrene, but had no effect on the yields of 2-acetoxymethylpyridine. This led to the opinion [175,176] that the free radicals are formed by a side-reaction, the main reaction proceeding by an ionic mechanism. The reaction with butyric anhydride in the presence of sodium acetate provided unambiguous evidence of the intramolecular character of the process, and identified the XXVa as an intermediate, since 2-pyridylmethyl butyrate was the only product.

The above mechanisms for the reaction of *N*-oxides with acid anhydrides do not cover all the aspects of this interesting reaction. They do not explain why the acetoxy-group sometimes assumes the β-position in the pyridine [177], quinoline [178], and isoquinoline [165] rings. In practice, the β-hydroxy-derivative is often formed in considerable amounts, as for instance in the reaction of isoquinoline *N*-oxide with the *p*-toluenesulphonyl chloride [165,179,180]. Ochiai [179] suggested the following mechanism for this reaction:



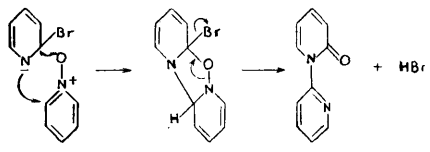
It is noteworthy that, although pyrimidine *N*-oxide and its methyl analogues react with acetic anhydride to form *C*-acetoxy-derivatives [168], purine oxides under these conditions suffer cleavage of the pyrimidine ring, yielding derivatives of imidazole [181].

Reactions with the cyanide ion. It was shown in 1936 that acridine *N*-oxide reacts with potassium cyanide forming 9-cyanoacridine [182]. Quinoline *N*-oxide reacts with a benzoyl chloride–potassium cyanide mixture forming 2-cyanoquinoline [183]. The reaction of the cyanide ion with *N*-oxides has recently been shown to be general [184]. For instance, the reaction of *N*-alkoxypyridinium salts under mild conditions with potassium cyanide yields 4-cyanopyridine (42%). The authors assumed that the first stage of this reaction consists of the addition of a cyanide ion to the quaternary pyridinium salt to form an *N*-alkoxyanhydronium base, which subsequently eliminates the alkoxy-group forming 4-cyanopyridine.



Quaternary *N*-alkoxyquinolinium and *N*-alkoxyisoquinolinium salts also react with the cyanide ion yielding 2-cyanoquinoline and 1-cyanoisoquinoline, respectively, in quantitative yields. Electron-accepting substituents in the pyridine ring do not inhibit this reaction. *N*-Alkoxy-4-cyanopyridine reacts with potassium cyanide forming 2,4-dicyanopyridine.

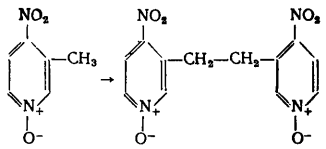
Reaction with α-bromopyridine. Heating pyridine *N*-oxide with α-bromopyridine at 100° yields 1-(2-pyridyl)-2-pyridone [185–187]. The reaction mechanism suggested by the authors is the following:



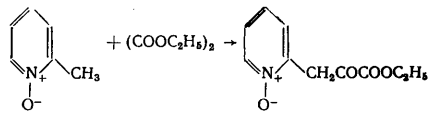
Villers and Hertog [188] ascribed the same mechanism to the reaction of 2-pyridyl *p*-toluenesulphonate with pyridine *N*-oxide, which also yields 1-(2-pyridyl)-2-pyridone. The same compound was observed as a by-product in the reaction of *p*-toluenesulphonyl chloride with pyridine *N*-oxide [189].

3. Effect of the *N*-Oxide Group on the Reactivity of Substituents in Aromatic Heterocyclic Compounds

The hydrogen atom in the methyl groups of α- and γ-picoline, quinaldine, or lepidine is characterised by remarkable reactivity which is caused by the conjugation of σ-electrons with the electrons in the ring. The mobility of the hydrogen atom is increased by transition to the corresponding quaternary compounds. Similarly, the mobility is higher in aromatic heterocyclic *N*-oxides. 2-Picoline and 4-picoline and quinaldine *N*-oxides react with aromatic aldehydes in the presence of basic reagents forming ethylene derivatives [190]. The increased mobility of the hydrogen atom in *N*-oxides as compared with non-oxidised compounds is brought out by the fact that 3-ethyl-4-nitropyridine *N*-oxide [191,192] and 2,5-dimethylpyrazine dioxide [50] react with benzaldehyde, while the corresponding non-oxidised bases do not. The mobility of the hydrogen atom in 3-methyl-4-nitropyridine *N*-oxide is evidenced by the fact that in alkaline solution this compound undergoes oxidative dimerisation and forms 4,4′-dinitro-3,3′-bipicoline 1,1′-dioxide [193].

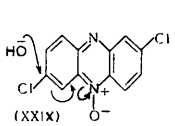


In contrast to the corresponding bases, 2- and 4-picoline *N*-oxides enter the Claisen condensation [28,194,195]. For instance, 2-picoline *N*-oxide undergoes condensation with ethyl oxalate forming a derivative of pyruvic acid:



Nevertheless, the electron-accepting power of the *N*-oxide group in quinaldine *N*-oxide is insufficient to cause the hydrogen mobility required for reaction with *p*-nitrosodimethylaniline [196].

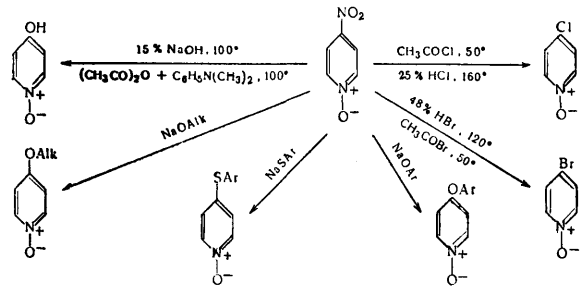
The ability of the *N*-oxide group to lower the electron density at the α- and γ-positions in the ring results in an increased mobility of halogen substituents in these positions. The halogen atoms in *N*-oxides, *e.g.* pyridine *N*-oxide, are more active than in the corresponding bases. 2-Bromopyridine *N*-oxide reacts with the sodium derivatives of malonic, acetoacetic, benzoylacetic, and cyanoacetic esters, while 2-bromopyridine itself is inactive in this reaction [112]. The halogen substituent in phenazine *N*-oxides is especially reactive: it hydrolyses on boiling with alkali [197-199], and is replaced by an amino-group on heating with amines [200]. In these reactions the *N*-oxide group activates the halogens in *meta*-positions, and not those in *para*-positions [201]. This behaviour is typically shown by compound (XXIX).



(XXIX)

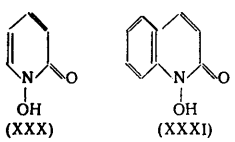
The *N*-oxide group also activates nitro-groups in positions α and γ of the heterocyclic compound. Such nitro-groups can easily be replaced by various reagents. As the nitro-group is readily introduced into position 4, its replacement is one of the preparative methods for obtaining 4-substituted aromatic heterocyclic compounds.

Typical replacements of the nitro-group in 4-nitropyridine *N*-oxide are summarised below [10,103]. The nitro-group in 4-nitronicotinic acid *N*-oxide can similarly be replaced [202].



The nitro-group in 4-nitroquinoline *N*-oxide can be replaced under milder conditions, *e.g.* by chlorine, on boiling with hydrochloric acid. The reduction of nitro-substituted *N*-oxides is sometimes accompanied by replacement of the nitro-group.

The effect of the *N*-oxide group on the properties of 2- and 4-hydroxy- and amino-groups is most interesting, as is the comparison of the structure of these substituted *N*-oxides with those of the corresponding non-oxidised bases. In his comparative study of the spectra of the *N*-oxides of 2-hydroxy-, 3-hydroxy-, and 2-benzyloxy-pyridines, and of *N*-benzyloxy-2-pyridone, Shaw established that 2-hydroxypyridine *N*-oxide has the *N*-hydroxy-2-pyridone structure (XXX) [203]. 2-Hydroxyquinoline *N*-oxide has a similar structure (XXXI) [204].



(XXX) (XXXI)

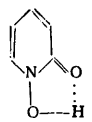
It could be assumed that 4-hydroxypyridine *N*-oxide also had the pyridone structure, but the experimental evidence is that both hydroxy- and oxo-forms were present. For instance, 4-hydroxypyridine *N*-oxide reacts with diazomethane forming a mixture of *N*-methoxy-4-pyridone and 4-methoxypyridine *N*-oxide [205]. 2-Amino- and 4-amino-substituted *N*-oxides were shown to have an amine, not an imine structure. They can easily be diazotised and coupled with β-naphthol [10]. 4-Aminopicoline *N*-oxides take part in the Skraup reaction [206].

Katritzky *et al.* [23,125,207,208] established the structure of the hydroxy- and amino-derivatives of pyridine *N*-oxide on the evidence of basicity and spectral studies, and also investigated the structure of the *N*- or *O*-alkyl derivatives corresponding to both tautomeric forms. It was shown that 2- and 4-aminopyridine *N*-oxides exist in the form of amino-derivatives, that 4-hydroxypyridine *N*-oxide consists of a mixture of equal amounts of the hydroxy- and oxo-forms, and that only 2-hydroxypyridine *N*-oxide exists in the pyridone form. Quantitative relationships are collected in Table 6.

TABLE 6. Correlation between the benzenoid and quinonoid structures.

Compound	Ratio of benzenoid to quinonoid structure			
	4-Amino	2-Amino	4-Hydroxy	2-Hydroxy
Pyridine	10^7	10^8	1	—
N-oxide	$2 \cdot 10^3$	$2 \cdot 10^5$	$4 \cdot 10^{-4}$	$3 \cdot 10^{-3}$
Pyridine				

The pyridone form of 2-hydroxypyridine *N*-oxide is stabilised by a strong hydrogen bond, which makes it impossible to calculate the quantitative ratio of hydroxy- and oxo-forms. The *N*-oxides of the mercaptopyridines exist mainly in the thione form[209]



IV. USES OF AROMATIC HETEROCYCLIC *N*-OXIDES

N-Oxides are widely used as intermediate products in the synthesis of various heterocyclic derivatives. Many such uses have already been discussed. It may now be noted that they are intermediates in the synthesis of certain alkaloids, *e.g.* ricinine[210], alstyrine[211], and 2-ethylisonicotinic thioamide[212]. Pyridinealkanol *N*-oxides are used in a convenient method for obtaining pyrrocolines[213,214]. The specific synthesis of isomeric alkylphenazinium salts using phenazine *N*-oxide is worthy of note[215].

The conversion of heterocyclic rings into corresponding *N*-oxides can be employed for the separation of high-boiling compounds. The lutidine fraction was separated by oxidation to 2,6- and 3,4-lutidine *N*-oxides followed by reduction to the corresponding bases[216]. The separation of the quinoline fraction has been done similarly[217]. Separation can be carried out either by fractional distillation *in vacuo* or chromatographically[218].

Aromatic heterocyclic *N*-oxides are not very important biologically. It has already been mentioned that the antibiotics iodinin and aspergillic acid are *N*-oxides. Attempts to enhance the biological activity by preparing *N*-oxide structures of this type have met with slight success[219]. Nicotinic and isonicotinic acid *N*-oxides are physiologically less active than the corresponding bases[220]. On conversion to *N*-oxides the activity of a number of tuberculostatic compounds (pyridine derivatives) usually drops[221,222]. Purines *N*-oxides are at the moment attracting attention as potential antimetabolites and as possible products of the biological transformations of purines[223,224].

Certain authors report bactericidal action in the *N*-oxides of certain heterocyclic compounds which are otherwise inactive[169,125]. Finally, certain *N*-oxides, *e.g.* 4-nitroquinoline *N*-oxide, have recently been shown to possess carcinogenic activity[226,227].

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CYANOETHYLATION, DECYANOETHYLATION, and TRANSCYANOETHYLATION

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INTRODUCTION

The β-cyanoethyl group $-CH_2CH_2CN$ is most frequently introduced into compounds containing a mobile hydrogen atom by reacting them with acrylonitrile. The cyanoethylation with acrylonitrile has in the last 15–20 years been widely studied on many organic compounds. Alcohols, phenols, mercapto compounds, oximes, amides, aliphatic and aromatic amines, heterocyclic bases, phosphines, arsines, and compounds in which a mobile hydrogen atom is linked to carbon (certain hydrocarbons, polyhalogeno-alkanes, nitro-compounds, aldehydes, ketones, acid derivatives, compounds of the acetoacetic and malonic ester type, and sulphones) have all been cyanoethylated. Several hundreds of original publications and patents and several reviews have dealt with this subject[1-3]. Cyanoethylation is a very simple and convenient method for the preparation of a large number of compounds otherwise difficult to obtain, which are indispensable for the development of various fields of chemical industry.

Cyanoethylation with acrylonitrile proceeds according to the following scheme:

$$R{-}H + CH_2{=}CHCN \rightarrow R{-}CH_2CH_2CN.$$

Cyanoethylation is reversible. Hence by introducing a new compound capable of cyanoethylation into a system in equilibrium transcyanoethylation products can be obtained:

$$R{-}CH_2CH_2CN \underset{+R{-}H}{\overset{-R{-}H}{\rightleftharpoons}} CH_2{=}CHCN \underset{-R'{-}H}{\overset{+R'{-}H}{\rightleftharpoons}} R'{-}CH_2CH_2CN$$

In certain cases decyanoethylation occurs, when acrylonitrile is eliminated (sometimes as a polymer or as acrylic acid):

$$R{-}CH_2CH_2CN \rightarrow R{-}H + CH_2{=}CHCN.$$

Cyanoethylation and its reverse are base catalysed[4].

This review covers all the methods of cyanoethylation with reagents other than acrylonitrile, as well as decyanoethylation and transcyanoethylation. This last reaction can hardly be discussed separately, since it consists in simultaneous cyanoethylation and decyanoethylation:

$$R{-}CH_2CH_2CN + R'{-}H \rightarrow R'{-}CH_2CH_2CN + R{-}H.$$

In addition to acrylonitrile, β-halopropionitriles, ethylene cyanohydrins, β-alkoxypropionitriles, cyanoethyl esters, β-aminopropionitrile and its *N*-substituted derivatives, and certain other compounds can also be used as cyanoethylating agents. In cases where cyanoethylation with acrylonitrile yields polymers, by using some of the above agents the reaction can be carried out under milder conditions and arrested at the monomer stage. These agents are also known to give positive results in cases where acrylonitrile failed to react or gave too low yields of the product. Certain cyanoethyl compounds can only be obtained by transcyanoethylation.

The course of decyanoethylation and transcyanoethylation provides the evidence that the bond attaching β-cyanoethyl groups to oxygen, sulphur, nitrogen, carbon, *etc.*, is, as a rule, more labile than the bonds between alkyl radicals or other groups with these atoms. The mobility of the β-cyanoethyl group is clearly demonstrated by the decyanoethylation of certain cyanoethyl derivatives on distillation.

Decyanoethylation and transcyanoethylation are interesting both from the theoretical and preparative viewpoints. For instance, β-cyanoethyl group can be used for protecting an amino-group[5,6]:

$$R{-}NH_2 + CH_2{=}CHCN \rightarrow RNH{-}CH_2CH_2CN \rightarrow$$

$$\xrightarrow{\text{alkylation}} \begin{matrix} R' \\ R \end{matrix}\!\!>\!N{-}CH_2CH_2CN \xrightarrow{\text{heating}} \begin{matrix} R' \\ R \end{matrix}\!\!>\!NH + CH_2{=}CHCN.$$

1. β-HALOPROPIONITRILES AS CYANOETHYLATING AGENTS

(a) Cyanoethylation with β-chloropropionitrile. The β-halopropionitrile most widely used in cyanoethylations is β-chloropropionitrile.