THE CHEMISTRY OF THE AROMATIC HETEROCYCLIC *N*-OXIDES

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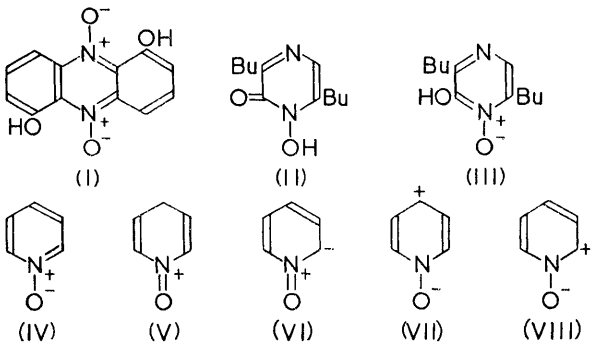
IN general, little interest was taken in the chemistry of heterocyclic *N*-oxides* until about 15 years ago. The discovery that the antibiotics iodinin and aspergillic acid were, respectively, a phenazine dioxide (I) [1] and the cyclic hydroxamic acid tautomer (II) of a pyrazine oxide (III) [2] attracted some attention,[3] but more important to the development of the subject was the determination of the dipole moment of pyridine 1-oxide.[4] This showed



that, in addition to (IV), the canonical forms (V) and (VI) must make important contributions to the resonance hybrid. Ochiai predicted, and confirmed, that this would facilitate electrophilic substitution in the 4-position; following this lead, Japanese workers have completed a very large amount of work [5] on heterocyclic *N*-oxides since 1943. In Holland, den Hertog independently discovered the ready nitration of pyridine 1-oxide and did much to develop the field.[6] Colonna's work in Italy should also be mentioned.[7]

It has become apparent [5] that structures (VII) and (VIII) also contribute to the pyridine 1-oxide resonance hybrid; the fact that the *N*-oxide function is strongly polarisable in both directions is of considerable theoretical

[1] Clemo and McIlwain, *J.*, 1938, 479; Clemo and Daglish, *J.*, 1950, 1481.

[2] Dutcher and Wintersteiner, *J. Biol. Chem.*, 1944, **155**, 359; cf. Dunn, Gallagher, Newbold, and Spring, *J.*, 1949, S 127.

[3] See, *inter alia*, papers by Spring, Shaw, and Landquist, and their co-workers.

[4] Linton, *J. Amer. Chem. Soc.*, 1940, **62**, 1945.

[5] Summarised to 1953 by Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

[6] Latest paper: den Hertog, van Ammers, and Schukking, *Rec. Trav. chim.*, 1955, **74**, 1171.

[7] Colonna, *Gazzetta*, 1956, **86**, 705.

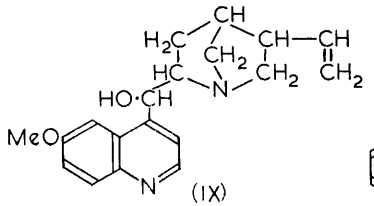
* Throughout this Review the representation $N^+–O^-$ has been used for *N*-oxides in preference to N→O. The former has the advantage that comparison with other canonical forms is clearer (cf. IV—VIII).

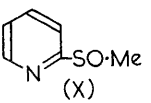
interest,[8] and in this respect the $N^+–O^-$ group of an *N*-oxide is similar to a nitroso-group attached to a benzene ring.[9] The ability of the *N*-oxide group both to accept or to donate electrons is clearly shown by a comparison of dipole moments of alkyl, phenyl, 4-pyridyl, and (4-pyridyl 1-oxide) compounds.[10]

Attention is directed to compilations on amine oxides,[11] derivatives of pyridine,[12] quinoline and *iso*quinoline,[13] acridine,[14] furazans and isatogens,[15] and quinoxalines and cinnolines.[16]

Preparation of Aromatic Heterocyclic *N*-oxides

Direct oxidation.[5, 11] This is the most generally applicable method of preparation. The most convenient oxidising agent is peracetic acid (*i.e.*, a mixture of glacial acetic acid and 30% hydrogen peroxide); monoperphthalic acid and perbenzoic acid have also been used. Hydrogen peroxide alone is usually without effect.


(IX)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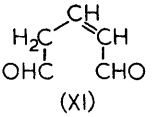
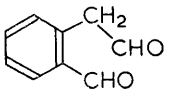
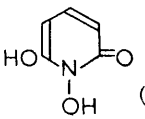

(XI)


(XII)


(XIII)

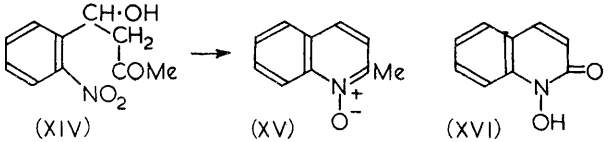
An aromatic nitrogen-heterocyclic compound is converted less readily than a tertiary amine into the *N*-oxide or than a sulphide into the sulphoxide, but more readily than a monosubstituted ethylenic bond into an epoxide. Quinine (IX) gives successively the quinuclidine mono-*N*-oxide and the di-*N*-oxide,[5] whereas 2-methylthiopyridine gives the corresponding sulphoxide (X).[17] Pyrimidines give mono-oxides only.[18]

The reaction is subject to steric hindrance and gives anomalous results with some quinoxaline derivatives:[11] electron-attracting groups interfere.[16a]

Cyclisation of a dicarbonyl compound with hydroxylamine. Glutaconic dialdehyde (XI) is cyclised by ammonia to pyridine and by hydroxylamine

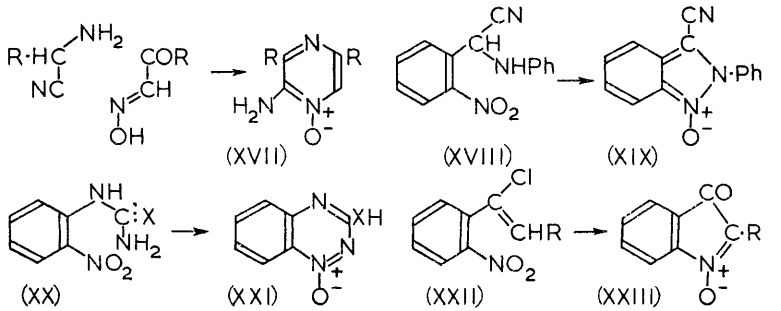
[8] See, *e.g.*, Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.
[9] Robinson, *Chem. and Ind.*, 1925, **44**, 456.
[10] Katritzky, Randall, and Sutton, *J.*, in the press.
[11] Culvenor, *Rev. Pure Appl. Chem.* (*Australia*), 1953, **3**, 83.
[12] Cislak, *Ind. Eng. Chem.*, 1955, **47**, 800.
[13] Elderfield, "Heterocyclic Compounds", Wiley, New York, 1952, Vol. IV, pp. 121, 237.
[14] Albert, "The Acridines", Arnold, London, 1951, p. 144.
[15] Smith, *Chem. Rev.*, 1938, **23**, 193.
[16] Simpson, "Condensed Pyrazine and Pyridazine Ring System", Interscience, New York, 1953, pp. 9, 54, 232, 311, 348.
[16a] Landquist, *J.*, 1953, 2816; Landquist and Stacey, *ibid.*, p. 2822.
[17] Shaw, Bernstein, Losee, and Lott, *J. Amer. Chem. Soc.*, 1950, **72**, 4362.
[18] Ochiai and Yamanaka, *Pharm. Bull.* (*Japan*), 1955, **3**, 175.

to pyridine 1-oxide,[19] and homophthalaldehyde (XII) similarly gives *iso*-quinoline 2-oxide.[20] Glutaconic acid with hydroxylamine gives the cyclic hydroxamic tautomer (XIII) of 2 : 6-dihydroxypyridine 1-oxide, and other examples of this type of reaction are known.[21]



(XIV) (XV) (XVI)

Cyclisation of a substituted hydroxylamine.[11] In the preparation of quinolines by reductive cyclisation of *β-o*-nitrophenylpropionic acid derivatives, the corresponding quinoline 1-oxide is often obtained as a by-product. The quinoline is formed by the cyclisation of an intermediate amine, the *N*-oxide by cyclisation of the corresponding hydroxylamine. In this way quinaldine 1-oxide (XV) has been prepared from the ketone (XIV), and derivatives of 1-hydroxyquinol-2-one (XVI) and 2-aminoquinoline 1-oxide from *o*-nitrophenylacrylic esters and nitriles,[11, 22] respectively; α-*o*-nitrobenzoyl-ketones are reduced to 4-hydroxyquinoline 1-oxides [22a] and the reaction has also been extended to afford 2 : 9-diazaphenanthrene 9-oxides.[23] The similar preparation of 5-membered ring compounds is exemplified by the mild reduction of *o*-nitro-azo-compounds to benzotriazole 1-oxides,[23a] and *o*-nitroanilides to benziminazole 1-oxides.[23b] The reaction between α-aminonitriles and oxo-aldoximes to give 2-aminopyrazine 1-oxides (XVII),[24] and the use of benzyloxyurea in the Traube pyrimidine synthesis to afford derivatives of pyrimidine 1-oxide,[25] are related reactions.



(XVII) (XVIII) (XIX)

(XX) (XXI) (XXII) (XXIII)

[19] Baumgarten, Merländer, and Olshausen, *Ber.*, 1933, **66**, 1802.

[20] Schöpf, Hartmann, and Koch, *Ber.*, 1936, **69**, 2766.

[21] Ames and Grey, *J.*, 1955, 631, 3518; Nielsen, Elming, and Clauson-Kaas, *Acta Chem. Scand.*, 1955, **9**, 9, 30.

[22] Taylor and Kalenda, *J. Org. Chem.*, 1953, **18**, 1755.

[22a] Gabriel and Gerhard, *Ber.*, 1921, **54**, 1067, 1613; Cornforth and James, *Biochem. J.*, 1956, **63**, 124.

[23] Hansen and Petrow, *J.*, 1953, 350.

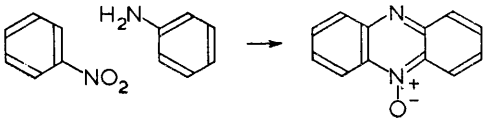
[23a] Elbs, *J. prakt. Chem.*, 1924, **108**, 209; Ross and Warwick, *J.*, 1956, 1724.

[23b] Niementowski, *Ber.*, 1910, **43**, 3012 and refs. therein.

[24] Sharp and Spring, *J.*, 1951, 932.

[25] Lott and Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 70.

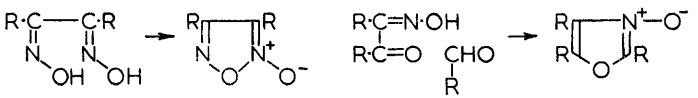
Internal cyclisation of a nitro-compound. In this group of reactions the N=O bond of a nitro-compound undergoes a reaction of the carbonyl-addition type. α-Amino-*o*-nitrophenylacetonitriles (as XVIII) are cyclised to indazole 1-oxides (*e.g.*, XIX) by treatment with alkali,[26] and *o*-nitrophenylurea derivatives (XX; X = O, S, NH, NPh) give benzotriazine 1-oxides (XXI) with sodium hydroxide.[27] The preparation of isatogens (indolenin-3-one 1-oxides) (XXIII) by heating 1-*o*-nitrophenylvinyl chlorides (XXII) with pyridine [15] is probably of the same type.



(XXIV)

The Wohl–Aue reaction,[11] in which phenazine 9-oxides (XXIV) are prepared by heating aromatic amines with nitro-compounds, has probably a related mechanism, initiated by nucleophilic attack of Ph·NH⁻ on the nitrobenzene; this is supported by the isolation of *p*-nitrodiphenylamines as by-products.[28]

N-Hydroxyacridones are formed together with acridones by the reaction of *o*-nitrobenzaldehydes with benzene.[29]



(XXV) (XXVI) (XXVII)

Miscellaneous cyclisations. *o*-Aminophenyl ketoximes are cyclised by nitrous acid to 4 : 5-benzo-1 : 2 : 3-triazine 1-oxides.[29a] 1-Oxa-2 : 5-diazole 2-oxides (XXVI) are obtained by the mild oxidation of dioximes (XXV) and the spontaneous dimerisation of nitrile oxides (RNCO),[15] which can also undergo an alternative dimerisation to 1-oxa-2 : 4-diazole 2-oxides, or trimerise to *s*-triazine 1 : 3 : 5-trioxides.[29b] Certain γ-bromo-nitro-compounds cyclise to *iso*oxazoline 2-oxides.[29c] Aldehydes react with α-diketone monoximes to give oxazole 3-oxides (XXVII).[30]

Reactions of Aromatic Heterocyclic *N*-Oxides

Because of the possibility of electron movement both into the heterocyclic ring from the $N^+—O^-$ group, and in the opposite direction, as shown for, *e.g.*, pyridine 1-oxide by the contribution of canonical forms (IV—VIII)

[26] Behr, *J. Amer. Chem. Soc.*, 1954, **76**, 3672.

[27] Wolf, Wilson, Pfister, and Tishler, *ibid.*, p. 4611; Arndt, *Ber.*, 1913, **46**, 3522; Arndt and Rosenau, *Ber.*, 1917, **50**, 1248.

[28] Wohl, *Ber.*, 1903, **36**, 4135.

[29] Albert, "The Acridines", Arnold, London, 1951, pp. 99—101.

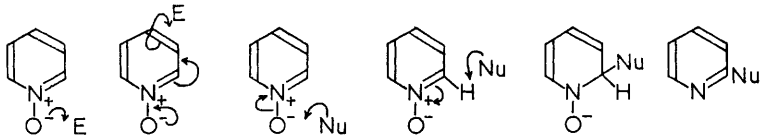
[29a] Meisenheimer, Senn, and Zimmermann, *Ber.*, 1927, **60**, 1736; cf. Ockenden and Schofield, *J.*, 1953, 1915.

[29b] Wieland, *Ber.*, 1909, **42**, 803.

[29c] Smith and Scribner, *J. Amer. Chem. Soc.*, 1956, **78**, 3412 and refs. therein.

[30] Selwitz and Kosak, *ibid.*, 1955, **77**, 5370.

to the resonance hybrid, *N*-oxides show great variety in their chemical reactions.



(XXVIII) (XXIX) (XXX) (XXXI) (XXXII) (XXXIII)

An electrophilic reagent (E) may attack the oxygen (as in XXVIII) or the γ-carbon atom (as in XXIX). (A reaction of this type at the α-carbon atom is hardly ever found, being presumably prevented by the powerful adverse inductive effect of the neighbouring positively charged nitrogen atom.) Acids, alkyl halides, and certain Lewis acids receive electrons at the oxygen atom, giving, respectively, salts, quaternary salts, and co-ordination compounds. The species responsible for nitration, mercuration, and some other electrophilic substitutions receive electrons from the γ-carbon atom in the transition state, and finally displace a proton from this point, giving γ-nitro-*N*-oxides, etc.

A nucleophilic reagent (Nu) may attack the oxygen (as in XXX), the α-carbon (as in XXXI), or the γ-carbon atom. Reducing agents, and some other electron donors such as phosphorus trichloride, supply an electron pair to the oxygen atom and cause deoxygenation. Some powerful nucleophiles, *e.g.*, Grignard reagents, attack the α-carbon atom, giving an intermediate (XXXII) which spontaneously loses a proton and an oxide ion, thus affording the corresponding α-substituted deoxygenated heterocyclic compound (XXXIII). Weaker nucleophilic agents, *e.g.*, chloride, cyanide, and acetoxy-ions, are able to attack the α- or the γ-carbon atom if the *N*-oxide first forms a co-ordinated intermediate with an electron acceptor (as in XXVIII) : this happens when the *N*-oxide reacts with sulphonyl chloride, benzoyl chloride–potassium cyanide, acetic anhydride, etc. In certain of these reactions it is possible that α-substitution results from reaction of the co-ordinated intermediate by way of a cyclic transition state. In reactions with nucleophilic reagents heterocyclic *N*-oxides sometimes behave similarly to the nitrones $R{\cdot}N^{+}(\cdot O^{-}){:}CR_2$, as emphasised by Colonna.[31]

Finally there is a group of reactions in which a substituent is attached to a carbon atom β or δ to the N^{+}–O^{-} group, *i.e.*, either on the β-carbon atom of the ring or on the first carbon atom of an α- or γ-side-chain. The mechanism here is not clear ; in certain cases a free-radical attack has been suggested.

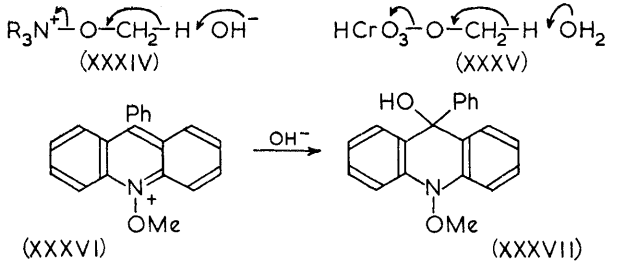
These various reactions are now discussed in more detail ; it will be noted that most of the illustrations are taken from the pyridine and the quinoline field, which is because much more work has been done there than with other *N*-oxides.

Electrophilic Attack on Oxygen (cf. XXX).—*Salt formation.* *N*-Oxides

[31] Colonna, *Boll. Sci. Fac. Chim. ind. Bologna*, 1940, **4**, 134 ; *Chem. Abs.*, 1940, **34**, 7290.

form stable salts with strong acids unless other negative groups are present. The basicity is however considerably less than that of the corresponding deoxygenated compound: the pK values [32] of the conjugate acids of, *e.g.*, pyridine, pyridine 1-oxide, and 4-nitropyridine 1-oxide are respectively 5·29, 0·79, and − 1·7. The basicities of a series of substituted pyridine 1-oxides were found [32] to conform to the Hammett equation with $\rho = 2{\cdot}09$. Picrolonates are convenient for the characterisation of N-oxides.[32a]

Quaternary salts. N-Oxides, with some difficulty, give quaternary salts. These are often converted by alkali into the corresponding deoxygenated base and aldehyde,[5, 33] just as are the quaternary salts from aliphatic N-oxides. The mechanism of this reaction (XXXIV) may be compared



(XXXVI) (XXXVII)

with the oxidation of alcohols with chromic acid (XXXV). In favourable cases the quaternary salt with alkali gives a *pseudo*-base, *e.g.*, (XXXVI) → (XXXVII).[34] Quinoxaline 1-oxide adds methyl iodide solely on the 4-nitrogen atom.[16a]

Co-ordination compounds. Very little is known about their formation from heterocyclic N-oxides. Pyridine 1-oxide and sulphur trioxide give $C_5H_5N{\cdot}O{\cdot}SO_3$.[35]

Electrophilic Attack on the Ring (XXXI).—*Nitration.* Pyridine 1-oxide is nitrated by mixed acid at 100° to give 4-nitropyridine 1-oxide in very good yield.[5] If the reaction is carried out at 150° some 2-nitropyridine is also obtained; presumably this is formed by deoxygenation of 2-nitropyridine 1-oxide (cf. below).[5] This nitration α to the $N^+–O^-$ group is exceptional; if the γ-position is occupied, nitration is usually either not effected (*e.g.*, in 4-alkylpyridine 1-oxides),[36] takes place in another ring (*e.g.*, in *iso*quinoline 2-oxide in the 5-position [37]), or, when a very strongly electron-releasing group is in the α- or the γ-position, nitration takes place in the β-position (as, *e.g.*, in 4-hydroxypyridine 1-oxide [5, 38]).

[32] Jaffé and Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.

[32a] Katritzky, *J.*, 1956, 2404.

[33] Ochiai, Katada, and Naito, *J. Pharm. Soc. Japan*, 1944, **64**, 210; *Chem. Abs.*, 1951, **45**, 5154.

[34] Lehmstedt and Dostal, *Ber.*, 1939, **72**, 1071.

[35] Baumgarten and Erbe, *Ber.*, 1938, **71**, 2603.

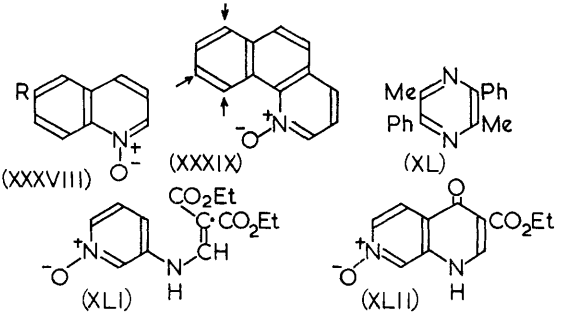
[36] Ishikawa, *J. Pharm. Soc. Japan*, 1945, **65**, 6; *Chem. Abs.*, 1951, **45**, 8529.

[37] Ochiai and Ishikawa, *J. Pharm. Soc. Japan*, 1945, **65**, 4*A*, 17; *Chem. Abs.*, 1951, **45**, 8527.

[38] Naito, *J. Pharm. Soc. Japan*, 1947, **67**, 246; *Chem. Abs.*, 1951, **45**, 9541.

The position substituted in quinoline 1-oxide (XXXVIII ; R = H) varies ; at 10° 5- and 8- and at 70° mainly the 4-nitro-derivative are formed ; at still higher temperatures initial deoxygenation again directs substitution into the benzenoid ring.[5] The nitrations of some other quinoline 1-oxides (XXXVIII ; R = Me, Cl, Br) show a similar temperature dependence, but in the ether (XXXVIII ; R = OMe) substitution is entirely at the 5-position, and in the derivative (XXXVIII ; R = NO_2) entirely at the 4-position.[39]

The directive power of the $N^+–O^-$ group is very great compared with that of other substituents in the same ring ; 2- and 3-ethoxypyridine 1-oxide are both nitrated exclusively in the 4-position.[40] However, 2-hydroxypyridine 1-oxide [or its hydroxamic acid tautomer, cf. (II)] is nitrated in



the 5-position,[25] and in 3 : 5-dimethoxy-, 3-bromo-5-methoxy-, and 3 : 5-diethoxy-pyridine 1-oxide substitution even occurs in the 2-position, probably partly for steric reasons.[6, 41]

In phenazine 5-oxide (XXIV) nitration occurs more easily than in the deoxygenated parent, and the nitro-group enters the 3-position ; similar behaviour is found with chlorophenazine 5-oxides, but in methoxy-compounds the methoxyl group directs the orientation of nitration.[41a]

Little is known about more complicated systems ; 4-phenylcinnoline 1-oxide on nitration gives four different products, none of which has been orientated,[16] and 7 : 8-benzoquinoline 1-oxide is nitrated in the positions shown in (XXXIX).[42] 3 : 4-Benzocinnoline 1-oxide was originally considered [42a] to be nitrated mainly in the 2- and partly in the 3-position, but dipole-moment evidence [42b] showed that the major product could not be the 2-isomer, and chemical evidence showed that it was not the 1-, 3-, 8-, or 10-isomer.[42c] It is of interest that both 2 :5-dimethyl-3 : 6-diphenylpyrazine

[39] Naito, *J. Pharm. Soc. Japan*, 1948, **68**, 209 ; *Chem. Abs.*, 1953, **47**, 8075 ; Okamoto, *J. Pharm. Soc. Japan*, 1951, **71**, 727.

[40] den Hertog, Kolder, and Combé, *Rec. Trav. chim.*, 1951, **70**, 591.

[41] den Hertog, Henkens, and Dilz, *ibid.*, 1953, **72**, 296.

[41a] Otomasu, *Pharm. Bull., Japan*, 1954, **2**, 283 ; 1956, **4**, 117.

[42] Iwai, *J. Pharm. Soc. Japan*, 1951, **71**, 1291.

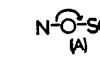
[42a] King and King, *J.*, 1945, 824.

[42b] Calderbank and Le Fèvre, *J.*, 1951, 649.

[42c] Arcos, Arcos, and Miller, *J. Org. Chem.*, 1956, **21**, 652.

(XL) and the corresponding 1 : 4-dioxide give *m*-nitrophenyl compounds on nitration.[43]

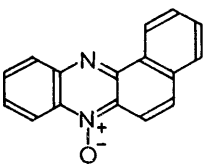
Other electrophilic substitutions. Pyridine 1-oxide is mercurated in the 4-position under mild conditions; quinoline 1-oxide, however, forms the 8-mercuri-derivative,[44] probably through a cyclic transition state.[45] Bromination of pyridine 1-oxide could not be effected,[46] but 4-bromoquinoline 1-oxide was prepared by direct halogenation.[47] Treatment of pyridine 1-oxide with 20% fuming sulphuric acid and mercuric sulphate at 220—240° gave 3-sulphopyridine 1-oxide in 51% yield, but no substitution could be induced under milder conditions;[46] presumably under the forcing conditions the co-ordination complex with SO_3 is formed (see above) in which the activating character of the $N^+–O^-$ group is lost (cf. A).

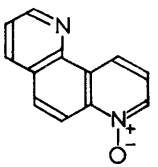

(A)

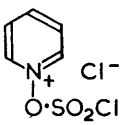
Although the Friedel–Crafts reaction fails with pyridine 1-oxide,[46] the derivative (XLI) cyclises into the 4-position, giving the oxo-ester (XLII). The deoxygenated analogue cyclises less readily and into the 2-position.[48]

Nucleophilic Attack on Oxygen (cf. XXXII).—The ease of reduction of heterocyclic *N*-oxides varies. Some phenazine and quinoxaline *N*-oxides liberate iodine from acidified potassium iodide [11, 23] but pyridine and quinoline 1-oxides are generally very resistant to reduction, as shown by the values of their reduction potentials (C_5H_5NO — 1·2786; cf. Me_3NO — 0·4562).[5] Other groups in the molecule can often be reduced selectively without simultaneous loss of the N–O group (see below). Iron–acetic acid,[40, 41, 49] and sodium dithionite [24] remove the *N*-oxygen atom efficiently.

Heterocyclic *N*-oxides may also be deoxygenated by an oxygen acceptor. This method is most useful when it is desired to leave unaffected other groups susceptible to reduction. Phosphorus trichloride converts 4-nitropyridine 1-oxide into 4-nitropyridine. The method fails with 4-nitroquinoline 1-oxide, but phosphorus tribromide may then be used.[5] An early example of this type of reaction in the benzopyrazole series is recorded.[50] Triphenyl phosphite has also been used as an oxygen acceptor.[51]


(XLIII)


(XLIV)


(XLV)

[43] Beech, *J.*, 1955, 3094.

[44] Ukai, Yamamoto, and Hirano, *J. Pharm. Soc. Japan*, 1953, **73**, 823; *Chem. Abs.*, 1954, **48**, 9946 (cf. also *J. Pharm. Soc. Japan*, 1955, **75**, 490).

[45] Yamamoto, Hirano, and Yotsuzuka, *Pharm. Bull.* (*Japan*), 1955, **3**, 105.

[46] Mosher and Welsh, *J. Amer. Chem. Soc.*, 1955, **77**, 2902.

[47] Ochiai and Okamoto, *J. Pharm. Soc. Japan*, 1947, **67**, 87; *Chem. Abs.*, 1951, **45**, 9538.

[48] Murray and Hauser, *J. Org. Chem.*, 1954, **19**, 2008.

[49] den Hertog and Combé, *Rec. Trav. chim.*, 1951, **70**, 581.

[50] Reissert and Lemmer, *Ber.*, 1926, **59**, 351.

[51] Hamana, *J. Pharm. Soc. Japan*, 1955, **75**, 139.

Pyridine 1-oxides are deoxygenated in poor yield by heating them alone or in concentrated sulphuric acid.[11] Hydrogen peroxide will also cause deoxygenation if re-oxidation is prevented by steric hindrance — *e.g.*, 1 : 2 - benzophenazine 7 : 12 - dioxide gives the 7 - monoxide (XLIII).[52]

Nucleophilic Attack on the Ring (cf. XXXIII and XXXVI).—*Grignard reagents.* As mentioned above, Grignard reagents convert the group —$N^+(O^-)$:CH— into —N:CR—; *e.g.*, quinoline 1-oxide and phenylmagnesium bromide give 2-phenylquinoline.[53] Good results are also obtained with benzoquinolines,[54] but pyridine 1-oxides give poorer yields.[13] Here the yields may be improved by using the complex between pyridine 1-oxide and benzoyl chloride.

Action of sulphuryl chloride or phosphorus oxychloride.[11] As already indicated, nucleophilic attack on the ring is enhanced by previous co-ordination of the oxygen atom. Pyridine 1-oxide and sulphuryl chloride give a mixture of 2- and 4-chloropyridine, which can be separated because the weakly basic 2-chloropyridine does not form a picrate.[55] The reaction has been used most where the formation of two products is prevented. A 2- or a 4-substituted quinoline 1-oxide is converted into the corresponding 2 : 4-disubstituted quinoline;[56] *iso*quinoline 2-oxides give exclusively 1-chloro*iso*quinolines[57] (only one true *ortho*-position); and the *N*-monooxide (XLIV) gives only the α-chloro-compound, probably because the γ-position is sterically hindered.[58] Phosphorus oxychloride reacts with phenazine *N*-oxides, where there is no free α- or γ-position, chlorine being introduced into the side rings.[59]

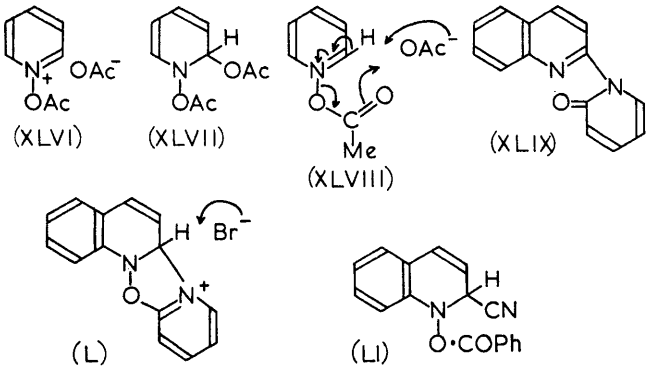
Although α- and γ-nuclear attack on complexes such as (XLV) preponderated, it has been shown that reactions of this type give some β-nuclear[60] and side-chain[61] chlorination.

Action of acetic anhydride. This reagent converts *N*-oxides (without an alkyl group α or γ to the N^+–O^-, see below) into α-oxo-compounds, *i.e.*, —CH:N(O)— becomes —CO·NH—. Ochiai has emphasised the formal similarity to the last reaction, by writing (XLVI) and (XLVII) as intermediates, but it is possible that the reaction involves a cyclic transition state (XLVIII; of course, the electrons can also be considered to move in the opposite direction). This reaction is known in the benziminazole and quinoline series,[5, 62] etc.

[52] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1951, **73**, 4958.
[53] Colonna and Risaliti, *Gazzetta*, 1953, **83**, 58.
[54] Colonna and Fatutta, *ibid.*, p. 622.
[55] Bobranski, Kochanska, and Kowalewska, *Ber.*, 1938, **71**, 2385.
[56] Reitsema, *Chem. Rev.*, 1948, **43**, 58.
[57] Robinson, *J. Amer. Chem. Soc.*, 1947, **69**, 1939.
[58] Kermack and Tebrich, *J.*, 1945, 375.
[59] Postovskii and Abramova, *Zhur. obshchei Khim.*, 1954, **24**, 485; *Chem. Abs.*, 1955, **49**, 6273.
[60] Gouley, Moersh, and Mosher, *J. Amer. Chem. Soc.*, 1947, **69**, 303.
[61] Kato, *J. Pharm. Soc. Japan*, 1955, **75**, 1236, 1239.
[62] Montanari and Risaliti, *Gazzetta*, 1953, **83**, 278.

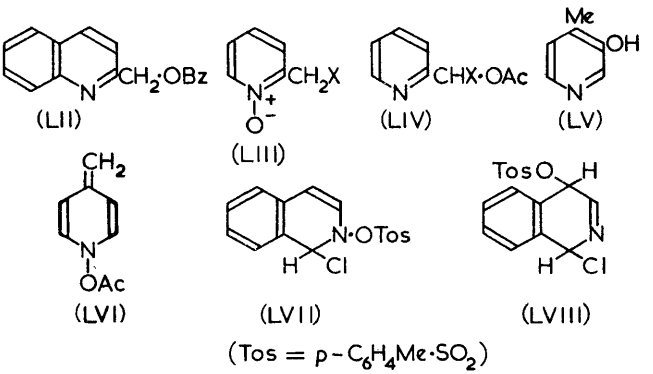
Quinoline 1-oxide and 2-bromopyridine give the pyridone (XLIX);[63] it is suggested that this reaction involves an analogous cyclic transition state (L).

Benzoyl chloride and potassium cyanide. With these reagents quinoline 1-oxide gives 2-cyanoquinoline, probably by way of the intermediate (LI). This discloses an obvious analogy to the Reissert reaction, and other examples



are given in a comprehensive review of the latter reaction.[64] Benzoyl chloride and potassium hydroxide with quinoline 1-oxides give carbostyrils,[54, 62] and diethyl sodiomalonate with preformed benzoyloxyquinolinium chloride gives diethyl 2-quinolylmalonate.[13] Recently, examples of these reactions in the pyrimidine series have been described.[18]

Reactions leading to Substitution β or δ to the N^+–O^-.—Pachter[65] showed that the reaction between quinaldine 1-oxide, benzoyl chloride, and sodium



hydroxide gave 2-benzoyloxymethylquinoline (LII). Acetic anhydride acetoxylates the alkyl group of α- or γ-alkylpyridine 1-oxides, *e.g.*, (LIII;

[63] Takeda and Hamamoto, *J. Pharm. Soc. Japan*, 1953, **73**, 1158; *Chem. Abs.*, 1954, **48**, 12748.

[64] McEwen and Cobb, *Chem. Rev.*, 1955, **55**, 543.

[65] Pachter, *J. Amer. Chem. Soc.*, 1953, **75**, 3026.

X = H, Me, or OAc) → (LIV).[66–69] With 2-picoline 1-oxide (LIII ; X = H) some 6-methylpyrid-2-one is also formed.[66] The reaction can be used to make hydroxymethyl- and formyl-pyridines by hydrolysis of the acetates (LIV ; X = H, Me, or OAc).[67]

4-Picoline 1-oxide gives, in addition to 4-acetoxymethylpyridine, some 3-hydroxy-4-methylpyridine (LV). It was suggested that these both came from a common anhydro-base intermediate (LVI).[69] A free-radical mechanism has also been suggested for this reaction.[70] A mixture of products appears to be generally formed ; thus, lepidine 1-oxide gives 2- and 3-hydroxylepidine as well as 4-quinolylmethanol.[71]

Another reaction, giving β-substitution, is the production of β-hydroxy-compounds from *N*-oxides with toluene-*p*-sulphonyl chloride ; *e.g.*, *iso*quinoline 2-oxide is converted into 4-toluene-*p*-sulphonyloxy*iso*quinoline ; Ochiai has suggested [72] that the compounds (LVII) and (LVIII) are intermediates in this reaction.

N-Oxides with substituted groups

Alkyl groups. In the α- or γ-position to the $N^+–O^-$ groups, alkyl groups show enhanced reactivity ; thus 2- and 4-methylpyridine 1-oxide undergo Claisen condensations with ethyl oxalate [73] and give cyanine dyes.[74]

Nitro-groups and halogen atoms. When α or γ to the $N^+–O^-$, these groups readily undergo nucleophilic replacement by amines, sodium alkoxides, phenoxides, and thio-derivatives.[6, 49, 17, 75] Attempts at replacement with carbanions have been less successful.[76] Halogen atoms in phenazine *N*-oxides are more reactive than those in phenazines.[77] 4-Nitropyridine 1-oxides are converted into 4-chloro(or -bromo)pyridine 1-oxides by treatment with acetyl chloride,[5] or with boiling hydrochloric (hydrobromic) acid.[5, 49] Heating them with acetic anhydride and dimethylaniline (acceptor for nitrous acid) gives 4-hydroxypyridine 1-oxides.[5] The nitro-group in 2 : 6-dimethyl-3-nitropyridine 1-oxide does not show this reactivity.[36]

Catalytic reduction of 4-nitropyridine 1-oxides in neutral media affords the corresponding 4-aminopyridine 1-oxide ; in acid the $N^+–O^-$ group is also lost. Reduction under other conditions leads to azo-, azoxy-, and hydrazo-compounds.[5]

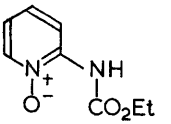
[66] Kobayashi and Furukawa, *Pharm. Bull.* (*Japan*), 1953, **1**, 347 ; *Chem. Abs.*, 1955, **49**, 10948. [67] Boeckelheide and Linn, *J. Amer. Chem. Soc.*, 1954, **76**, 1286.
[68] Bullitt and Maynard, *ibid.*, p. 1370.
[69] Berson and Cohen, *ibid.*, 1955, **77**, 1281.
[70] Boeckelheide and Harrington, *Chem. and Ind.*, 1955, 1423.
[71] Kobayashi, Furukawa, Akimoto, and Hoshi, *J. Pharm. Soc. Japan*, 1954, **74**, 791 ; *Chem. Abs.*, 1955, **49**, 11659 ; cf. also Kato, *J. Pharm. Soc. Japan*, 1955, **75**, 1233.
[72] Ochiai, Abs. Papers, XIVth Internat. Congr. Pure Appl. Chem., Zurich, 1955, p. 375 ; cf. Ochiai and Ikehara, *Pharm. Bull.* (*Japan*), 1955, **3**, 454.
[73] Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 3168.
[74] Takahashi and Satake, *J. Pharm. Soc. Japan*, 1952, **72**, 1188 ; *Chem. Abs.*, 1953, **47**, 7500. [75] Katritzky, unpublished work.
[76] Nakayama, *J. Pharm. Soc. Japan*, 1951, **71**, 1391.
[77] Pachter and Kloetzel, *J. Amer. Chem. Soc.*, 1952, **74**, 971.

2-Nitropyridine 1-oxides have been made by oxidation of 2-amino-pyridine 1-oxides with Caro's acid.[78]

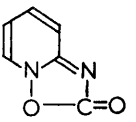
Amino- and hydroxy-groups. Comparison of ultraviolet spectra shows that 2-hydroxypyridine 1-oxide exists in the tautomeric, cyclic hydroxamic acid form, *i.e.*, 1-hydroxy-2-pyridone [79, 80] (cf. II and III), but 2-amino- [75] and probably 4-amino- and 4-hydroxy-pyridine 1-oxide exist mainly in the *N*-oxide form.[81, 82]

2- and 4-Hydroxypyridine 1-oxide may be prepared by dealkylation of 2- and 4-alkoxypyridine 1-oxide ; [5, 79, 80] 2- and 4-amino-derivatives are made respectively by oxidation of a 2-acylaminopyridine followed by removal of the acyl group,[83, 75] and by reduction of the readily available 4-nitropyridine 1-oxides.[5]

Reaction of 4-hydroxypyridine 1-oxide with diazomethane gives a mixture of 1-methoxypyrid-4-one and 4-methoxypyridine 1-oxide.[81] 4-Aminopyridine 1-oxide with methyl iodide gives 4-amino-1-methoxy-



(LIX)



(LX)

pyridinium iodide.[33] 4-Aminopyridine 1-oxides can be diazotised, and the diazonium compounds subjected to the various Sandmeyer reactions, etc. ; [5] the diazo-group can also be replaced by hydrogen.[38]

2-Aminopyridine 1-oxide can also be diazotised in dilute acid.[75] 2-Ethoxycarbonylaminopyridine 1-oxides (as LIX) lose ethanol when heated, forming bicyclic products (as LX).[84]

2-Hydroxy- and 2-amino-*N*-oxides give intense red and blue colours respectively with ferric chloride ; [23, 24, 79] under forcing alkaline conditions the 2-amino- may be converted into a 2-hydroxy-group.[24]

The importance of *N*-oxide intermediates in synthetic work is likely to increase ; thus in recent syntheses of ricinine [85] and alstyrine,[86] in each case the pyridine 4-substituent was introduced by nitration of a 1-oxide and further transformation of the nitro-group.

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[78] Brown, Abs. 128th meeting Amer. Chem. Soc., 1955, p. 10-o.

[79] Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67.

[80] Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2091.

[81] Ochiai and Hayashi, *J. Pharm. Soc. Japan*, 1947, **67**, 151 ; *Chem. Abs.*, 1951, **45**, 9540.

[82] Jaffé, *J. Amer. Chem. Soc.*, 1955, **77**, 4445 ; but see also Hayashi, *J. Pharm. Soc. Japan*, 1951, **71**, 213.

[83] Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 2785.

[84] Katritzky, *J.*, 1956,

[85] Taylor and Crovetti, *J. Amer. Chem. Soc.*, 1956, **78**, 214.

[86] Lee and Swan, *J.*, 1956, 771.