ORGANIC CHEMISTRY

A Series of Monographs — Volume 19

CHEMISTRY of the HETEROCYCLIC *N*-OXIDES

ORGANIC CHEMISTRY

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CHEMISTRY of the HETEROCYCLIC *N*-OXIDES

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Foreword

The first heteroaromatic *N*-oxides were prepared a century ago, but these compounds remained largely chemical curiosities for the next 70 years. In the early 1940's the Japanese began their extensive study of the chemistry of the heteroaromatic *N*-oxides, however the western world was not aware of their work until about 1951 owing to the breakdown in communications resulting from World War II. Since then, the *N*-oxides have been actively studied, and their manifold reactions have already found extensive application in synthetic work; their reactivity pattern is also of considerable theoretical importance. It is apparent, however, that the *N*-oxides have great potential for future development in both synthetic and theoretical directions.

Our own long-standing interest in the heteroaromatic *N*-oxides prompted us to undertake the preparation of this monograph in 1960. The task proved to be slow, and our working outline underwent several major modifications. We have specifically directed our attention towards the *chemistry* of the heterocyclic *N*-oxides as reflected in the methods of their preparation and chemical reactivity: spectral and other physiochemical properties are discussed primarily from the light they shed on understanding their chemical reactivity. Particular emphasis has been placed on the systematic arrangement of the reactions according to mechanism, and it is hoped that this treatment will be of considerable value to those interested in new reactions. Extensive tabulations of data are included with the hope that they will indicate the most appropriate conditions for syntheses. We have attempted to survey the published literature available through March 1970 (references to papers appearing during the last six months are given in the Appendix), paying particular attention to the collection and collation of reports in the non-Japanese literature and studies concerned with *N*-oxides of heteroaromatic systems other than pyridine. Although our main concern is with heteroaromatic *N*-oxides, partially reduced heterocyclic *N*-oxides are also treated as are compounds such as cyclic hydroxamic acids which are tautomeric with *N*-oxides. The arrangement of the material within the book is discussed in the first part of Chapter 1, and a detailed subject index is included to facilitate location of reactions applied to specific ring systems. To avoid duplication of the thorough treatment of the historical development and the spectral and biological properties of *N*-oxides included in E. Ochiai's authoritative work "Aromatic Amine Oxides," which appeared in 1967 and covers the literature up to about 1965, we have placed less emphasis on these subjects.

Our system for dealing with the references is new, and whilst economical of space, allows for easy identification. This system has simplified the preparation of the manuscript, and we hope it has minimized the number of errors in the bibliography. Errors of interpretation and of fact, however, are almost inevitable in a book of this nature; the responsibility for these is ours, and we would appreciate having them brought to our attention.

The preparation of this book would not have been possible without the help of a great many people. We would like to thank particularly Mrs. P. Jones, Mrs. C. Jenvey, Mrs. H. Stedman, and Miss L. Metcalf for their help with the compilation and checking of the material, and Miss B. Futter and Mrs. J. Hall for typing the manuscript. The structural formulae drawn by Misses L. Metcalf and A. Turner for inclusion in the manuscript were deemed satisfactory for reproduction in the monograph by the publisher. We also want to express our appreciation to our colleagues at the University of East Anglia for their helpful criticisms of the manuscript, and to the Academic Press staff for their assistance during the preparation of this volume. Last, but not least, we wish to thank our spouses for their understanding and encouragement during the years this manuscript was in preparation.

A. R. Katritzky
J. M. Lagowski

1st September 1970

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REACTIONS AT *N*-OXIDE RINGS

CHAPTER IV

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CHAPTER I

1. Introduction and Historical Aspects

A. ARRANGEMENT OF THE BOOK

i. Chapters of the Book

Chapter I affords rather cursory treatment of the physical properties and biological activities of heterocyclic *N*-oxides, their use as catalysts, and the historical development of *N*-oxide chemistry.

The bulk of the material in this monograph is arranged in the subsequent three chapters, one on the preparation of heterocyclic *N*-oxides and two on reactions of these compounds. Chapter II is concerned with the synthesis of *N*-oxides from compounds which are not themselves cyclic *N*-oxides. The material in Chapter II is subdivided into two major categories: direct *N*-oxidation and ring synthesis. Direct *N*-oxidation reactions are further subdivided on the basis of the type of oxidizing agent employed. Ring syntheses are first classified according to the mechanism of the cyclization reaction, and then by the type of ring system prepared.

Chapter III deals with the reactions of *N*-oxide ring systems, including reactions at ring carbon, hydrogen, or nitrogen atoms, at the *N*-oxide oxygen atom, and at fused benzene rings, but excluding those involving substituents. As far as possible, this material is logically arranged according to the reaction type: reactions at the *N*-oxide oxygen atom with electrophilic reagents are discussed first, followed by reactions involving nucleophilic reagents; reactions at ring carbon atoms with electrophilic and nucleophilic reagents are then considered successively. Free-radical reactions, reactions at ring nitrogen atoms, and reactions involving a cyclic transition state are also discussed. Those reactions proceeding by mechanisms which are not yet fully understood are placed in the category that appears most probable and appropriate cross-references are given.

Chapter IV treats the reactions of substituents. These are classified according to the substituent type, specifically according to the atom linked directly to the *N*-oxide ring. Thus, carbon-linked, oxygen-linked, nitrogen-linked, etc., substituents are distinguished. Many substituent reactions also involve the ring or, more frequently, the *N*-oxide oxygen atom. These reactions are generally treated as substituent reactions on the grounds that they are not typical of the unsubstituted ring systems, and an attempt to give pertinent cross-references has been made.

Chapter V comprises a comprehensive bibliography of all references. The system of referencing is explained in an introductory section.

It will be apparent that the chemistry of the *N*-oxide(s) of one particular ring system, e.g. pyrimidine 1-oxides, is scattered throughout the book. To partially surmount this problem, which is an inevitable consequence of the arrangement of the material, a detailed subject index is included.

ii. Nomenclature, Sections, and Tables

Nomenclature, as far as possible, follows the I.U.P.A.C. rules and/or *Chemical Abstracts* conventions. For reasons of clarity and simplicity as well as logic, tautomeric compounds are generally named in the tautomeric form which predominates in aqueous solution or in the crystalline state (cf. the discussion in reference 65CI331).

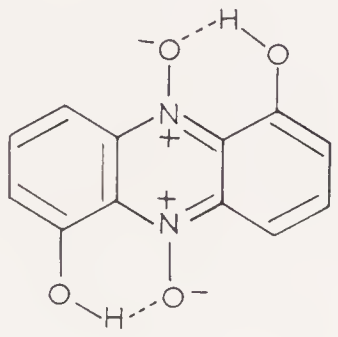
As explained in the preceding section, this book is primarily arranged according to reaction types. Within each section dealing with reactions of any one type, examples from the various ring systems are considered in unique order. Ring systems are classified first by ring size, *six*-membered rings followed by *five*, followed by *others*; then by the *number* of hetero-atoms in the ring; next by the type of hetero-atoms, nitrogen before oxygen before sulphur; and finally according to the number of rings fused together, *monocyclic* before *bicyclic*, etc.

The tables are comprehensive in that we have tried to include each relevant reference; however, all individual examples of a reaction are not recorded separately. Tables are ordered first by ring system (as outlined in the previous paragraph) and then by substituents, in alphabetical order. References occurring in the discussion section of the text are also included in the tables, where relevant.

B. THE HISTORICAL DEVELOPMENT OF *N*-OXIDE CHEMISTRY

Historically, *N*-oxide chemistry falls into four periods: the early period, from 1870–1920, which consists largely of fragmentary work; the steady but unspectacular progress of the classical period from 1920–1940; the post-classical period, from 1940–1955, which includes the rapid development of the field by the work of Ochiai's group in Japan; and the modern period, from 1955 to the present. The first heterocyclic *N*-oxide appears to have been prepared by Weselsky in about 1870 (71CB613). Many of the *N*-oxides which were obtained in the early period (1870–1920) were not recognized as such, and revisions of early structural assignments have continued from the 1920's to the present. Pyridine 1-oxide was first prepared by Meisenheimer (26CB1848) by perbenzoic acid oxidation of pyridine. Largely due to further work by Meisenheimer and by Bobranski, the heteroaromatic *N*-oxides were a well-recognized group of compounds by the end of the 1930's.

In 1940, Linton (40JA1945) measured the dipole moment of pyridine 1-oxide and found that its value indicated a considerable back-polarization of electrons into the pyridine ring from the *N*-oxide group. Ochiai, realizing that this might facilitate electrophilic substitution, discovered in 1942 the facile nitration of pyridine 1-oxide in the 4-position (42PJ561) and subsequently observed the ready nucleophilic displacement of the nitro group of 4-nitropyridine 1-oxide. He also quickly recognized the increased stability of aromatic *N*-oxides which sharply differentiates them from their aliphatic analogues. Thus was founded the well-known Japanese school of *N*-oxide chemistry (43JJ307; 43PJ307) from which has come so much of our knowledge of the chemistry of these compounds. The discovery that the antibiotics iodinin (*1*) and aspergillic acid (*2*) are *N*-oxides gave further impetus to the study of the general chemistry of *N*-oxides.



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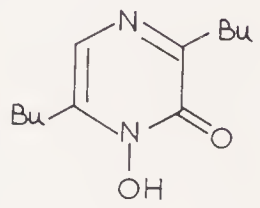

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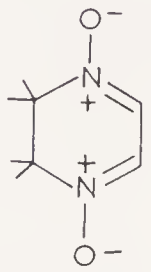

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Because of the breakdown in communications resulting from World War II, the Japanese work remained unknown in the western world until about 1951. In the Netherlands, den Hertog, applying the same reasoning as Ochiai, independently discovered the nitration of pyridine 1-oxide (50R468) and founded a school of *N*-oxide chemistry at Wageningen. A third early centre of *N*-oxide research was that of Colonna and his group in Italy, which emphasized particularly the analogy between heterocyclic *N*-oxides and nitrones (40BS134). Heterocyclic *N*-oxides can indeed be considered as cyclic nitrones, and in this monograph an attempt is made to include the chemistry of those *N*-oxides which do not contain a completely unsaturated ring and which are therefore often classified as cyclic nitrones (for a review of nitrone chemistry, including both cyclic and acyclic derivatives, see reference

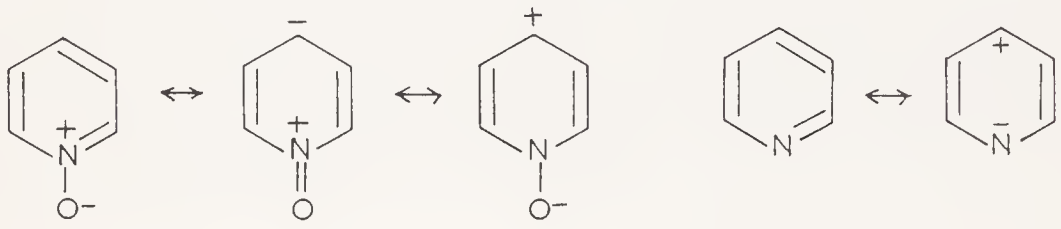
64CR473). Nitrones are usually more reactive than heteroaromatic *N*-oxides; however, their reactivity may be reduced by suitable structural modifications, as for example in the bis-nitrone *3* [66J(C)2300].

Within the last fifteen years, many additional research groups have become concerned with the chemistry of *N*-oxides. Reviews of the subject, arranged in chronological order, are listed in Table 1.01.

2. Structure-reactivity Relations in *N*-Oxide Chemistry

A. SURVEY OF REACTIVITY TYPES

Fundamental to the chemistry of *N*-oxides is the fact that the dipolar *N*-oxide group $=N^{+}(O^{-})-$ is both an electron donor and an electron acceptor by the resonance effect (in addition to being an inductive electron acceptor). Taking pyridine 1-oxide (*4*) as an example, this "push–pull" character is expressed by the fact that canonical forms of type *5* in addition to those of type *6* contribute to the resonance hybrid. This situation is in fundamental contrast to that appertaining to pyridine (*7*) and to coordination complexes such as pyridine–boron trichloride (*9*), where significant resonance is limited to canonical forms of types *7*↔*8* and *9*↔*10*, respectively. In its dual role as an electron donor or acceptor, the *N*-oxide group resembles the nitroso group (57T170).



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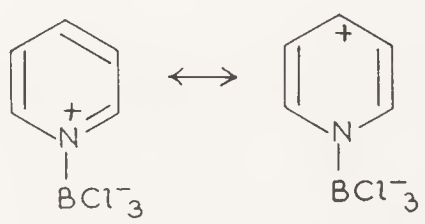

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Much evidence has been amassed from physical measurements regarding the electron-donating and electron-accepting properties of the N^{+}-O^{-} group in pyridine 1-oxides, and these data are discussed under the various methods which have been applied: dipole moments, infrared stretching frequencies, infrared intensities, and ultraviolet absorption frequencies. Most of the data that were obtained initially by these methods are of a qualitative character.

Table 1.01. Reviews of *N*-Oxides and Their Chemistry

Subject	Author(s)	References	Language
Analogy between *N*-oxides and nitrones	Colonna	40BS134, 52G503	Italian
Pyridine 1-oxides	Ochiai	48KK1	German
Amine oxides	Ochiai	49JJ1	Japanese
Japanese work on pyridine 1-oxides, etc.	Ochiai	53JO534	English
Pyridine 1-oxides	Talikowa	53WC169	Polish
Amine oxides	Culvenor	53RV83	English
Pyridine 1-oxides	Cislak	55IE800	English
Heteroaromatic *N*-oxides	Katritzky	56QR395	English
Substitution reactions in pyridine and pyridine 1-oxide	den Hertog	56CW387	Dutch
Aromatic *N*-oxides	Colonna	57BS1	Italian
Substitution in the pyridine ring via *N*-oxides	Thomas and Jerchel	58AG719	German
Pyrimidine and quinazoline *N*-oxides	Hayashi, Yamanaka, and Higashino	58SY24	Japanese
Electrophilic reactions on pyridine 1-oxide	van Ammers	61MIa	Dutch
Heteroaromatic *N*-oxides	Ioffe and Efros	61RU569	English translation
Recent work on heteroaromatic *N*-oxides	Ochiai	62AI43	Japanese
Aromatic amine oxides	Kubota	62NK97	Japanese
Electronic spectra of *N*-oxides	Kubota	62SJ83	Japanese
Pyridazine *N*-oxides	Itai	64BH1	Japanese
Formation of *N*-oxides from *o*-substituted nitrobenzenes	Loudon and Tennant	64QR389	English
Nitrones	Delpierre and Lamchen	65QR329	English
Hydrogen bonding and coordination complexes of pyridine 1-oxides	Szafran	66WC545	Polish
Comprehensive monograph on aromatic amine oxides	Ochiai	67MIa	English
Coordination chemistry of *N*-oxides	Garvey, Nelson, and Ragsdale	68CD375	English
Purine *N*-oxides and cancer	Brown	68MI209	English

Quantitative measurements of electronic interactions, and hence of reactivities or physicochemical properties, are achieved by application of the Hammett equation and by molecular orbital techniques. In the following consideration of electronic interactions, it is considered important to include a discussion of the cations of pyridine and other *N*-oxides. *N*-Oxides are bases and exist predominantly as cations in acidic solutions; since many of the reactions of *N*-oxides are carried out in acidic media, the relevance of the cations is obvious. Qualitatively it is to be expected that the protonated (N^+-OH) or coordinated group (N^+-OX) would be a far weaker electron donor and a much stronger electron acceptor than is the free *N*-oxide group: this has been amply confirmed.

B. EVIDENCE OF ELECTRONIC INTERACTIONS FROM PHYSICAL METHODS

i. Dipole Moments

Katritzky, Randall, and Sutton (57J1769) showed that the mesomeric moments for 4-substituted pyridine 1-oxides are greater in magnitude for both electron-withdrawing and electron-donating substituents than for the

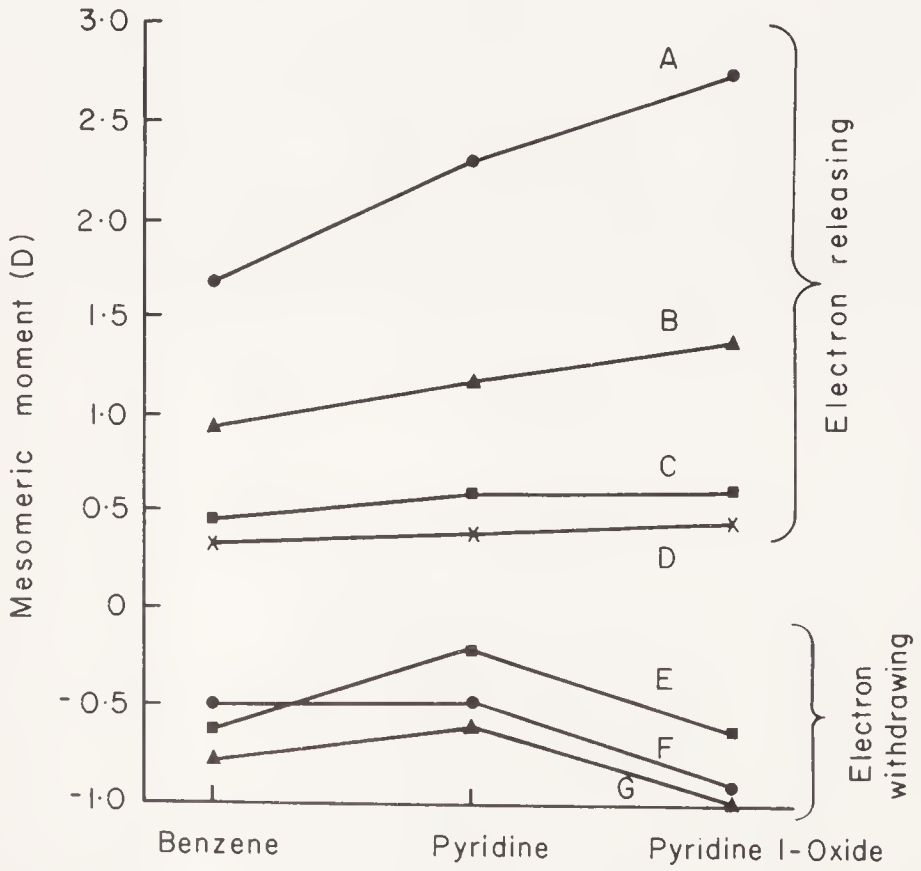


Fig. 1. Comparison of mesomeric moments of substituted benzenes, 4-substituted pyridines and 4-substituted pyridine 1-oxides: (A) NMe_2, (B) OMe, (C) Cl, (D) Me, (E) COMe, (F) CO_2Et, (G) NO_2.

corresponding 4-substituted pyridines (Figure 1). The mesomeric moment is defined by Equation 1, where Z is the substituent and PyO denotes the pyridine 1-oxide system. The mesomeric moment thus measures the π-electron

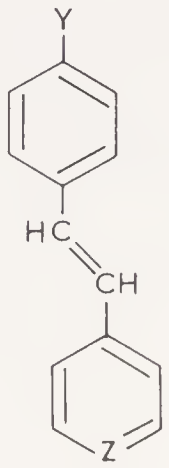
interaction between a ring and a substituent group, and the results quoted

$$\mu_m(\text{PyO}) = \mu(\text{Z-PyO}) + \mu(\text{Z-Me}) - \mu(\text{PyO}) \quad (1)$$

demonstrate that the N^+-O^- group can behave as *both* an electron donor and an electron acceptor. This is in contrast to the N^+-$BCl_3^{\ominus}$ group in pyridine–boron trichlorides which was shown by dipole moments to be capable of receiving electrons from, but not donating electrons to, the ring (58J1254; cf. 58J1258).

Dipole moments have been used by Sharpe and Walker to compare the electron-accepting ability of the pyridine 1-oxide ring system with that of nitrobenzene and of pyridine (61J4522); these authors also correlated the dipole moments with Hammett substituent constants. Similar work has been carried out with the dipole moments of 9-substituted acridine 10-oxides (60J3367; 61PC619). The moments of certain pyrazine *N*-oxides (65BF3150) also indicate considerable back-donation of electrons from the oxygen atom into the pyrazine ring.

Dipole moments have been used to demonstrate that interactions between substituents and the N^+-O^- group decrease rapidly with distance. From these studies of 4-(*p*-substituted-styryl)-pyridines and -pyridine 1-oxides (*11*, Z = N, N^+-O^-), and also the corresponding phenyl and phenylethynyl derivatives, there is no detectable interaction between the heterocyclic group and the substituent in the *para*-position of the benzene ring [66J(B)822].



(11)

(12) (13)

ii. Infrared Stretching Frequencies

The infrared stretching frequencies of substituents can serve as a measure of the electron-donating ability of the *N*-oxide ring at the 3- and 4-positions. In a compound of type *12*, if the electron-donating ability of the ring were to

be increased, the contribution of canonical forms of type *13* would also increase and, hence, the single bond character of the AB bond. Thus, the AB stretching frequency affords a measure of the AB bond order, and comparison of *v*AB for a series of ring systems with the same substituent enables a direct comparison of the electron-donating ability of the rings within this series. The electron-donating ability at the 3- and 4-positions of the pyridine, the pyridine 1-oxide, and the pyridine–boron trichloride rings was found to vary in the order: 4-PyBCl_3 < 4-Py ~ 3-PyO < 3-Py ~ 4-PyO < Ph. This result was obtained by studying changes in *v*(C=O) for the following substituents: ethoxycarbonyl, methoxycarbonyl, formyl, and acetyl (58J2182). Similar deductions were made from the variation of the asymmetric stretching mode of the nitro group in a series of nitropyridines and nitropyridine 1-oxides (60R361). Essentially the same conclusions have been reached by Shindo who has also investigated *N*-oxide–substituent interactions by studying *v*(N^+-O^-)(58MIb).

Infrared stretching frequencies can also measure the electron-accepting ability of a ring. If a substituent has a lone electron pair on the atom adjacent to the ring (*14*, X = OR or NR_2), resonance of type *14*↔*15* occurs, leading to an increase of the C-X bond order. It is more difficult to locate and to measure *v*(C-O) and *v*(C-N) frequencies, and indeed the group frequency approximation itself is far less valid for the vibrations of single bonds which occur below ca. 1400 cm^{-1} because of a very considerable degree of coupling between the vibrational modes. Nevertheless, from the infrared spectra of compounds with methoxy and ethoxy groups (59J2062) and with amino, methylamino, and dimethylamino groups (59J3674), a clear indication was obtained that the pyridine 1-oxide ring is a better electron acceptor than the pyridine ring, which in turn is superior to a benzene ring.

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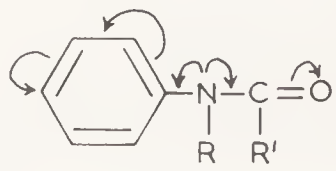


(16)

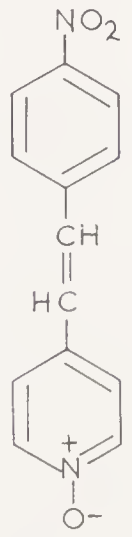
Electron-accepting ability may also be estimated from infrared frequencies by a competitive method: in acetamido and benzamido compounds of type *16*, the greater the electron-accepting ability of the ring, the less developed

will be the flow of electrons from the amide nitrogen atom to the carbonyl oxygen. Hence, the carbonyl stretching frequency ν(C=O) for the acyl group can be utilized as an indirect measure of the electron-accepting ability of the ring; this method gives results in agreement with those described in the previous paragraph (59J2067).

iii. Infrared Intensities

The infrared intensities of some group vibrations are directly related to the conjugation between the substituent and ring. For aromatic cyano compounds, the intensity of the ν(C≡N) stretching band increases with increasing electron-donating character of the ring. This criterion has been used to show that the electron-donating ability of the pyridine 1-oxide ring at the 4-position is much greater than that of the pyridine ring at the 4-position, but that this pattern is reversed for the 3-positions. At the 2-position, the electron-donating abilities are approximately the same for the pyridine and for the pyridine 1-oxide ring, reflecting the influence of the adjacent positive charge on the *N*-oxide group in pyridine 1-oxide (59R995; 61JJ27). For compounds of types ArCH=CHAr′ and ArC≡CAr′, the intensities of the ν(C=C) and ν(C≡C) stretching bands are zero when the groups Ar and Ar′ have identical electron-withdrawing or -accepting character. For non-identical Ar and Ar′ groups, the intensity is a measure of their difference in electron-donating or -accepting ability. Study of a series of 2- and 4-(*p*-substituted-styryl)pyridine 1-oxides and 2- and 4-(*p*-substituted-phenylethynyl)-pyridine 1-oxides indicated that the 1-oxido-2- and -4-pyridyl rings behave as strong electron-accepting substituents: in particular, a *para*-nitro group, as in *17*, is unable to back-polarize the N^+-O^- electrons (60J1519). The electron-donating effects of the *N*-oxide group evidently are only called into play by substituents in the *same* ring.

The infrared intensities of ring stretching bands also indicate electron donation can occur at the 4-position, but not at the 3-position, of pyridine 1-oxides (58J4162; 59QR353; 69JA636).



(17)

iv. NMR Chemical Shifts

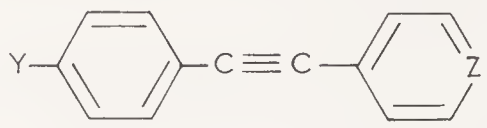
Nuclear magnetic resonance spectra [61J43; 66J(B)1137] demonstrate the dual electron-donating and -accepting properties of the *N*-oxide group, and the pure acceptor character of the protonated *N*-oxide group. The order of field strength for the chemical shifts of the various protons is:

	Pyridine	*Pyridine 1-oxide*
unprotonated	$\alpha\text{-H} < \gamma\text{-H} < \beta\text{-H}$	$\alpha\text{-H} \ll \beta\text{-H} < \gamma\text{-H}$
protonated	$\alpha\text{-H} \leqslant \gamma\text{-H} < \beta\text{-H}$	$\alpha\text{-H} < \gamma\text{-H} < \beta\text{-H}$

In agreement with the infrared spectral data, the NMR chemical shifts show no evidence for back-coordination in complexes of pyridine with boron trichloride, arsenic trichloride, or phosphorus trichloride [66J(B)235].

v. Ultraviolet Absorption Frequencies

Ultraviolet spectral frequencies afford information about electronic interactions in excited states. The spectra of *p*-substituted-styryl and -phenylethynyl compounds of types *11* and *18*, where Z = CH, N, $\overset{+}{\text{N}}\text{H}$, or $\text{N}^+\text{-O}^-$, afford evidence for appreciable long-range interaction between the substituent Y and the heterocyclic group Z in the first excited state in contrast to the lack of interaction in the ground state (60J2954). For similar work involving (*o*-, *m*-, *p*-nitrophenyl)pyridine 1-oxides and (*o*-, *m*-, and *p*-aminophenyl)pyridine 1-oxides, see reference 60J4901. Shifts of the ultraviolet spectral maxima of 3- and 4-(*β*-ethoxycarbonylvinyl)pyridines and the corresponding 1-oxides provide further support for the relative electron-donating ability of the various ring positions in the monocyclic compounds (58J3721).



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C. HAMMET EQUATION TREATMENT

The application of the Hammett equation to heterocycles in general and *N*-oxides in particular was pioneered by Jaffé, who has reviewed the field (64MI209). The basicities of 3- and 4-substituted pyridine 1-oxides are correlated with a ρ value of 2·09 (cf. 5·71 for pyridines) (55JA4441): for the best fit, σ^+ must be used for electron-donating substituents and σ^- values for electron-accepting substituents (58JO1790), a fact which again reflects the ability of the *N*-oxide group to enter into strong conjugative interaction with both electron donors and strong electron acceptors.

The Hammett equation has been applied to the hydrolysis of ethoxycarbonyl- (60J1171) and (*β*-ethoxycarbonylvinyl)-pyridine 1-oxides (62J2148)

by Falkner and Harrison. Their results indicate that the pronounced electron-withdrawing effect of the N^+-O^- group decreases rapidly with distance. Other Hammett treatments have concerned the pK_a values of 2-substituted pyridine 1-oxides (64JA2033), tautomeric equilibria (55JA4445; cf. Sections IV-3Bia and IV-3Cia), and infrared intensities (61JJ27; 69J636) and frequencies (58CT117). Recently, the Hammett treatment has been applied to the kinetics of electrophilic substitution of pyridine 1-oxides. The acid-catalysed deuteration of 4-aminopyridine 1-oxide indicates $\sigma_m^+ = 1{\cdot}99$ for the protonated *N*-oxide group [68J(*B*)864].

Sigma constants for pyridine 1-oxide rings considered as substituents attached to benzene have been obtained by measurement of the basicities of (aminophenyl)pyridine 1-oxides (60J1511). The σ values are in the range $+0{\cdot}23$ to $+0{\cdot}33$, disclosing a moderate electron-withdrawing effect.

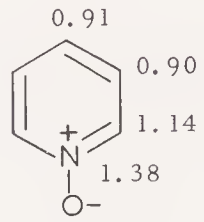
It has recently been suggested that a new set of *sigma* constants should be devised from data on pyridine 1-oxide for use with other reaction series involving *N*-oxides (67JH591). The paper contains a useful collection of data, but the present authors do not feel that it is advantageous to set up a new *sigma* scale in this way. Further progress in correlations of the Hammett type will probably come when the contributions of resonance and induction field effects to *sigma* constants are better understood.

D. MOLECULAR ORBITAL TREATMENT

Molecular orbital treatments for pyridine 1-oxide have been reported by Jaffé (54JA3527) and Barnes (59JA1935). A major difficulty is the question of the parameters to be used. These were originally derived by Jaffé from Hammett's substituent constants and were used to calculate localization energies for electrophilic and nucleophilic substitution. The relative ease of reaction was deduced to be 4- > 2- > 3-position for electrophiles, and 4- > 3- > 2-position for nucleophiles. The reason for the incorrect prediction of the order for nucleophilic substitution (the experimentally determined order is 4,2 > 3) was considered to be anomalous behaviour at the *ortho*-position. The π-electron density was calculated and values are given in structure *19*. It was pointed out that no single charge distribution could of itself predict that both electrophilic and nucleophilic substitution would occur preferentially at the same 4-position.

In somewhat later work, Barnes (59JA1935) used as parameters $\alpha_N = \alpha_C + 0{\cdot}5\beta$ and $\beta_{CN} = \beta$, together with a range of values for β_{NO} of $0{\cdot}5\beta$ to $1{\cdot}5\beta$. Calculated localization energies then predicted the following orders of reactivity: for radical substitution, 2 > 4 > 3; for nucleophilic substitution, 4 > 2 > 3, provided $\beta_{NO} < 0{\cdot}82\beta$. In the case of electrophilic substitution, the problem of cation formation was recognized, and it was suggested that nitration at the 4-position occurs on the free base, but sulphonation at the

3-position occurs on the conjugate acid. This hypothesis is now known to be correct; see Section III-3A. However, the 2-position was predicted to be more reactive towards electrophiles than the 4-position, and this discrepancy was ascribed to steric hindrance. The π-electron density for $\beta_{NO} = 0{\cdot}75$ was calculated and values are given in structure *20*. Recent calculations indicate that the introduction of an *N*-oxide group increases the aromaticity of pyridine (69CP1174).



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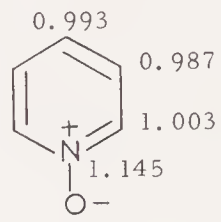

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The results of the Japanese school, particularly those of Kubota, on the molecular orbital treatment of the reactivity of pyridine 1-oxide have been summarized by Ochiai (67MIa).

In the majority of molecular orbital treatments, the reagent is not specifically considered; however, this refinement has been incorporated in a more recent treatment which demonstrates that each of the positions of the pyridine 1-oxide ring could become the most susceptible to attack by an electrophilic reagent depending on the differing "softness" or "hardness" of the reagent (68JA223). The following further theoretical work is also available: molecular orbital treatments which are reported in Japanese (59JJ388; 59NK579); extension of the method to polycyclic derivatives [61P613; 61CO(253)277]; and an unacceptable paper (57N633). Recently, a molecular orbital treatment of acridine 10-oxide has appeared (69RR125).

Few quantitative tests of the theory are available, although kinetic work on the nucleophilic displacements has been carried out by a Belgium group (61BB480). Attempts to calculate the positions of tautomeric equilibria by molecular orbital methods (55JA4448) have had only limited success (see Sections IV-3Bia and IV-3Cia).

3. Physical Properties

A. ULTRAVIOLET ABSORPTION SPECTRA

A general discussion of the ultraviolet spectra of *N*-oxides is beyond the scope of this monograph; however, a general survey is available (62SJ83, in Japanese; see also reference 58CR689). Lists of individual *N*-oxides for

which ultraviolet spectral data are available are given in various compilations, for example, in reference 61MIb. Papers which are principally concerned with the ultraviolet spectroscopy of *N*-oxides and their substituted derivatives are listed in Table 1.02.*

Table 1.02. The Ultraviolet Spectra of *N*-Oxides: Bibliography of Important Papers

N-Oxide ring	Substituents	References
Pyridine	various	52BS157, 52SR121, 55BJ260, 58NK930, 69JH859
	various, conjugate acids	55JA4451, 59JO943
	alkyl, various	54CT400, 58JA559
	carboxyl	58BJ255
	ethoxycarbonylvinyl	58J3721
	4-halogeno	56BJ82
	hydroxymethyl	58BJ224
	phenyl	58AN1395
	phenylazo	60G1203
	(nicotine alkaloids)	60IZ1119
Quinoline	various	55BJ260, 56JT495, 58NK930, 59BS19, 65BG448
	dihydro	58CB1978
	2-phenyl	53AL809
Isoquinoline	—	58NK930
Acridine and phenazine	various	55BJ260, 56JT495, 58NK924, 58NK930, 68TL3161
Azanaphthalene and azophenanthrene	various	61CT948
Cinnoline	bromobenzo	66J(C)1306
	polycyclic	61J1363, 62J1812
Quinazoline	various	67PC(35)225
Pyrazine	various	59JA5160, 62BJ946, 65BG448
Quinoxaline	various	62JJ1434, 66JJ1109
Benzotriazoles	various	55BJ260, 56JT495
Pyrroline	methyl	68J(C)1085
Furoxans and benzofuroxans	various	57JA1748

The photochemical decomposition of adenine 1-oxide, to unknown end products, has been reported (64B883), and certain polysubstituted nitropyridine 1-oxides are phototropic (53R296). Other photochemical reactions are discussed in Sections III-2Giii and III-5B.

* See addendum in the Appendix.

The solvent sensitivity of the ultraviolet maximum of pyridine 1-oxide has been suggested by Kosower as a measure of solvent polarity (56JA5838; 58JA3253), and various applications of these "Z-values" have been made (58JA3261; 58JA3267). For further discussion of the effects of solvents on the ultraviolet spectra of *N*-oxides, see reference 62BJ555. The role of the solvent in alkyl-substituent effects has been studied in the pyridine 1-oxide series [59T(5)194].

Ultraviolet spectroscopy has been used to study various aspects of the chemistry of *N*-oxides. Areas in which it has played a particularly significant role are listed in Table 1.03, together with representative references to the original literature and cross-references to the relevant sections of this monograph.

For a discussion of the fluorescence spectra of heterocyclic *N*-oxides, see references 58NK916, 58NK924, 61CT948, 65B2612, and 65BG448.

Table 1.03. Applications of Ultraviolet Spectral Data on *N*-Oxides: Cross References and Typical Papers

Topic	Cross reference	Typical reference
pK_a values	III-1Aii	53JJ140
Intermolecular hydrogen bonding	III-1Aiiia	54JJ831, 55JJ1540, 56SR31
Intramolecular hydrogen bonding	III-1Aiiib	56J614
Complexes with non-metals	III-1Ci	65JA458
Non-chelated complexes with metals	III-1Cii	62IC285
Chelated complexes with metals	III-1Ciii	58CT563, 59CT84
Covalent hydration	III-4Cia	62J5030
Photochemical deoxidation	III-2Giii	61BJ1444, 62JT(36)2072
Charge-transfer complexes	III-6C	56JA3625
Ring-opening reactions	III-4Cib	65T2205
Tautomerism of hydroxy *N*-oxides	IV-3Bia	49J2091
Tautomerism of amino *N*-oxides	IV-3Cia	57J4375
Tautomerism of mercapto *N*-oxides	IV-3Di	60J2937

B. INFRARED AND RAMAN ABSORPTION SPECTRA

A detailed treatment of the infrared spectra of heterocyclic compounds, including *N*-oxides, is given by Katritzky and Ambler (63MI161; cf. 59QR353). Indexes are also available which list infrared spectra by name, e.g. reference 61MIc. A detailed theoretical treatment of the vibrational spectrum of pyridine 1-oxide has been reported (65OP119; cf. 64MI1). Table 1.04 lists principal papers which are concerned with the infrared spectra of *N*-oxides, and Table 1.05 refers to topics in which the application

Table 1.04. Infrared Spectra of *N*-Oxides: Bibliography of Important Papers

N-Oxide ring	Substituents	References
Pyridine	various	55BJ353, 55G1085, 55ZP(4)24, 58CT117, 61J18, 63AL530, 69JH859
	alkyl	56CT460, 63BA169
	complexes	63IC286[a], 63SA201, 67JN1527
	hydroxy (*N*-hydroxypyridones)	60J2947
	carboxylic acids	56IM238
	salts	66BA335
	2- and 4-substituted	58J2192, 58J2195
	3-substituted	59J3680
Quinoline	various	60CT845
Acridine	various	66RR243
Pyrimidine	various	57JA2233
Pyrazine	various	60CT33
Phenazine	various	50J1481, 57ZE976
1,2,3-Triazole	various	66J(B)1243
Furoxans	various	55JA4238, 57JA1748, 65KG825

[a] Complexes of 2,2′-bipyridine 1,1′-dioxide.

Table 1.05. Applications of Infrared Spectra of *N*-Oxides: Cross References and Typical Papers

Type	Cross reference	Typical reference
Formation of basic salts	III-1Aib	64BA289
Hydrogen bonding	III-1Aiii	59CT791, 63SA829
Non-chelated complexes with non-metals	III-1Ci	62J5128
Non-chelated complexes with metals	III-1Cii	63SA189, 64J5008, 65IC97
Mechanism of *N*-oxide reactions	—	58J2182, 59R995, 61JJ27, 64IC374
Tautomerism, hydroxy *N*-oxides	IV-3Bia	56ZP(7)123, 59JJ428
Tautomerism, amino *N*-oxides	IV-3Cia	56ZP(7)123

of infrared spectroscopy has been of major importance, with cross-references to the appropriate sections of this monograph.

The Raman spectra of some simple alkylpyridine *N*-oxides are discussed in references 59PI213 and 62PI221. Comparison of the infrared and Raman spectra of benzotrifuroxan enables various alternative structures, including both those with greater and lower symmetry, to be eliminated (67TF833).

C. PROTON MAGNETIC RESONANCE SPECTRA

The nuclear magnetic resonance spectrum of pyridine 1-oxide itself has been completely elucidated (68JA141). Other papers which deal specifically with the NMR spectra of *N*-oxides are collected in Table 1.06. The relative sign of the coupling constant in diazine *N*-oxides has been discussed by Moritz and Paul (69AJ1305).

Table 1.06. NMR Spectra of *N*-Oxides: Bibliography of Important Papers

N-Oxide ring	Substituents	References
Pyridine	—	67ZP202
	various	66J(B)1137
	4-substituted	61J43
Quinoline	4-nitro	65CT396
Acridine	—	67RR1137
Benzazine and benzodiazine	—	63CT681
Pyridazine	various	63CT235, 63JJ523
Pyridazine (1,2-dioxide)	various	68TL1855
Pyrido [2,3-*d*] pyridazine	—	69AJ1745
Pyrazine	—	64J1507
Phenazine mono- and di-*N*-oxide	—	66CT419
Thiazole 3-oxide	—	64CC2375
Benzofuroxan	various	61ZE854, 61ZN413, 63J197
Benzodiazepine	various	68AP444, 69AP969
Methyl-substituted *N*-oxides	—	67CT1015

NMR spectroscopy has been used to particular advantage in the elucidation of certain rearrangements (Section II-Dic), in the investigation of the tautomerism of hydroxypyridine 1-oxides (Section IV-3Bia), and in the determination of the structure of the isomeric cinnoline 1- and 2-oxides (62CT-1123). The NMR spectra of phenazine 5,10-dioxides have been used (67H716) to disprove the claim that certain of these compounds possess an N^+-O-O^- structure (66TL4867). The NMR spectrum of pyridine 1-oxide in benzene solution shows a large dependence on the mole fraction, reflecting strong solute-solvent interactions [67ZP(55)202]. For a discussion of ^{15}N-C-H coupling constants in *N*-oxides, see reference 67JA2765.

D. DIPOLE MOMENTS

Applications of dipole moment measurements in heterocyclic chemistry, including *N*-oxide chemistry, have been summarized by Walker (63MI189). Dipole moments have been particularly valuable in determining the structures of diazine and triazine *N*-oxides formed by direct oxidation where two

or more isomeric products could be obtained (Table 1.07). The application of dipole moment measurements to the electronic interactions of the ring with the substituent in *N*-oxides is discussed in Section I-2Bi. Dipole moments are also important in connection with complex formation (cf. Section III-1Ci).

Table 1.07. Dipole Moments of *N*-Oxides: Applications to Determination of Structure in Ambiguous Cases

N-Oxide ring	Substituents	References
Pyridazine	methyl	63CT39
	alkoxy	64CT714
Cinnoline	benzo	62J5292
Pyrimidine	alkyl, alkoxy	64TL19, 64CT714
1,2,4-Triazine	various	64CT1329
Benzothiazole	2-alkyl-5- and -6-chloro	69CT1598

Molecular orbital methods have been used to calculate dipole moments, and the results show reasonable agreement with experimental values (63BJ1093). Dipole moments of the following *N*-oxides have been reported: pyrazine (65BF3150), acridine (58ZO2702), phenazine (58ZO2702), oxadiazole (59AT1), furoxans (59AT1), and various nitrogen-containing heterocycles (56DA1098).

E. CRYSTAL STRUCTURES

Compounds for which X-ray structure determinations have been carried out are listed in Table 1.08. Other more limited crystallographic data are also available for a number of *N*-oxides (57CX382).

F. MASS SPECTRA

An important feature of mass spectra of *N*-oxides, originally discovered by Bryce and Maxwell, is the presence of an intense characteristic (M-16) peak; this serves as a diagnostic test for the *N*-oxide group (65CH206; cf. 67TL715; 67CH893). This criterion has also been used by Amiet and Johns in their study of the dibenzodiazepinone *N*-oxides (67AJ723). However, pyrroline 1-oxides show only small (M-16) peaks, and the peak is also much reduced in α-substituted pyridine 1-oxides [66J(B)218]. Benzimidazole 3-oxides often show both strong (M-16) and (M-17) peaks, as do quinoxaline 1-oxides (67TL2985). A systematic survey of the mass spectra of thirty-eight *N*-oxides indicates that (M-16) and (M-17) peaks are characteristic for heteroaromatic compounds, but often do not appear for aliphatic amine oxides (67H1885).

Mass spectral data indicate that quinoline 1-oxides undergo molecular rearrangements on electron impact similar to those found on UV irradiation (see Section III-5Bii) (67CT1079); for similar work including also isoquinoline 2-oxides, see references 68CT1533 and 68T3139. Meta-stable peaks indicating molecular rearrangements have also been found for some fused pyrazine and pyridazinone *N*-oxides (67AJ2545).

Table 1.08. Crystallographic X-Ray Structure Determinations of *N*-Oxides

N-Oxide ring	Substituents	References
Pyridine*	HCl and HBr salts	60BJ1618, 61CX914
	metal complexes	67IC51, 68CH852
	4-nitro	56CX787
(Pyridine 1-oxide)$_2$HAsF$_6$	—	63P216
(Pyridine 1-oxide)$_2$ZnCl$_2$	2,6-dimethyl	68IC1358
(Pyridine 1-oxide)$_2$CuCl$_2$	2,6-dimethyl	69IC308
*		
(Pyridine 1-oxide)$_4$Cu(ClO$_4$)$_2$	—	69CX1378
4,4′-Azopyridine 1,1′-dioxide	—	59CX746
Phenazine 5-oxide	—	60CX55, 60RL129, 61CX133
Phenazine 5,10-dioxide	—	60RL117, 60RL129, 60RS1570, 61BJ889
Furoxan*	4-methyl-3-*p*-bromo-phenyl	69CX1126, 69CX1133
Benzofuroxan	5-bromo and-chloro	62JO3218
*		
Benzotrifuroxan	complexes	65J4838, 65J4882, cf. 66CH664

* See addendum in the Appendix.

Mass spectra have also been reported for quinoline hydroxamic acids (69OM681), acridine 10-oxides (69RR550), phenazine 5-oxides (66CT426), benzocinnoline 5-oxides (68AJ1233), 1,2,4-triazine 1- and 2-oxides (69T1021), furoxans (64JH61; 66CI2009), and benzotrifuroxan [69J(B)681].†

G. MISCELLANEOUS

The optical rotatory dispersions of (2-pyridyl 1-oxide)-derivatives of amino acids (67CH321; 68G316; 68G324) and amines (68AN286; 68RS57) have been studied. For optical measurements of furoxans, see reference 27CB2122.

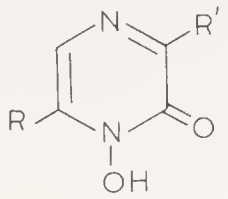
The analysis of mixed pyridine bases has been carried out by conversion to *N*-oxides and separation by paper chromatography (54AG298). The chromatographic behaviour of phenazine *N*-oxides has also been studied.

† See addendum in the Appendix.

4. Natural Occurrence and Biological Activity

In 1917 Polonovski (17BF191) isolated from Calabar beans the first naturally occurring heterocyclic *N*-oxide, geneserine, which is the *N*-oxide of the alkaloid eserine. Most of the plant alkaloid *N*-oxides carry the *N*-oxide oxygen atom on a bridgehead nitrogen atom. Relatively few aromatic heterocyclic *N*-oxides occur in nature, and an appreciable number of those that do contain a pyrazine or reduced pyrazine moiety.

The isolation of iodinin, a potent antibiotic, from *Chromobacterium iodinum* in 1938 (38J479) was followed in 1943 by isolation of the antibiotic aspergillic acid from the mold *Aspergillas flavus* (43JX433). Iodinin was identified as 1,6-dihydroxyphenazine 5,10-dioxide (*1*) (50J1481) and aspergillic acid as a 1-hydroxy-2-pyrazinone (*2*) (47JB321, 49J126S). Other closely related compounds with antibiotic activity have since been isolated from a variety of microbial sources: 1,6-dihydroxyphenazine 5-oxide (65B176); myxin, which is the 6-methoxy derivative of iodinin (67H716, 67TL715); hydroxyaspergillic acid [*21*, R = $C(OH)(CH_3)C_2H_5$, R′ = $CH_2CH(CH_3)_2$], muta-aspergillic acid [*21*, R = $C(OH)(CH_3)_2$, R′ = $CH_2CH(CH_3)_2$], and neo-aspergillic acid [*21*, R = R′ = $CH_2CH(CH_3)_2$] (67SC1443); pullcheriminic acid (*22*) (56J4133); mycellianamide (*23*) (56J3717); and emimycin (*24*) (63JK182). The fungistat 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (*25*) occurs as the glycoside in some plant



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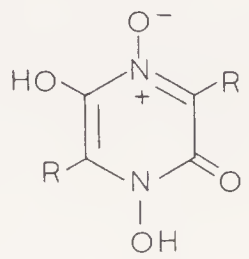

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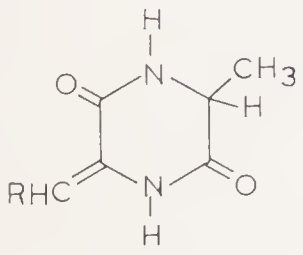

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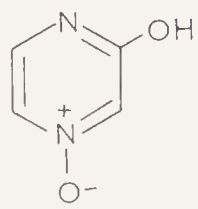

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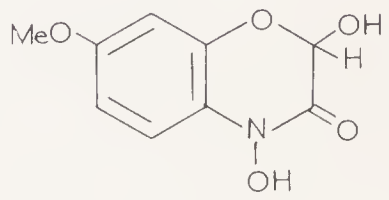

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seedlings (60AS499). Compounds containing the —CON(OH)— group, which is an oxidized peptide bond, are frequently called hydroxamic acids. The naturally occurring hydroxamic acids and their role in iron metabolism have been reviewed (67SC1443). A more general discussion of

the natural occurrence and metabolism of *N*-oxides appears in a recent review by G. B. Brown (68MI209).

Not surprisingly, the realization that the antibiotics iodinin and aspergillic acid are heterocyclic *N*-oxides stimulated interest in the biological activities of compounds of this type. Added interest was provided by claims that the conversion of certain alkaloids into their *N*-oxides led to a reduced toxicity without a parallel decrease in biological activity (see, e.g., 46JA192, 54MI96). A large number of heterocyclic *N*-oxides have been synthesized and tested for pharmacological activity. The biological activities of synthetic heteroaromatic *N*-oxides that had been reported up to 1964 have been summarized by Ochiai (67MIa). Purine *N*-oxides are the subject of a recent comprehensive review by G. B. Brown (68MI209). Physiological activities ranging from antibiotic, antibiotic antagonist, fungistatic, mutagenic, oncogenic, carcinostatic, sedative, and anti-convulsant activities have been reported. No well-defined mechanism for the biological activity of the heterocyclic *N*-oxides has emerged, although suggestions have been advanced that the primary reaction may involve modification of enzymes or biological redox systems, and/or alteration of the nucleic acids (see, e.g., 67NA749, 68MI209). A few examples will serve to illustrate the variety of *N*-oxides which possess biological activity and the range of this activity. 4-Nitroquinoline 1-oxide, which is both a potent mutagen and oncogen and also possesses antifungal and the antibiotic activities, has been extensively studied; this compound is reduced *in vivo* to 4-hydroxyaminoquinoline which is the active principle. 2-Mercaptopyridine 1-oxide and some of its derivatives are effective pesticides and fungicides for a broad spectrum of organisms. Several 3*H*-benzo[*e*]-(1,4)-diazepine 4-oxides find use as sedatives and anti-convulsants. The *N*-oxides of some of the naturally occurring purines are potent oncogens.

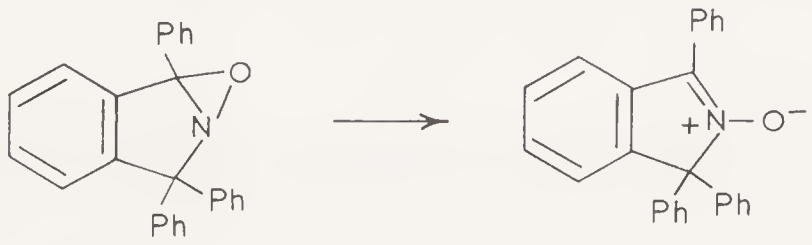
5. Catalytic Activity of *N*-Oxides

Pyridine 1-oxides show marked catalytic activity in a number of diverse reactions: (*a*) conversion of isocyanates into carbodiimides (62JO3851); (*b*) ozonolysis of olefins (58JA915); (*c*) lithium aluminium hydride reduction of 1-hexyne (60JA3560); (*d*) the reaction of phenyl isocyanate with alcohols or phenols (62JO474); (*e*) *N*-oxidation of amines [59AK(14)237]; (*f*) alkylation of sodiomalonic ester (60JA2895; 60JA2903). The last reaction was investigated in some detail; the catalytic activity is probably due to specific coordination of the sodium cations (cf. Section III-2B).

CHAPTER 11

The Preparation of Heteroaromatic *N*-Oxides

Practically all known methods for the preparation of heteroaromatic *N*-oxides may be classified in one of three major groups: (*a*) direct *N*-oxidation of the corresponding heterocyclic base, (*b*) formation of the ring carrying the *N*-oxide group by a cyclization reaction, and (*c*) chemical modification of an existing cyclic *N*-oxide with preservation of the *N*-oxide function. The first two of these categories are discussed systematically in the present chapter, but all preparative work falling into the third category is considered in Chapters III and IV under the reactions of the particular cyclic *N*-oxide which serves as the starting material. One of the very few methods that cannot be classified in this way is the curious formation of 2-styrylquinoline 1-oxide by the reaction of "*N*,*N*-dibromo-2-styrylquinoline" with sodium ethoxide [62PC(18)175]. This report needs to be confirmed. Another reaction which defies this classification, but which is well authenticated, is the isomerization of the tricyclic oxaziridine *1* to the nitrone *2* (68JA3893). The oxidation of cyclic hydroxylamines and the rearrangement of oxaziridines to the corresponding *N*-oxides, although strictly not belonging in category *a*, are considered in this chapter for convenience (Section II-1E).



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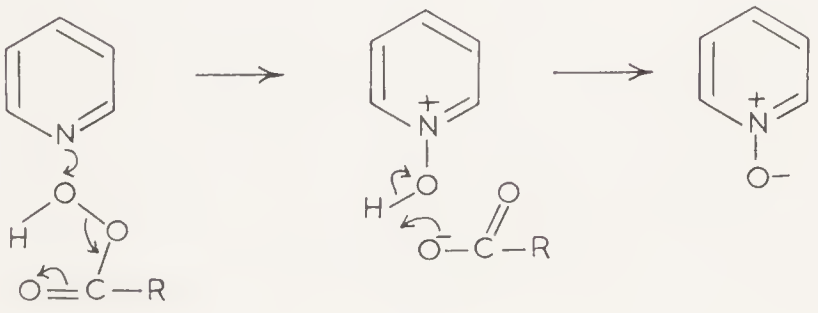

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1. Formation of Heteroaromatic *N*-Oxides by Direct *N*-Oxidation

All of the important oxidizing agents are percarboxylic acids, of which a variety have been used. The percarboxylic acids are discussed with respect to their relative convenience and oxidizing strength; then the rare cases in which hydrogen peroxide and other reagents are effective are considered. Mechanistically the peracid oxidation reaction is well understood (cf. *3* → *5*), and the kinetics have been determined for peracetic and perbenzoic acid *N*-oxidations (Section II-1Dii). The steric and electronic effects of substituents on the *N*-oxidation of compounds containing a single ring nitrogen atom, as well as the behaviour of the substituents towards the oxidizing agents, are discussed (Section II-1Di). In certain *N*-oxidations, compounds resulting from attack on the ring carbon atoms are formed as minor or major reaction products (Section II-1Cii). Finally, the selectivity of the *N*-oxidation reaction with compounds containing two or more ring nitrogen atoms in different rings or in the same ring is treated (Section II-1Diii).

A. *N*-OXIDATION WITH PERCARBOXYLIC ACIDS: PREPARATIVE ASPECTS

Peracetic acid is the most commonly used reagent for the *N*-oxidation of heterocyclic compounds. *N*-Oxidations with perbenzoic acid and some other aryl analogues are generally carried out in ether solution, and these reagents are particularly useful for sensitive compounds. Performic and pertrifluoroacetic acid, which are much stronger oxidizing agents than peracetic acid, are the reagents of choice for compounds which are difficult to oxidize. A few other peracids have been used occasionally. *m*-Chloroperbenzoic acid, a commercially available stable crystalline compound, has been recommended as a convenient general reagent for *N*-oxidation (64JO2806); it is certainly being employed with increasing frequency.

i. Peracetic Acid

Peracetic acid is the reagent that has been utilized for the conversion of the greatest number of nitrogen-containing heterocycles into their *N*-oxides; available examples are collected in Table 2.01. To effect *N*-oxidation, the heterocyclic compounds, glacial acetic acid, and 30% aqueous hydrogen peroxide are usually heated at a temperature between 20 and 90° for 3–24 h; a temperature of 70° is frequently selected and reactions are commonly allowed to proceed "overnight". In most cases, the product has been isolated by dilution and evaporation of excess peracetic acid followed by distillation, but recently a procedure involving extraction of the purified mixture has been recommended (69JO655). In a few cases, anhydrous peracetic acid has been used (62J1475); this reagent can be prepared from aqueous hydrogen peroxide and acetic anhydride in a non-polar solvent such as chloroform.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine	1	—	78–98	45JJ73, 47JJ33, 51R581, 60TU24, 62RC539, 63OS828
	1	2- and 3-acetamido	39–85	54JA2785, 56JO1077, 57JA3565, 60JO1716, 60JO2242
	1	2,6-diacetamido	79	54JA2785
	1	2-acetamido-3-, -4-, -5-, and -6-alkyl	65–78	54JA2785, 57JA3565, 60JO2242
	1	2-acetamido-4,6-dialkyl	70	57JA3565
	1	3-acetamido-2,6-dialkyl	(data)	63RC273
	1	4-acetamido-3-alkyl	—	61JO418
	1	4-acetoxymethyl	(data)	62CT961, 63J3440
	1	2,6-diacetoxymethyl	(data)	58J3594
	1	2-acetoxymethyl-3-alkyl	ca. 23	57JA481
	1	3-acetoxymethyl-2-alkyl	—	58CT222
	1	2-acetoxypropyl	—	56USP2735851
	1	3- and 4-acetyl	ca. 84	53JJ120, 56J2404, 58J2182
	1	N^4-acetylsulphonamido	see note [b]	47J52, 58JO67, 59USP2881166
	1	3- and 4-(β-acrylic acid)[c]	95 and 50	58J150
	1	2-, 3-, and 4-aldoxime	34–62	58J150, 60AS1253
	1	3-alkoxy	ca. 78	48J1864, 57R58

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "1 and 2", for example, indicates that a mixture of the 1- and 2-mono-*N*-oxides is obtained, while "1,2-di" means that the product is the 1,2-di-*N*-oxide.

[b] N^4-Acetyl-*N'*-hydroxysulphonamidopyridine also formed.

[c] Ethyl esters (96 and 51%) and corresponding amides (50 and 18%) also reported.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2-alkoxy-3-, -4-, or -6-alkyl	(data)	49J2091, 59JA2537[d]
	1	2-alkoxycarbonyl	87	59CB155
	1	3-alkoxycarbonyl	48–85	49J231S, 52JJ1474, 56J2404, 58AP330, 58J2182, 59J3680, 65TL2737
	1	4-alkoxycarbonyl	73–82	52JJ1474, 56J2404, 58J2182, 58JA2716
	1	2,5-bis(alkoxycarbonyl)	80[e]	60JO565
	1	6-alkoxy-2-alkyl	66	54JA3168
	1	3-, 4-, and 5-alkoxycarbonyl-2-alkyl	70–85	58BF694, 60CT427, 63J1841, 64LA(670)69
	1	3,4-bis(alkoxycarbonyl)-6-alkyl	75	61JJ182
	1	2-alkoxycarbonylamino	68	57J191
	1	2-(alkoxycarbonylamino)-5-, -6- and -4,6-di-alkyl	67–86[f]	57J4385
	1	2-, 3-, and 4-alkoxycarbonylmethyl	68–79	54JA3168[g], 65TL2737
	1	2-, 3-, and 4-(2′-alkoxycarbonyl-vinylene)	50–95	58J150, 58J3721, 59J3680
	1	2-alkoxymethyl	31	67JO1270
	1	6-alkoxymethyl-2-alkyl	—	65CT233

[d] If "old" peracetic acid is used, a mixture of 2-methoxy-6-methylpyridine 1-oxide and 1-methoxy-6-methyl-2-pyridone is obtained.
[e] 5-Methoxycarbonyl-2-carboxypyridine 1-oxide formed.
[f] In the case of 5-alkyl-2-alkoxycarbonylaminopyridine, *N*,*N*′-di-(5-methyl-2-pyridyl)urea 1,1′-dioxide (7%) is formed as a by-product.
[g] *N*-Oxide of corresponding pyridinecarboxylic acid formed.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2-alkyl	52–75	58CC949, 58J1306, 58LA(618)152, 59JJ487, 59ZO915, 61LA(643)136,[h] 62J1475, 62RC539
	1	3-alkyl	55–92	51JJ1385, 54JA4184, 56H505, 58CI582, 58IZ748,[i] 58IZ900,[j] 58J3230,[i] 58JA2716, 58LA(618)152, 59AP496, 59J3680, 59JO275, 60J4953, 61AP292, 62J1475
	1	4-alkyl	42–82	51JJ1385, 55JA1281, 58CI582, 58J150, 58LA(618)152, 59AP496, 61AP292, 62J1475, 63J3440, 69JO655
	1	2,3-dialkyl	70–87	57JA481, 59CT241, 61J5556, 69J(B)54
	1	2,4-dialkyl	—	51JJ1385, 61J5556, 67J(B)1222
	1	2,5-dialkyl	76–95	55JO1461, 56J771, 57H1016, 57H2428, 57JO936, 58BF694, 60JJ709, 61J5556, 61NK616

[h] 2-(1-Imidazolyl and -benzimidazolyl)ethylenepyridine 1-oxide.
[i] Nicotine di-*N*-oxide.
[j] Nicotine and *N*-methylanabasine; both yield di-*N*-oxides.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2,6-dialkyl	ca. 75	51JJ1385, 58CI582, 58J3594,[k] 61AP292, 61NK616, 62RC539
	1	3,4-dialkyl	69	58JA1181, 69J(B)54
	1	3,5-dialkyl	55	60J4953, 69JO655
	1	2,3,6- and 2,4,6-trialkyl	—	59J1312, 61J5556, 67J(B)1222
	1	2,3,5,6-tetraalkyl	32	60J4953
	1	2,4,6-trialkyl-3-amino (substituted)	71	58JA3649
	1	6-alkyl-2-arylvinylene[l]	(data)	58J3594
	1	*6-alkyl-2- and -3-carboxy	64–78	37LA(530)87, 58J3594, 61JJ182
	1	4- and 4,5-di-alkyl-3-carboxy	(data)	57J551
	1	2- and 3-alkyl-4-cyano	(data)	59JJ492, 61JJ917, 62JA3393
	1	2,6-dialkyl-4-cyano	(data)	59JJ492, 61JJ917
	1	2-alkyl-5-cyano-4-hydroxy	73	65CT878
	1	6-alkyl-2-cyanomethyl	(data)	66CT762
	1	4-alkyl-3-formamido	(data)	60JO2242
	1	2-alkyl-4-halogeno	ca. 38	59PC(9)164, 65J2096
	1	2,6-dialkyl-3- or -4-halogeno	54–90	62JO1329, 65CT963
	1	2,6-dialkyl-3,4,5-trihalogeno	96	56CT1
	1	*4- and 6-alkyl-2-(2-ketocyclohexyl)[m]	(data)	66CT762
	1	2,4,6-trialkyl-3-nitro	50	67J(B)1213
	1	2,4,5-trialkyl-3-substituted	9–33	59JO1032

[k] 1,2-Bis-(6-methyl-2-pyridyl)ethane di-*N*-oxide.
[l] 1,2-Bis-(6-methyl-2-pyridyl)ethylene di-*N*-oxide.
[m] 2-Carboxy-4- and -6-methylpyridine 1-oxide.
* See addenda in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2,6-dialkyl-4-sulphonic acid (sodium salt)	(data)	62JO1329
	1	3- and 4-amino, *N*-benzoyl	(data)	60T(9)194
	1	2-, 3-, and 4- and 2,6-di-aryl[n]	poor–94[n]	58H2059, 58J1754, 58JO1903, 60AK(15)387, 60J1511, 60JA186, 62JO640, 64MC446, 69JO655
	1	2-aryl-4-aryl-azo and -azoxy[o]	(data)	61CT87
	1	2- and 4-arylazo[p]	(data)	53BS101, 55G1148, 56G1067, 59G1843
	1	3-aryloxycarbonyl	32–38	58AP330
	1	6-aryl-2,3-tri-, -tetra- and -penta-methylene[q]	64–76	63RC403
	1	3- and 4-(2′-arylvinylene)	30–60	65JJ565
	1	*2-, 3-, and 4-(*N*′-benzene-sulphonylhydrazinocarbonyl)	40–48	58J150
	1	2-, 3-, and 4-benzoyl	(data)	66JJ1022
	1	3-(2-benzoylamino-3-hydroxy-3,3-disubstituted-propenyl)[r]	(data)	66T35

[n] Aryl = 2-[5-amino-1,3,4-thiazolyl], poor yield (58H2058); 2-, 3-, and 4-phenyl, 88–94% yield (58J1754); 2-(10-phenothiazolyl 5,5-dioxide), 80% yield (58JO1903); 3-(2-[3,4-dimethyltriazinyl]), nicotinic acidamide *N*-oxide isolated [60AK(15)387]; 2-, 3-, and 4-(*x*-nitrophenyl), 46–78% (60J1511); 4-(2-oxazolyl) (60JA186); 2,6-bis(2′-pyridyl), 88% yield of tri-*N*-oxide (62JO640); 3-(3-coumaryl), 75% yield (64MC446).

[o] Obtained from the oxidation of 4-azidopicoline.

[p] The *beta* nitrogen in the azo group is also oxidized; aryl = phenyl.

[q] 2,3-Trimethylenepyridine corresponds to pyrindane or 6,7-dihydro-1,5-pyrindine; 2,3-tetramethylene corresponds to 5,6,7,8-tetrahydroquinoline.

[r] Carbinol *N*-oxide not isolated; cyclizes directly to pyrindine *N*-oxide.

* 4-Azolyl; see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2- and 4-benzyl	ca. 95	58J1754, 62PH2434
	1	2-carboxamido (and *N*-substituted)	40–84	49J133S, 57JO984, 60J3371, 60J3387
	1	3-carboxamido (and *N*-substituted)	73–82	58AK(12)559, 60AK(15)387,[s] 63OS704
	1	4-carboxamido (and *N*-substituted)	66–80	58BF694, 58J150, 60USP2945040
	1	3-carboxamido (*N*,*N*-disubstituted -3-hydroxy	76–95	60J3371
	1	2-carboxy	ca. 70	34LA(513)129, 61JO428
	1	3-carboxy	70–80	49J231S, 50BS137, 58AK(13)225, 58AP330,[t] 58JA2716
	1	4-carboxy	—	42CB1318, 59AK(13)439[u]
	1	2,5-, 2,6-, and 3,4-dicarboxy	47–86[v]	59JO1569, 61J5216, 60USP2953572
	1	2-carboxy-3-hydroxy	76	60J3371
	1	5-chloro-2-phenylsulphonyl	—	62R604
	1	2-, 3-, and 4-cyano	47–70	56JO1077, 59J3680, 59R995, 61JJ917, 61JO428
	1	3-cyanomethyl	87	59JA740
	1	2,6-decamethylene	61	57JA5558
	*			

[s] In some cases, nicotinic acid *N*-oxide isolated, in others an *N*-oxide of *N*-substituted 3-pyridinecarboxamide.
[t] Oxidation carried out on the potassium salt.
[u] Starting material was pyridine-4-aldehyde.
[v] For the 2,5-dicarboxylic acid, the best yield (86%) was obtained using the sodium salt (59JO1569).
* 2-(2,4-Dinitrobenzyl); see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1,1′-di	4-ethoxy-3-(4-ethoxy-3-pyridylethyl)	(data)	61JO3796
	1	2-(2-furyl)vinyl	87	66JJ1014
	1	2-halogeno	70–80	50JA4362, 56JO1077, 56USP2745826, 57J191, 59JA2674, 62RC539
	1	3-halogeno	19–95[w]	54JO2008, 56JO1077, 58JO1616, 59J3680, 59JO1008, 60J4953, 62J2379, 63J4007, 64RC777
	1	4-halogeno	—	56J2404
	1	3,5-dihalogeno	(data)	57JO984
	1	2- or 4-heptadecyl	—	69J(C)823
	1	3-hydroxy	70–80	57R58, 69AS2075
	1	2-(1′-hydroxy-alkyl and -alkylidene)[x]	18–43	59AK(13)439, 60CB2591, 69RC653
	4	1*H*-imidazo[4,5-*d*]	66	65JO4066
	1	3-nitro	ca. 40	57CT56, 59J3680
	1	*m*- and *p*-nitrophenyl (various)	46–78	60J1511
	1	2- and 4-oximinomethyl	42–94	69AP494
	1	*3-(2-piperidyl)	—	64IZ2241
	1	2-(2-pyridyl)	(data)	55JJ731, 56NK682, 67J(B)106

[w] The following yields have been reported: 3-bromo, 46–95%; 3-chloro, 35–80%; and 3-fluoro, 19%.
[x] 2,2′-Pyridoin 1,1′-dioxide.
* 3- and 4-(α-Phenyl)acetic acids; see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine *cont'd.*	1,1′-di	2-(2-pyridylethyl)	74	66BA505
	1,1′-di	2-(2-pyridylvinyl)	34	66BA505
	1	2-semicarbazone	65	58J150
	1	2- and 4-styryl	28–78	58J150, 59JJ487
	1	2-sulphanilamino	—	58AK(13)225
	1	4-sulphonamido	49	58J3514
	1	2-, 3-, and 4-sulphonic acid (sodium salt)	40–44	58CI1559, 62JO1329
	1	2-, 3-, and 4-trifluoromethyl	72–81	69CT510
	1	2,3-tri-, -tetra-, and -penta-methylene[l]	78–94	58JA6254, 61AP759, 63RC403
	1	3-trimethylsilyl	—	67JJ1374
Quinoline	1	—	ca. 73	45JJ73, 50JJ265, 51JJ1385, 57CM388
	1	2-alkoxy	—	48J1864
	1	5-alkoxy	—	51JJ297
	1	6-alkoxy	80 (data)	47USP2416658, 53G58, 57JJ1243
	1	8-alkoxy	61	58ZO2386
	1	2-alkoxy-4-alkyl	—	49J2091
	1	6-alkoxy-2-cyano	70	57JJ1244
	1	6-alkoxy-4-(1-hydroxyalkyl)	(data)	47JJ101,[y] 48JJ109,[z] 58CT273,[aa] 59EGP16921

[y] Quinine di-*N*-oxide; dihydroquinine reacts analogously.
[z] Quinuclidine; a 1,1′-dioxide is obtained.
[aa] *al*-*N*-Hydroxydihydronichin *ar*-*N*-oxide.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoline, *cont'd.*	1	2-alkyl	33–80	50JJ265, 56USP2748141, 57CT188, 59PC(9)54, 60CT126,[bb] 60JJ339
	1	4-alkyl	75–excellent	48JJ123, 57CT621, 60CT126[cc]
	1	5-alkyl	(data)	61JJ1601
	1	6-alkyl	81 (data)	50JJ265, 53G58, 59WZ93, 60AF1029
	1	2,8-dialkyl	—	50JJ265
	1	3-alkyl-2-aryl	(data)	56RS2512
	1	2-alkyl-5,6-benzo	—	50J703
	1	2,3-dialkyl-4-carboxy	25	50J703
	1	2-alkyl-4-chloro-3-(chloroethyl)	—	63JJ234
	1	2-alkyl-5,6,7,8-tetrahydro	77	67CT1385
	1	2-alkyl-5- and -8-nitro	(data)	51JJ1078
	1	7,8-dialkyl-5-nitro	(data)	58AK(12)553
	1	2-aryl	—	51BS82, 54RS2351[dd]
	1	3-aryl	25–38	58JO271
	1	2-aryl-4-carboxy	75	50J703
	1	2-aryl-5-nitro	50	58JO271
	1	3- and 5-azido	84 and 70	61JJ1743
	1	5,6- and 7,8-benzo	(data)	51JJ1288, 52JJ985, 53G622

[bb] In case of quinaldine, the following products have been reported: quinaldine 1-oxide (60–65%), 3-hydroxyquinaldine 1-oxide (3–4%), and 3-hydroxyquinoline (trace).
[cc] From 4-methylquinoline, 3-hydroxy-4-methylcarbostyril (0·4%) is also formed.
[dd] From 2-phenylquinoline, *N*-benzoylanthranilic acid is also formed.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoline, *cont'd.*	1	3-bromo	ca. 30	54JO2008, 56JO1077
	1	6-carboxaldehyde	65[ee]	60JJ339
	1	2-, 4-, and 6-carboxy	58 (data)	51BS82, 56RS2512, 60CI402, 60JJ339
	1	7-chloro	84	46JJ60
	1	4-(α-cyanobenzyl)[uuu]	—	63AI5
	1	2-cyano-6-halogeno	76	57JJ1244
	1[ff]	4-(4-dimethylaminostyryl)	—	63JJ342
	1	2-ethoxycarbonylamino	ca. 90	57J4385, 59JJ1063
	1	3-, 5-, 6-, and 7-fluoro	—	63J4007, 68CT1742
	1	2-halogenomethyl	67 (data)	53JJ1326, 60JJ339
	1	8-hydroxy	ca. 20	54NK1180, 58ZO2386, 62PI360
	1	3-hydroxy-6-nitro	—	60CT126
	1	4-(1-hydroxyalkyl)[gg]	43	58CT208, 59CT744
	1	11*H*-indeno[1,2-*b*]	—	61JO3812
	1	6,7-methylenedioxy	54	60JO1365
	1	6-nitro	32–41	60AK(15)283, 60CT126[hh]
	1	2-(2-oxocyclohexyl)	see note [ii]	63CT1331
	1	2-phenylcarbamoyl	—	60J3387
	1	(quinine alkaloid)	(data)	62AI11, 62AI29
	1	*2-(vinyl, 2-substituted)	—	60G1179

[ee] The product is 6-carboxyquinoline 1-oxide.
[ff] Amino group also oxidized.
[gg] Dihydrocinchonine.
[hh] 3-Hydroxy-6-nitroquinoline 1-oxide (27%) and 3-hydroxy-6-nitroquinoline (1%) also formed.
[ii] 2-Carboxyquinoline 1-oxide is obtained.
* 3- and 4-Trifluoromethyl; see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Isoquinoline	2	—	53–63	51JJ1385, 54CT109, 56JO1337, 57JO514
	2	5-acetoxy	(data)[jj]	62JO4571
	2	4-bromo	(data)	54CT72
	2	1- and 3-carboxy	(data)	58JO900
	2	1-cyano	(data)	69RC473
	2	1-ethoxycarbonylamino	—	59JJ1063
	2	fluoro (various)	23–82	64J4561
	2	7-hydroxy-8-methyl	—	45JA860
	2	1-methyl	(data)	65JJ565
	2	3-methyl	69	56JO1337
	2	1-(vinylene, substituted)	—	65JJ565
Acridine	10	9-*H* and -phenyl-octahydro	80	65RO947
Phenanthridine	5	—	88	60JJ834
	5	6-alkyl	70	67J(C)2066
	5	9-aryl	—	50J703
	5	mono- and di-nitro	—	50J703
	5	6-substituted, various[kk]	—	61JJ1033
o-, *m*-, and *p*-Phenanthroline	di-*N*-oxide	—	68–71[ll]	46JA403
	1[mm]	—	(data)	58JA2745, 65JO288
Androstano-[3,2-*b*]pyridine	1′	17 β-acetoxy	(data)	64CT77

[jj] The corresponding 5-hydroxy compound is formed.
[kk] 6-Carboxamido, -cyano, and -hydroxy; the 6-hydroxy derivative obtained from oxidation of the 6-carboxylic acid.
[ll] *o*-Phenanthroline di-*N*-oxide was difficult to isolate because of its extreme water solubility; characterized as the picrate.
[mm] *o*-Phenanthroline.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
1,5-Naphthyridine	1 and 5	—	—	67JO241
	5	1-, 2-, and 6-substituted	(data)	49J1157
*1,6-Naphthyridine	6; 1,6-di	—	(data)	69CT1045
1,8-Naphthyridine	1,8-di	7-ethoxy-2,4-dimethyl	—	51BS82
7-Azaindoline	7	1-ethoxycarbonyl	46	59JA743
†1*H*-Imidazo[4,5-*b*]pyridine	4	6-halogeno-5,7-*H* or -substituted	—	59JO1455
1*H*-Imidazo[4,5-*c*]pyridine	5	—	74	64CT866
Pyridazine	1	—	(data)	58JO1603, 68TL1855
	1,2-di	—	poor	68TL1855
	2; 1 and 2	3-acetamido	—; 50 (total)	62CT347, 63CT114
	1	3-acetyl	77	68JH379
	1	3-acetyl-6-methoxy	20	68JH379
	1	3-alkoxy	70–84	59CT938, 61JJ708
	1 and 2	4-alkoxy	11–45 and 8–28	62CT643, 65JJ344
	1	3,6-dialkoxy	30–47[nn]	55JJ966, 61CT149, 65JJ344, 66JJ314
	1	3-alkoxy-4-alkyl	—	62JJ1005
	1	3-alkoxyl-6-alkyl	70	62JJ249
	1,2-di	3-alkoxy-6-alkyl- or -aryl-mercapto	see note [oo]	56JJ1293
	2	6-alkoxy-3-amino	70	63CT114
	1	3,6-dialkoxy-4-azido	19	63CT1073
	1	6-alkoxy-3-chloro	18[pp]	62JJ244
	1	5-alkoxy-3,4-dichloro	35	68CT142
	1	3-alkoxy-6-halogeno	<30	62CT989

[nn] Rearrangement products also formed (65JJ344); see text.
[oo] With 3 moles of peracetic acid, the trioxide is formed.
[pp] 3-Chloro-6-pyridazinone and 3-alkoxy-6-pyridazinone also formed.
* See addendum in the Appendix.
† 1,6-Phenanthroline; see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridazine, *cont'd.*	1 ; 1 and 2	3,6-dialkoxy-4-methyl	(data)[pp,qq]	65JJ344
	1 and 2[rr] ; 1,2-di	3-alkyl	ca. 45 and 7 ; poor	60NK350, 60NK1148, 61JJ1817, 62JJ249, 63CT29, 68TL1855
	1 and 2 ; 1,2-di	4-alkyl	(data) ; poor	63CT35, 68TL1855
	1 ; 1,2-di	3,6-dialkyl	52 ; poor	61CT149, 68TL1855
	1 and 2	3,4-dialkyl	35 and 16	63CT721
	1	2,5-dialkyl-3,6-diaryl	(data)	59AK419
	2	3-alkyl-6-chloro	63	61CT1017, 63CT29
	1 and 2	3,4-dialkyl-6-chloro	<1 and 83	63CT721
	(mono)	3-alkylmercapto-6-chloro	—	56JJ1293
	2	3-amino (and substituted)	ca. 20	62CT347, 62CT936, 63CT261
	2	3-amino (substituted)-6-chloro	—	62CT347, 62CT936, 63CT114
	1 and 2	3-aryl	1 ≫ 2 (data)	63CT1522
	(mono)	3-arylmercapto-6-chloro	—	56JJ1293
	1	6-carboxamido (disubstituted)-3-hydroxy	28	60J3371
	1	3,6-dihalogeno	<30	62J989
	1	3-hydroxy-6-phenylcarbamoyl	28	60J3387
Cinnoline	1 and 2	—	(data)[ss]	62CT1123, 63CT1527
	2 and 1,2-di	—	(data)	68J(B)316
	1, 2, and 1,2-di	4-alkyl and 3,4-dialkyl	(data)	68J(C)2621

[qq] 3,6-Dimethoxy yields only the 1-oxide ; 3,6-diethoxy yields a mixture of 1- and 2-oxides.
[rr] Exclusive formation of the 2-oxide has been reported (61JJ1817).
[ss] Ratio of 1- to 2-oxides is 1 : 1·4.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Cinnoline, *cont'd.*	1	3-chloro	(data)	63CT1527
	1	3-chloro-5,6-tetramethylene	(data)	62CT1123
	1 and 2	4-methyl	(data)[tt]	62CT1123, 63CT1527
	1,2-di	4-methyl	4	66CI157
	1	3-methyl-4-phenyl	—	47J1649
	1 and 2	5-nitro	18 and 43[uu]	65CT713
	1	6-nitro	(data)	59AK(14)237
	2	8-nitro	6–26[vv]	65CT713
	1 and 2	3-phenyl	60	66MC670
Phthalazine	2	5,6,7,8,9,9-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethano	ca. 90	59JA382
Benzo[*c*]cinnoline	5	—	(data)	59J3025, 67CT1088
	6	1- and 4-bromo	ca. 89	64J1265, 66J(C)1306
	5	1,7- and 2,9-dibromo	—	61J3695, 61J5029
	5 and 6	1-nitro	(data)	62J2454
	5 (or 6)	4-nitro	(data)	62J2454
Dibenzo[*c*,*h*]cinnoline	6	—	(data)	66J(C)890
Naphtho[1,2-*c*]cinnoline	6	—	75–85	60J3646
	6	benzo[*f*]	75–85	60J3646
	6	7,8,9,10-tetrahydro	(data)	62J3671
	(mono)	benzo[*h*]	(data)	59J3025
Naphtho[2,1-*c*]cinnoline	7	9,10,11,12-tetrahydro	(data)	62J3671
*	(mono)	benzo[*f*]	(data)	59J3025

[tt] Ratio of 1- to 2-oxides is 1:2.
[uu] 4-Nitroindazole also formed.
[vv] 8-Nitro-4-cinnolinol and 7-nitroindazole also formed.
* Pyrido[2,3-*d*]pyridazine; see addendum in the Appendix.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
4,9-Diazapyrene	4,9-di	5,10-dimethyl or -diphenyl	(data)	60J2553
4,5,9-Triazapyrene	(mono)	—	(data)	64J6090
1,2,9-Triazaphenanthrene	(mono and di)	4,10-diphenyl	(data)	66J(C)2053
4,5,9,10-Tetrazapyrene	di (4,9?)	—	(data)	60J3216, 64J6090
Pyrimidine	1	—	7–21	57JA2233, 58DI64, 58CB2832, 58JO1603, 58AG571(B), 59J525
	1	4-alkoxy	29	59CT297, 67JJ1096
	1	4,6-dialkoxy	7	62MC1335
	1	2-alkoxy-4-alkyl	—	55CT175
	1	4-alkoxy-6-alkyl	46–77	55CT175, 58CT633
	1	2,4-dialkoxy-6-alkyl	(data)	55CT175
	1[ww]	2-, 4-, and 5-alkyl	27–36	55CT175, 57JA2233, 58AG571(B), 58CB2832
	1	2,6- and 4,6-dialkyl	57–75	55CT175, 58AG571(B), 58CB2832, 59J525
	1	4-alkyl-6-phenyl	74	58CB2832
	1	7-aminothiazolo[5,4-*d*]	60	63MC825
	1	4-phenyl	25	67JJ1096
	1	6-phenyl	74	58AG571(B)
	(mono)	2,4,6-trimethyl	30–36	57JA2233
Quinazoline	1	3-aryl-4-hydroxy-2-methyl	(data)[xx]	65JJ507
	1	6-chloro-2-methyl-4-phenyl	(data)	60JA475
	1 (?)	4-hydroxy-2-methyl	—	60J2157

[ww] 2-, 4-, and 5-Methyl derivatives reported to give "mono-*N*-oxides" (57JA2233).
[xx] Products are 3-aryl-2-methyl-4-quinazolinone and aryl *o*-nitrobenzoate.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Purine	3	6-alkoxy	(data)	69BJ750
	1	9-alkyl-6-amino	40–70	66CI1598
	1	6-amino	ca. 85	57AA(132)22-P, 58AK(13)185, 58JA2755, 60MI111
	1	2,6-diamino	13	57AA(132)22-P, 58JA2755
	1	6-amino-9-(3′-amino-3′-deoxyribosyl)	—	64MC204
	1	6-amino-8-hydroxy	ca. 70	58JB1513, 60MI111
	1	6-amino-9-ribosyl	95 (data)	57AA(132)22-P, 58AG571(A),[yy] 58JA2755, 59JA1734[zz]
	1	6-amino-9-ribosylphosphate	ca. 70	66B746
	1 (?)	8-hydroxy	33	62JO567
	1	8-hydroxy-6-methyl	62	62JO567
	1	6-hydroxy-9-ribosylphosphate	ca. 70	66B746
	1	6-methyl	70	62JO567
	1	9-ribosyl	—	62JO567
2-Azapurine	1	6-amino	52	60JA3189
	1	6-amino-9-ribosyl	13	60JA3189
8-Azapurine	1	6-amino	56	60JA3189
Pyrazine	1	—	ca. 60	58JO1603, 59AA(135)75-O, 59JA5160
	1,4-di	—	ca. 90	58JO1603, 59JA5160

[yy] ADP.
[zz] AMP-2′ 1-oxide (17%); AMP-3′ 1-oxide (25%); AMP-5′ 1-oxide (62%).

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyrazine, *cont'd.*	1 and 1,4-di	—, methyl	—	58DI64
	1 and 4; 1,4-di	2-acetamido	(data)	68KG725
	1 and 1,4-di	2-acetoxymethyl	(data)	59JJ1273
	1	3-alkoxy	45	64JO2623
	1	2-alkoxy-3-methyl	82	64JO2623
	1 and 4[aaa]	2-alkyl	29 and 40–57	58JO1603, 59AA(135)75-O, 59JA5160, 59JJ1273, 64JO2477
	1,4-di	2-alkyl	57–76	59JA5160, 59JJ1273, 63JO1682
	1 and 1,4-di	2,5-dialkyl	60–90	58JO1603, 59AA(135)75-O, 59JA5160
	1 and 4; 1,4-di	2,6-dialkyl	29–84	59AA(135)75-O, 59JA5160
	1,4-di	2,5,6-trialkyl	50–72	59JA5160
	1 and 1,4-di	2,3,5,6-tetraalkyl	ca. 90	59AA(135)75-O, 59JA5160
	1	2-alkyl-3-chloro	37–81	63JO1682, 64JO1645
	1	2-alkyl-6-chloro	63	63JO1682
	1	2,5-dialkyl-3,6-diphenyl	—	59CB2266
	1	2-carboxamido (disubstituted)-3-hydroxy	48–68	60J3371, 60J3387
	1	2-carboxamido (disubstituted)-4-methyl-3-oxo	46–48	60J3387
	1	3-chloro	49	63JO1682
	1	3,5-dichloro	—	66F805
	1 and 1,4-di	2,3-diphenyl	(data)	56J1885

[aaa] 2-Methylpyrazine 4-oxide (57 %) was the only mono-*N*-oxide isolated [59AA(135)75-O, 59JA5160].

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyrazine, *cont'd.*	4	2,6-diphenyl	—	56J1885
	4	3-phenyl-2-methoxy	97	56JA4071
Quinoxaline	1 and 1,4-di	—	(data)	43J322, 53J2816
	1	2,3-acenaphthyleno	100	59ZO228
	1 and 1,4-di	2-, 5-, and 6-acetamido	(data)	53J2816, 53J2822, 63ZO1544
	1,4-di	2-acetoxymethyl	40–42	56J2052, 61ZO1018
	1 and 1,4-di	2,3-di(acetoxymethyl)	—	61ZO1018
	1 and 1,4-di	2-acetoxymethyl-3-alkyl	(data)	56BC455, 56J2052
	1 and 1,4-di	3-(3-acetoxypropyl)	52	65RO1169
	1,4-di	6-acetyl-2,3-dialkyl	(data)	56J2058
	4- and 1,4-di[bbb]	2-acrylic acid	71–75	58ZO1378
	4	2-alkoxy	35	61J1246
	1 and 1,4-di	5-alkoxy	(data)	53J2816
	1,4-di	6-alkoxy	33–60	49J3012, 53J2816
	1 and 1,4-di	5,6- and 6,7-dialkoxy	(data)	49J3012, 53J2816
	1,4-di	5-, 6-, and 6,7-di-alkoxy-2,3-dialkyl	(data)	53J2822
	1,4-di	2,3-dialkoxy-5,6,7,8-tetrahydro	66	49J3012
	1,4-di	2-alkyl	(data)	43J322, 53J2822, 56J2052, 59ZO2763
	1 and 1,4-di[ccc]	5- and 6-alkyl	(data)	53J2816
	1 and 1,4-di	2,3-dialkyl	(data)	43J322, 53J2822, 56J2052,[ddd] 56J2551,[eee] 61ZO1018, 66JJ1109

[bbb] Acrylic acid group oxidized to propionic acid.
[ccc] The 6-alkyl compound is reported to give only the 1,4-dioxide.
[ddd] 2,3-Bis(bromomethyl)quinoxaline 1-oxide obtained.
[eee] 2,3-Cyclohepteno- and bornyleno(2′,3′,2,3)-quinoxaline 1,4-dioxides.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoxaline, *cont'd.*	(mono)	5,6-dialkyl	—	58AK(12)559
	1,4-di	6,7-dialkyl	(data)	53J2816
	1	2,3,5-trialkyl	—	53J2822
	1,4-di	2,3,6- and 2,6,7-tri-, and 2,3,6,7-tetra-alkyl	—	53J2822
	1 and 4; 1,4-di[fff]	2-alkyl-3-aryl	—	53J2822, 62JO1674, 64JA1830
	1 or 4	7-alkyl-2,3-diaryl	89	59ZO228
	1	2-alkyl-3-arylbenzo[*f*]	—	46G239
	1 and 1,4-di	7-alkyl-6-halogeno	(data)	53J2816
	1,4-di	2,3,7-trialkyl-6-halogeno	—	53J2822
	1	4-alkyl-3,4-dihydro-3-oxo-2-substituted	20–64	57J439, 60J3387
	1	2,3-dialkyl-5-substituted	—	53J2822
	1,4-di	2,3-dialkyl-6-substituted[ggg]	(data)	53J2822, 56J2058
	1	2,3-dialkyl-5,6- or -6,7-disubstituted	—	53J2822
	1	3-alkyl-sulphonyl or -thio	(data)	57J3236
	1 and 1,4-di	2,3-diaryl	80–90	46G239, 46JA403, 53J2822, 59ZO228[hhh]
	1 and 1,4-di	5,6-benzo	—	53J2816, 66JJ687
	1	5,6,7,8-dibenzo	—	53J2816
	1,4-di	2-carboxamido (disubstituted)	90	60J3371, 60J3387
	1	3-carboxy and -ethoxycarbonyl	80	55ZO161

[fff] Formation of the 1-oxide (64JA1830), the 4-oxide (62JO1674), and the 1,4-dioxide (53J2822, 62JO1674) has been reported.
[ggg] Substituents in 6-position; acetamido, acetyl, carbethoxy, cyano, halogeno, hydroxy, nitro, trifluoromethyl.
[hhh] The 1-oxide (80% yield) was the only product reported.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoxaline, *cont'd.*	1	3-chloro	—	66J(C)157
	1 and 1,4-di	2-, 5-, 6- and 6,7-di-halogeno	(data)	53J2816
	1,4-di	6-hydroxy	(data)	49J3012
	1	2-(*N*-methyl-*N*-phenylcarbamoyl)	30–50	65CC3424
	1 and 1,4-di	11*H*-indeno[1,2-*b*]	—	62JO1674
	1,4-di	2-phenyl	—	62JJ1093
	1 and 1,4-di	2- and 2,3-di-substituted	(data)	64JJ163
Phenazine	5,10-di[iii]	—	—	38J479, 54ZO485, 56DA1098,[jjj] 60AA(138)14-P[kkk]
	5 and 5,10-di	—	25 and 29	59ZO228
	5,10-di	1- and 2-acetoxy	(data)	52JJ1301
	(mono)	1,9-diacetoxy[lll]	—	54CT25
	5,10-di	1,7-, 1,8-, and 2,7-diacetoxy[lll]	(data)	53CT66, 54CT25
	5,10-di	2,3-diacetoxy-1,4-quinone	—	60TU34
	5 and 10	2-alkoxy	29 and 71	59ZO1306
	5,10-di	6-alkoxy-2-aryl	—	59ZO1299
	10	1-alkoxy-4-bromo	(data)	59CT581
	5,10-di	8-alkoxy-2-substituted	—	56JO1034
	5	1-chloro	—	59ZO1306
	5 and 10	2-chloro	47 and 53	59ZO1306
	5,10-di	2,3- and 2,8-dichloro	—	55CT365
	5,10-di	1-chloro-2,6,7-trihydroxy	—	57CC1423

[iii] Early attempts to effect this oxidation reportedly failed (01CB2442).

[jjj] Two forms of phenazine 5,10-dioxide are reported, one melting at 189–191°, the other melting at 202–203°. The high-melting form reverts to the low-melting form on standing one week at room temperature in benzene.

[kkk] 1-Hydroxy- and 1,4-dihydroxy-phenazine 5,10-dioxide are also formed.

[lll] Product is the corresponding hydroxy compound.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Phenazine, *cont'd.*	5,10-di	2,3-bis(dimethylamino)	—	60TU34
	5,10-di	1,2,3,4-tetrahydro-7-substituted	—	56J2551
	5,10-di	1-hydroxy	(data)	52JJ1301
	5,10-di	1,3-, 1,4-, 1,6-, and 2,3-dihydroxy	(data)	52JJ1301, 54CT53, 60NK515
	10 and 5,10-di	2-methyl	24 and 5·5	56CT391, 59ZO228
	10	1,6-dimethyl	(data)	56CT391
	5	1,2-naphtho	—	46G239
	5,10-di	2-nitro	—	67G1826
	5,10-di	1-phenyl-8-*H* or -substituted	83–92 or 7–16	60ZO2033
	5,10-di	2-phenyl-7-*H* or -substituted	38–62	60ZO2033
5-Azaquinoxaline	(mono)	7-bromo	—	48J1389
Alloxazine	(mono)	monoacetyl	—	60TU34
Pyrido[3,2-*f*]quinoxaline	(tri)	—	(data)	46JA874
	(di)	2,3-dimethyl	87	46JA874
1,2,4-Triazine	2	3-amino-5,6-dimethyl	(data)[mmm]	64CT1329
	2	3-amino-5-phenyl	(data)	66JO3917
	1 and 2[nnn]	3,5,6-triphenyl	33 and 8	59CB2266, 64J4209
	1	5,6-diphenyl-3-oxo	—	65CT1168
1,3,5-Triazine	1	2,4,6-triamino	<25	61AA(140)28-Q
	1	2,6-diamino-4-alkyl and -aryl	2–91	61AA(140)28-Q, 62JO3890
1,2,4-Benzotriazine	1	—	16	57J3186
	1,4-di[ooo]; 2[ppp]	3-amino	72	17CB1248, 57J3186
	4	3-amino-7-chloro or -methoxy	39–64	57J3186
	1,4-di[ooo]	3-amino-7-chloro or -methoxy	34–47	57J3186

[mmm] 3-Amino-6-methyl-*as*-triazin-5-one also formed.
[nnn] Only the 1-oxide reported to be formed (59CB2266).
[ooo] Prepared from the corresponding mono-*N*-oxide.
[ppp] Reference 17CB1248.

Table 2.01. Formation of *N*-Oxides by Oxidation with Peracetic Acid—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
1,2,4-Benzotriazine, *cont'd.*	1	3-aryl-6-substituted	—	57J3186
	1	3,4-dihydro-4-methyl-3-oxo	—	50IU91
	1	3-hydroxy	—	50IU91
	1 or 2[qqq]	3-phenyl	86 or 48	57J3186
	2	3-phenylamino	—	17CB1248
1,2,3-Triazolo[5,1-*c*]-[1,2,4]benzotriazine	5	7-*H* and -methyl-3-phenyl	70–80	67J(C)1279
Dibenzo-1,4,5-thiadiazine	5	1,1-dioxide[rrr]	ca. 80	53JA6338, 57JA4382, 57JA5583
Pyrazole	2	3-alkyl-5-amino-1-phenyl	70[sss]	57JA3175
Δ^1-Pyrazoline	2	3-benzoyloxy-3,5,5-trimethyl	—	61TL749
Benzimidazole	3	1-methyl	—	66JH51
Pyrrolo[2,3-*d*]imidazole	1	—	(data)	58AK(13)185
Isoxazoline	2	5,5-bis(ethoxycarbonyl)-3,4-diphenyl	—	26JA1770
Thiazole	3	4-, 2,4-, and 2,5-di-methyl	27–58	47JJ34, 60JA186
	3	2-sulphanilylamino	—	58AK(13)225
Benzothiazole	3	2-acylamino	low	42CB935,[ttt] 64CI368
*2*H*-1,4-Benzodiazepine	4	1-alkyl-7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2-oxo	67	68MC774
	4	7-chloro-1,3-dihydro-5-phenyl	—	62JO562
11*H*-Dibenzo[*c*,*f*]-[1,2]-diazepine	5	3,8-dihalogeno	63–82	64JH178
1,4,5-Triazepine	5	dibenzo	73	63J1436
Dibenzo-1,4,5-oxadiazepine	5	—	56	56JA458, 63J1436
Dibenzo-1,4,5-thiadiazepine	5	dimethyl 1,1-dioxide	96	66J(B)255

[qqq] See text.
[rrr] Each benzo ring carries a trifluoromethyl group *meta* to the nitrogen atoms.
[sss] Compound isolated was di-(3-methyl-1-phenyl-5-pyrazyl)amine 2,2′-dioxide.
[ttt] Incorrectly formulated as a sulphoxide.
[uuu] Converted into 4-benzoyl.
* Benzotriazole; see the addendum in the Appendix.

Ochiai, Katada, and Hayashi (47JJ33) found that optimum yields of pyridine 1-oxide were obtained using 1·2–1·7 times the theoretical amount of hydrogen peroxide. For certain quinoxalines, traces of mineral acid have been employed as catalyst (56J2058), but this is not a common practice. A patent suggests the use of tungstic acid as catalyst (62USP3047579).

ii. Aromatic Peracids

N-Oxidations with the aromatic peracids are generally carried out in non-polar solvents at room temperature, conditions that are considerably less severe than those for peracetic acid oxidation. The aromatic peracids are therefore particularly suitable reagents for the *N*-oxidation of sensitive substrates.

a. Perbenzoic Acid. Perbenzoic acid is the second most frequently used reagent for the conversion of nitrogenous bases into their *N*-oxides (Table 2.02.). Reactions are commonly conducted in chloroform solution, and there are fewer side reactions than with peracetic acid. Perbenzoic acid, for example, is the reagent choice for the *N*-oxidation of acridines (55DA257). The reaction is usually effected by adding the base to a chloroform solution of perbenzoic acid and allowing the mixture to stand at room temperature for several days. In some cases the reaction is carried out at a lower temperature, and reaction times from "overnight" to nine days have been reported.

b. m-*Chloroperbenzoic Acid. m*-Chloroperbenzoic acid, which is crystalline, stable, and commercially available, is rapidly gaining in popularity as a convenient alternative to perbenzoic acid for effecting *N*-oxidation. *N*-Oxides which have been prepared using this reagent are listed in Table 2.03.

c. Perphthalic Acid. Perphthalic acid is a popular reagent for the synthesis of *N*-oxides (Table 2.04) because of its ease of formation from phthalic anhydride and hydrogen peroxide (37CB379; 55OS619) and its relative stability. Furthermore, the reagent can be used under very mild conditions. Typically, the heterocyclic base is allowed to react with an ethereal solution of perphthalic acid at a temperature between -20 and $+20°$ from a few hours to a week or longer. Alternatively, but less frequently, an ethereal solution of perphthalic acid is added to a solution of the base in ethanol, benzene, dioxane, or chloroform, and the reaction occurs in the mixed solvent (see footnotes to Table 2.04). Acetic acid has also been used for bases with difficultly soluble phthalates (62AI19).

A method which does not involve the use of ether is to add phthalic anhydride to the heterocyclic base dissolved in aqueous hydrogen peroxide (47OK147).

Russian authors (49UK296) report that 2-phenylquinoline, which is converted into the *N*-oxide by an ethereal solution of perphthalic acid, is unaffected if the reaction is carried out in acetic acid or acetone. Perphthalic acid oxidation of 9-arylphenanthridines proceeds in better yield than does the

Table 2.02. Formation of *N*-Oxides by Oxidation with Perbenzoic Acid in Chloroform Solution

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine	1	—	80–90	26CB1848, 47JJ33, 58AJ200, 60G702
	1	3-acyloxy-2,4,5-trialkyl	60–74	63J4600
	1	2-, 3-, and 4-alkoxy	45–85	49JA67, 55R1160
	1	3,5-dialkoxy	—	57R261
	1	2,6-dialkoxy-4-alkyl	(data)	55J631
	1	3-alkoxy-2-halogeno	52	50JA4362
	1	5-alkoxy-3-halogeno	60	67R655
	1	3-alkoxycarbonyl-4-alkyl-5-vinyl[b]	—	56N251
	1	2-, 3-, and 4-alkyl	ca. 70	60G702, 61G613, 62J1475, 63J3440
	1	2,4- and 2,6-dialkyl	40–71	60G702, 61G613,
	1	2,4,6-trialkyl	—	60G702, 61G613
	1	4-alkyl-5-aryl-3-hydroxy	(data)	55JA3417, 59JA6041
	1	3-, 4-, 5-, and 6-alkyl-2-halogeno	59–67	50JA4362, 56J3684
	1	4-alkyl-3-halogeno	95	67R655
	1	2-aryl	67–77	53CC457
	1	2-, 3-, and 4-arylazo[c]	? –75	52R1145, 56G1067, 59G1843, 60T194, 63G404, 64AN180
	1	3-benzoyloxy	(data)	59J2844
	1	2-benzyloxy-4- and -5-substituted	25–53	49JA70
	1	2,5- and 3,5-dibromo	6–"good"	50JA4362, 53R296, 58R340
	1	2-(*p*-dimethylaminostyryl)[d]	—	61T151

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "1 and 2", for example, indicates that a mixture of the 1- and 2-mono-*N*-oxides is obtained, while "1,2-di" means that the product is the 1,2-di-*N*-oxide.

[b] The alkaloid gentianine.

[c] For the isomeric *p*-dimethylaminophenylazopyridines, the 3-isomer yields mainly the amino-oxide together with a small amount of the *ar*-1-oxide; the 4-isomer gives a mixture from which only the 1-oxide was isolated; and the 2-isomer yields only the amino-oxide.

[d] The amino nitrogen is oxidized more readily than the pyridine nitrogen atom.

Table 2.02. Formation of *N*-Oxides by Oxidation with Perbenzoic Acid in Chloroform Solution—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2-, 3-, and 4-halogeno	ca. 60	50JA4362, 61G613
	1	3-hydroxy	65	49JA67
	1	3-hydroxy-2-hydroxymethyl	67	57AS1496
	1	3-methyl-4-(4-pyridyl)	(data)	61J5216
	1	4-phenethynyl	—	60J1516
	1	2,6-diphenyl	6	53CC457
Quinoline	1		—	26CB1848, 58AJ200
	1	alkoxy (various)	12–55	52ZO1224, 56J3079
	1	amino, substituted (various)	40–55	56J3079
	1	2-aryl-6- and -7-methyl	54–93	46JA979, 46JA2017
	1	5,6-benzo-2-chloro-4-methyl	40	56J3684
	1	4-benzyloxy-7-chloro	65	49JA70
	1	4,7-dichloro	42	64JH6
	1	5-chloro-8-hydroxy	—	52ZO1224
	1	4-chloro-2-methyl	(data)	28PC138
	1	7-chloro-4-substituted-amino	19	56J3079, 64JH6
	1	4-ethoxycarbonyloxy-2-*n*-heptyl	—	56BC(63)124
	1	2-*n*-heptyl (Na salt)	—	56BC124
	1	8-hydroxy	—	52ZO1224, 58ZO2386
	1	2-mesityl	(data)	56RS2512
	1	2-methyl	—	25CB2334
	1	6-nitro	—	58AK(12)559
Isoquinoline	2	*	—	26CB1848, 60H265
Acridine	10	—	19	36CB197, 36CB1155, 55DA257, 60J3367
	10	9-alkyl	80–90	61ZO2362, 62ZO2217
	10	3,9-dichloro	41	62MC1159
	10	6,9-dichloro	—	59USP2880210, 60ZO3476
	10	6,9-dichloro-2-methoxy	81	62MC1159
	10	6-chloro-2-methoxy-9-substituted	25	55DA257, 59TU36, 62MC1159

* 5-, 6-, or 7-Tritio; see addendum in the Appendix.

Table 2.02. Formation of *N*-Oxides by Oxidation with Perbenzoic Acid in Chloroform Solution—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Acridine, *cont'd.*	10	6-chloro-9-phenoxy	—	60ZO3476
	10	9-chloro-2- or -3-substituted	—	55DA257
	10	5,8-dichloro-2- and -3-substituted	—	60BP829728
	10	9-hydroxy	—	36CB1155
	10	9-phenyl	—	60J3367
	10	9-substituted (various)	—	66RR243
9-Azaphenanthrene	9	—	—	67BB230
1,5-Naphthyridine	5 and 1,5-di	2- and 3-bromo	11	63R988
p-Phenanthroline	1,8-di	—	(data)	58AK(13)185, 58AK(13)225
Pyridazine	1	3-benzyloxy	(data)	62JJ244
	1	3- and 3,6-di-chloro	(data)	60CT559, 62JJ244
	1	6-chloro-3-methoxy	—	61JJ1048
	1	3-chloro-4-, -5-, and -6-methyl	ca. 85	61JJ1048, 62JJ249, 63CT35
	1 and 2	6-chloro-3-phenyl	1 >2(data)	63CT1522
Phthalazine	2	5,6,7,8,9,9-hexachloro-1,4,4a,5,-8,8a-hexahydro-1,4,5,8-dimethano	91	59JA382
Purine	1 (?)	—	(data)	62JO567
Phenazine	5,10-di	—	—	38ZO151, 56DA1098[e]
	5	alkoxy (various)	—	52ZO1915
	5,10-di	1,6-dihydroxy	(data)	50DA645
Δ^1-Pyrazoline	1 and 2	3-benzoyloxy-3,5,5-trimethyl	see note [f]	61TL749
Dibenzo[*c*,*f*][1,2]diazepinone	5	11-oxo	(data)	67AJ723
	6	2- and 2,4-di-nitro-11-oxo	(data)	67AJ723
2,1,5-Benzothiadiazocine	5	3,4-dihydro-1*H*-6-phenyl 2,2-dioxide (various)	72–92	68M1117

[e] Two forms of phenazine 5,10-dioxide are reported, one melting at 189–191°, the other melting at 202–203°. The high-melting form reverts to the low-melting form on standing one week at 20° in benzene.

[f] The 1-oxide is the major product; only a small amount of the 2-oxide is formed.

Table 2.03. Formation of *N*-Oxides by Oxidation with *m*-Chloroperbenzoic Acid

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoline	1	2-cyano; 2-cyano-3-, -4-, and -6-methyl (various); 2-phenyl-3-, -4-, and -6-methyl (various)	65–95	67AS1841
Indolo[2,3-*g*]isoquinoline	2	—	49	69JH389
Cinnoline	1	3-aryl	ca. 80	66MC670
Pyrimidine	3	4-amino-2-oxo-1-*H* and -β-D-ribofuranosyl	21 and 41	65JO2766
	3	4-amino-2-chloro-5-fluoro	(data)	68M847
Quinoxaline	1	2,3-bis(4-bromophenyl)	65	68AS877
Phenazine	5 and 5,10-di	1,6-dimethoxy	—	67TL715
1,3,5-Triazine	3	2,4-diamino-6-chloromethyl	27	67JH268

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "5,10-di", for example, means that the product is the 5,10-di-*N*-oxide, while "5 and 5,10-di" indicates that a mixture of the mono- and di-*N*-oxides is obtained.

* See addendum in the Appendix.

† 2*H*-1,4-Diazepin-2-one 4-oxide; see addendum in the Appendix.

Table 2.04. Formation of *N*-Oxides by Oxidation with Perphthalic Acid in Ether Solution

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine	1	—	85–90	38CB2385, 47JJ33, 47OK147, 49JP177949
	1	4-acyl	(data)	57F705
	1	2- and 4-alkoxycarbonyl	70	53AN87, 53NK547

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "1 and 2", for example, indicates that a mixture of the 1- and 2-mono-*N*-oxides is obtained, while "1,4-di" means that the product is the 1,4-di-*N*-oxide.

Table 2.04. Formation of *N*-Oxides by Oxidation with Perphthalic Acid in Ether Solution—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Pyridine, *cont'd.*	1	2-alkyl	71	43JJ78
	1	2,4-, 2,5-, and 2,6-dialkyl	36–71	43JJ78, 61NK616
	1	2,4,6-trialkyl	—	43JJ78
	1	2-alkyl-4-halogeno	13	65J2096
	1	3-benzoxy-4,5-bis(benzoxymethyl)-2-methyl	76	66MC620
	1	3-bromo	40–85	46JJ21, 50R468
	1	2- and 4-formyl (various)[b]	37–45	58JJ957
Quinoline	1	—	70	53G58
	1	2-acetoxymethyl	95	60JJ339
	1	2-(1-alkoxyalkyl)[c]	69–80	63MC628
	1	7,8-benzo	—	44JO302
	1	2-bromomethyl	82	53JJ1326
	1	6- and 8-halogeno	—	44JO302, 63J4007
	1	8-hydroxy	—	54J570, 54NK1180
	1	6-methoxy	—	44JO302
	1	3,4-trimethylene-5-nitro	—	65JJ645
	1	3-, 6-, and 7-nitro[d]	(data)	44PJ599, 56J1885
	1	2- and 4-phenyl (various)	10–98[e]	49UK296
Acridine	10	1,2,3,4-tetrahydro-5-nitro	—	65JJ645
Phenanthridine	5	—	88	50J703
	5	6-alkyl and -aryl	87–91	50J703, 67JJ651
	5	7,8,9,10-tetrahydro-4-nitro	—	65JJ645
	5	6-(1-oxido-4-pyridyl)[f]	71	50J703
1,6-Naphthyridine	6	—	9	69CT1045

[b] Prepared by oxidation of the acetal or diacetyl derivative.
[c] Oxidation carried out in ethanol–ether solution.
[d] Benzene–ether or dioxane–ether mixtures used as reaction medium.
[e] 2-Phenyl derivatives obtained in 10–12% yield, 4-phenyl in 96–98% yield.
[f] Oxidation occurs on the pyridine nitrogen atom first.
* Diethoxymethyl (various); see addendum in the Appendix.

Table 2.04. Formation of *N*-Oxides by Oxidation with Perphthalic Acid in Ether Solution—*continued*

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
4,9-Diazapyrene	4,9	5,10-dimethyl and -diphenyl[g]	37–46	60J2553
Pyridazine	1 and 2	3-acylamino	2 and 82	62CT347
	1	amino-dichloro	43–47	66CT303
	1	6-chloro-3- and 3,4-di-methoxy	30–50	62CT643
	1 and 2	4-chloro-3,6-dimethyl	23 and 11	63CT337
	1	3,6-dichloro	ca. 30	62CT989
	1 and 2	3,6-dichloro-4-methoxy	12 and 5	62CT643
Cinnoline	1 and 2	—	14 and 40	63CT1527
	1 and 2	4-chloro, -methoxy, and -methyl	18–28 and 33–44	63CT1527, 64CT619
Phthalazine	2	—	—	62JJ584
	3	1-alkoxy	—	62JJ584
	3	1-aryl-4-*H* and -alkyl	—	66JJ576, 67JJ940
	2 and 3	1-methyl, 1-benzyl	1:2	68JJ1333
Pyrimidine	1	4-alkoxy- and -aryloxy-6-methyl	58–77	58CT633
Quinazoline	1	4-alkoxy and -aryloxy[h]	10–45	59CT152
	1 (?)	4-hydroxy-2-methyl	—	60J2157
	1	4-isopropyl[i]	40	64CT43
Purine	1	6-amino-7-substituted (various)[j]	10–21	64ZN1043
	3	6-chloro	—	69BJ750
Quinoxaline	1,4-di	2-alkyl	(data)	67JJ643
	1,4-di	2,3-cyclopenteno	(data)	56J2551
	1	2,3-dimethyl-5-nitro	(data)	53J2822
1*H*-Imidazo[4,5-*c*]pyridine	5	—	42	64CT866
3*H*-Imidazo[4,5-*c*]pyridine	5	3-glycosyl	43	64JO2611
Thiazole	3	2,4-dimethyl	55	47JJ34, 61NK616

[g] Oxidation effected in chloroform–ether solution.
[h] 4-Alkoxy-1-hydroxy-2-quinazolinone also formed.
[i] 4-Isopropyl-2-quinazolinone (23%) and 4-quinazolinone (10%) also formed.
[j] The reaction medium was dimethylformamide–ether. Adenine- and 2-methyladenine-cobamide (pseudovitamin B_{12} and "factor A").

reaction with peracetic acid (50J703), whereas 4-methylthiazole can be *N*-oxidized with peracetic acid but not with perphthalic acid (47JJ34).

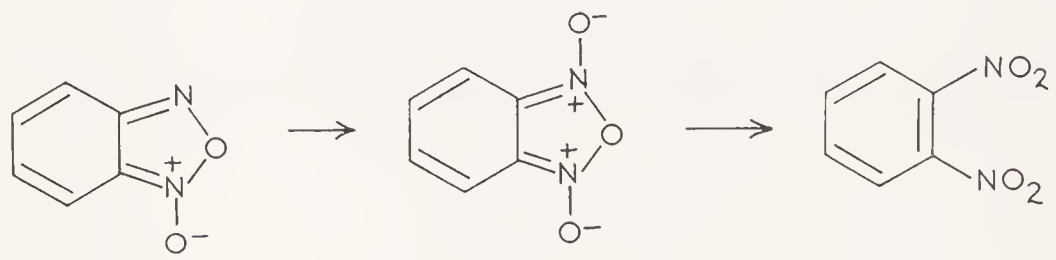
iii. Performic, Pertrifluoroacetic, and Permaleic Acids

These peracids are stronger oxidizing agents than peracetic acid, and consequently they are generally used to effect the *N*-oxidation of compounds which are resistant to the milder reagents. Pertrifluoroacetic acid has been the most extensively used.

a. Performic Acid. *N*-Oxidations that have been carried out with performic acid are summarized in Table 2.05. Frequently the same results are obtained as with peracetic acid; however, performic acid oxidation sometimes gives the desired product when peracetic acid fails, for example, in the preparation of 3,6-dichloropyridazine 1-oxide without hydrolysis of the chlorine atoms (63CT269), and in the preparation of 2-phenylquinoxaline 1,4-dioxide (53J2822). Performic acid has also been recommended for use in the preparation of pteridine *N*-oxides; steric factors are important here in determining the orientation of the oxidation [65AG(E)175].

b. Pertrifluoroacetic Acid. Pertrifluoroacetic acid is a strong oxidizing agent and has been used in a number of cases where peracetic acid fails or gives poor yields of the *N*-oxide (Table 2.06). It is often the reagent of choice for the preparation of α-halogeno *N*-oxides. Pentachloropyridine has recently been converted into its *N*-oxide with pertrifluoroacetic acid, although in this case care is needed since prolonged heating causes deoxygenation [67CH893, 68J(C)1537]. 1,3-Dihalogenoisoquinolines, however, are apparently unaffected (64J4561).

On treatment with pertrifluoroacetic acid, benzofuroxan (*6*) is oxidized to *o*-dinitrobenzene (*8*), possibly via the unstable benzofurazan 1,3-dioxide *7* (59JO2038). Guanine is converted into the 3-oxide [not the 7-oxide (*9*) as first thought], but caffeine undergoes ring cleavage (66JO178; 69JO978).



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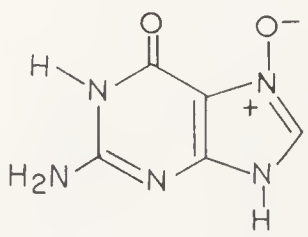

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Table 2.05. Formation of *N*-Oxides by Oxidation with Performic Acid

Ring system	Position of oxidation[a]	Substituents	Reaction conditions	Yield, %	References
Pyridine	1	N^4-acetylsulphonamido	20°, 12 h	(data)	58JO67, 59USP2881166
Pyrazine	1	3-methyl-2-piperidino	20°, 4 days	1[b]	64JO1645
Quinoxaline	1 and 1,4-di	5,6-benzo	50°, 15 h	(data)	53J2816
	1,4-di	6-chloro	50°, 15 h	(data)[c]	53J2816
	4 and 1,4-di	2-phenyl	50°, 15 h	(data)	53J2822
Pteridine	5	*C*- and *N*-methyl-2,4-dioxo (various)	20°, 15 h	20–70	65AG(E)1075
	8	3,4-dihydro-3-methyl-2-methylthio-4-oxo-6-phenyl	20°, 15 h	—	65AG(E)1075
Alloxazine	5,10-di	8-chloro	65°	88	63JS1192

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "1,4-di", for example, means that the product is the 1,4 di-*N*-oxide, while "1 and 1,4-di" indicates that a mixture of the mono- and di-*N*-oxides is obtained.

[b] The major product (84 %) is the *al*-*N*-oxide, 1-hydroxy-1-(3-methyl-2-pyrazinyl)piperidinium hydroxide.

[c] 6-Chloro-2,3-quinoxalinedione is formed as a by-product.

Table 2.06. Formation of *N*-Oxides by Oxidation with Pertrifluoroacetic Acid

Ring system	Position of oxidation	Substituents	Reaction conditions	Yield, %	References
Pyridine	1	3-amino[a]	CH_2Cl_2, reflux 1 h	21	60JO1716
	1	2,6-dibromo	3 h, 100°	70–75	59R408
	1	2-bromo-5-chloro	3 h, 100°	69	61R1066
	1	2,6-dichloro	4 h, 100°	62	65JH196
	1	pentachloro	5 h, 50°	20	67CH893, 68J(C)1537
	1	2,6-dicyano	7 h, 50°	83	69T295
	1	2-sulphonyl	3 h, 100°	79	62R604
	1	2,4- and 2,6-bis(trifluoromethyl)	—	(data)	69CT510
Quinoline	1	2-chloro	—	8	61JJ1743
Pyrimidine	3	*2,4-diamino-6-(*p*-bromoanilino)-5-nitroso	14 h, 20°	73	66MC573
	1 and 1,3-di	2,4,6-triamino-5-nitroso[b]	overnight, 20°	28 and 48	68JH449
	1 and 1,3-di	2,4,6-triamino-5-nitro	overnight, 20°	—	68JH449
Purine	7	2-amino-6-oxo	overnight, 20°	62	66JO178
Benzotriazole	3	2-acetamido	"CH_2Cl_2-Na_2CO_3"	83	64CI368

[a] 3-Aminopyridine oxidized to 3-nitropyridine 1-oxide using a mixture of trifluoroacetic anhydride and hydrogen peroxide in dichloromethane.

[b] 5-Nitroso group is converted into a 5-nitro group.

* 2-Trifluoromethyl; see addendum in the Appendix.

Table 2.07. Formation of *N*-Oxides by Oxidation with Permaleic Acid

Ring system	Position of oxidation[a]	Substituents	Yield, %	References
Quinoline	1	2-alkylmercapto-, -alkoxy, -amino- (substituted), -carboxamido-, -hydroxy-4-*H* and -methyl	43–100	66JJ749
*	1	2-benzoyloxy	58[b]	63CT1586
Pyridazine	1 and 1,4	3,6-dibutyl-5-chloro	—	69CT851
	1	3,6-dimethoxy-4-methyl	see note [c]	65JJ344
Pyrimidine	1	2-alkyl-4-chloro-6-methyl	34–74	68CT1337
Pyrazine	1 and 1,4-di	2,5-dichloro-3,6-diisobutyl	73 and 24	64CT125
Quinoxalino[2,3-*b*]-quinoxaline	5-mono; 5,11- and 5,12-di	—	total 85	68CB3913
1,2,4-Triazine	2	3-acetamido- and -ethoxycarbonyl-amino-5-phenyl	(data)	66JO3917
	2	3-methoxy- and -phenoxy-5,6-diphenyl	36 and 51	66JO3914
†				

[a] If *N*-oxidation leads to a single mono-*N*-oxide, only one position is indicated. The notation "1,4-di", for example, means that the product is the 1,4-di-*N*-oxide, while "1 and 1,4-di" indicates that a mixture of the mono- and di-*N*-oxides is obtained.

[b] *N*-Benzoyloxycarbostyril, not the *N*-oxide, is obtained.

[c] 1,3-Dimethoxy-4-methyl-6-pyridazinone also formed.

* Acridine; see addendum in the Appendix.

† Benzothiazole; see addendum in the Appendix.

c. Permaleic Acid. *N*-Oxidations which have been effected with permaleic acid are recorded in Table 2.07. Use of permaleic acid appears to be advantageous for the *N*-oxidation of some compounds which are difficult to oxidize. 2-Halogenoquinolines (66JJ749), chloropyrimidines (68CT1337) and chloropyrazines (64CT125) have been converted into the corresponding *N*-oxides in good yield with this reagent.

iv. Other Percarboxylic Acids

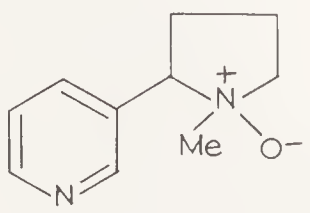
A patent claim refers to the use of higher fatty peracids for the *N*-oxidation of 1,7- and 4,7-phenanthroline, 2,3-diphenylquinoxaline, and 8-hydroxyquinoline (50USP2518130). Perlauric acid has been used to prepare nicotine *N*,*N*′-dioxide (59JO275), and 2-chloroquinoline 1-oxide has been obtained in poor yield from 2-chloroquinoline by the action of permonochloroacetic acid (61JJ1743). Pertrichloroacetic acid has been used successfully to effect *N*-oxidation in the pteridine series (67JH124). Succinic and tartaric acids have also been used successfully with hydrogen peroxide (47JJ33). *p*-Nitroperbenzoic acid is another alternative to perbenzoic acid (69JH389).

B. *N*-OXIDATION BY HYDROGEN PEROXIDE AND BY OTHER REAGENTS

Reactions of this type are of relatively little preparative importance. The oxidation of heteroaromatic compounds with hydrogen peroxide generally involves the intermediate formation of a peracid. Examples of oxidations involving inorganic peracids are sparse.

i. Hydrogen Peroxide

Hydrogen peroxide alone does not normally react with nitrogen-containing heteroaromatic compounds, although saturated tertiary amines are smoothly converted into the corresponding *N*-oxides, as was first shown many years ago (98CB1553); (cf. 92CB3123; for more recent work, see, e.g., reference 54AP326). Thus, the alkaloids nicotine (58IZ748; 59JO275), quinine (47JJ101), and quiterine (47JJ248), each of which contains both a heteroaromatic and a tertiary amine nitrogen atom, are converted into mono-*N*-oxides (cf. *10*, *11*) by hydrogen peroxide, but give di-*N*-oxides on treatment with peracetic acid (see also 52TA3; 61JO3045; 62JO1903). Similarly, 10-(2-pyridyl)phenothiazine reacts with hydrogen peroxide to give the 5-mono-*S*-oxide as the sole product (58JO1903).*



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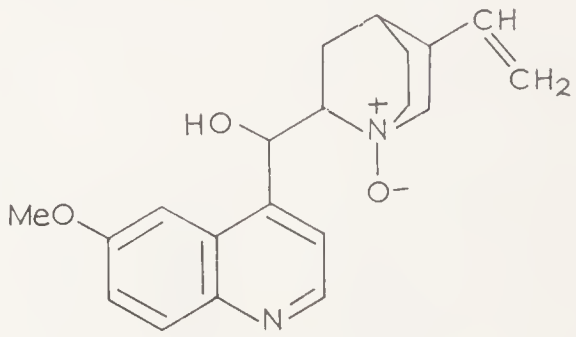

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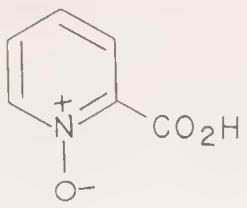
* See addendum in the Appendix.



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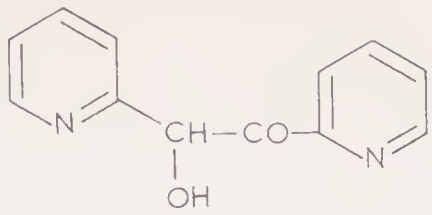

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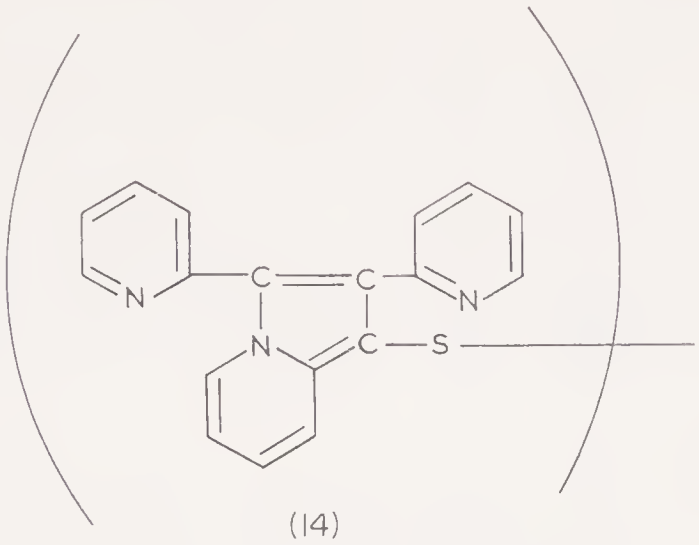

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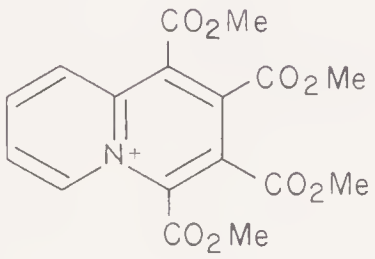

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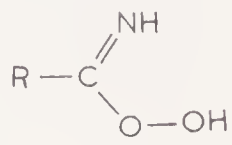

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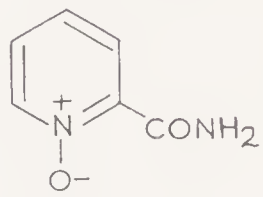


(17)

In the presence of an acid such as acetic or phthalic acid, hydrogen peroxide is in equilibrium with the corresponding peracid, which can readily effect *N*-oxidation, as discussed above. Acids formed *in situ* are also effective, thus oxidation of isoquinoline 3-aldehyde with hydrogen peroxide yields 3-carboxyisoquinoline 2-oxide (58JO900). Similarly, 2-carboxypyridine 1-oxide (*12*) is formed by the hydrogen peroxide oxidation of α-substituted pyridine derivatives such as *13* (51CB452), *14* (53CB205), and *15* [33LA(505)103]. 4-Phenylquinoline 2-carboxylic acid acts as its own acid catalyst for *N*-oxidation (49UK296).

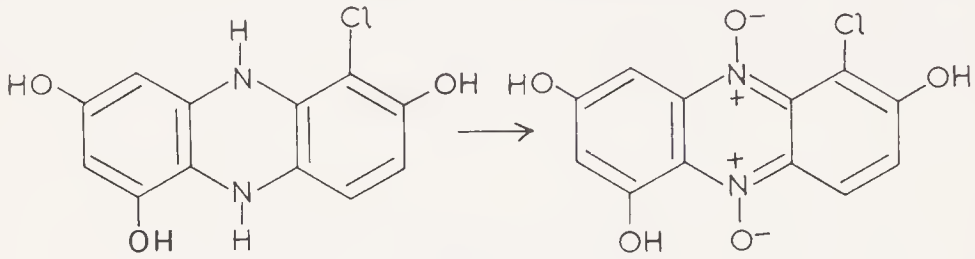
The *N*-oxidizing ability of hydrogen peroxide is also enhanced by the presence of a cyanide. Thus, pyridine is converted into its *N*-oxide by a mixture of hydrogen peroxide and benzonitrile, with simultaneous formation of benzamide; probably an intermediate of type *16* is involved (61JO659).

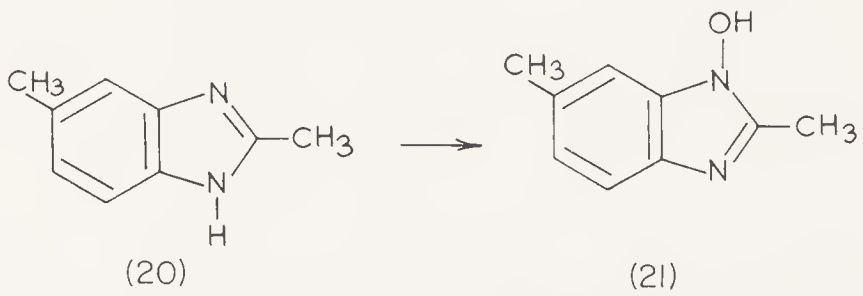
Hydrogen peroxide alone converts 2-cyanopyridine into the amide-oxide *17* (61JO668). Although the direct oxidation of amides to hydroxamic acids has succeeded with a mixture of ferric chloride and hydrogen peroxide, this reagent does not convert 2-pyridone into the cyclic hydroxamic acid 1-hydroxy-2-pyridone (49JA70).

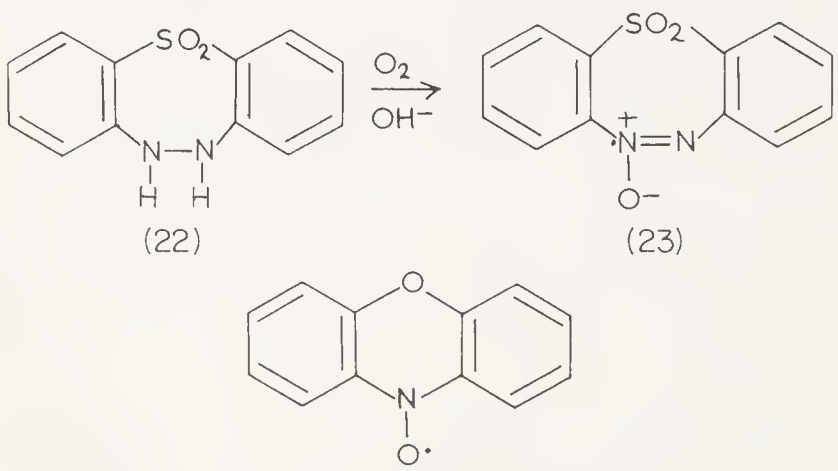
True oxidation of heteroaromatic nitrogen atoms by hydrogen peroxide may occur, but examples are rare. Adenosine 5′-monophosphate and deoxyadenylic acid give 1-oxides in low yield (59JA1734), but perphosphoric acids may actually be involved here. Quinoxaline also reacts to give the 1-oxide, but the yield is very poor (53J2816). The reported *N*-oxidation of 3-benzenesulphonamido-2,4,6-trimethylpyridine by hydrogen peroxide (58JA3649) may well be a typographical error. Prolonged reaction (40 days) of anabasine with hydrogen peroxide is also reported to yield the aromatic *N*-oxide (58IZ788).

ii. Other Reagents

Table 2.08 records the isolated instances of the use of potassium peroxymonosulphate, peroxymonosulphuric acid, perphosphoric acid, and chromic acid for the preparation of heterocyclic *N*-oxides. Although potassium permanganate has been reported to oxidize 4-azaindole to its *N*-oxide (50J2952), the compound obtained is unlikely to be an *N*-oxide.*







* See addendum in the Appendix.

Table 2.08. Formation of *N*-Oxides by Direct Oxidation with Miscellaneous Reagents

Oxidizing agent	Substrate	Product	Yield, %	Reference
Potassium peroxymonosulphate–glacial acetic acid	pyridine	pyridine 1-oxide	13	60JO1901
Peroxymonosulphuric acid	quinoxaline	quinoxaline 1-oxide	poor[a]	53J2816
	phenazine	—	—	38J479
	2,2′-bibenzimidazole	2,2′-bibenzimidazole 3,3′-dioxide	27	58LA(615)99
Perphosphoric acid	quinoxaline	quinoxaline 1-oxide	poor[a]	53J2816
Chromic anhydride–glacial acetic acid	phenazine-2-carboxylic acid	2-carboxyphenazine 5,10-dioxide	—	52AN519
Chromic anhydride–glacial acetic acid	3,8-dichloro-11*H*-dibenzo-[*c*,*f*]-[1,2]diazepine	3,8-dichloro-11*H*-dibenzo[*c*, *f*]-[1,2]diazepin-11-one 5-oxide	40	64JH178

[a] *N*-oxidation is accompanied by the formation of "much tar and insoluble, high-melting by-products".
[b] Both *C*- and *N*-oxidation occur.

Sodium perborate is reported to oxidize the dihydrophenazine *18* to the phenazine 5,10-dioxide *19* (57CC1423), and treatment of the benzimidazole *20* with bromine followed by alkali is said to give the *N*-hydroxy derivative *21* (92CB860). The thiadiazepine trioxide *23* was prepared by aerial oxidation of the dihydro compound *22* in a basic medium (56JA458). The oxidation of phenoxazine with *t*-butyl hydroperoxide yields the phenoxazinyl *N*-oxide radical *24* (68TL3619), and *N*-oxides are formed as by-products in the reaction of benzoyl peroxide with pyridine and quinoline (58AJ200; 58MI8). The ozonolysis of olefins to yield carbonyl compounds is facilitated by the presence of pyridine, and it was originally thought that pyridine 1-oxide was formed in the reaction (58JA915; 59MI162), but this suggestion has been refuted (66CH920).

C. SIDE REACTIONS ACCOMPANYING *N*-OXIDATION

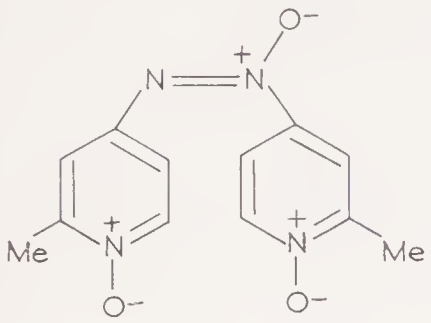
Although many common substituents are resistant to peracetic acid and still more are resistant to perbenzoic acid under the typical conditions for *N*-oxidation with these reagents, substituents can be modified completely or in part in the course of these reactions. By-products involving attack on the ring carbon atoms are not infrequently encountered.

i. Transformation of Substituents

Most of the side reactions of substituents involve hydrolysis or oxidation. As a general rule, if hydrolysis is an undesirable side reaction in peracetic acid *N*-oxidation, it can be avoided by the use of perbenzoic acid in a non-polar solvent. A few examples of other reaction types are known. 4-Azido-2-methylpyridine is converted into the azoxy compound *25* on treatment with peracetic acid (61CT87). Methoxyl groups are normally stable, but rearrangement was reported to accompany *N*-oxidation of 2-methoxy-6-methylpyridine with "old" peracetic acid (59JA2537); a mixture of 1-methoxy-6-methyl-2-pyridone and the expected *N*-oxide was obtained. Some 6-methoxypyridazine 1-oxides spontaneously rearrange to 1-methoxy-6-pyridazinones (cf. Section III-B3b) (65JJ344).

a. Hydrolytic Side Reactions. Peracetic acid causes partial hydrolysis of carboxamido groups to carboxyl groups (57JO984), and alkoxycarbonyl groups in an α-position also show a tendency to be hydrolysed to carboxyl groups (60JO565). Cyano groups are converted, in part or completely, into carboxamido groups (59JJ492), but good yields of cyano *N*-oxides can be obtained (see, e.g., 57JJ1244). Although the hydrolysis of amides and esters is largely suppressed by the use of an aromatic peracid in a non-polar solvent, *N*-oxidation of cyano compounds with perphthalic acid is stated to yield more of the amide by-product than is peracetic acid oxidation (64JJ163). Nucleosides are also frequently hydrolysed in part during *N*-oxidation (64MC204).

Acyloxy groups directly attached to a ring are very sensitive towards hydrolysis. Although 3-benzoyloxypyridine gives the corresponding 1-oxide with perbenzoic acid, the 4-benzoyloxy analogue yields dibenzoyl peroxide together with 4-pyridone and 1-hydroxy-4-pyridone (59J2844). Evidently a reaction of the type shown in structure *26* intervenes when X = H or O^-. Attempted *N*-oxidation of 4-acetoxy- and 4-benzoyloxy-quinolines by perbenzoic acid failed (56J3079).



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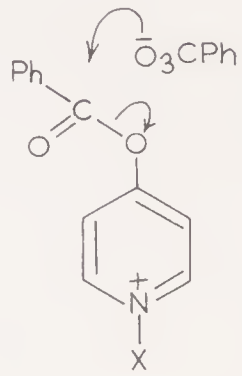

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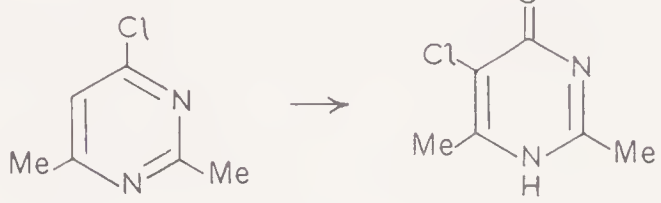
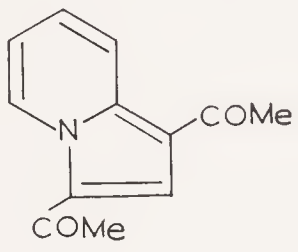


(27) (28)

Halogen atoms are sometimes sensitive to peracetic acid; thus, chloro (58JO1071) and fluoro groups (64J4561) in the 1-position of isoquinoline are hydrolysed. Substituents on diazines are more reactive and side reactions are more common than for correspondingly substituted pyridines. Thus, chloro groups (62JJ244; 63CT269) and benzyloxy groups (61CT149) in pyridazines can be hydrolysed. More complex products are sometimes formed: the hydrogen chloride liberated by hydrolysis of the chloropyrimidine *27* is oxidized to chlorine and converts the pyrimidinone into *28* (68CT1337). Whereas 1-phenoxyphthalazine yields the 3-oxide with perphthalic acid, the phenoxy group is largely hydrolysed on peracetic acid treatment (62JJ584).

b. Oxidative Side Reactions. We consider successively substituents linked to the ring through C, S, and N atoms. Several classes of functional groups which are attached to the ring through a carbon atom are oxidized, usually to a carboxyl group, although surprisingly styryl and ethoxycarbonylvinyl groups are unaffected by peracetic acid (58J150). Formyl and piperidinomethyl groups (58J150; 60JJ339), some ketonic side chains (63CT1331), and α- and γ-ethoxycarbonylmethylene groups (54JA3168; 56J2404) are oxidized to carboxyl groups by peracetic acid. However, 2-piperidinomethylquinoline is converted by perphthalic acid into the *N*-oxide before the ring nitrogen is

attacked (60JJ339). Peracetic acid degrades indolizines (pyrrocolines) (cf. *29*) to 2-carboxypyridine 1-oxides (cf. *30*) [37LA(530)87; 46J1069; 57JJ1347] and converts 6*H*-indeno[2,1-*b*]quinoline into the 6-oxo derivative; in the latter case the nitrogen is hindered from the α-position (61JO3817). Similar work on indeno-quinolines and indeno-quinoxalines has been reported (62JO1674). Carboxyl groups are usually stable, but phenanthridine-6-carboxylic acid (*31*) reacts with peracetic acid to give 6-hydroxyphenanthridine 5-oxide (61JJ1033). The 3-(2-piperidino) group of anabasine is oxidized and ring-opened to $-C(:NOH)CH_2CH_2CH_2CO_2H$ (62IZ2209). Certain substituents of type —CH(CN)R are oxidized to —COR (68AI1).*



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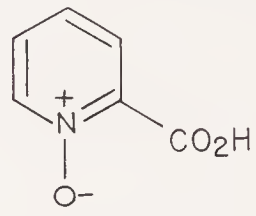

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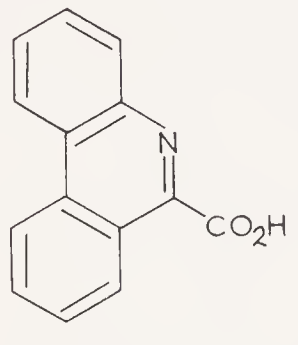

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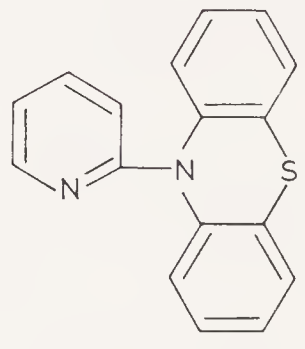


(32)

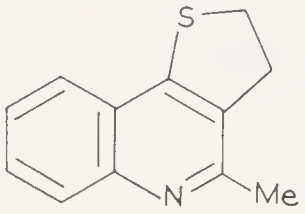
Hydroxyl groups tend to become oxidized, but may be stabilized by prior acetylation: thus pyridoxine triacetate gives a good yield of *N*-oxide in contrast to free pyridoxine (59JO1032).

Sulphur-containing groups are readily oxidized by peracids. Although the pyridylphenothiazine *32* does form the 2-substituted pyridine 1-oxide, the sulphur atom is simultaneously oxidized to the sulphone level (58JO1903). Simpler phenothiazines are also converted into sulphoxides and sulphones by hydrogen peroxide (57JA4375). If the sulphur-containing group is nearer to the nitrogen atom, *N*-oxide formation is hindered, thus 2-methylthiopyridine reacts with peracetic acid to give only the sulphoxide (50JA4362), and 2-benzylthiopyridine yields only the sulphoxide and sulphone [66LA(695)77]. However, certain 2-arylthiopyridines, although they first give sulphones, are converted into sulphone *N*-oxides on stronger treatment (62R604). The quinoline derivative *33* behaves similarly (63JJ234).†

Of the functional groups linked to the ring through a nitrogen atom, tertiary aliphatic amines are *N*-oxidized more readily than typical heterocyclic

*, † See addenda in the Appendix.

nitrogen atoms, whereas azo groups are converted into azoxy groups less readily. Thus, the *p*-dimethylaminophenylazo derivative *34*, which contains all three of these functional groups, is oxidized by perbenzoic acid first at the dimethylamino group, and then at the pyridine nitrogen atom, to yield successively the mono- and di-*N*-oxides (59G1843). Other phenylazopyridines also give *N*,*N*′-dioxides (e.g. *35*) with perbenzoic acid; again the pyridine nitrogen atom is attacked first (63G404). Similar results have been obtained with peracetic acid, but here azo groups tend to be simultaneously oxidized to azoxy groups (53BS101; 55G1148) although initial attack is at the pyridine ring nitrogen atoms (56G1067). 2-Dimethylaminopyridine yields only the aliphatic *N*-oxide (*36*) on treatment with peracetic acid (64R249), whereas 2-sulphonamidopyridine gives a mixture of the expected pyridine 1-oxide (*37*) and the hydroxyamino derivative *38* (58JO67). 3- and 4-(*p*-Dimethylaminophenyl)pyridines react with perbenzoic acid to give mixtures of the *N*-oxides formed by attack at the ring nitrogen atom and at the dimethylamino group [60T(9)194], whereas dimethylaminostyrylquinolines of type *39* undergo *N*-oxidation only at the dimethylamino group (63G1093; 64JH6). Pyridine-2-carboxaldehyde phenylhydrazone gives the corresponding pyridine 1-oxide derivative (64AN180). For recent work on the oxidation of amino-perfluoropyridines, see 69J(C)1485.



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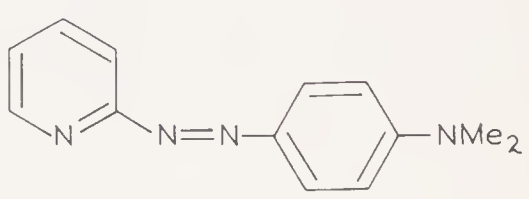

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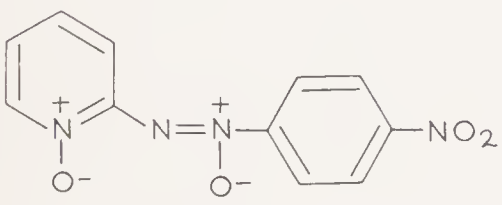

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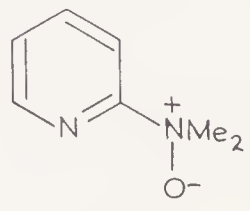

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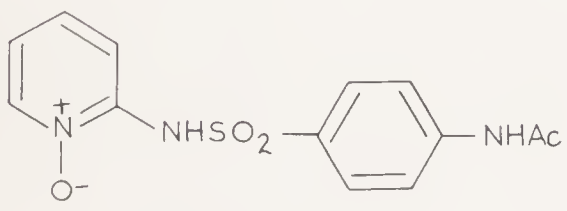

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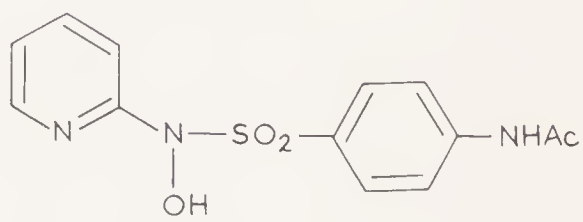

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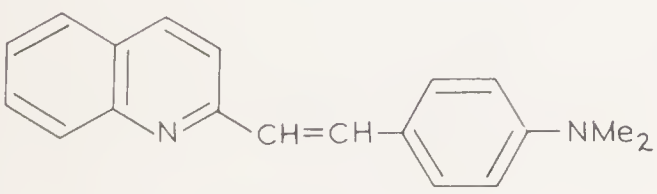

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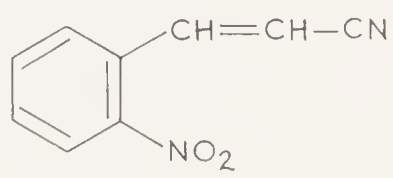

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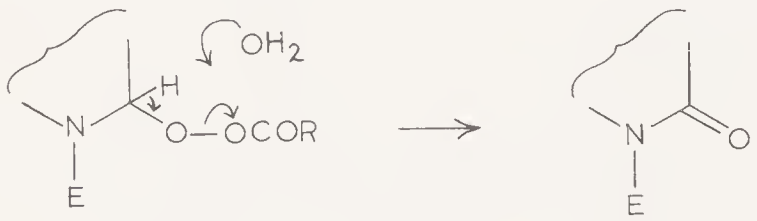
Pertrifluoroacetic acid converts 3-aminopyridine into 3-nitropyridine 1-oxide (60JO1716), an example of its known ability to oxidize aromatic amino groups into nitro groups. 2,4-Diamino-6-(*p*-bromoanilino)-5-nitrosopyrimidine is converted by pertrifluoroacetic acid into the 5-nitro 3-oxide (66MC573). On treatment with peracetic acid, 2-methylaminoquinoline yields *o*-nitrocinnamonitrile (*40*), possibly via the *N*-oxide (64CT350).

Tri-2-pyridyl-phosphine and -arsine are converted by peracetic acid only into the *P*- and As-oxides (48JO502).

ii. By-products Arising from Attack at Ring Carbon Atoms

It has become apparent that attack at ring carbon atoms is not a rare occurrence in the reactions of heteroaromatic compounds with peracids, particularly with peracetic acid. (In this section, the reagent is peracetic acid unless otherwise specified.) These by-products are generally α-oxo heterocycles and *N*-hydroxy-α-oxo heterocycles, or β-hydroxy heterocycles and their *N*-oxides. Compounds of the first and second types probably arise from nucleophilic attack of peracyl ions on the protonated or *N*-oxidized heterocycles (cf. discussion of such reactions in Section III-4Civb), respectively, to give an intermediate of type *41* which breaks down as shown: *41* → *42*. The mechanism for the production of the β-hydroxy derivatives (*43* → *45*) is speculative, but it may involve electrophilic attack at the β-position of an adduct formed by nucleophilic attack at the γ-position (cf. the mechanism for the nitration of *N*-oxides in a β-position, Section III-3C).



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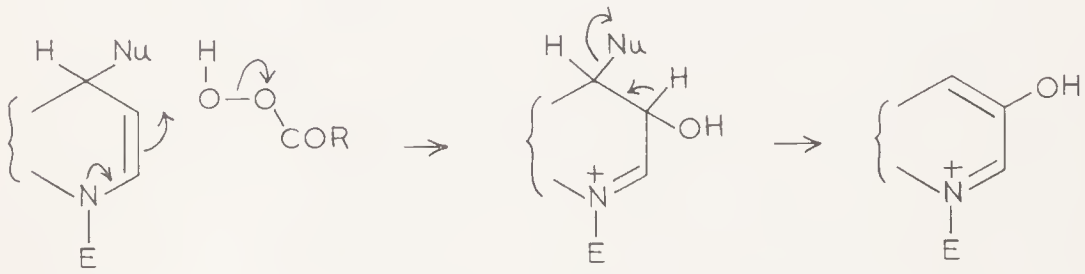

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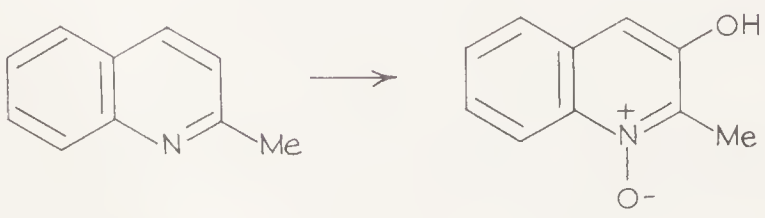

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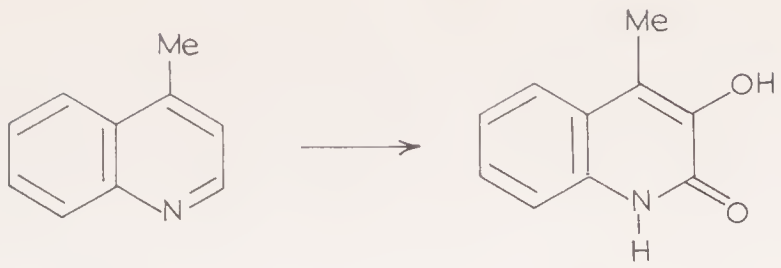


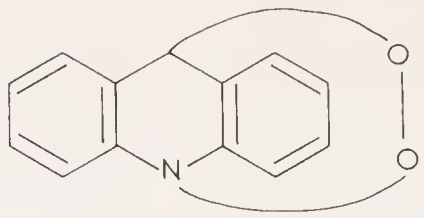
(48) (49)

Sometimes the amounts of these by-products are very small, which means that they may have passed undetected in many other reactions. Ochiai and his co-workers have shown that *N*-oxidation of 2-methylquinoline (*46*) gives 4% of the 3-hydroxy *N*-oxide *47* (57CT188), while that of 4-methylquinoline (*48*) gives 0·5% of the 3-hydroxy-2-oxo compound *49* as by-products. 6-Nitroquinoline was originally stated (45JJ448) to yield 6-nitro-2-quinolone as a by-product, but its structure was later corrected to 3-hydroxy-6-nitroquinoline (57CT621; 60CT126). 8-Substituted quinolines generally yield 3-hydroxy derivatives (69CT126). Treatment of 6-nitroquinoline, at least, with perbenzoic acid yields only the expected *N*-oxide. Occasionally ring degradation occurs: thus 2-phenylquinoline yields in addition to the expected *N*-oxide some *N*-benzoylanthranilic acid (54RS2351), and 1-methoxyisoquinoline gives phthalimide as the only product identified (58JA3443).* Ring attack also occurs with trifluoromethylpyridines (69CT510).

Perbenzoic acid oxidation of acridine was claimed to give the endo peroxide *50* as well as the normal *N*-oxide (36CB1514), but later work indicated that the alleged peroxide was 9-hydroxyacridine *N*-oxide (59CT152). A more recent paper has suggested that the "endo peroxide" may have the curious structure *51*, and that 2-(*o*-hydroxyanilino)benzaldehyde is formed as a second by-product [68J(C)1045]. In suitable cases an α-substituent can be lost. Thus, peracetic acid treatment of phenanthridine-6-carboxylic acid yields a mixture of 6-phenanthridone and 5-hydroxy-6-phenanthridone (61JJ1033). 4,10-Diazapyrene is converted by peracetic or monoperphthalic acid exclusively into the 5,9-dioxo derivative (65J3379), and some attack occurs at the 2-position of 1,6-naphthyridine (69CT1045).

Little is known of the occurrence of ring attack in the *N*-oxidation of pyridazines, but cinnolines can undergo extensive modification: 5- and 8-nitrocinnolines yield 4- and 7-nitroindazoles as by-products, and the former additionally gives the 4-hydroxy derivative (65CT713). 4-Methyl-8-nitrocinnoline yields the 4-cinnolinone *52* with loss of the methyl group; several alternative mechanisms were suggested [68J(C)2621]. Ring attack is commonly observed with pyrimidines unless substituents are present in the 4- and 6-positions (67JJ1096), and quinazolines are often converted into 4-quinazolinones by peracetic acid treatment (57JJ507). Even with perphthalic acid, 2-unsubstituted quinazolines (*53*) sometimes simultaneously

* See addendum in the Appendix.



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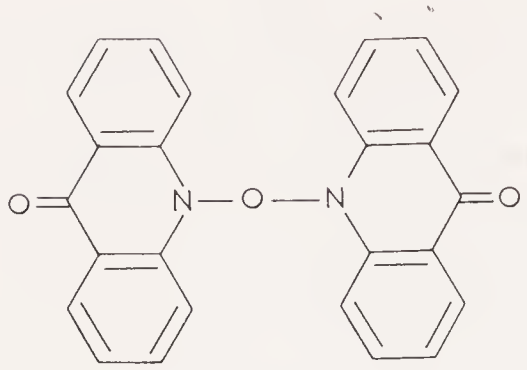

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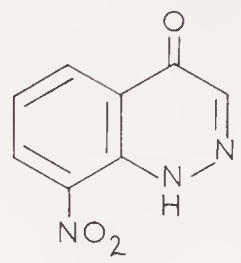

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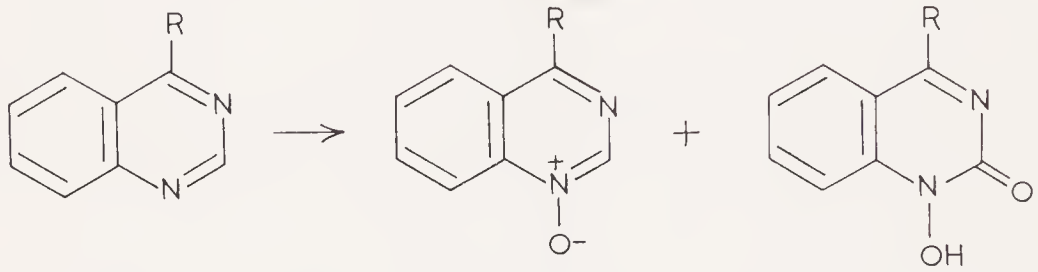
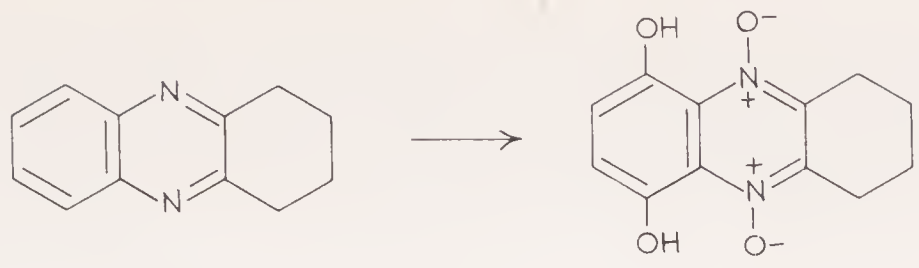


(53) (54) (55)

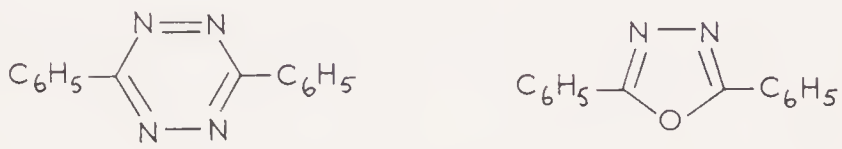
yield 1-hydroxy-2-quinazolinones (*55*) in addition to the expected 1-oxides (*54*) (59CH152); the formation of 2- and 4-quinazolinones (64CT43) and even imidazoles (53J2822) as by-products has also been reported. Electron-withdrawing substituents in quinoxalines promote ring attack with the formation of 2,3-quinoxalinediones (53J2816; 57J3236), and 3-quinoxalinone 1-oxide itself is converted into 1-hydroxy-2,3-quinoxalinedione (53J2830; 63J2428). Certain 2,3-disubstituted quinoxalines yield 5,8-dihydroxy dioxides, as in the transformation of the tetrahydrophenazine *56* into *57* [60AA(138)14-P]. Although pteridine was originally reported to yield an *N*-oxide on treatment with perphthalic acid (51J474), the compound was subsequently shown to be 4-pteridinone (52QR197). Recently other examples of pteridinone formation have been reported [69J(C)1408].

More complex reactions can occur with triazines and tetrazines. Certain triazinones (*58*, R = H, Me), which were first thought to yield *N*-oxides on reaction with peracetic acid (65CT1168), are now claimed to give curious bicyclic derivatives of type *59* (66CT1448). 3,6-Diphenyl-1,2,4,5-tetrazine (*60*) is converted by peracetic acid into the oxadiazole *61* (62JO1463). Peracetic acid reacts with benzimidazoles to give benzimidazolones rather than *N*-oxides (66JH51).



(56) (57)

(58) (59)



(60) (61)

D. KINETICS AND SELECTIVITY OF *N*-OXIDATION

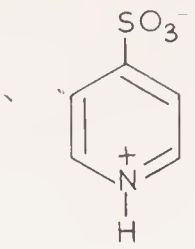
The steric and electronic effects of substituents on *N*-oxidation as qualitatively judged from relative yields, together with kinetic investigations of the quantitative effects of substituents, and deductions regarding the reaction mechanisms, are considered in this section. The question of selectivity in the oxidation of heterocycles containing two or more ring nitrogen atoms is also discussed.

i. Steric and Electronic Effects of Substituents and Extra Ring Hetero Atoms

N-Oxidation reactions are subject to steric hindrance. 2,6-Diphenylpyridine gives the *N*-oxide in poor yield under conditions (perbenzoic acid) which lead to *N*-oxidation of 2-phenylpyridine in good yield (53CC457). The *N*-oxide of 2,6-dimethoxy-4-methylpyridine is likewise obtained in low yield (55J631), and 2,6-dibenzyloxy- and 2,6-dibromo-4-methylpyridine cannot be *N*-oxidized with perbenzoic acid (55J631). In bicyclic compounds, substituents *peri* to the ring nitrogen atoms also seriously hinder the reaction; thus, 8-nitroquinoline (47JA303), 8-alkoxyquinolines (52ZO1224), and 2-aryl-8-methylquinolines (46JA979; 46JA2017) are unaffected by peracetic acid.

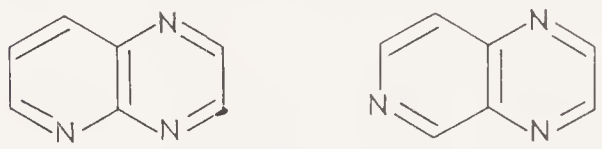
The *N*-oxidation reaction requires that the heterocyclic nitrogen atom be in the form of its free base. Thus, pyridinesulphonic acids are not attacked by peracetic acid because they exist as zwitterions (cf. *62*), but the corresponding sodium salts are smoothly *N*-oxidized (58CI1559; 62JO1329). Attempted *N*-oxidation of quinoline-6-sulphonic acid with perphthalic acid

also failed (60JJ339). Picolinic acid (61PC58) and pyridine-2,5- and -2,6-dicarboxylic acids, which are relatively strong acids, are unaffected by peracetic acid (59JO1569; cf. 60JO565).



(62)

Electron-withdrawing substituents clearly hinder the reaction, and compounds with an inductive or mesomeric electron-accepting substituent in the α-position often require use of pertrifluoroacetic acid if good yields are to be obtained (see Section II-1Aiiib). The reaction rarely fails completely because of substituent influence, although 2-nitropyridine is a case in point (47JJ79).



(63) (64)

Neither pyrido-pyrazines (*63*, *64*) (59JO1455) nor quinolo-pyrimidines (57J3718) yield *N*-oxides on treatment with peracetic acid. Attempts to prepare *N*-oxides of adenosine [59AK(13)439] and ribonucleic acid using peracetic acid failed [59CB266; 60AK(16)187]. Examples of the reaction failing have been reported in the pyridazinone, pyrazinone (60J3387), and quinazoline series (60J2157). Benzo-1,2,4-triazines are often resistant to *N*-oxidation, although reaction does occur in certain cases (57J3186).

Table 2.09. Second-order Rate Constants for the Oxidation of Pyridines with Perbenzoic Acid[a]

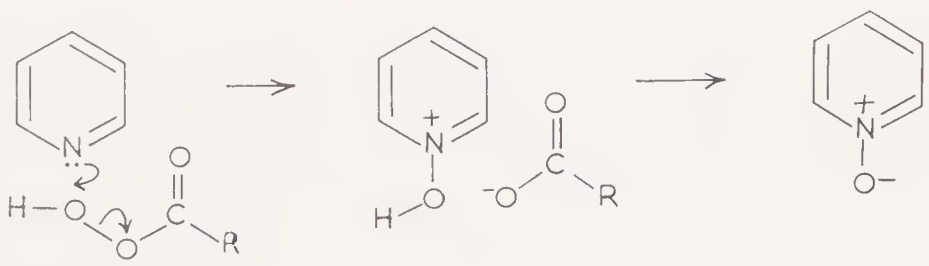
Pyridine	$k \times 10^3$ ($sec^{-1}mole^{-1}$/litre)	pK_a value
—	4·80	5·17
4-Methyl	7·25	6·02
2,4-Dimethyl	10·2	6·79
2,4,6-Trimethyl	10·2	7·50

[a] Data taken from reference 60G702.

Among phenazines, the 2,8-diacetoxy derivative was not converted into its *N*-oxide (54CT25). Attempted *N*-oxidation of 2,5-diphenyloxazole failed, although the *N*-oxide of the dimethyl analogue was successfully prepared (60JA186). *N*-Oxidation by peracetic acid fails in the benzimidazole series (67JJ648).

ii. Kinetics and Mechanism

A kinetic study (60G702) showed that the reaction of pyridine with perbenzoic acid in aqueous dioxane is of second order and involves the pyridine as free base and the peracid as such. The rate falls off at low pH values due to formation of the pyridinium cation, and a corresponding rate drop at high pH values is due to formation of the peracid anion. Electron-donating alkyl groups enhance the reaction rate, as is illustrated by the second-order rate constants measured under standard conditions at 25°, which correlate with the pK_a values of the pyridines as bases (Table 2.09). These findings are in accord with a mechanism of the type illustrated in the scheme *65* → *66*. However, steric effects are also reflected in the lower-than-expected rate found for 2,4,6-trimethylpyridine.



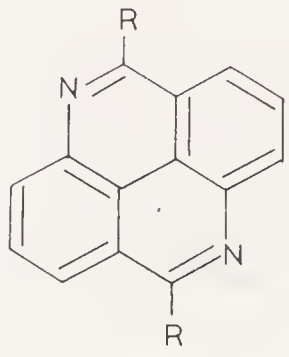
(65) (66)

More recently, the kinetics of perbenzoic acid *N*-oxidation have been extended to cover a wider variety of alkyl-substituted pyridines and also the mono-chloropyridines (61G613). Linear relationships were found between the second-order rate constants and the Hammett *sigma* constants for the mono-substituted compounds: *rho* for the reaction has, as expected, a large negative value of −2·35. For all the compounds studied, a satisfactory linear relationship was found between the second-order rate constants and the pK values, except for the 2,6-disubstituted derivatives, where steric hindrance obviously interferes with *N*-oxidation. An analogous kinetic study has been concerned with the *N*-oxidation of quinoline, isoquinoline, and azaphenanthrenes: the *N*-oxidation reaction is less sensitive to steric effects than is the formation of quaternary salts with methyl iodide (66BB17).

Although no kinetic work has been reported for the peracetic acid *N*-oxidation of pyridines, rate studies of the oxidation of ring-substituted anilines give a Hammett *rho* value of −1·86, indicating that the lone pair of electrons on nitrogen attack the outermost oxygen atom of peracetic acid. It was concluded that the mechanism of *N*-oxidation of heteroaromatic bases is similar to that shown in scheme *65* → *66*.

iii. Selectivity in the N-*Oxidation of Compounds with Two or More Ring Nitrogen Atoms*

a. Compounds Containing Two Nitrogen Atoms in Different Rings. Bipyridyls are usually converted quite normally into bis-*N*-oxides (55JJ731; 56NK682). Dipyridylalkanes give bis-*N*-oxides, but mono-*N*-oxides can also be isolated (62J1475). Polymers derived from 2-vinylpyridine can be oxidized to the poly-*N*-oxides [69J(C)1012]. 1,6-Naphthyridine undergoes oxidation first at the less hindered 6-position, but the 1,6-dioxide is also obtained (69CT1045). Diazapyrenes (*67*) yield the normal bis-*N*-oxides (60J2553).



(67)

b. Pyridazines, Cinnolines, and Phthalazines. Pyridazines normally form only mono-*N*-oxides by direct oxidation, but it has recently been shown that 1,2-dioxides can be prepared under forcing conditions (68TL1855). *N*-Oxidation of unsymmetrically substituted pyridazines often occurs at both the 1- and 2-positions; however, 3-substituents favour oxidation at the 1-position (63CT114), presumably for steric reasons. In the *N*-oxidation of 3,6-disubstituted pyridazines in which the substituents are different, the directive effect of the substituents is in the order Cl $\approx$ OR > Me > NH_2 and towards the position furthest away from the substituent. For further details and references, see Tables 2.01, 2.02, and 2.04.

Cinnolines can give either 1- or 2-oxides on *N*-oxidation: determination of the orientation of the products by NMR and chemical methods has been carried out by Japanese workers (62CT1123). Cinnoline 1,2-dioxides are formed as by-products in peracetic acid oxidations (66CI157), and can be obtained from either cinnoline or its mono-*N*-oxides under vigorous reaction conditions (66TL2899; 67CT1088). Cinnoline itself yields a mixture of the 1-, 2-, and 1-2-di-oxides, which are separable by column chromatography [68J(B)316]. A 4-carboxylic acid group directs *N*-oxidation to the 2-position, but a 3-nitro group to the 1-position: 4-alkyl groups favour 2-oxidation and 3,4-dialkylcinnolines form only the 2-oxide and the 1,2-dioxide [68J(C)2621].

1-Substituted phthalazines generally undergo *N*-oxidation at the 3-position (62JJ584), but considerable amounts of 2-oxide are also produced (68JJ1333).

c. Pyrimidines and Condensed Pyrimidines. Pyrimidine *N*-oxides are readily formed only from 4,6-disubstituted derivatives; oxidative ring attack

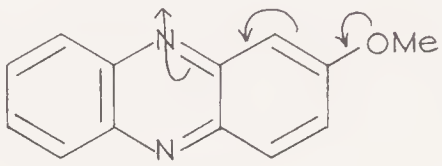
occurs with other derivatives (67JJ1096). The reaction is sterically hindered by phenyl groups but not by simple alkyl groups (67JJ1096). Contrary to the assumption of previous workers, the *N*-oxidation of 4-methylpyrimidine actually gives somewhat greater amounts of the 3-oxide than of the 1-oxide (64TL19). The first pyrimidine 1,3-dioxide has recently been reported: it is the 5-nitro-2,4,6-triamino compound prepared from the corresponding 5-nitrosopyrimidine by pertrifluoroacetic acid oxidation (68JH449). The factors influencing the orientation of oxidation at the 1- or 3-position of 4-substituted pyrimidines, and analogous 4-substituted quinazolines and 6-substituted purines, have been discussed (69JO2153).

4-Substituted quinazolines are *N*-oxidized in the 1-position (59CT152; 64CT43). 6-Methylpurine (62JO567) and most other purines (see Table 2.01) are selectively *N*-oxidized at the 1-position, but the 6-alkoxy (69BJ750) and 6-halogeno derivatives (69JO2157) are oxidized at the 3-position. Guanine (2-aminopurin-6-one) is also *N*-oxidized at the 3-position (69JO978), although 7-oxidation was originally considered to have occurred (66JO178).

d. Pyrazines, Quinoxalines, and Phenazines. Pyrazines can be converted into mono- or di-*N*-oxides. Thus, 2-methylpyrazine yields the 1- and 4-oxides, and with a large amount of peracetic acid the 1,4-dioxide is obtained (59JJ1273). In unsymmetrically substituted pyrazines, the most basic and least sterically hindered nitrogen atom is oxidized first (63JO1682); a compromise is sometimes reached, thus 2-acetamidopyrazine yields approximately equal amounts of the 1- and 4-oxides (68KG725). Some polysubstituted pyrazines form only mono-*N*-oxides (47J1183; 48J1859). *N*-Oxidation of 2-dialkylaminopyrazines occurs mainly at the amine nitrogen atom, but some of the 1-oxide is also formed (64JO1645).

In the quinoxaline series, the strength of the peracetic acid determines whether mono- or di-oxidation occurs (61ZO1018). 5-Substituted quinoxalines usually form only the 1-oxides, which is a reflection of steric hindrance by a *peri*-substituent (53J2816; 53J2822). 2-Methylquinoxaline yields the 1-oxide, but the 2-alkoxy derivative gives the 4-oxide (62JJ1434). The size of the substituents is also important: 2,3-dimethylquinoxaline forms the 1,4-dioxide, 2-methyl-3-isopropylquinoxaline gives a mono-*N*-oxide, and 2,3-diisopropylquinoxaline is not readily *N*-oxidized (53J2822). The effect of substituents in an α-position on the *N*-oxidation of quinoxalines has been carefully studied more recently by Hayashi *et al.* (64JJ163). Their conclusions are in general agreement with those given above: methyl groups slightly facilitate the reaction; other primary-alkyl groups have little effect; and secondary-alkyl groups, aryl groups, and most other functional groups offer considerable hindrance. However, they point out that it is difficult to predict the course of *N*-oxidation of a 2,3-disubstituted quinoxaline on the basis of the reactions of mono-substituted compounds.

The orientation of the *N*-oxidation of substituted phenazines has been investigated by Russian workers (59ZO1306; 60ZO2033, cf. 64JJ1080). Substituents in an α-position exert an important steric effect, whereas substituents in a β-position display an electronic effect. Thus, 1-chlorophenazine yields the 5-oxide, 2-chloro- and 2-methyl-phenazine yield mixtures of the 5- and 10-oxides, but 2-methoxyphenazine forms mainly the 10-oxide (cf. *68*). Treatment of the benzophenazine 12-oxide *69* with peracetic acid gives a mixture of the 5,12-dioxide and the isomeric 5-oxide *69b*, demonstrating the reversibility of the reaction and presumably reflecting the steric hindrance present in *69a* (51JA4958).



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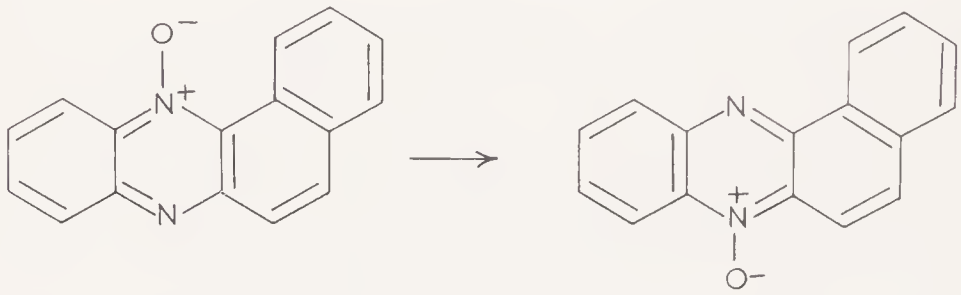

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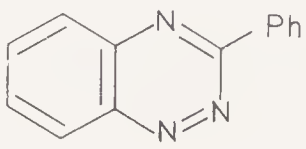


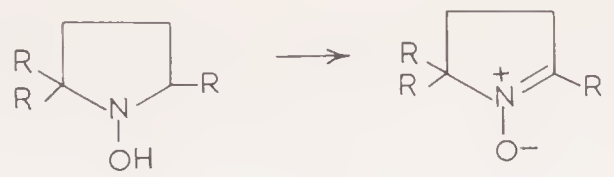
(70)

e. Benzotriazines. At 20°, 3-phenyl-1,2,4-benzotriazine (*70*) is converted into the 2-(or 4)-oxide, while oxidation at 45–50° yields the 1-oxide (57J3186).

E. OXIDATION OF CYCLIC HYDROXYLAMINES AND REARRANGEMENT OF AZIRIDINES

Cyclic hydroxylamines are readily oxidized to cyclic nitrones by oxidizing agents such as oxygen–cupric acetate–ammonia, potassium ferricyanide, and mercuric oxide. Cyclic *N*-oxides which have been prepared in this way include pyridine 1-oxides (57J3497), pyrroline 1-oxides (*71* → *72*) (56CB2159; 59CB1748; 59J2094; 59J2109), and 3,4-dihydroisoquinoline 2-oxides (*73* → *74*)[57LA(609)46]. 1,4-Dihydroxypyrazole can be oxidized to 4-oxo-4*H*-pyrazole 1-oxide (69JO187). 3,4,5,6-Tetrahydropyridine 1-oxides are probably formed analogously, but polymerize immediately to give cyclic dimers

(*75*) (56CB2159) or trimers (*76*) [57LA(609)46], depending on the reaction conditions.



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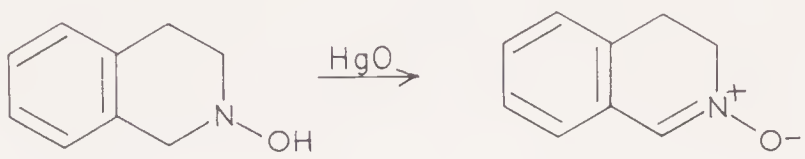

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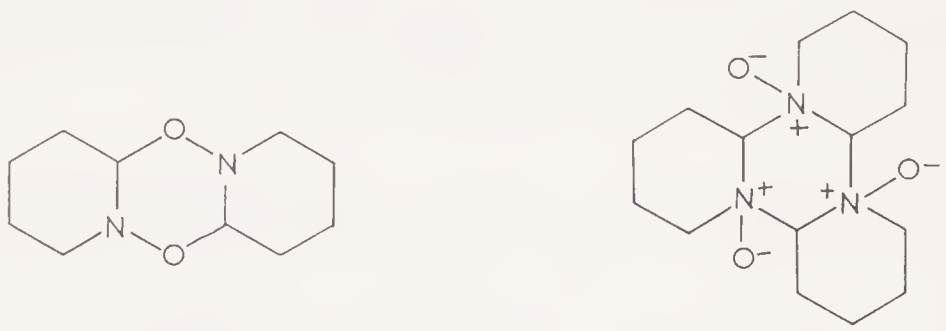

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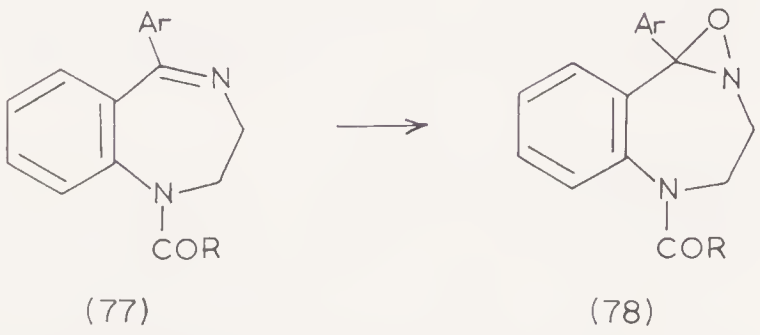


(77) (78)

The *N*-oxidation of heterocyclic nitrogen compounds is usually straightforward; however, the benzodiazepine derivative *77* yields initially the oxaziridine *78* which may be rearranged to the *N*-oxide (63JO2459). This behaviour is typical of open-chain imines, and the rearrangement of oxaziridines to *N*-oxides must therefore be considered a method for their preparation (cf. Section III-5Bvi).*

2. Formation of Heteroaromatic *N*-Oxides by Cyclization Reactions

Cyclizations leading to the formation of an *N*-oxide function are classified, for convenience in discussion, into five groups depending on the structure of the compound which actually undergoes ring closure. The cyclization of hydroxylamine derivatives (including oximines) and of nitroso compounds form the first and second groups. The cyclization of nitro compounds by non-reductive methods is then discussed, sub-divided into nucleophilic

* See addendum in the Appendix.

attack on the nitro group nitrogen atom and those reactions in which both oxygens of the nitro group are retained. Finally, a group of miscellaneous reactions is considered.

The first group includes the reactions of hydroxylamine itself with suitable cyclic and acyclic precursors. In addition to cyclizations of preformed hydroxylamines and oximes, cyclization of derivatives of this type formed *in situ* by the partial reduction of another functional group—most frequently a nitro group—is important. Similarly, the cyclizations of nitroso compounds in which the nitroso group is formed *in situ* are included in the second group of reactions. Occasionally, available evidence does not allow a clear distinction of a reaction mechanism between the various classes; in such cases the reaction is placed in the class which we consider to be the most probable. The third group of reactions consists of miscellaneous cyclizations, e.g. of nitrile oxides, and reactions of obscure mechanism.

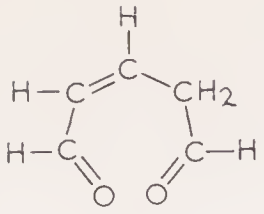
A. CYCLIZATION OF OXIMES AND OTHER HYDROXYLAMINE DERIVATIVES

This group of reactions is classified first according to the *N*-oxidized ring system obtained, and then according to whether the oxime or hydroxylamine derivative cyclized is preformed or formed *in situ*. The formation of six-, five-, and seven-membered ring *N*-oxides are considered in turn.

i. Pyridine and its Benzo Derivatives

a. Pyridine and Isoquinoline N-*Oxides*. A wide range of derivatives of glutaconic acid and aldehyde react with hydroxylamine to yield pyridine *N*-oxides; cyclic derivatives such as pyrones and pyrylium salts react similarly. The type of compound formed is related to the oxidation state of the starting material.

Baumgarten and co-workers (33CB1802) were the first to observe that various glutaconic dialdehydes (*79*) undergo ring closure to give pyridine 1-oxides. Substituted pyridine 1-oxides result from cyclization of cyano derivatives of type *80* (61J3566). Analogously, homophthalaldehyde (*81*) yields isoquinoline 2-oxide (*82*) (36CB2766), and the more complex isoquinoline derivative *83* can be prepared similarly (50JA1118). Pyridine 1-oxides have also been obtained from hydroxylamine and pyrylium salts (*84*) (58CB1488), although the reaction takes another course in some cases (68T5059). All of these reactions involve the formation of an intermediate oxime by nucleophilic attack of hydroxylamine on a carbonyl group or on the α-position of a pyrylium ring. The oxime undergoes ring closure, as indicated in structure *85*, followed by aromatization. The intermediate oxime can sometimes be isolated and then cyclized in a separate step; cf. *87* → *86*, *88* (66CB698). *o*-Formyl-β-phenethyl bromide reacts with hydroxylamine to give 3,4-dihydroisoquinoline 2-oxide (58CB1488).



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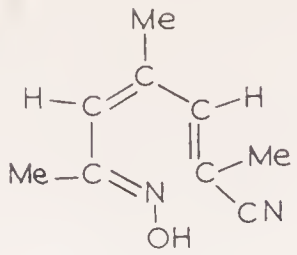

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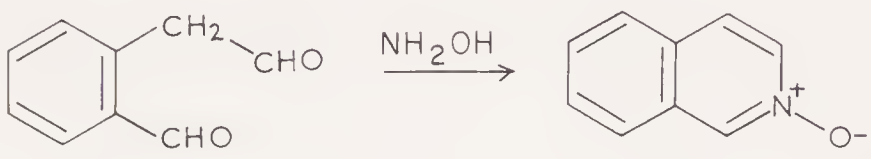
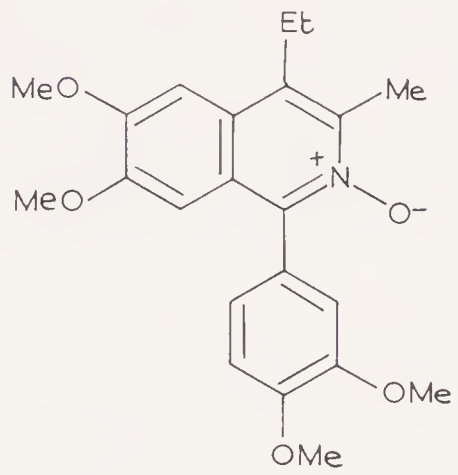


(81) (82)



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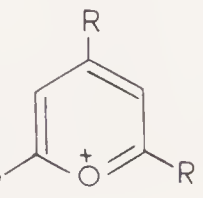

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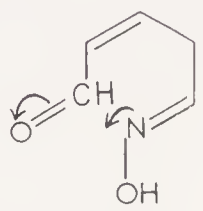

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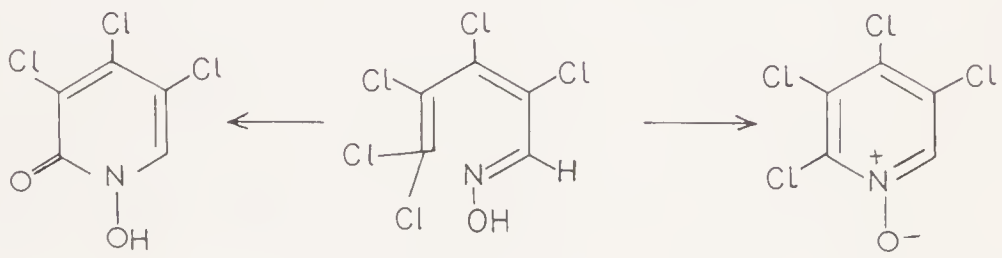


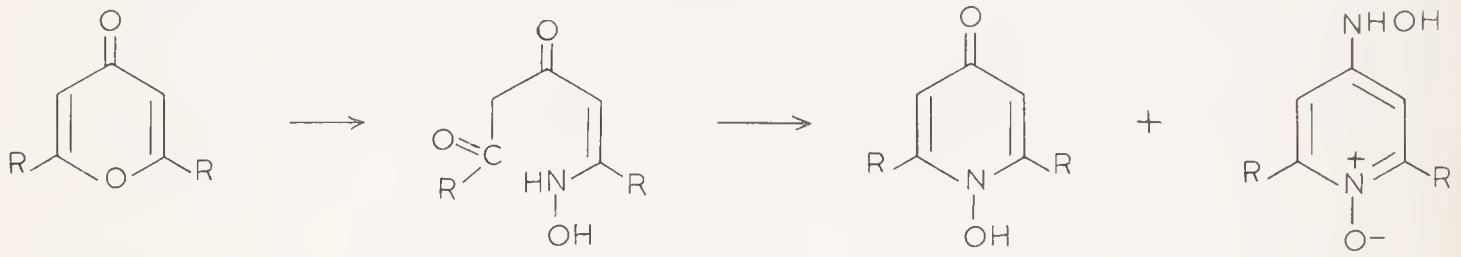
(86) (87) (88)

On treatment with hydroxylamine, γ-pyrones undergo facile ring opening and reclosure to give 4-hydroxypyridine 1-oxides (tautomeric with 1-hydroxy-4-pyridones; see Section IV-3Bia) and/or 4-hydroxyaminopyridine 1-oxides (*89* → *91*, *92*). The latter derivatives are formed by further reaction of hydroxylamine with the γ-carbonyl group, probably at the ring-opened stage (cf. *90*).

Table 2.10. Conversion of 4-Pyrones into Pyridine 1-Oxides by Hydroxylamine (89 → 91, 92)

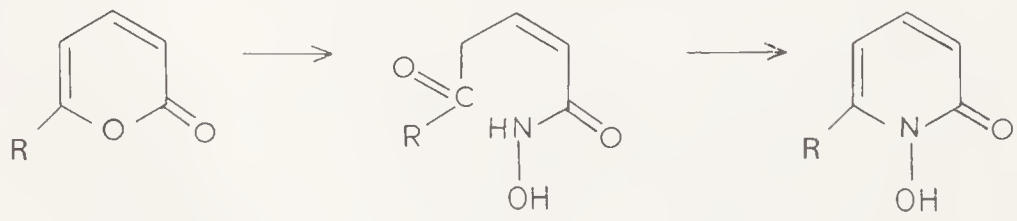
4-Pyrone	Reference	Pyridine 1-oxide formed (yield, %)	
		4-hydroxy	4-hydroxyamino
—	60G903, [cf. 84PC(29)378]	—	76
2-Carboxy	84PC(29)378, 11G619	yield not reported	—
2-Carboxy-5-ethoxy	11G619	yield not reported	—
2,6-Diethyl and -dimethyl	62CC2146, 62G1138	—	ca. 20
2,6-Diphenyl	62J1857	product obtained in ethanol (data)	product obtained in aqueous pyridine (data)

Examples of the reaction are collected in Table 2.10; however, other cases are known where reclosure of the ring does not occur (64CT381).*



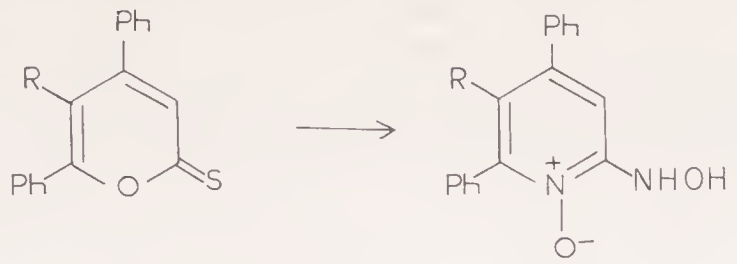
(89) (90) (91) (92)

b. Pyridine and Isoquinoline Hydroxamic Acids. α-Pyrones are converted by hydroxylamine into 1-hydroxy-2-pyridones: *93* → *95* (1-hydroxy-2-pyridones are tautomers of 2-hydroxypyridine 1-oxide; see Section IV-3Bia). 5-Benzoyl-2-pyrones (56JA2393) and a series of 4,6-diphenyl-2-pyrones react similarly (61J4490). 2-Hydroxyaminopyridine 1-oxides are not produced from α-pyrones; this is predictable since neither the lactone-type carbonyl group of a 2-pyrone nor the amide-type carbonyl in the ring-opened intermediate (*94*) would be expected to react with hydroxylamine. However, the corresponding 2-pyranthiones do possess the necessary reactivity and do indeed form 2-hydroxyaminopyridine 1-oxides (*96* → *97*) (61J4490). 2-Hydroxy-1-isoquinolones are formed by the cyclizations shown in schemes *98* → *99* (58JA3443) and *100* → *101* (03CB570).

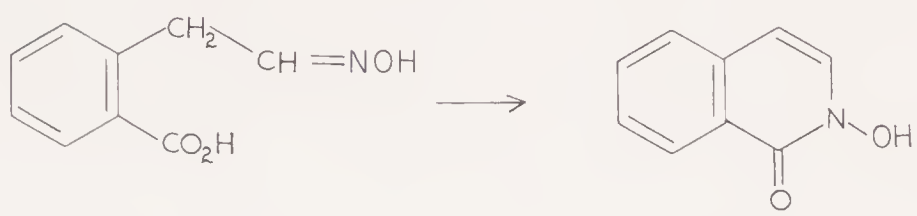


(93) (94) (95)

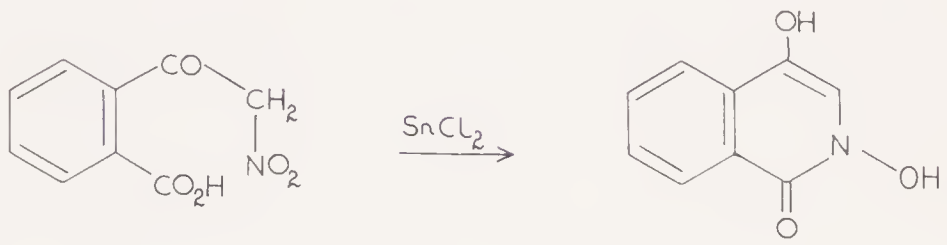
* See addendum in the Appendix.



(96) (97)

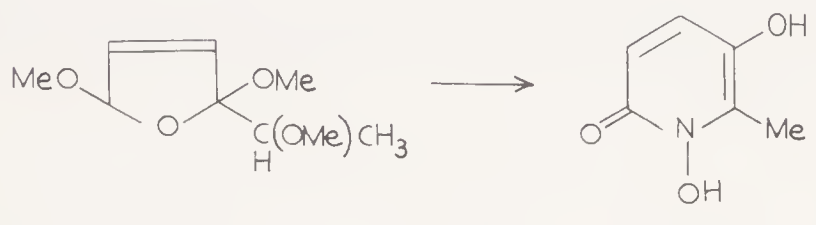


(98) (99)

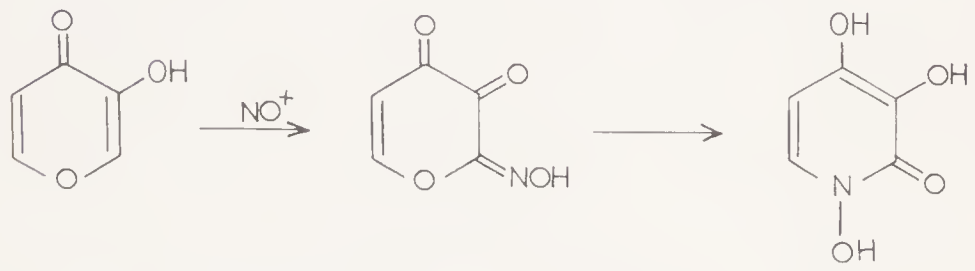


(100) (101)

A series of more complex reaction sequences is related to the transformation of α-pyrones into 1-hydroxy-2-pyridones just described. Certain 2-acyl-2,5-dimethoxyfuran derivatives yield 1-hydroxy-2-pyridones: cf. *102* → *103* (55AS9; 55AS30, 56USP2748142). Pyromeconic acid (*104*) reacts with nitrous acid to give the isonitroso derivative *105*, which readily undergoes ring opening and reclosure to form the hydroxamic acid *106* [79PC(19)177; 81PC(23)439].



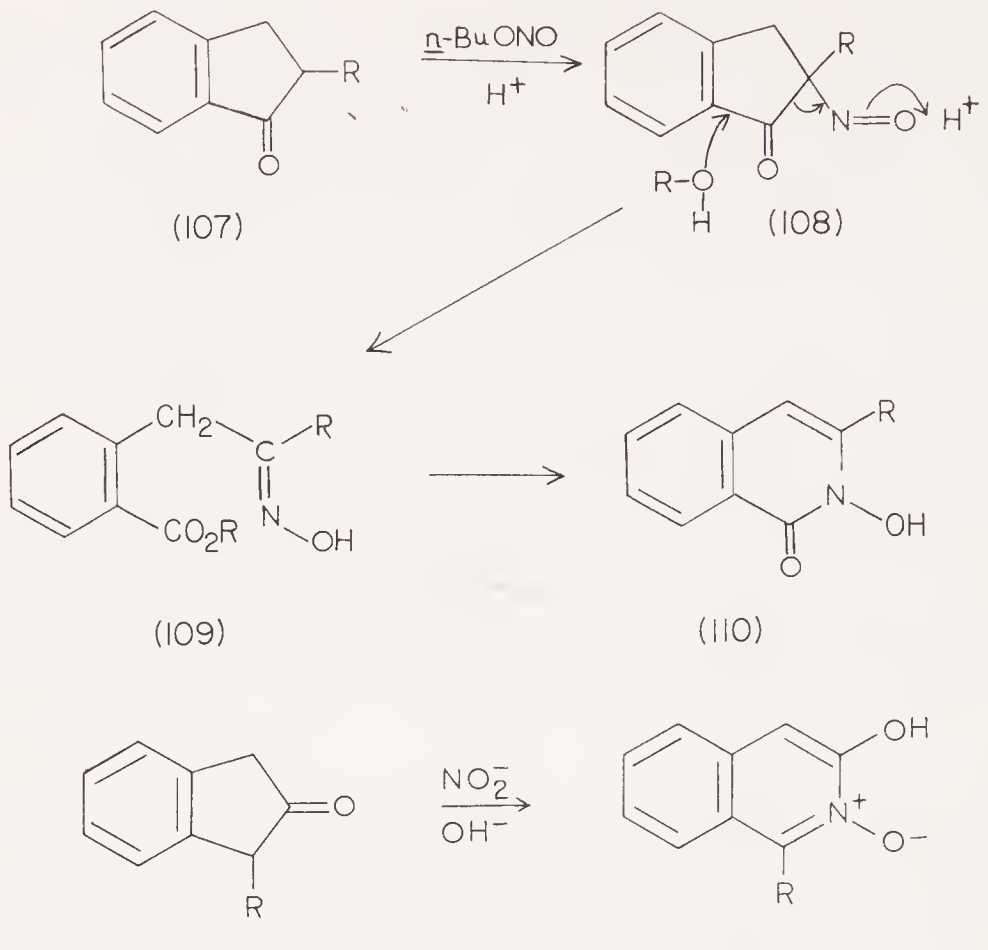
(102) (103)



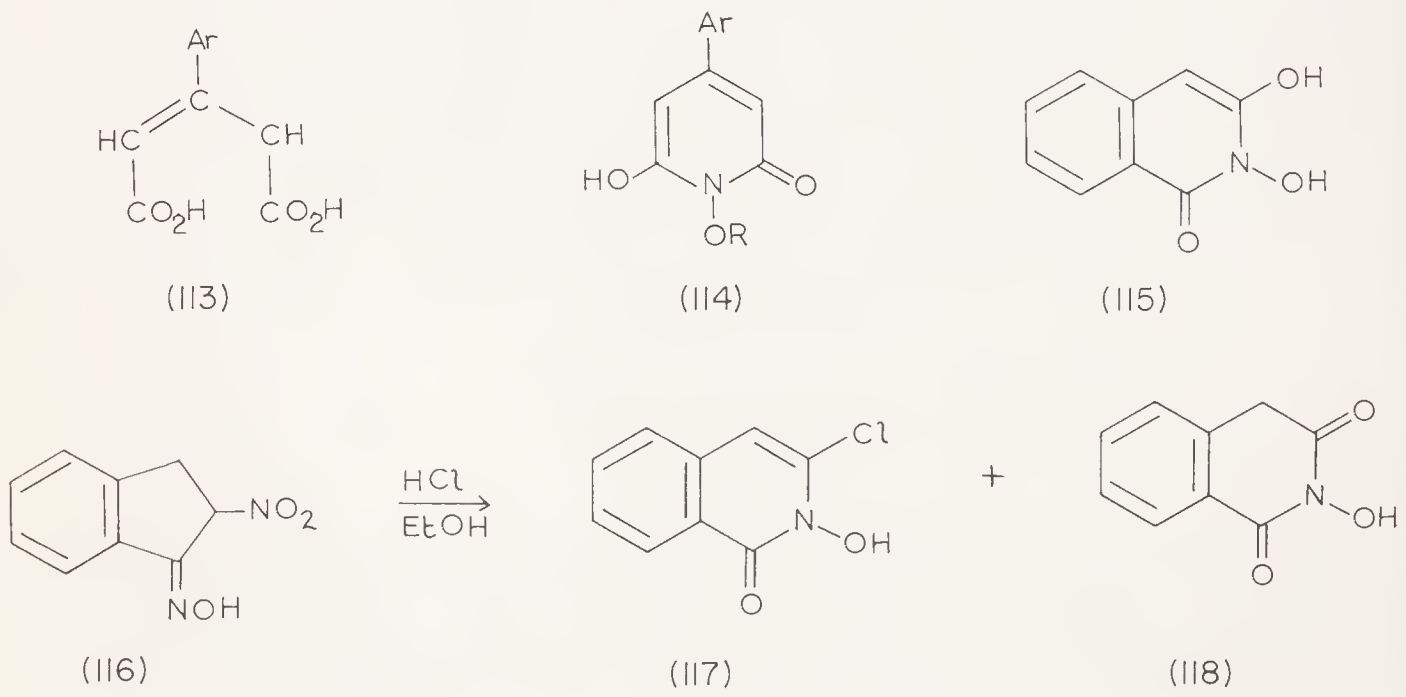
(104) (105) (106)

2-Substituted 1-indanones (*107*) on nitrosation under acid conditions are converted into 2-hydroxyisocarbostyrils (*110*) (63JO2215); probably, retro-Claisen ring opening of the nitroso derivative *108* gives the oxime *109* which

then undergoes acylative ring closure. 1-Substituted 2-indanones (*111*) are similarly transformed by nitrosation under alkaline conditions into 3-hydroxyisoquinoline 1-oxides (*112*) (61JO3761).



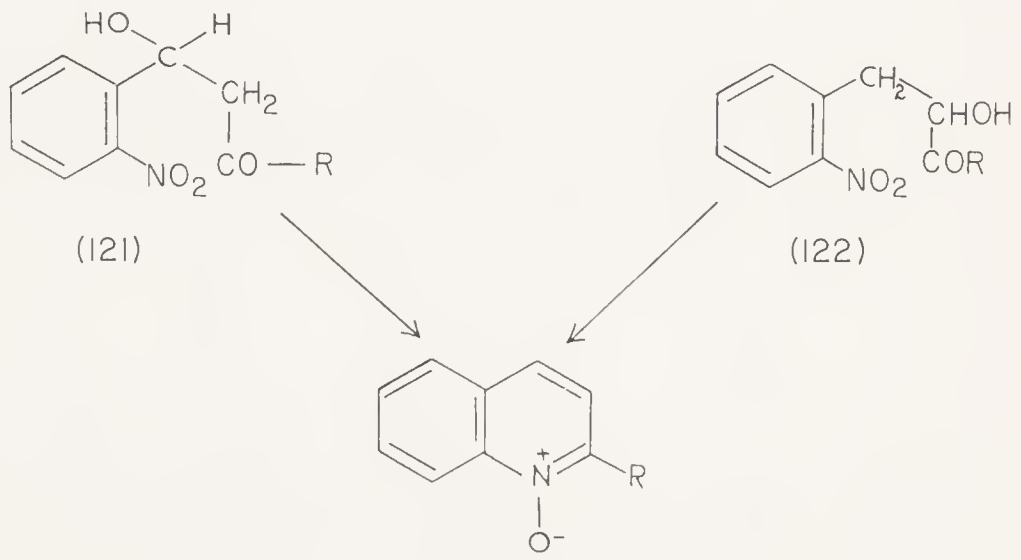
Glutaconic acids and their anhydrides (cf. *113*) are converted by hydroxylamine into 1,6-dihydroxy-2-pyridones (*114*, R = H) (59J2310), and homophthalic anhydrides yield the corresponding isoquinoline derivatives (*115*) (55J3518). The use of *O*-benzylhydroxylamine leads to compounds of type *114* (R = CH_2Ph) (55J631).



(119) (120)

2-Nitro-1-indanone oxime (*116*) on treatment with acid yields 3-chloro-2-hydroxyisocarbostyril (*117*) and *N*-hydroxyhomophthalimide (*118*) (64J3856; cf. 66CT1408). We suggest that ring opening of the reverse Dieckmann type yields the nitro-hydroxamic acid *119*, which is then transformed by a well-known acid-catalysed reaction into the bis-hydroxamic acid *120*.

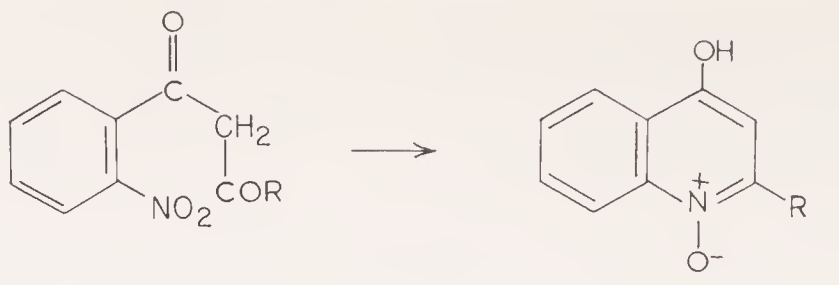
c. Quinoline 1-Oxides and Phenanthridine 5-Oxides. For the formation of quinoline 1-oxides, in contrast to the formation of pyridine and isoquinoline *N*-oxides, the hydroxyamino group usually has to be prepared *in situ* by the reduction of a suitably *ortho*-substituted nitrobenzene since phenolic hydroxyl groups generally do not react with hydroxylamine. The principal variations of the reaction lead to the following compounds by the schemes indicated: (*a*) simple quinoline 1-oxides: *121*, *122* → *123*, (*b*) 4-hydroxyquinoline 1-oxides: *124* → *125*, (*c*) 2-aminoquinoline 1-oxides: *126* → *127*, and (*d*) 1-hydroxy-2-quinolones: *128* → *129* (1-hydroxy-2-quinolones are tautomeric with 2-hydroxyquinoline 1-oxide; see Section IV-3Bia).* Examples of these reactions are given in Tables 2.11 and 2.12. An interesting extension of the reaction has been reported by Taylor and Bartulin (67TL2337), who found that active methylene compounds react with anthranil to give intermediates which ring-close to 1-hydroxy-2-quinolones or 2-aminoquinoline 1-oxides: cf. *130* → *131* (X = CO_2Et or CN, respectively). Rearrangement is also involved in the reduction of the indole derivative *132* to yield *133* (67CI1871).



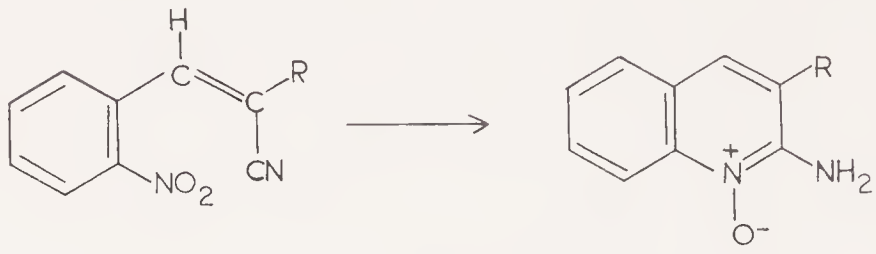
(121) (122)

(123)

* See addendum in the Appendix.



(124) (125)



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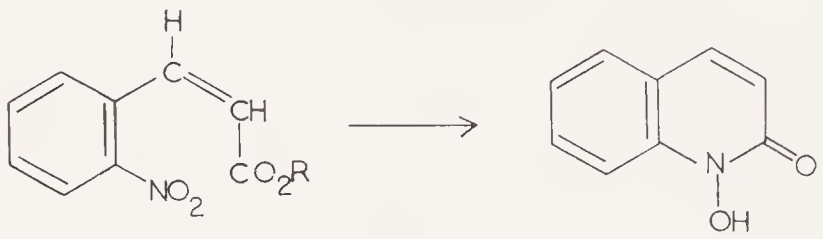

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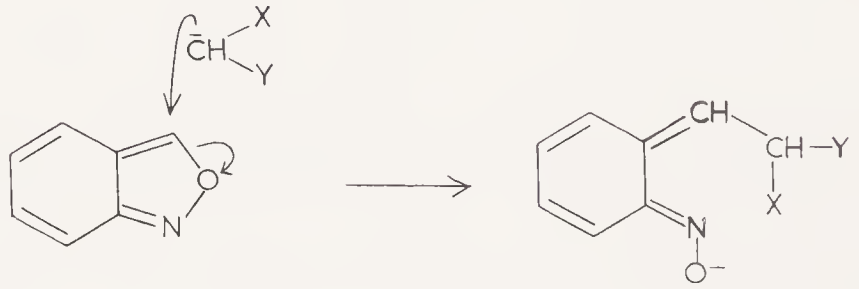
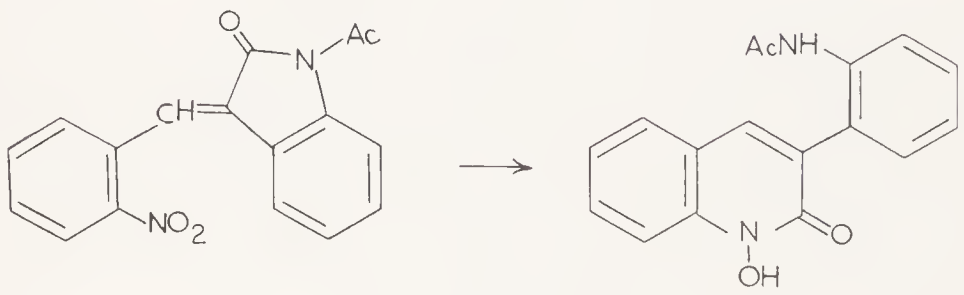


(130) (131)



(132) (133)

The early literature on these reactions contains errors. Quinaldine 1-oxide, prepared by reaction *121* or *122* → *123*, was first considered to be an "isomer" of 2-methyl-4-quinolone (08CB2692), but was later shown to be identical with the compound obtained by direct *N*-oxidation of quinaldine [25CB2334; 28PC(118)138]. 2-Aminoquinoline 1-oxides were originally formulated as

Table 2.11. Formation of Quinoline 1-Oxides by the Reduction of *o*-Nitrophenyl Compounds

R of *o*-NO_2-C_6H_4-R	Reaction sequence	Reducing agent	Quinoline 1-oxide formed	References
-COH=C(CO_2Et)CN	126 → 127	H_2/Pd–C	3-alkoxycarbonyl-2-amino-4-hydroxy	62J2518
-CO-CH(CO_2R)CO-CH_3	124 → 125	$NaBH_4$/Pd–C; $SnCl_2$–HCl–AcOH	3-alkoxycarbonyl-4-hydroxy-2-methyl	22JA1573, 63J4610
-CH=C($CONH_2$)CN	126 → 127	Zn–AcOH	2-amino-3-carboxamido	14CB1617,[a] 53JO1755, 55J203
-CH=C(CO_2R)CN	126 → 127	Zn–AcOH	2-amino-3-carboxy (or carboxylate)	55J203
-C(OH)=CH-CN	126 → 127	Zn–NH_3	2-amino-4-hydroxy	53CB957
-CH=C(4′-isoquinolyl)CN	126 → 127	H_2/Pd–C	2-amino-3-(4′-isoquinolyl)	63CC2265
-CH=C(C_6H_5)CN	126 → 127	H_2/Pt	2-amino-3-phenyl	38CB2226
-CO-CH_2-CO-alkyl	124 → 125	$SnCl_2$	4-hydroxy-2-*n*-heptyl, -*n*-nonyl-, and -*n*-undecyl	56BC(63)124
-CO-CH_2-CO-CH_3 (or -Ph)	124 → 125	$SnCl_2$	4-hydroxy-2-methyl (or phenyl)	21CB1067, 21CB1613
-CH(OH)CH_2CO-CH_3	121 → 123	Zn–AcOH	2-methyl	08CB2692, 25CB2334
-CH_2CH(OH)CO-CH_3	122 → 123	Zn–AcOH	2-methyl	08CB2692, 25CB2334

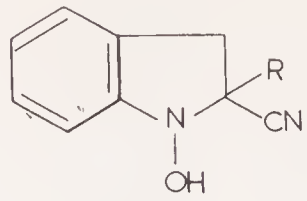
[a] Incorrectly formulated as an indole derivative.

Table 2.12. Formation of 1-Hydroxy-2-quinolones by the Reduction of *o*-Nitrophenyl Compounds (128 → 129)

R of *o*-NO_2-C_6H_4-R	Reducing agent	1-Hydroxy-2-quinolone formed	References
-CH=CH-CO_2H	NH_3–H_2S	—	81CB1916, 14CB3369
-CH=C(CO_2Et)$_2$	$NaBH_4$/Pd–C	3-alkoxycarbonyl	63J4610
-CH(CN)CH(CO_2Et)$_2$	(unknown)	3-alkoxycarbonyl-4-cyano	60J3462
-CH_2CR(CO_2Et)$_2$	$NaBH_4$/Pd–C	3-alkyl-2-hydroxy	66MC974
-CH_2C(CO_2Et)=NOH	H_2/Pt	3-amino-2-hydroxy	67J(C)2446, 69J(C)2207
*-CH=C(CO_2H)$_2$	Zn–AcOH	3-carboxy	14CB2889
-CH=C(H or CN)-CO_2CH_3	$NaBH_4$/Pd–C	3-cyano	63J4610, 69J(C)713
-CH=C(Me)-CO_2Et	$(NH_4)_2S$–EtOH	3-methyl	49J2091

* -CH_2C(CO_2Me)=NOH; see addendum in the Appendix.

indole derivatives (*134*) (14CB1617); the formulation was corrected by Taylor and Kalenda (53JO1755) and also by Tyler (55J203).



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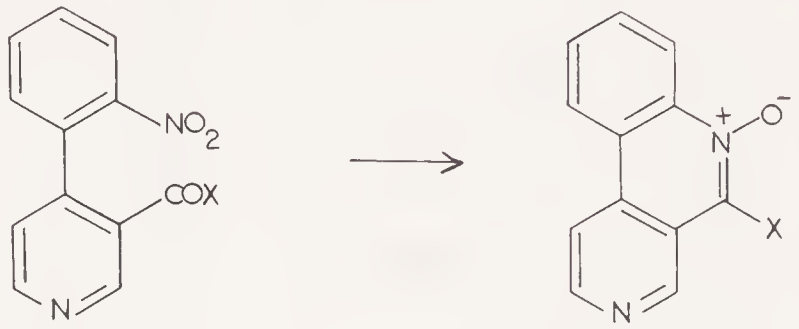

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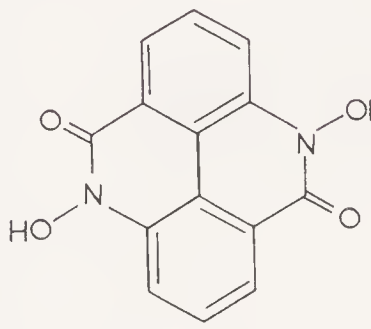
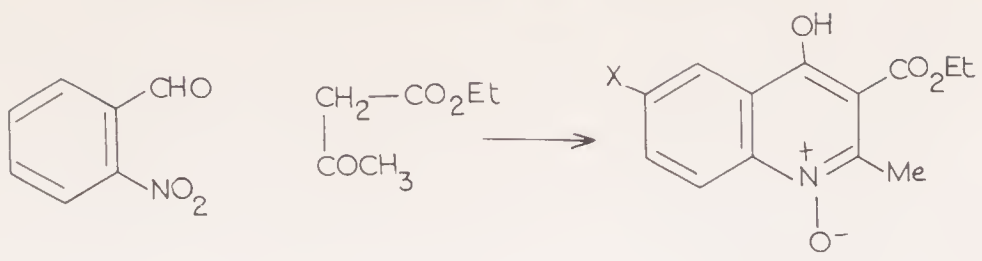


(137)

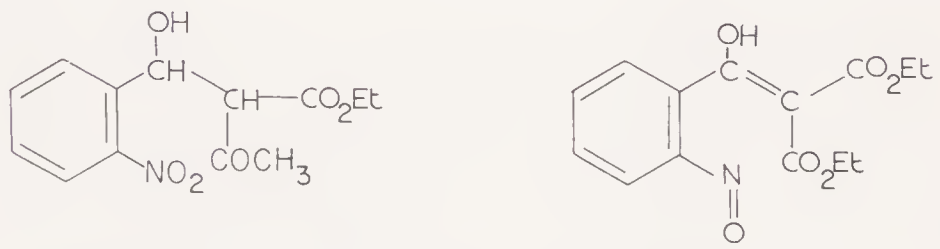
9-Hydroxyphenanthridones (67JO1106) and 2,9-diazaphenanthrene 9-oxides (*135* → *136*) (53J350) have been prepared by analogous reduction reactions. Hydrogenation of 2,2′-dinitro-6,6′-dimethoxycarbonylbiphenyl under acidic conditions gives the bis-hydroxamic acid *137*, and the 6,6′-dicyano analogue yields the corresponding diamino di-*N*-oxide (67JO1106).

4-Hydroxyquinoline 1-oxides are also produced by the acid-catalysed condensation of *o*-nitrobenzaldehyde with β-keto esters (*138* → *139*); β-diketones react similarly. If the acid catalyst is hydrogen chloride, a chlorine atom is introduced into the product (*139*, X = Cl) (60J3470), but no uptake of bromine occurs with hydrogen bromide (62J3092). The transformation of *140* into *141* is related (60J3466). The mechanisms of these reactions are unknown, but they may involve internal oxidation–reduction of intermediates of type *142* to yield nitroso compounds (*143*), which are either reduced by hydrogen bromide to hydroxylamines, or converted by hydrogen chloride into *p*-chlorophenylhydroxylamines. A final cyclization would then give the observed products (*139*).



(138) (139)

(140) (141)



(142) (143)

ii. Diazine Derivatives

a. Benzo[c]cinnoline 5-Oxides. Reduction of 2,2′-dinitrobiphenyl (*144*) can give benzo[c]cinnoline, together with the 5-oxide *145*, the 5,6-dioxide *146*, and 2,2′-diaminobiphenyl. The 5-oxide probably arises by ring closure of the nitrosohydroxylamine *147*, and the 5,6-dioxide is presumably formed via either the nitro-hydroxylamine or the dinitroso derivative (cf. also Section II-2Ciia). The mechanistic routes and the influence of the type of Raney-nickel catalyst on the yields of the various products have been discussed by Moore and Furst (58JO1504) and Kempter and Castle (68JH583). Holt and his co-workers studied the reaction using various reducing agents and found that sodium sulphide gives good yields of the 5-oxide (58J4073). Examples of the reaction are given in Table 2.13. Reduction of the tetranitro compound *148* in the presence of Raney nickel gives the di-*N*-oxide *149* (64J6090S2).

(144) (145)

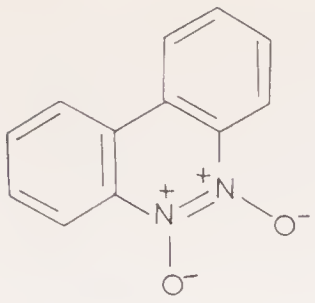
Table 2.13. Preparation of Benzo[*c*]cinnoline *N*-Oxides by Reduction of 2,2′-Dinitrobiphenyls (144 → 145, 146)

Cinnoline derivative	Position of *N*-oxide group	Reducing agent	References
Benzo[*c*]cinnoline	5 and 5,6-di	NaHS–MeOH, Na_2S–NaOH, Zn–KOH, H_2/Ni(R)	91CB3081, 04CB23, 52JA4122, 57J4,[a] 58JO1504
(various)*	5,6-di	H_2/Ni(R)	68JH583
8-amino	5	Na_2S_x	56JO651
3,8-dihalogeno-2,9-dimethyl	5	Na_2S	58J4073
1,10-dimethyl	5	Na_2S	34BJ393
3,8-bis(trifluoromethyl)	5	Na_2S	52JA1297
Naphtho[1,2-*c*]cinnoline	6	Na_2S–NaOH	60J3646
Naphtho[2,1-*c*]cinnoline	5 and 6	Na_2S–NaOH	60J3646
Benzo[*f*]naphtho[1,2-*c*]cinnoline	6	Na_2S–NaOH	60J3646
Benzo[*f*]naphtho[2,1-*c*]cinnoline	(mono-*N*-oxide)	Na_2S–NaOH	59J3025
Benzo[*g*]naphtho[2,3-*c*]cinnoline	6	Zn–NaOH	03CB4153
Benzo[*h*]naphtho[1,2-*c*]cinnoline	(mono-*N*-oxide)	Na_2S–NaOH, Zn–KOH	59J3025
4,5,9,10-Tetraazapyrene[b]	(di-*N*-oxide)	H_2/Ni(R)	64J6090

[a] Obtained as a by-product in the reduction of 2-amino-2′-nitrodiphenyl to 5-bromophenanthridine.

[b] Starting material was 2,2′,6 6′-tetranitropbiphenyl.

* See addendum in the Appendix.



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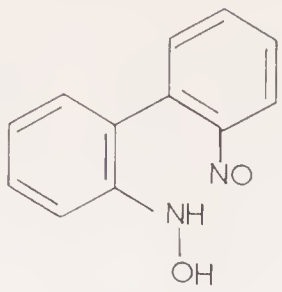

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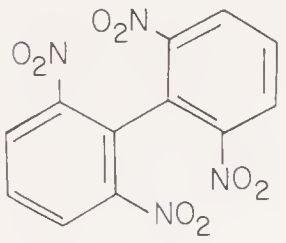
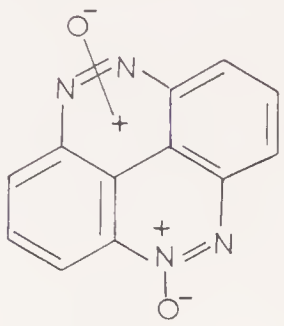


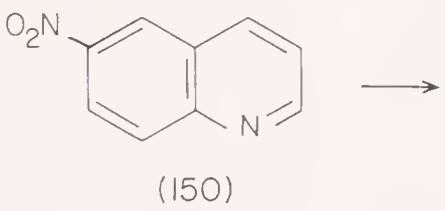
(148)



(149)

The compound obtained from the reaction of 6-nitroquinoline (*150*) with sodium methoxide, which was originally formulated [48LA(559)101; cf. 64R718] as a fused benzocinnoline oxide (*151*, Z = N), is actually a phenazine derivative (65J799) (see Table 2.21). However, the conversion of *150* into *151* (Z = N) can be effected with glucose and alkali (65J799), and further, 2-nitronaphthalene is reduced by phosphine to benzo[*f*]naphtho-[2,1-*c*]cinnoline *N*-oxide (*151*, Z = CH) (65T3285); the mechanism of these reactions may involve the dimerization of nitroso intermediates (cf. Section II-2Cii).

The oxidation of 2,2′-diaminobiphenyls with boric acid and hydrogen peroxide also gives benzocinnoline *N*-oxides (61J3695), but the sequence of the mechanistic steps in this reaction is not known.



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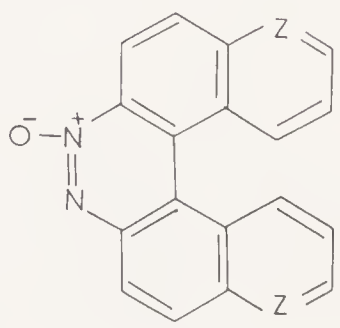
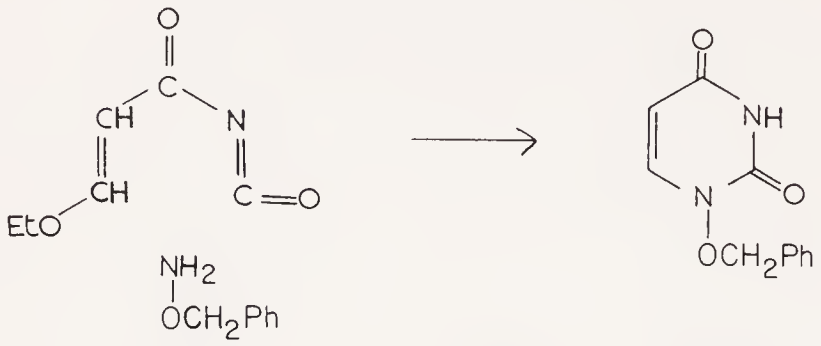


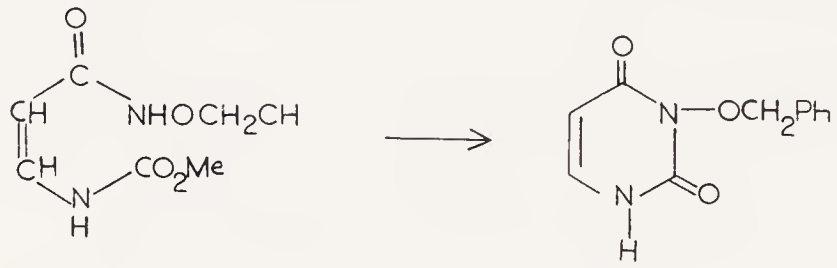
(151)

b. Pyrimidine N-*Oxides.* Klötzer has obtained 1-benzyloxy- (*153*) and 3-benzyloxy-uracil (*155*), both of which are derivatives of pyrimidine 1-oxide, by the routes indicated (*152* → *153*, *154* → *155*) (64M1729). For further work on analogues of *153*, see references 64M265, 65M1721, and 68IS123. The dihydro derivative *156* has been prepared by a similar method (54JO1140) and by a Lossen rearrangement (54JA2791; 55JO33). Cytosine 1-oxide has been synthesized from benzyloxyurea and β,β-diethoxypropionitrile (cf. *157*)

by catalytic hydrogenation of the 1-benzyloxy derivative *158* (65M169; see also 68M847). The isomeric cytosine 3-oxide (*161*) can be prepared from the benzyloxyurea derivative *159* via 3-benzyloxy-6-hydroxycytosine (*160*) (64M265; 65M169). 6-Aminouracil 1-oxide can be prepared similarly. The thiouracil derivative *163* has been made by the interesting route shown: *162* → *163* [66AG(E)511]. Steroidal pyrimidine *N*-oxides have been prepared by the reaction of suitable precursors with hydroxylamine (68CC2807).*



(152) (153)



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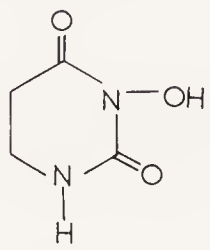
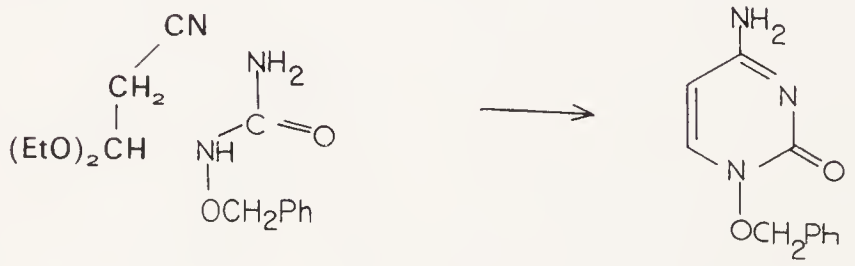


(156)



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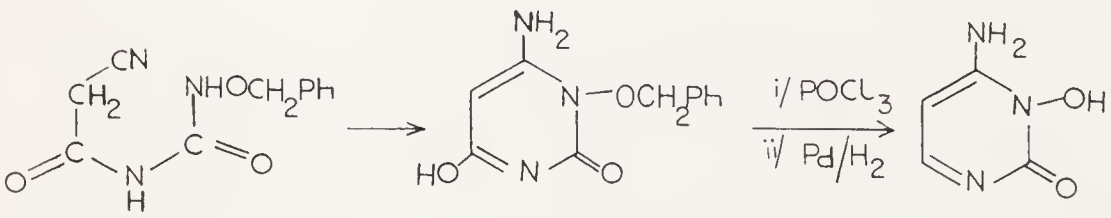
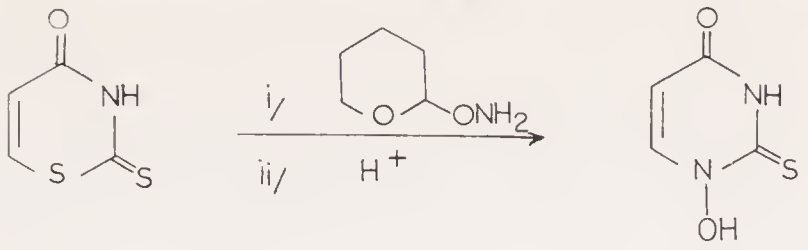


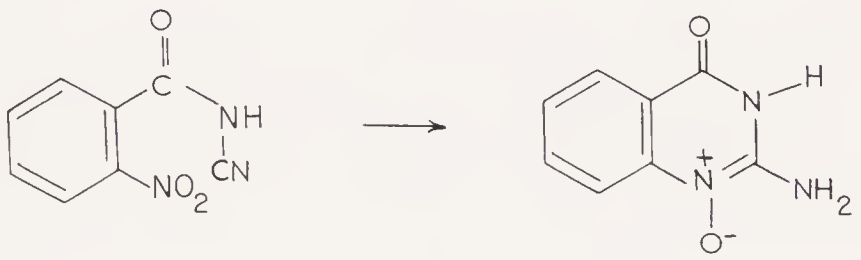
(159) (160) (161)

* See addendum in the Appendix.

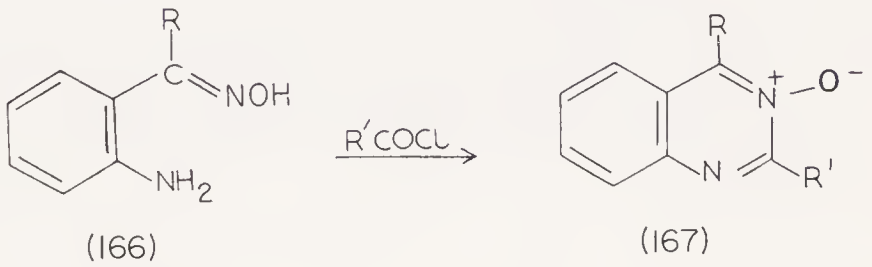


(162) (163)

c. Quinazoline 1-Oxides. 2-Amino-4-quinazolinone 1-oxide (*165*) can be prepared by reduction of the nitro compound *164*; the reaction probably involves cyclization of an intermediate hydroxylamine (63CI1559). Derivatives of 1-hydroxy-2,4-quinazolinedione have been prepared from ethyl *o*-hydroxyaminobenzoate (69CB1480).*



(164) (165)



(166) (167)

(168) (169)

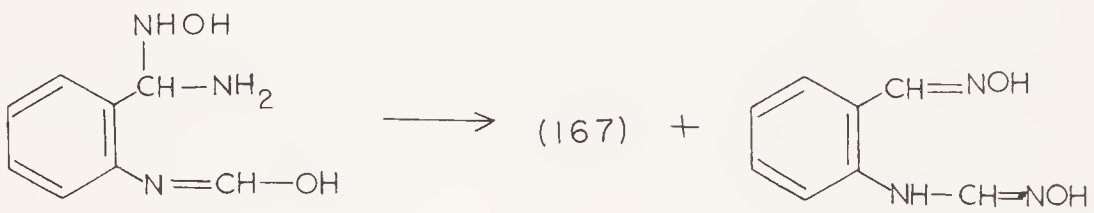
d. Quinazoline 3-Oxides. The reaction between *o*-aminobenzaldoximes (*166*) and acid anhydrides (or chlorides) has had a chequered history. The cyclization products were initially formulated by von Auwers (91CB2370; 24CB1723; cf. 54CB1814) as acylindazoles (*168*). Bischler (93CB1891) and Meisenheimer (24CB1715) pointed out the disadvantages in the indazole formulation and proposed the benzoxadiazepine structure *169*. Although von Auwers, after considerable experimental work, finally accepted the benzoxadiazepine structure [24LA(438)1; 25CB2081; 26LA(450)273], the acylindazole formulation was not finally disproved until 1954 (54CB1814). The position was finally clarified by Sternbach, Kaiser, and Reeder

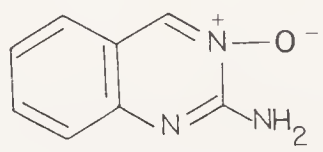
* See addendum in the Appendix.

(60JA475), and by Kövendi and Kircz (65CB1049), who demonstrated that both the preceding formulations were incorrect and proved the quinazoline 3-oxide structure (*167*). Confusion has undoubtedly arisen because the *syn* aldoximes form benzoxadiazepines, whereas the *anti* derivatives give the isomeric quinazoline 3-oxides (68IS569). The earlier investigators prepared a variety of quinazoline 3-oxides and studied many of their properties, although the products are wrongly formulated in the references quoted.

The formation of 4-arylquinazoline 3-oxides (*167*) from *o*-aminobenzophenone oximes (*166*, R = aryl) has been extensively investigated by Sternbach and others because compounds of type *167* (R = CH_2Cl) can be converted into analogues of the sedative Librium (cf. Section IV-2Ciiib). 4-Arylquinazoline 3-oxides which have been prepared in this way are listed in Table 2.14.

Another general route to quinazoline 3-oxides was reported by Adachi (57JJ507) and involves treatment of the corresponding quinazolines with hydroxylamine. The reaction probably involves an intermediate of type *170*, which undergoes both ring closure to give *167* (R = H) and further reaction with hydroxylamine to yield *171* (63MI31; cf. 59CT479). At a somewhat higher temperature 2-aminoquinazoline 3-oxide (*172*) is formed (57JJ510), presumably by subsequent amination of *167* (R = H) with excess hydroxylamine. The preparation of 4-methylquinazoline 3-oxide (57JJ514) and the conversion of 4-phenoxyquinazoline into 4-aminoquinazoline 3-oxide (67JJ578) are analogous.





(172)

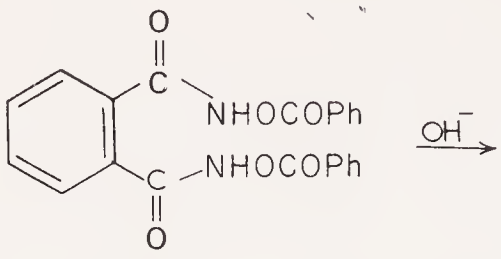
Quinazoline 3-oxides have also been obtained by the cyclization of hydroxylamine derivatives derived from a variety of other starting materials. The bis-hydroxamic acid derivative *173* undergoes a single Lossen-type rearrangement on treatment with alkali, and the product spontaneously cyclizes to the 3-oxide derivative *174* (R = COPh) (54JO1140; cf. 55JO33). 3-Hydroxy-4-quinazolinones (*176*), which are tautomeric with quinazoline 3-oxides, have been prepared from benzo-1,3-oxazin-4-ones (*175*) (02CB3480; 61JJ431; 65J6278), or benzo-1,3-thiazin-4-ones (61BF618) by reaction with

Table 2.14. Preparation of Quinazoline 3-Oxides from Aminobenzophenone Oximes (166 → 167)

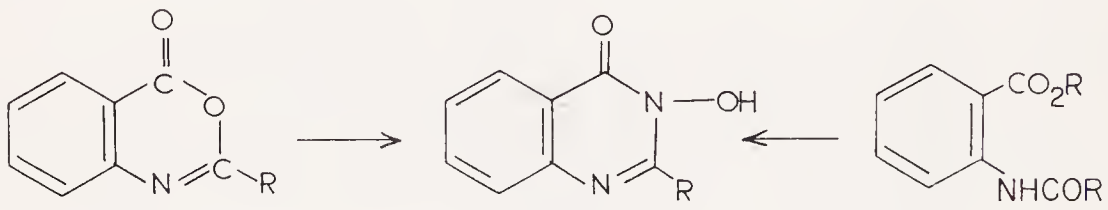
2-Aminobenzophenone oxime	Reagent	Quinazoline 3-oxide	References
5-Chloro	HCO_2H	6-chloro-4-phenyl	61JO4936
	$COCl_2$	6-chloro-2-hydroxy-4-phenyl[a]	62JO4424
	$ClCH_2COCl$–AcOH	2,6-dichloro-4-phenyl	59USP2893992
	RCHBrCOCl	2-(1-bromoalkyl)-6-chloro-4-phenyl	61JO1111
	MeNCS–EtOH	6-chloro-2-methylamino-4-phenyl	67M633
5-Chloro[b]	BF_3	6-chloro-2-dichloromethyl-4-phenyl	65JO4267
5-Methoxycarbonyl	$ClCH_2COCl$	2-chloromethyl-6-methoxycarbonyl-4-phenyl	63H1720
5-Nitro	$ClCH_2COCl$	2-chloromethyl-6-nitro-4-phenyl	63MC261
5-Nitro[b]	BF_3	2-dichloromethyl-6-nitro-4-phenyl	65JO4267
5-Trifluoromethyl	$ClCH_2COCl$	2-chloromethyl-4-phenyl-6-trifluoromethyl	62H2226
5-Substituted (various)	$ClCH_2COCl$	2-chloromethyl-4-phenyl-5-substituted	61JO4488

[a] Exists as a 2-quinazolinone derivative.
[b] Dichloroacetamido derivative, i.e. 2-dichloroacetamido-5-chloro(or nitro)benzophenone oxime.

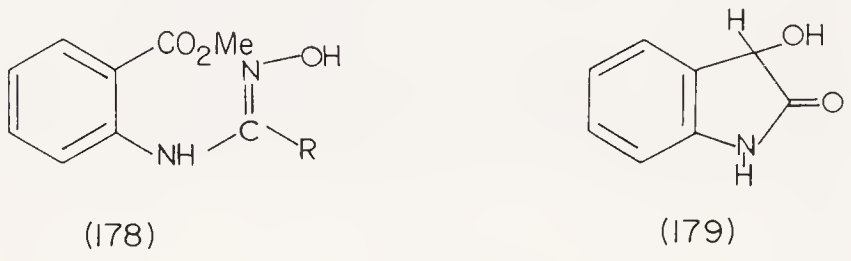
hydroxylamine, and from *o*-aminobenzoic acid derivatives of types *177* (60J2157) or *178* (66CB72). 3-Hydroxy-2,4-quinazolinedione (*174*, R = H) is formed by the condensation of dioxindole (*179*) with amyl nitrite (44G3): the mechanism involves a Claisen-type reaction followed by ring opening and reclosure.



(173) (174)



(175) (176) (177)



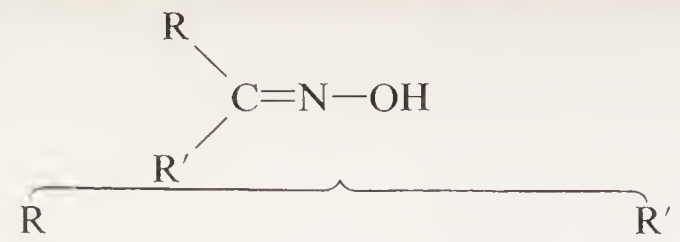
(178) (179)

1,2-Dihydroquinazoline 3-oxides have been prepared by the reaction of *o*-aminobenzoyl oximes with aldehydes or ketones (*180* → *181*); examples are given in Table 2.15.

e. Other Condensed Pyrimidine N-*Oxides*. The *N*-oxides of many other condensed pyrimidine ring systems have been obtained using analogous reactions on suitable precursors. Various purine 1- and 3-oxides have been prepared by the ring closure of imidazole derivatives (Table 2.16). This type of reaction has also been successfully applied in the pteridine series: *182* → *183* (55JA3927). Several other hydroxamic acids have been made by Lossen rearrangements: pyrazolo-pyrimidine *N*-oxide derivatives (*184* → *185*) (66JO2491; cf. 67JH325), imidazolo-pyrimidine hydroxamic acids (67JH216), and thiazolo-pyridine hydroxamic acids (68JH331). Pteridine hydroxamic acids of type *183* have also been made by the Lossen rearrangement of a bis-hydroxamic acid (66JH224). 4-Pteridinones are converted by hydroxylamine into 3-hydroxy-4-pteridinones (*186*) by a reaction which is similar to the opening and closing of the quinazoline ring mentioned earlier in this section [68J(C)919].*

* See addendum in the Appendix.

Table 2.15. Formation of 1,2-Dihydroquinazoline 3-Oxides from 2-Amino-aceto- or -benzo-phenone Oximes (180 → 181)



		Reagent	1,2-Dihydroquinazoline 3-oxide formed	Yield, %	References
2-Aminophenyl	methyl	PhCHO or *m*-NO_2-C_6H_4-CHO	4-methyl-2-phenyl or -*m*-nitrophenyl	—	37PC(150)1
See note [a]	*See* note [a]	50% aq. Me_2CO	4-methyl-2-nitromethyl	75	66J(C)1433
2-Alkyl- (or -aryl)-amino-3- or 5-bromophenyl	methyl	85% H_2SO_4	2-alkyl- (or -aryl)-6- or -8-bromo-4-methyl	76–95	65CB1049
2-Amino-5-chlorophenyl	phenyl	CH_3CHO	6-chloro-2-methyl-4-phenyl	30	65JO3957
		$ClCH_2CH(OEt)_2$–HCl	6-chloro-2-chloromethyl-4-phenyl	56	67JA332
	phenyl	Me_2CO–$CuSO_4$	6-chloro-2,2-dimethyl-4-phenyl	70	65JO3957
	phenyl	$(ClCH_2)_2CO$–MeOH–HCl	6-chloro-2,2-dichloromethyl-4-phenyl	45	67JA332
5-Chloro-2-methylamino	phenyl	Me_2CO–$CuSO_4$	6-chloro-1,2,2-trimethyl-4-phenyl	—	65JO3957

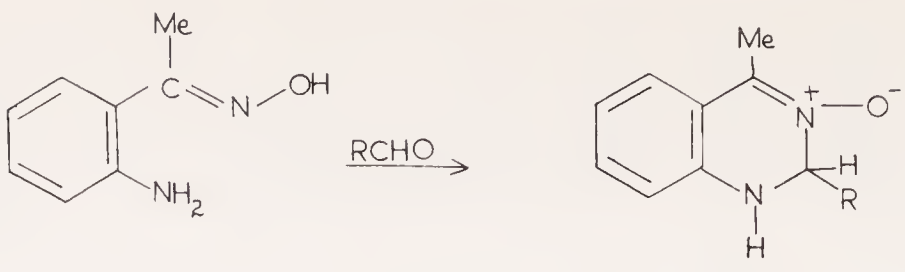
[a] The oxime formed by *o*-aminoacetophenone and methazonic acid was not isolated.

Table 2.16. Purine *N*-oxides Prepared by Ring Closure of Imidazole Derivatives

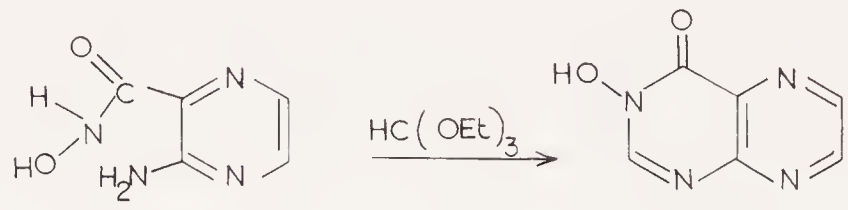
Imidazole substituents	Reagent	Purine formed	Yield, %	References
5-CN-4-NHOH-1-Me	$HC(=NH)NH_2 \cdot AcOH$[a]	6-amino-7-methyl 3-oxide	92	59JO2035
4-NH_2-5-CONHOH	$HC(OEt)_3$	1-hydroxy-6-oxo	(data)	57MI22, 59JO2019
*1-alkyl-4,5-diCONHO$^-$ Na^+	$PhSO_2Cl$	7-alkyl-1-hydroxy-2,4-dioxo	17–49	64JH275
4-NH_2-5-C(NH_2)=NOH	CS_2	6-amino-1-hydroxy 2-thione	69	63JO2560

[a] Formamidine acetate.

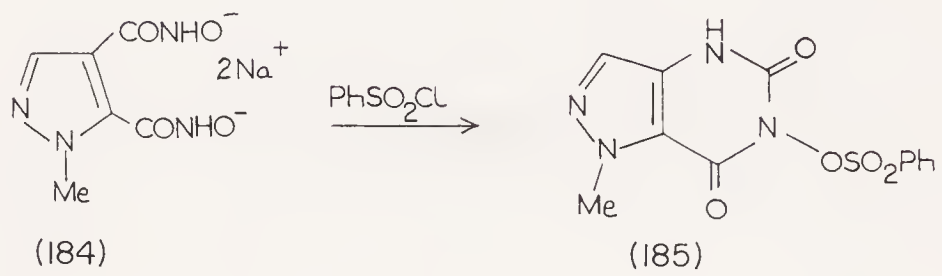
* Adenosine 1-oxide; see addendum in the Appendix.



(180) (181)



(182) (183)



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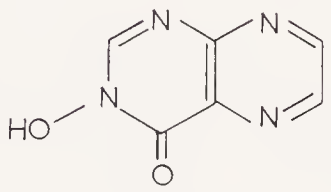
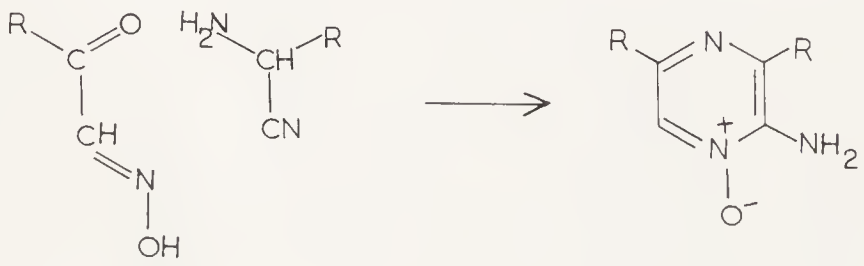


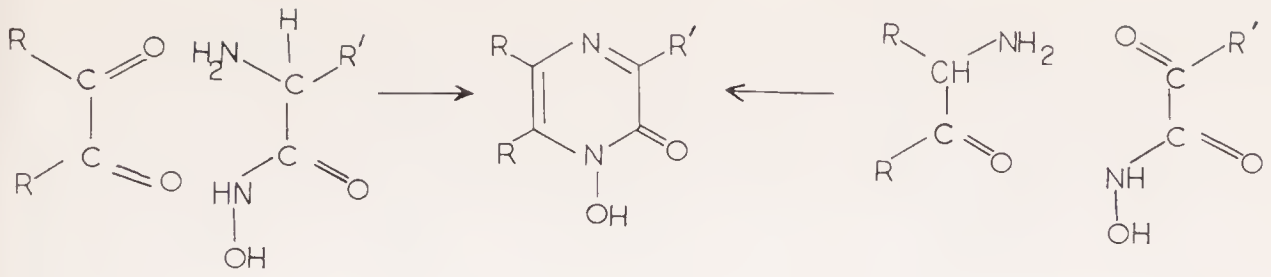
(186)

f. Pyrazine N-*Oxides.* Pyrazine *N*-oxides are formed from hydroxylamine derivatives by a variety of ring closures. 2-Aminopyrazine 1-oxides (*188*) are available from the reaction of α-aminonitriles with α-keto oximes (cf. *187*) (51J932; 51J2679; 68JA2424). 1-Hydroxy-2-pyrazinones (*190*), which are tautomeric with 2-hydroxypyrazine 1-oxides (see Section IV-3Bia), can be made by the condensation of either α-diketones with α-amino hydroxamic acids (*189*) (52JO1298; 63G339), or α-amino ketones with α-keto hydroxamic acids (*191*) (64JO3165). The naturally occurring neoaspergillic acid has been synthesized as shown: *192* → *193* (65TL4837; cf. reference 66JO4143 which also gives a synthesis of aspergillic acid). Muta-aspergillic acid (*194*) was later made by an analogous method (67TL845).*

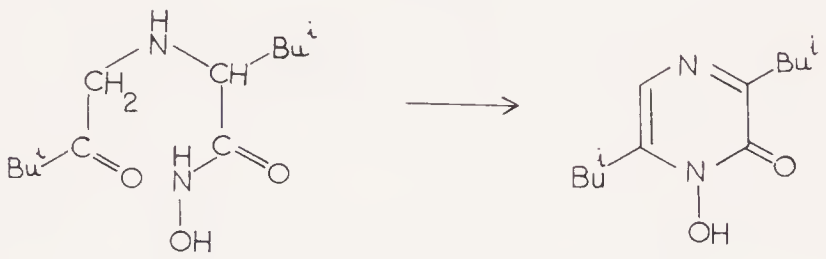


(187) (188)

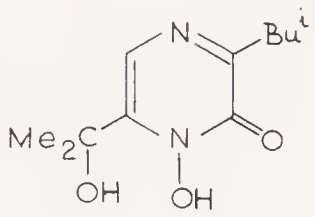
* See addendum in the Appendix.



(189) (190) (191)

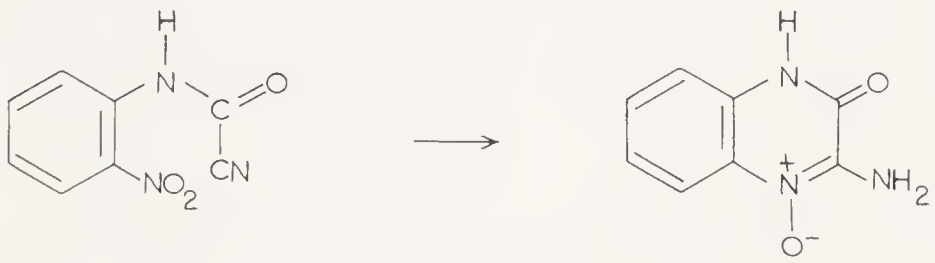


(192) (193)



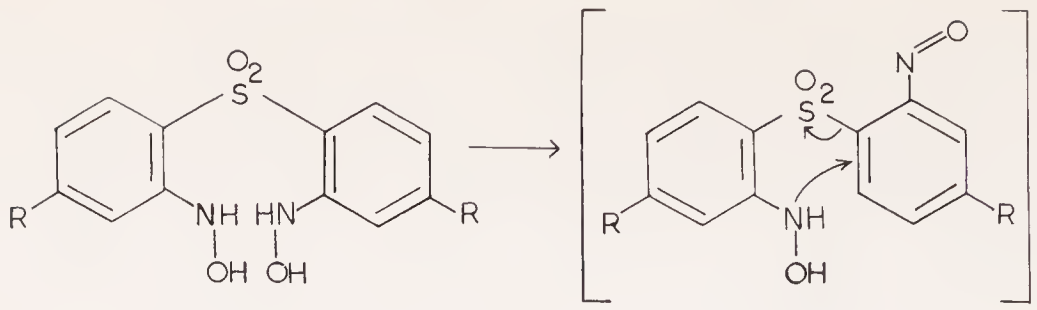
(194)

g. Quinoxaline 1-Oxides. The quinoxaline 1-oxide *196* has been obtained by reduction of the nitrobenzene *195* (63CI1559); evidently the reaction proceeds via the corresponding phenylhydroxylamine. Bis-2-hydroxyaminophenyl sulphones (*197*) yield phenazine *N*-oxides (*199*) on treatment with sodium hydroxide, possibly via a Smiles-type rearrangement of intermediate *198* [65CH67; 66J(B)260]. Pyridine-2-aldoxime reacts with α-bromo ketones to yield the 2-oxides of 2-azaquinolizinium salts: *200* → *201* [66JO941; 67J(C)2391].*



(195) (196)

* See addendum in the Appendix.



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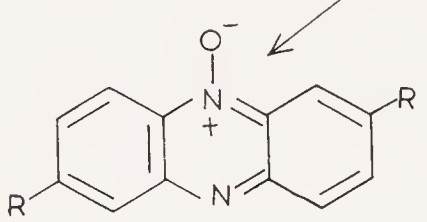

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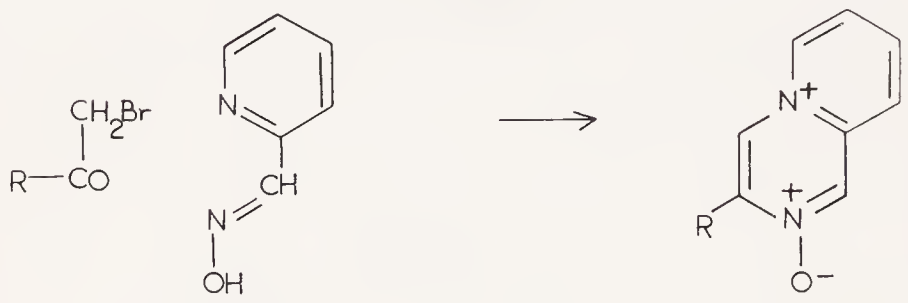
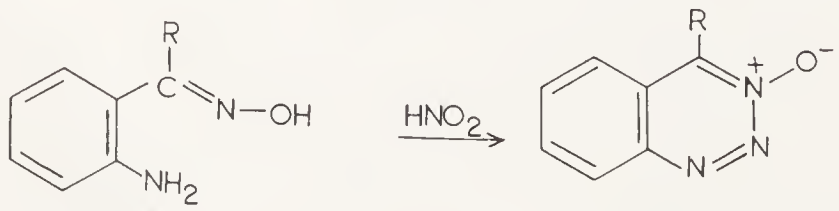


(200) (201)

iii. Derivatives of Triazine, Oxazine, and Thiazine

a. 1,2,3-Triazine N-*Oxides*. Benzo-1,2,3-triazine 3-oxides (*203*, R = Me) result from diazotization of *o*-aminoacetophenone oximes (*202*, R = Me) (27CB1736). The analogous amidoxime (*202*, R = NH_2) yields the amino 3-oxide (*203*, R = NH_2) (61J4930), although this product was originally assigned an alternative structure [96CB623; cf. 98PC(58)333; 03UJ131]. 3-Hydroxybenzo-1,2,3-triazin-4-one (*204*) is similarly prepared from *o*-aminobenzhydroxamic acid and nitrous acid (60J2157). Reactions of this type have been extended to other condensed 1,2,3-triazine 3-oxides. The 2-azapurine 1-oxide *205* results from the corresponding imidazole-amidoxime (63JO2560), and examples are known in the 2,8-diazapurine series (60JA3189). Ockenden and Schofield found that nitrous acid treatment of 3-amino-4-methylquinoline (*206*) gives the condensed triazine *N*-oxide *207* and proposed the intermediate formation of oxime *208* (53J1915).



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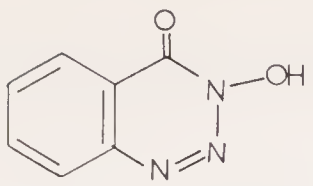

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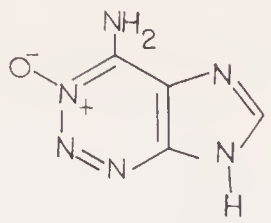

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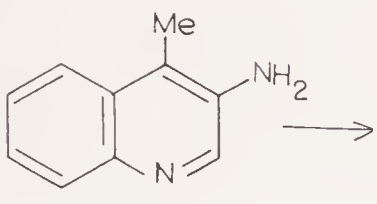

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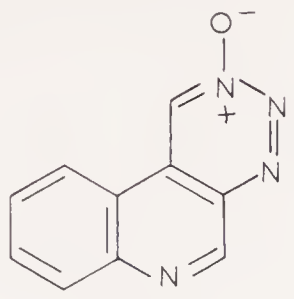

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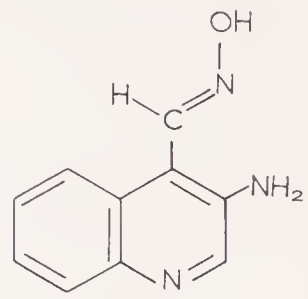
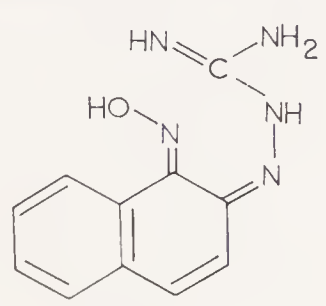


(208)

b. 1,2,4-Triazine N-Oxides. Certain naphtho-1,2,4-triazine 4-oxides have been prepared by the cyclization of oximes, as illustrated by the reaction sequence *209* → *210* (52AN584; 57G446); the isomeric amino *N*-oxide *211* and the oxo analogue *212* were similarly prepared (64TL641). However, attempts to apply similar methods in the monocyclic series gave triazinones, probably by further transformations of intermediate *N*-oxides (68JO4281). Later it was shown that the reaction course is highly dependent on the molecular geometry and that some products undergo ready deoxygenation [69J(C)1034]; ^{18}O-labelling indicates that *N*-oxide intermediates are *not* involved (69TL3059).



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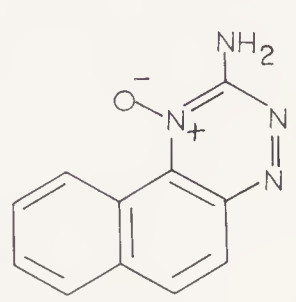

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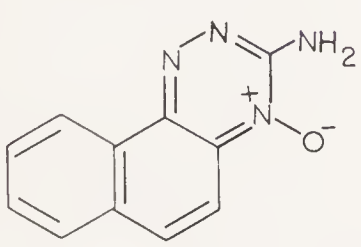

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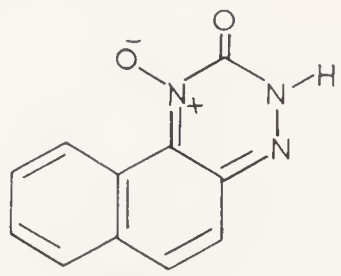

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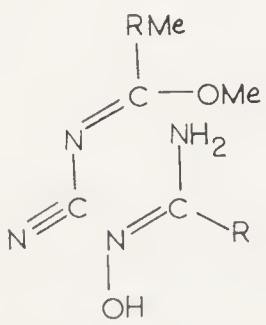

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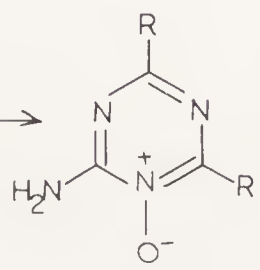

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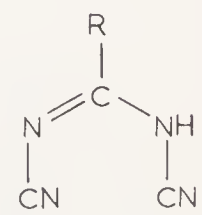
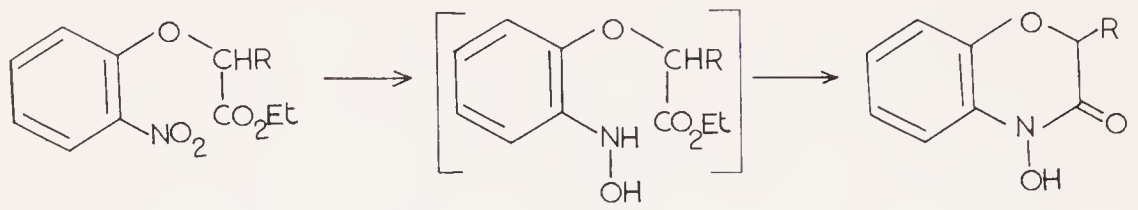


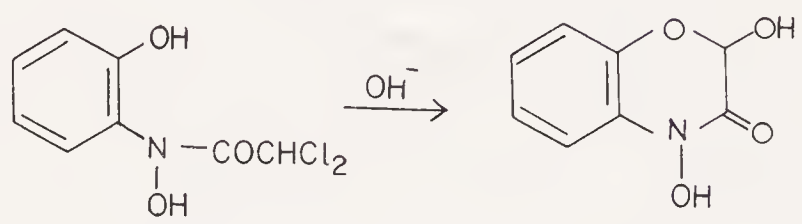
(215)

c. 1,3,5-Triazine N-*Oxides.* 1,3,5-Triazine 1-oxides (*214*) have been made from hydroxamic acids (*213*) (63JO1816) and from dicyanoamidines (*215*) (62JO3890).

d. 4-Hydroxy-1,4-benzoxazines and 1,4-Benzothiazine 4-Oxides. 4-Hydroxy-1,4-benzoxazines have been prepared by the reaction sequences *216* → *218* (60AS1214) and *219* → *220* (60AS504).



(216) (217) (218)



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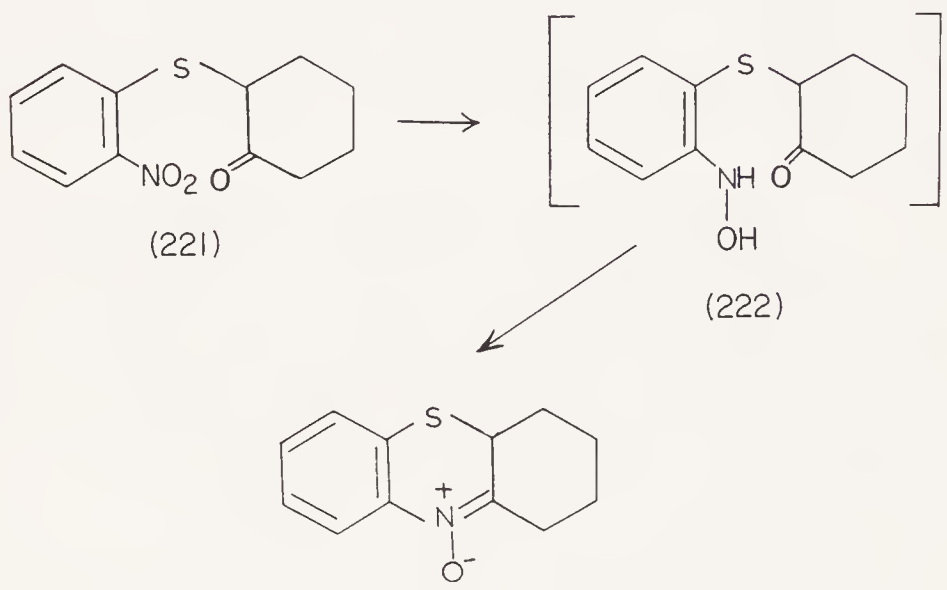
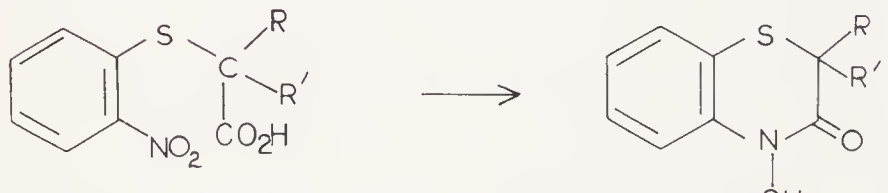


(221) (222) (223)



(224) (225)

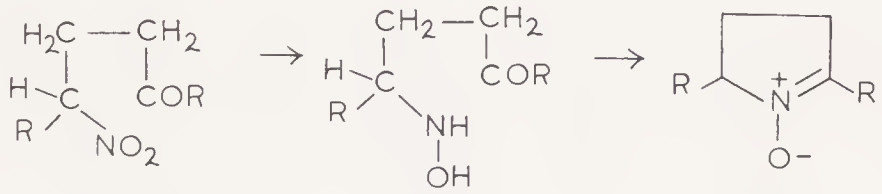
The 1,4-benzothiazine 4-oxide (*223*) can be prepared from the nitro derivative *221* by the sequence shown (57JJ352), and a similar reduction method (*224* → *225*) gives hydroxamic acids of the benzothiazine series (65CC3221; 66CC1733; 67CC975).

iv. Five-membered Ring Derivatives

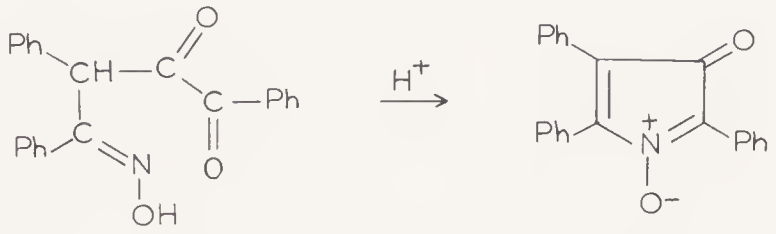
a. Pyrroline and Indolenine N-*Oxides.* γ-Nitro ketones (*226*) are converted on mild reduction into pyrroline 1-oxides (*228*) via hydroxyamino intermediates of type *227*; examples of this reaction are collected in Table 2.17. Bapat and Black (68AJ2483) recommend reduced iron in a mildly acid medium as the reagent of choice, in preference to the more frequently used zinc. Monocyclic analogues of the better-known bicyclic isatogens are formed by the cyclization of the mono-oximes of triketones: *229* → *230* (30JA1590).

The reaction of hydroxylamine with unsaturated diketones of type *231* yields 5*H*-pyrrole 1-oxides (*232*) (34JA2774).

Indolenine 1-oxides (*234*) (Section III-5D) are produced by the reduction of *o*-nitrotoluene derivatives (*233*) [65CO(260)2851; 67BF1296],* and a related reaction is the synthesis of isatogens by catalytic reduction: *235* → *236* (39H147).



(226) (227) (228)



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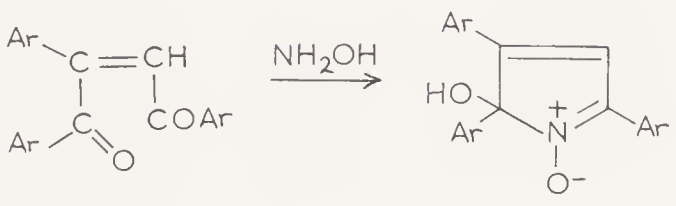
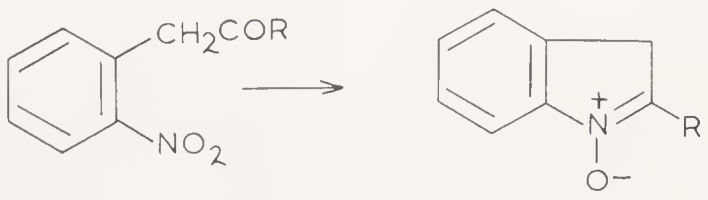


(231) (232)



(233) (234)

(235) (236)

* See addendum in the Appendix.

Table 2.17. Formation of Δ^1-Pyrroline 1-Oxides by the Reduction of γ-Nitro-ketones (226 → 228)

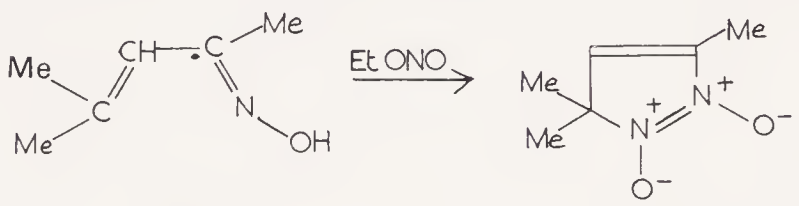
Starting material	Reducing agent	Δ^1-Pyrroline 1-oxide formed	Yield, %	References
4,4-Dialkyl-1,3-diaryl-4-nitro-1-butanone	Zn–aq. NH_4Cl, H_2/Ni(R), N_2H_4/Ni(R)	2,2-dialkyl-3,5-diaryl	28–75	61JA1128
3-Methyl-3-nitro-*n*-butyl cyanide	Fe–HCl, H_2/Ni(R), Zn–NH_4Cl	5-amino-2,2-dimethyl[a]	75[b]	47J1508
2,3-Dimethyl-3-nitro-*n*-butyl cyanide	H_2/Ni(R)	2-amino-4,5,5-trimethyl	60–75	65J1224
Ethyl 2-acetyl-2-ethyl-4-methyl-3-nitromethylpentanoate	Zn–aq. NH_4Cl	4-isopropyl-2-methyl	73	66J(C)1491
5-Nitro-2-pentanone	Zn–NH_4Cl	2-methyl	58	67AJ339
4-Methyl-5-nitro-2-pentanone	Zn–NH_4Cl	2,4-dimethyl	80	67AJ339
2-(3-Methyl-3-nitrobutyl)-1,3-dioxolane	Zn–aq. NH_4Cl	5,5-dimethyl	79	59J2094
4,4-Dimethyl-5-nitro-2-pentanone	Zn–aq. NH_4Cl	2,4,4-trimethyl	75	57P97, 59J2094
5-Alkyl-5-nitro-2-hexanone	Zn–aq. NH_4Cl	5,5-dialkyl	(data)	64T291(S1)
3,4-Dimethyl-4-nitropentanal	Zn–aq. NH_4Cl	4,5,5-trimethyl	51	57P97, 59J2094
3-(3,4-Methylenedioxyphenyl)-4-nitro-1-phenyl-1-butanone	Zn–aq. NH_4Cl	4-(3,4-methylenedioxyphenyl)-2-phenyl	40	59J2094
Phenyl and methyl derivatives of 4-methyl-4-nitropentanal	Zn–NH_4Cl; $NaBH_4$/Pd–C; Fe–HCl	phenyl and methyl derivatives of 5,5-dimethyl	(data)	68AJ2483

[a] Admixed with 5-amino-2,2-dimethylpyrrolidine if reductive cyclization effected by Fe-HCl.

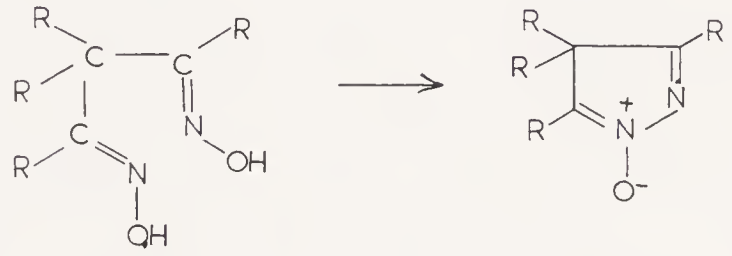
[b] Yield on reduction with H_2/Ni(R); data are given for other reducing agents.

b. Pyrazole N-*Oxides*. Mesityl oxide oxime (*237*) reacts with nitrite esters to yield the 5*H*-pyrazole 1,2-dioxide *238* (62JO1309).

4*H*-Pyrazole 1-oxides (*240*) are obtained by ring closure of certain β-dioximes (*239*) in the presence of thionyl chloride [65AG(E)1075; 66CB618]. 4-Oxo-4*H*-pyrazole 1,2-dioxides (*241*) are formed by the nitric acid oxidation of α-arylidene ketoximes (*242*, R′ = H) (36G479; 36G815; 67AP822); the same reaction produces 1-hydroxypyrazole 2-oxides (*243*) if the ketoxime contains an extra alkyl group (*242*, R′ = Me) (66JH544; 67AP822; 68TL1841; 69JO194), and nitrosation of α-arylidine ketoximes under nitrogen yields heterocyclic oximes corresponding to ketones of type *242* (69JO187; for older work that gives incorrect structures, see references 36G479 and 36G815). Compounds of type *241* are also formed by the action of nitric acid on acetone-dicarboxylic ester [these products were originally formulated differently (93CB997)]; presumably the intermediate dioxime is oxidized by more nitric acid (66KG766; 67KG904; 67TL4917; 69RO2).



(237) (238)



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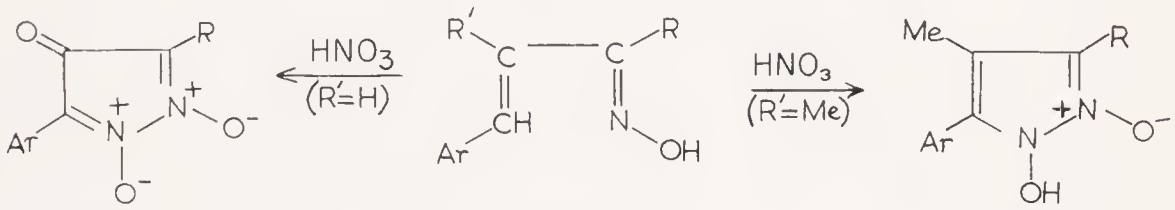
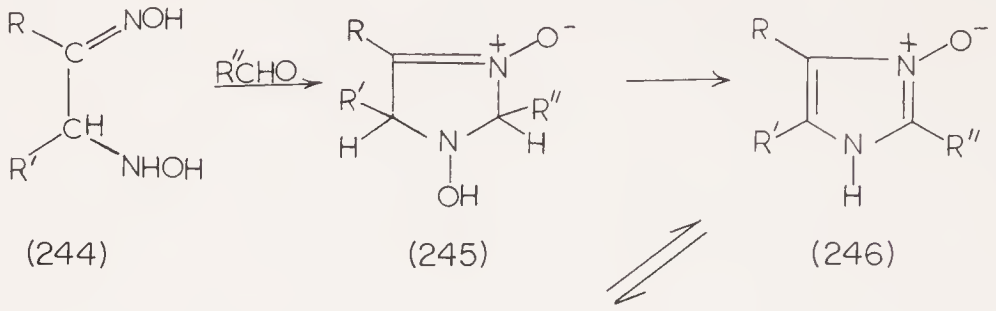


(241) (242) (243)

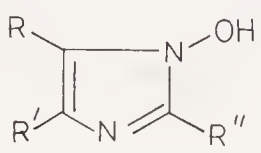
c. Imidazole N-*Oxides*. Imidazole 3-oxides (*246*), which are tautomeric with 1-hydroxyimidazoles (*247*) (See Section III-6Ai), are available by two main synthetic routes. (*a*) In a reaction similar to the formation of oxazole 3-oxides mentioned in Section II-2Aive, α-keto oximes react with aldehydes in the presence of ammonia to give imidazole 3-oxides (48J731; 64CI1837; cf. 18CB965; 19CB43; 52G252).* (*b*) α-Hydroxyamino oximes (*244*) react with aldehydes to form dihydro-1-hydroxyimidazole 3-oxides (*245*), which are readily converted into the aromatic *N*-oxides (*246*) (65TL1565).

* See addendum in the Appendix.

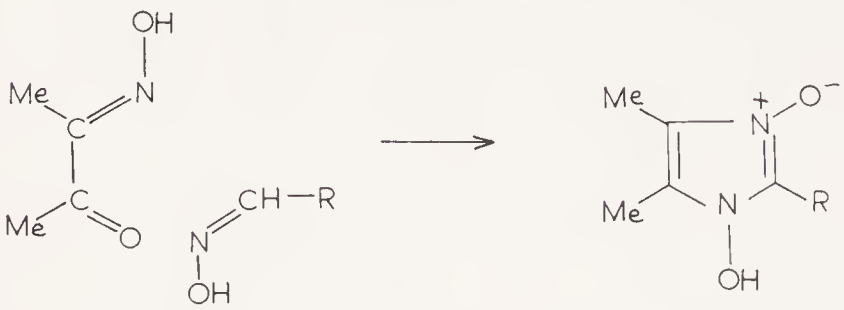
1-Hydroxyimidazole 3-oxides (*249*) are formed when α-keto oximes condense with aldehyde oximes (cf. *248*) (64JO1620; 65AP293), although the products were originally formulated differently (05CB3357). An alternative route to this type of compound is illustrated by the reaction of dimethyl glyoxime with benzaldehyde to give 1-hydroxy-2-phenylimidazole 3-oxide (45G216).



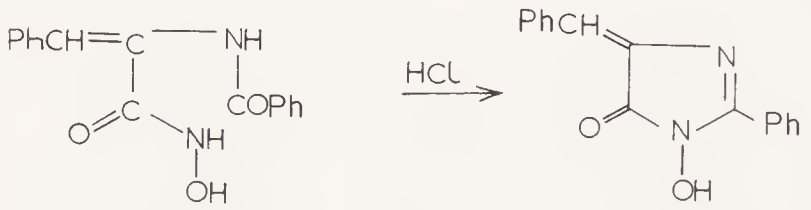
(244) (245) (246)



(247)



(248) (249)



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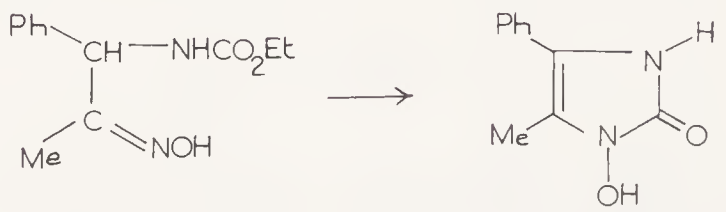

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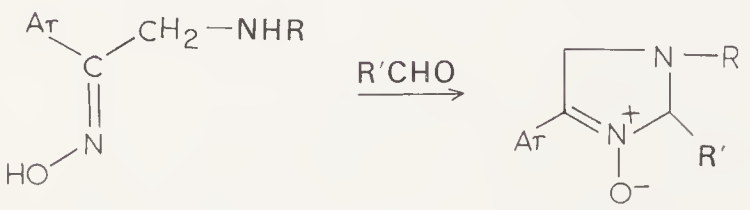


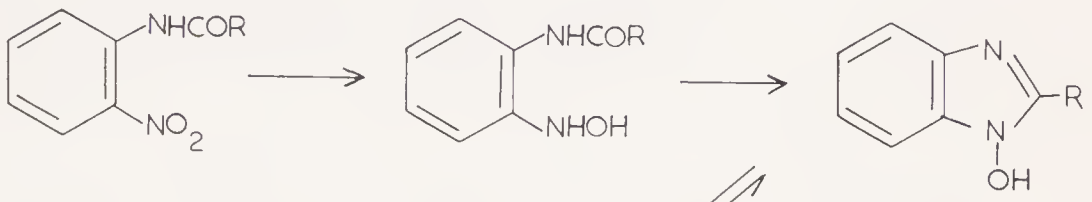
(254) (255)

Hydroxamic acids of the imidazolone series have been prepared by the cyclization reactions *250* → *251* (49JA1691) and *252* → *253* (64CB2169). The

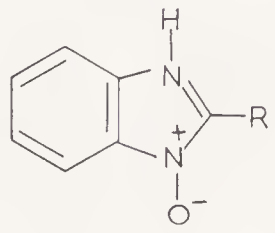
preparation of dihydroimidazole *N*-oxides (*254* → *255*) has been reported by Busch *et al.* [30CB649; 31CB1816; cf. 37PC(150)1].

d. Benzimidazole N-*Oxides.* *o*-Nitroanilides (*256*) can be reduced under mild conditions to yield 1-hydroxybenzimidazoles (*258*), which are in tautomeric equilibrium with benzimidazole 1-oxides (*259*) (see Section III-6Ai). The reaction probably involves cyclization of an intermediate phenylhydroxylamine (*257*). *N*-Substituted anilides (*260*) yield *N*-oxides of type *261* in which tautomerism is not possible. Both variations were discovered by von Niementowski; available data are recorded in Table 2.18.

Benzimidazole 3-oxides have also been prepared from benzal-*o*-nitroanilines (*262*) by prolonged heating (64JO1537), and from *o*-benzylaminonitrobenzenes (*263*) by treatment with sodium hydride (66JH51). This last reaction may involve nucleophilic attack on the nitro group by the benzyl carbanion centre, but the failure of the *N*-methyl derivatives corresponding to *263* to react argues against this route. 1-Hydroxybenzimidazole 3-oxides can be obtained by the reaction of aldehydes with *o*-quinone dioximes: *264* → *265* (66CH741).



(256) (257) (258)



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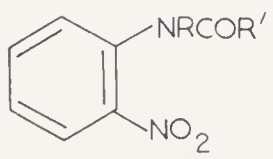

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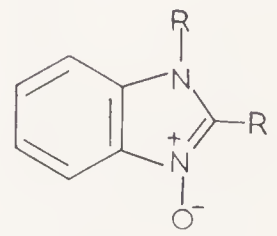

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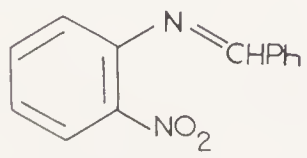

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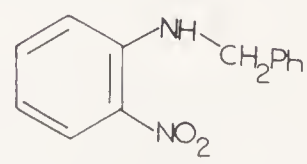

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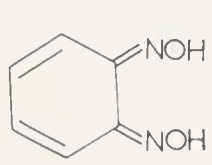

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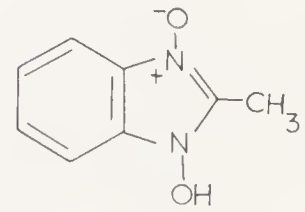
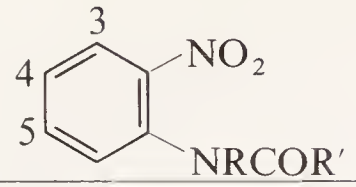


(265)

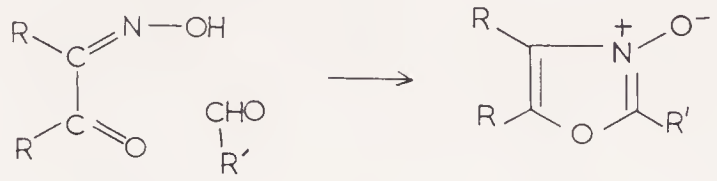
Table 2.18. Formation of Benzimidazole 1-Oxides by the Reduction of *o*-Nitroanilides (256 → 258 259; 260 → 261)



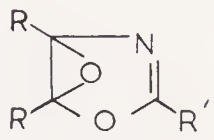
R	R′	Other substituents	Reducing agent	Benzimidazole 1-oxide formed	Yield, %	References
H	H	—	H_2S–NH_3; Zn–NH_4Cl	—	60–70	10CB3012, 58LA(615)99, 63CT1375
H	Me	4-NHAc, 5,6-benzo	H_2/Pd	6-acetylamino-5,6-benzo-2-methyl	96	67T1863
Alkyl	H	—	H_2S–NH_3	3-alkyl (various)	ca. 40	63CT1375
Alkyl or aryl	Me	—	H_2S–NH_3	3-alkyl- or -aryl-2-methyl	50–80	63CT1375
H	Me	4-NO_2, 5,6-benzo	Zn	6-amino-4,5-benzo	—	07PC(75)88
H	$C_6H_4 \cdot NO_2(o)$	—	Zn–HCl	2-(*o*-aminophenyl)	(data)	99CB1456
H	Me	4-Br, 6-Me	Zn–HCl	6-bromo-2,4-dimethyl	—	92CB860
H	Me	4,6-diBr	Sn–HCl	4,6-dibromo-2-methyl	—	02ZB940
H	Me	4-OMe	$Na_2S_2O_4$	6-methoxy-2-methyl	(data)	67MC211
H	H	—	H_2S–NH_3	2-methyl	60	10CB3012
Me	Me	—	Sn–HCl(?); H_2/Pd–C	2,3-dimethyl	—	87CB1874, 00PC(62)505, 66CT1219
H	Me	4-Me	H_2S–NH_3	2,6-dimethyl	—	89CB1396
H	Me	4-NO_2	NH_3–EtOH	2-methyl-6-nitro	25	67J(C)1764
H	Me	4-Me, 6-NO_2	H_2S–NH_3	2,6-dimethyl-4-nitro	—	88CB2402
Ph	CH_2Cl	—	H_2/Pt	2-methyl-3-phenyl	50–75	65JO1279
Me	Ph	—	H_2/Pt	3-methyl-2-phenyl	60	66JH51
H	H	4-NO_2	H_2S–NH_3	6-nitro	(data)	64CT282
H	$C_6H_4 \cdot Cl(p)$[a]	—	NaOH–MeOH	2-phenyl (various)	(data)	67MC211

[a] Group in 1-position is $NHCH_2.C_6H_4.Cl(p)$.

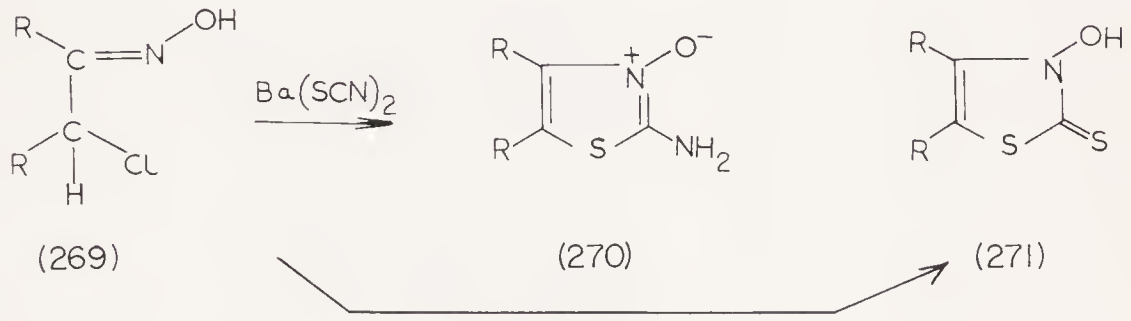
e. Oxazole N-*Oxides*. Dilthey and Friedrichsen showed that α-keto oximes condense with aldehydes to give oxazole 3-oxides (*266* → *267*); the products were initially formulated as epoxides (*268*) [30PC(127)292; cf. 15CB897], but the *N*-oxide structure is now generally accepted (cf. 47J96). More recent examples of this reaction have since been reported and are listed in Table 2.19.



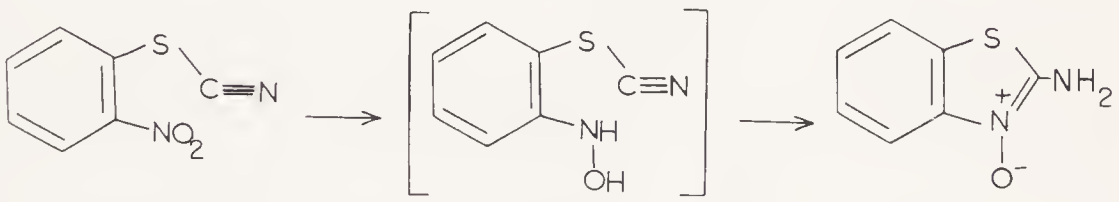
(266) (267)



(268)



(269) (270) (271)



(272) (273) (274)

f. Thiazole and Benzothiazole N-*Oxides*. Derivatives of thiazole 3-oxide have been prepared by the reactions *269* → *270* and *269* → *271* (64CB2165). Catalytic or chemical reduction of *o*-thiocyanatonitrobenzenes (*272*) yields 2-aminobenzothiazole 3-oxides (*274*), probably via the hydroxylamine *273* (64CI368).

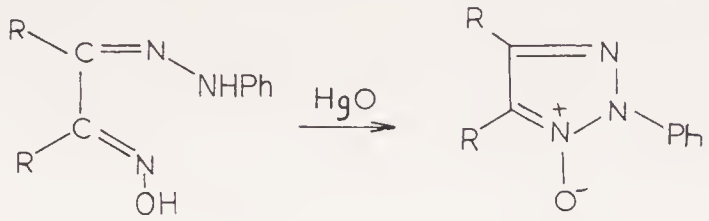
g. Triazole N-*Oxides*. 1,2,3-Triazole 1-oxides (*276*) are formed by the gentle oxidation of α-oximino hydrazones (*275*) [98G(1)173; 98PC(57)160; 00G(2)459]. The formation of 1-hydroxy-1,2,3-triazoles from *o*-keto oximes and tosyl hydrazide (*277* → *278*) is a related reaction (66CI420); such 1-hydroxytriazoles have also been prepared from the nitrosoimino oximes *279* [89LA(255)148; 01NW45]. A 4-phenylazo-1,2,3-triazole 1-oxide (*281*) is formed by diazo coupling of the nitroisoxazole *280* (42G399); an intermediate of type *282* is probably involved.

Table 2.19. Formation of Oxazole 3-Oxides from α-Diketone Monoximes by Reduction with Aldehydes (266 → 267)

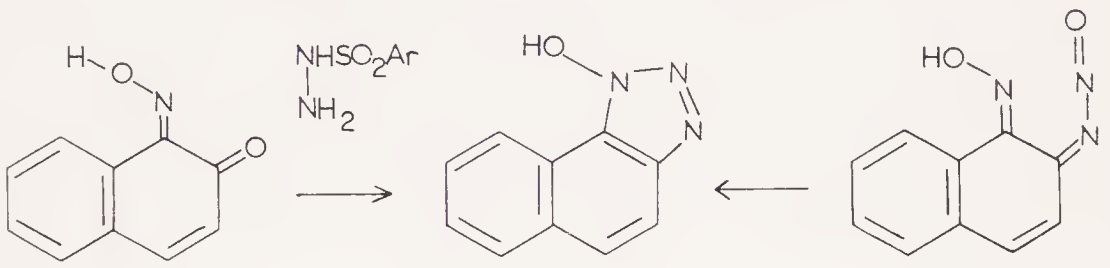
R—C(=O)—C(=NOH)—R′ R	R′	Aldehyde	Oxazole 3-oxide formed	Yield, %	References
Methyl, phenyl	acetal	Aryl-CHO, PhCH=CHCHO	4-acetyl-2-aryl (or -styryl)-5-methyl (or -phenyl)	62–92	65CI1340, 68J(C)1397
See note[a]	See note[a]	PhCHO	4,5,6,7-tetrahydro-7-hydroxyimino-2-phenylbenzoxazole	28	55JA5370
Phenyl	methyl	PhCHO	4-methyl-2,5-diphenyl	24	65AP293
Methyl	methyl	PhCHO	4,5-dimethyl-2-phenyl	27	55JA5370
Phenyl	phenyl	PhCHO	2,4,5-triphenyl	62	55JA5370

[a] 1,2,3-Cyclohexanetrione 1,3-dioxime.

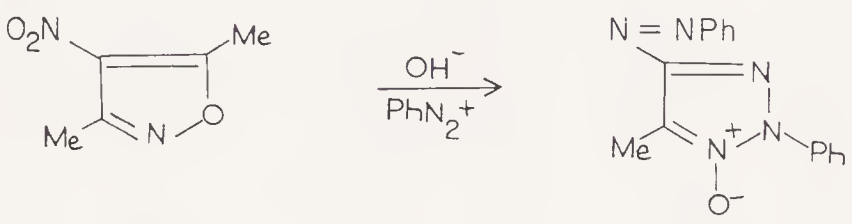
4-Hydroxy-1,2,4-triazoles, which are tautomeric with 1,2,4-triazole 4-oxides, are produced by the reaction *283* → *284* [06PC(73)288], and also by the spontaneous cyclization of azido-oximes of type $RC(N_3):NOH$ (09J183; 10AL218).



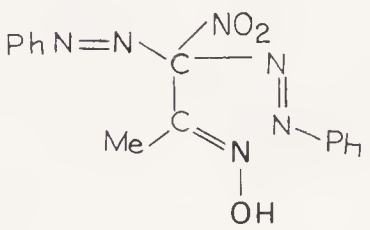
(275) (276)



(277) (278) (279)



(280) (281)



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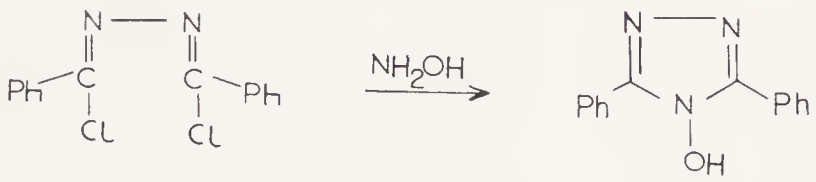
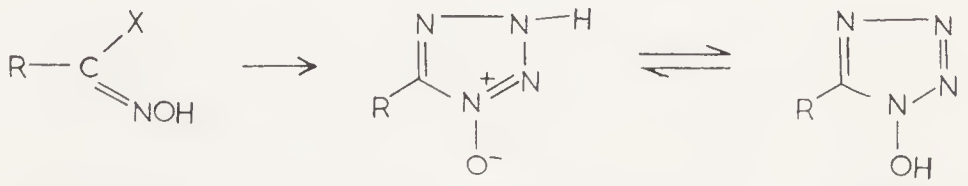


(283) (284)

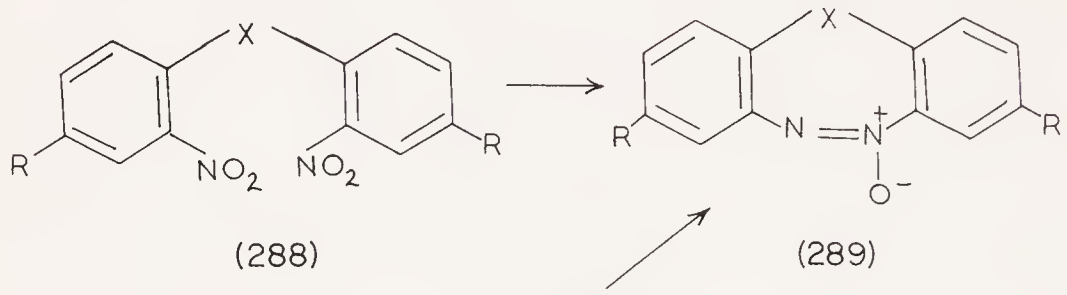
h. Tetrazole N-*Oxides*. Tetrazole 1-oxides (*286*), tautomeric with 1-hydroxytetrazoles (*287*), are obtained by the reaction of hydroxamoyl chlorides (*285*, X = Cl) with sodium azide (61JO952), or of nitrolic acids (*285*, $X = NO_2$) with hydrazoic acid (56AN812). Tetrazole 1-oxides can also be prepared from fulminic acid [10AL221; 13G(1)69].



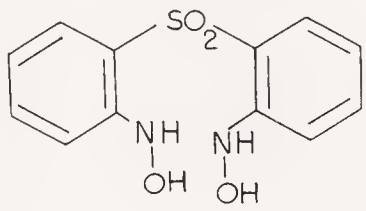
(285) (286) (287)

v. Seven-membered Ring N-*Oxides*

Reduction of nitro compounds of type *288* (X = CH_2, SO_2, NH) under certain conditions gives the corresponding *N*-oxide *289*; for examples, see Table 2.20. However, reduction of *288* (X = O) did not give an *N*-oxide (63J1436). Sulphone oxides (*288*; X = SO_2) can also be prepared from intermediates of type *290* [66J(B)260]. Benzodiazepine *N*-oxides (*292*) are prepared by the cyclization reactions indicated: *291* → *292* (62JO562), and *293* → *292* (61JO4936; 65JO4267; 67JO2417).



(288) (289)



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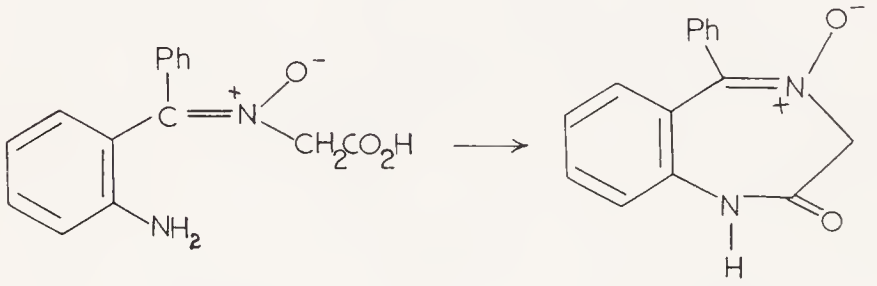
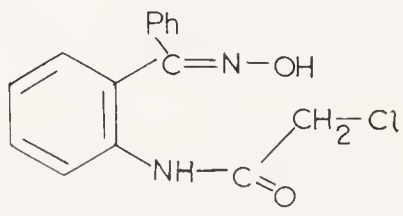


(291) (292)



(293)

B. RING CLOSURES OF NITROSO COMPOUNDS

Two well-defined reaction types may be distinguished: electrophilic attack by the nitroso group on an (activated) aromatic ring, usually intramolecular, and the spontaneous cyclization of suitably *o*-substituted nitroso compounds as shown in scheme *294* → *295* (X=Y is N=C, N=N, and N=O); the nitroso compounds are usually prepared *in situ*. Finally, there remains a

Table 2.20. Formation of *N*-Oxides with Seven-membered Rings by Reduction of Di-(*o*-nitrophenyl) Derivatives (288 → 289)

Nitro compound (288)		Reducing agent	*N*-Oxide formed (289)	Yield, %	References
X	R				
C=O	halogeno	Zn–NH_4Cl	11*H*-dibenzo[*c*, *f*][1,2]diazepine 5-oxide, 3,8-dihalogeno	18–100	64JH178
CH_2	amino	Zn–NH_4Cl	11*H*-dibenzo [*c*, *f*][1,2]diazepine 5-oxide, diamino[a]	—	05CO(141)198
SO_2	CF_3	H_2/Ni(R)	dibenzo[1,4,5]thiadiazepine 1,1,5-trioxide	(data)	53JA6338
NH	H	Zn–NaOH	dibenzo[1,4,5]triazepine 5-oxide	13	63J1436

[a] A series of dinitro compounds was reduced.

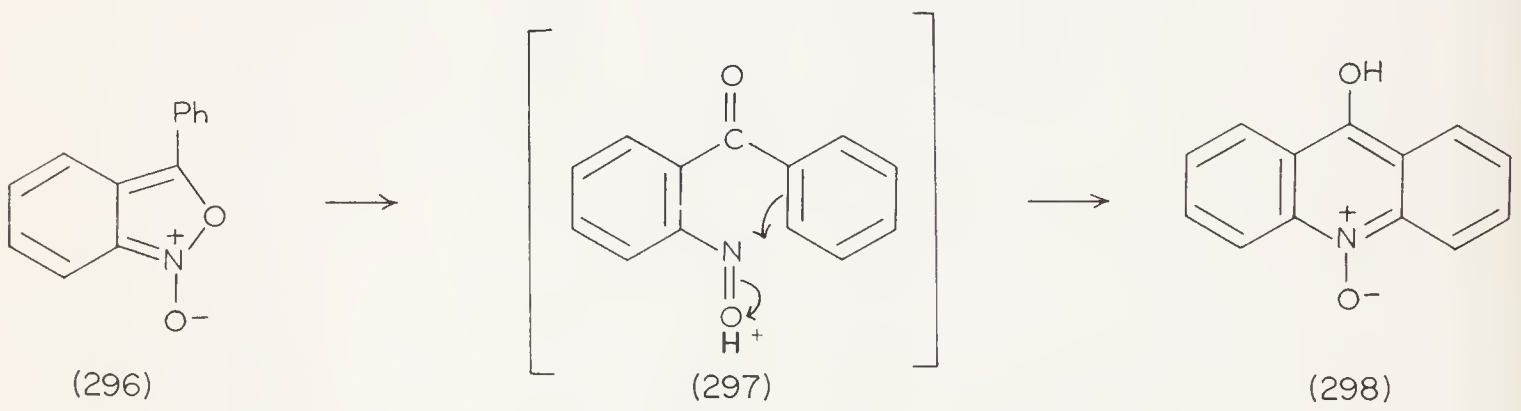
miscellaneous set of ring closures involving nitroso groups; the mechanism of some may be easily rationalized, others less easily.

(294) (295)

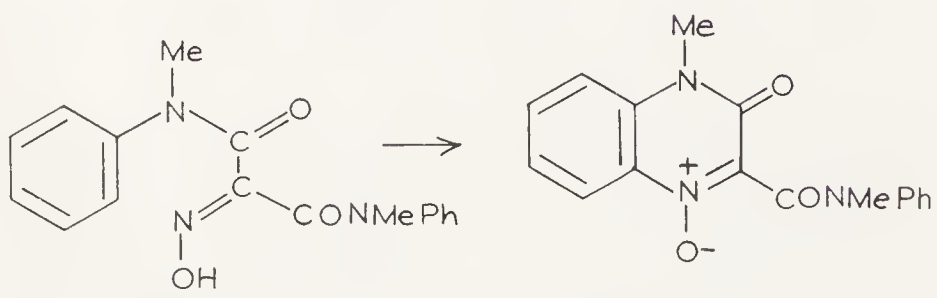
i. Electrophilic Attack by a Nitroso Group on an Activated Aromatic Ring

This group of reactions includes the well-known Wohl-Aue preparation of phenazines as well as some less familiar transformations. The preparation of phenoxazine *N*-oxides, considered in Section II-2Ciiic, may also proceed by a mechanism of this type.

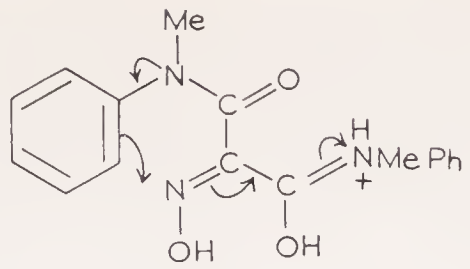
a. 9-Hydroxyacridine 10-Oxides. Because the final ring-closure step probably involves a nitroso compound, we also consider here the reaction of *o*-nitrobenzaldehydes with benzenes in sulphuric acid to yield 9-hydroxyacridine 10-oxides (*298*) (32CB834; 35CB1455; 60AR105; 60BF693; cf. 09CB1707; 34CB336). This reaction probably proceeds by a reaction of the Friedel-Crafts type to form the anthranil oxide *296* followed by ring opening to the nitroso intermediate *297*; for discussion and additional references, see reference 65RR1035. This interpretation of the reaction is supported by the fact that anthranil oxides do yield acridine 10-oxides on treatment with sulphuric acid (14CB1629; 59JA962). Anthranil oxides may exist in equilibrium with the open-chain nitroso compound *297* (cf. Section III-5Ciiic). For further discussion of the preparation of anthranil oxides, see Section II-2Diib.



(296) (297) (298)



(299) (300)

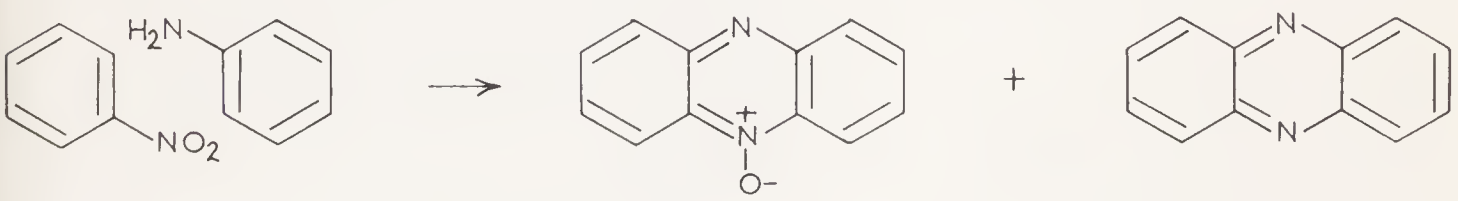


(301)

b. Quinoxaline N-*Oxides.* 3-Quinoxalinone 1-oxides (*300*) have been prepared by the chromic acid oxidation of isonitrosomalonanilides (*299*) (23J1069); these structures have been confirmed more recently (57J439; 60J3887). The mechanism of the reaction is not clear, but may involve an electrophilic ring-closure as indicated in *301* followed by oxidation of the 2-carboxy-quinoxaline 1-oxide derivative thus produced.

c. Phenazine N-*Oxides.* The Wohl-Aue reaction (01CB2442) involves the condensation of nitrobenzenes with anilines in the presence of alkaline catalysts to yield mixtures of phenazines and their mono-*N*-oxides: *302* → *303* + *304* (it is considered in the present section because a nitroso compound probably undergoes the cyclization). In the early work, potassium or sodium hydroxide was used as catalyst, often in refluxing toluene, but yields were generally poor. Improved yields (15–25 %) have been claimed using sodamide as catalyst (56CT391) and benzene as solvent (43USP2332170). Examples of the reaction are summarized in Table 2.21. The mechanism of the reaction is still not completely clear, but probably involves nucleophilic attack of the aniline on the *ortho*-position of the nitro compound, followed by ring closure of an intermediate nitroso compound of type *305* (52ZO502; 55UK350; 56JJ1051). For early work on the reaction mechanism, see reference 03CB4135.

para-Substituted nitrosobenzenes are converted by sulphuric acid, in a reaction reminiscent of the Wohl-Aue reaction, into disubstituted phenazine *N*-oxides: *306* → *307* [84M605; 11LA(382)82; cf. 72LA(162)273].



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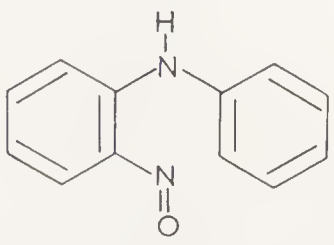

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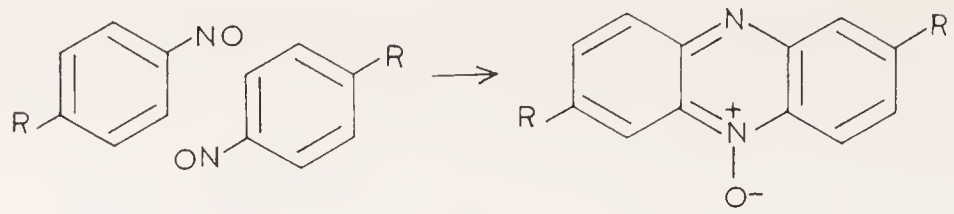

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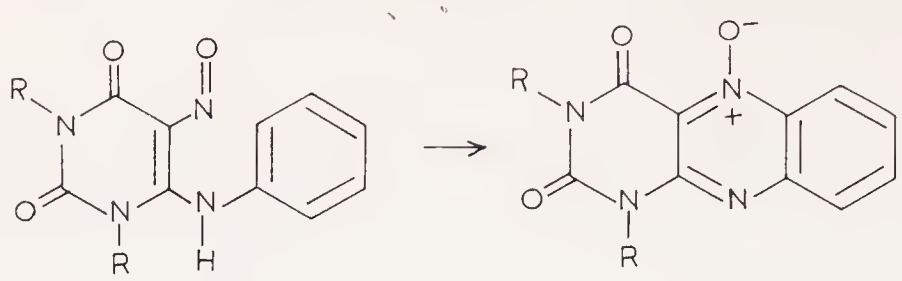


(308) (309)

Table 2.21. Phenazine *N*-Oxides Prepared by the Wohl-Aue Reaction (302 → 303 + 304)

Phenazine 5-oxide	References
—	01CB2442, 43USP2332179, 54CT292, 56JJ1051
1,2-Benzo	51JA4958, 52AN519
1,2-Benzo-11-methoxy	56JJ30
3- and 4-Bromo	56ZO3032
Carboxy (various)	52AN519, 53AN611
Chloro (various)	55CT365, 59ZO228, 59ZO1306
Chloro-1-methoxy (various)	59JJ896
8-Chloro-1-phenyl	60ZO2033
2-Chloro-7-phenylsulphonyl	62J4438
1,6-Diethoxy	50DA645
1-Fluoro	55ZO2161
Dihalogeno (various)	11LA(382)82, 55CT365
2-Hydroxy	55ZO2161
2- and 3-Iodo	56ZO3465
Methoxy (various)	52JJ1128, 53CT66, 53JJ23, 54CT25, 54CT53, 54CT292, 56JJ1051, 59ZO1306
Dimethoxy (various)	49DA651, 53CT66, 54CT25, 57CT81
Methyl (various)	37ZO151, 52AN519, 56CT391, 59ZO228
1-Methyl-7- and -9-methoxy	61JJ861
1,6- and 2,7-Dimethyl	11LA(382)82, 56CT391
1-Phenyl and 1,6-diphenyl	58J4492
2-Phenyl-7-substituted	59ZO1299, 60ZO1661, 60ZO2033
3-Phenyl-8-*H* or -substituted	59ZO1299, 60ZO1661
Dipyrido[3,2-*a*:3′,2′-h][a]	65J799
2- and 3-Trifluoromethyl	55ZO2161

[a] Shown to be a phenazine *N*-oxide by synthesis of the parent base (oxidation of 6-aminoquinoline with hypobromite); compound was previously formulated as a pyridazine *N*-oxide (pyridazino[4,3-*f*:5,6-*f*′]diquinoline 1-oxide)[48LA(559)128; 64R718].

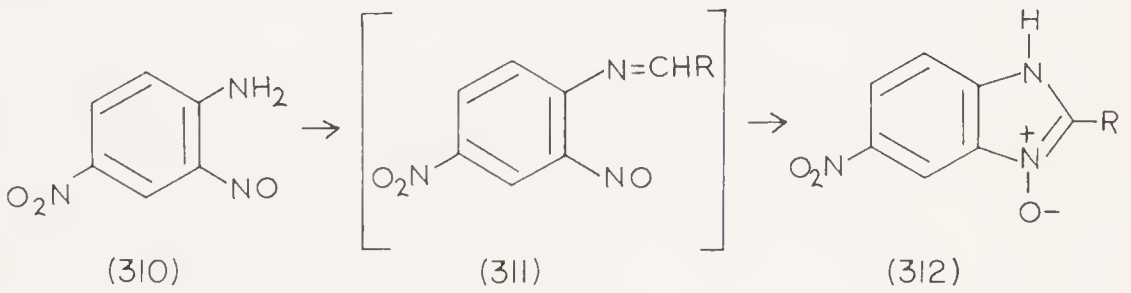
d. Alloxazine N-*Oxides.* Alloxazine 5-oxides (*309*) are formed by the oxidative cyclization of 6-arylamino-5-nitrosouracils of type *308* [64ZC454; 66LA(694)142]. Certain related cyclizations [61T(16)80] are considered to occur via *N*-oxides, although these were not isolated.

ii. Cyclization of a Nitroso Compound with an alpha N=C, N=N, *or* N=O *Group*

This set of reactions forms a well-defined group leading to the preparation of benzimidazoles, benzotriazoles, benzofuroxans, and analogous compounds such as purines. The reactions usually proceed spontaneously; the starting materials can be obtained in various ways. The only known example of this reaction in the monocyclic series is the oxidation of α-dioximes to furoxans, presumably via α-dinitroso olefins.

a. Benzimidazole and Purine N-*Oxides.* Benzimidazole 1-oxides are also available by the condensation of *o*-nitrosoanilines with aldehydes: *310* → *312* (65CH498; 64CH567). A somewhat similar reaction is involved in the rearrangement of benzofuroxan quaternary salts to 3-hydroxybenzimidazole 1-oxides, cf. Section III-5Ciiib.

Reactions of this type have been extended to the synthesis of purines. 6-Alkylidine-5-nitrosouracils (*313*) change spontaneously into the tautomeric purine 7-oxides (*314*⇌*315*). The alkylidine derivatives (*313*) can be prepared from the aminouracil and an aldehyde (64JA4721) or by dehydrogenation of the alkylaminouracil [64ZC454; 66LA(693)233]. If the alkylidine carbon atom does not carry hydrogen, pseudoxanthine 7-oxides of type *316* result [64ZC454; 66LA(692)134]. Purine 9-oxides have been analogously prepared from 5-amino-6-nitrosopyrimidines (57MI138).



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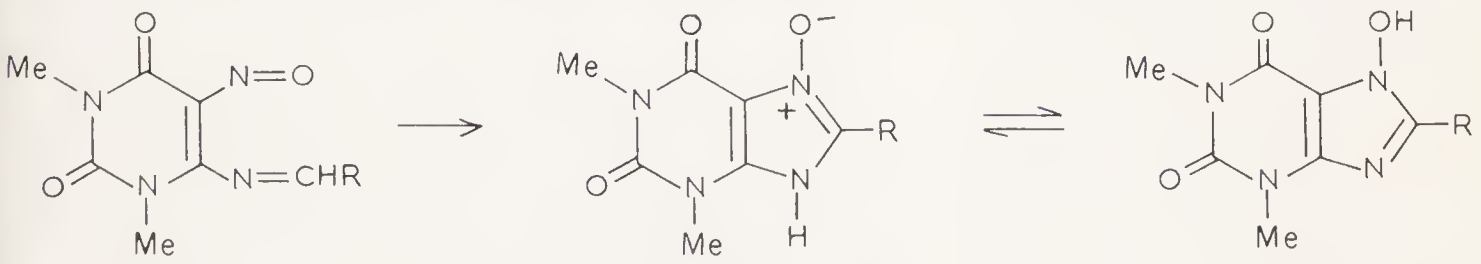

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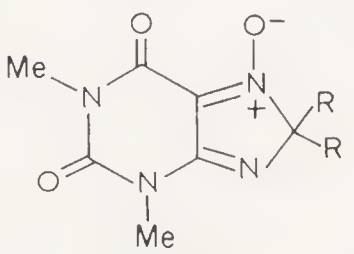
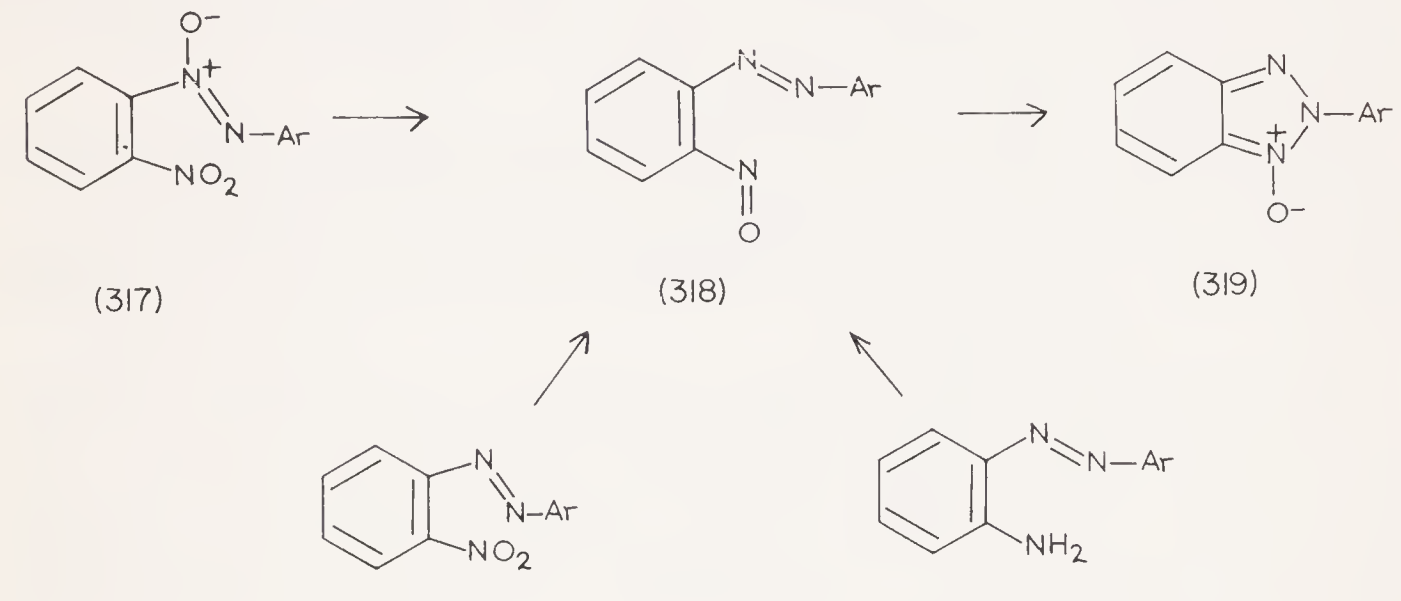
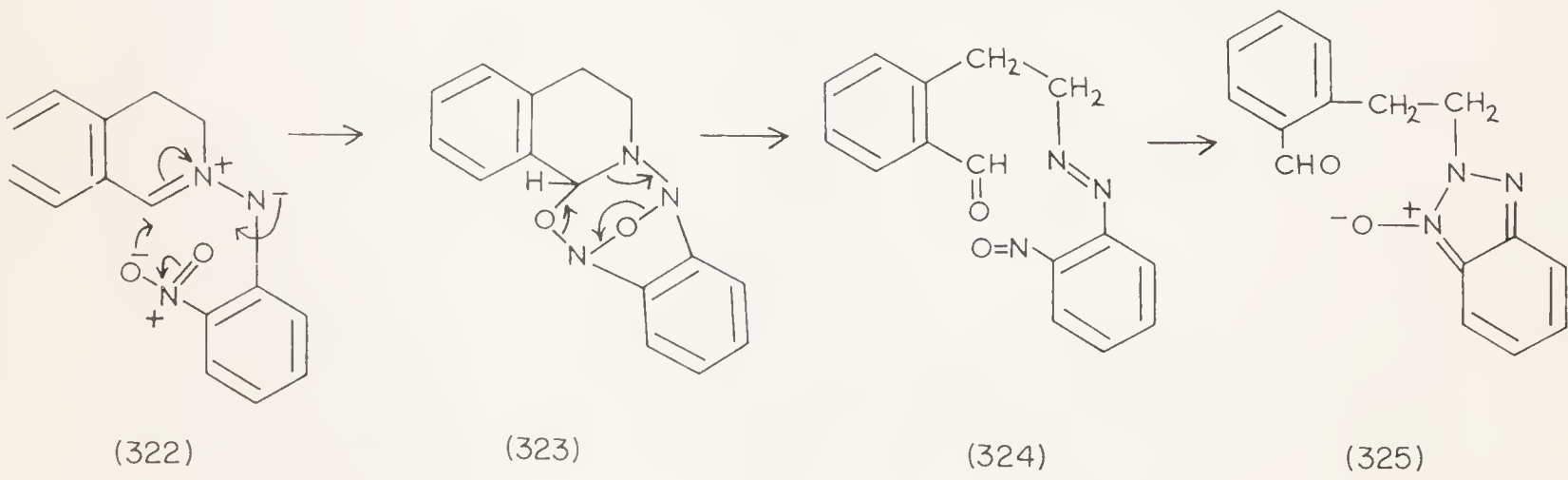


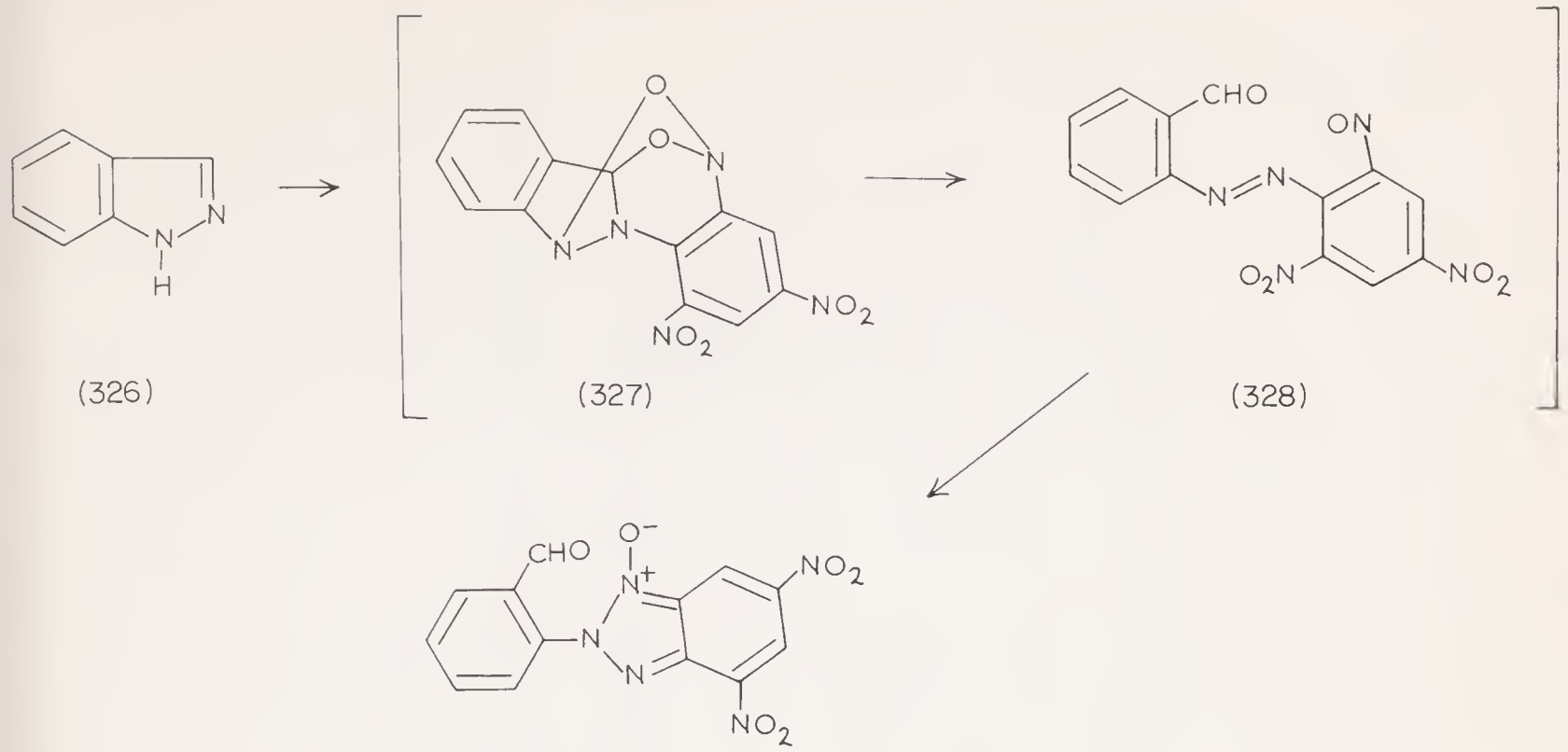
(316)

b. Benzotriazole 1-Oxides. The first benzotriazole 1-oxide was prepared by Zinin by reduction of an *o*-nitroazoxybenzene (*317* → *319*) [1860LA(144)217], although the benzotriazole 1-oxide structure was not proved until later (99CB3256). Ammonium sulphide reduction of *o*-nitroazobenzenes (*320*) also yields benzotriazole 1-oxides (*319*) [03B3822; 24PC(108)209], as does the hydrogen peroxide oxidation of *o*-aminoazobenzenes (*321*) (23G462; 26G207). These reactions probably involve the spontaneous cyclization of an intermediate *o*-nitrosoazobenzene (*318*), although other mechanisms can be postulated. Available examples of these reactions are summarized in Table 2.22.

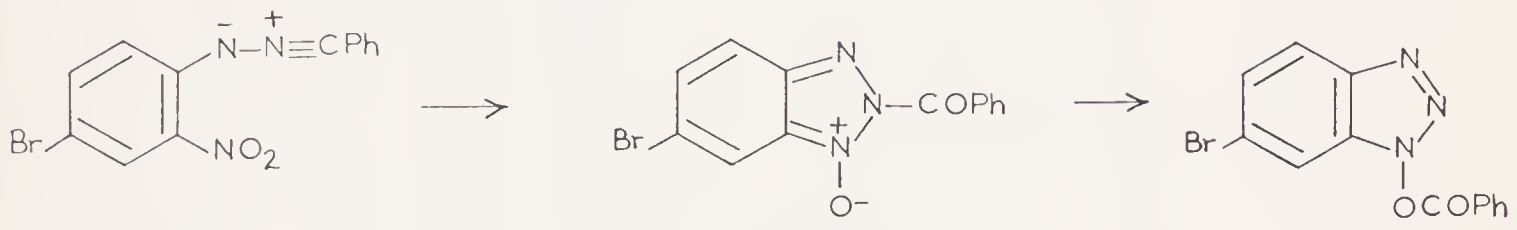


Intermediate *o*-nitroso-azo compounds can also be formed in more complex ways. The spontaneous internal 1,3-dipolar addition of the *N*-imine *322* yields the complex benzotriazole 1-oxide *325* via intermediates *323* and *324* (62AG155). A similar reaction path is involved in the reaction of indazole (*326*) with polynitrohalobenzenes to give the benzotriazole 1-oxide *329* via intermediates *327* and *328* (67BF2619; 68BF3331). The nitrile-imine *330* forms the benzoyloxy compound *332* by way of oxygen transfer to a nitroso-azo derivative which yields the *N*-oxide intermediate *331* [65CI1699; cf. 67CB71; 68J(C)8].





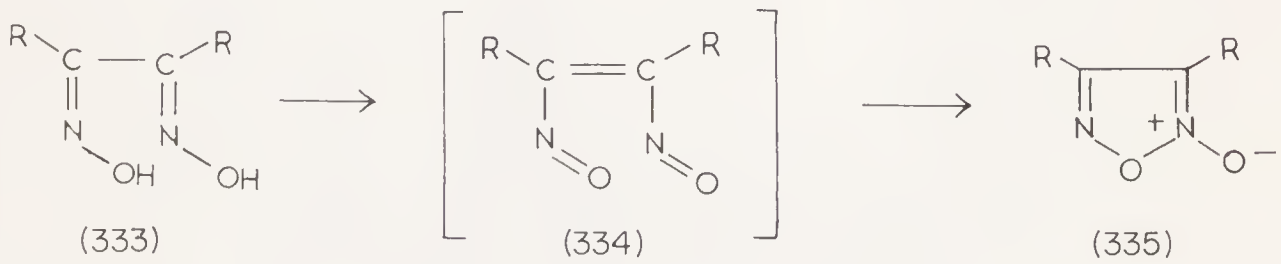
(326) (327) (328) (329)



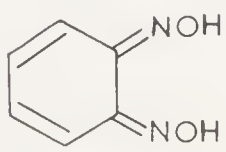
(330) (331) (332)

c. 1,2,5-Oxadiazole 2-Oxides (Furoxans). α-Dioximes (*333*) are smoothly oxidized by a variety of oxidizing agents to furoxans (*335*), presumably α-bis-nitroso compounds (*334*) are intermediates. Examples are collected in Table 2.23. For a general review of the preparation of furoxans, see reference 38CR193.

A large number of miscellaneous methods have also been used to prepare furoxans. Often these involve complex oxidations of olefins or ketones and may well involve intermediate nitroso compounds. Examples of these miscellaneous methods are collected in Table 2.24.



(333) (334) (335)



(336)

Table 2.22. Formation of Benzotriazole 1-Oxides by the Oxidation of *o*-Aminoazo Compounds or the Reduction of *o*-Nitro-azo or -azoxy Compounds

Starting material	Reagent	Benzotriazole 1-oxide	Yield, %	References
2-Amino-4,5-diethoxy-2′-nitroazobenzene	$Na_2S_2O_4$	2-(2-amino-4,5-diethoxyphenyl)	—	60GP1088060
2-Aminoazobenzene	H_2O_2	2-aryl	(data)	23G462, 26G207
2-Nitroazoxybenzene	—	2-aryl	—	1860LA(144)217
2,4-Dichloro-1-naphthylhydrazine	N_2H_4	4,5-benzo-6-nitro	—	25PC(111)277
4,5-Dichloro-2-nitrophenylhydrazine	N_2H_4	5,6-dichloro	—	25PC(111)277
4-Di-(2-chloroethyl)amino-2′-nitroazobenzene	$(NH_4)_2S_2$–EtOH	2-[4-di-(2-chloroethyl)amino]phenyl	quant.	56J1724
3- and 4-Chloro-2-nitroazobenzene	Na_2S	5- and 6-chloro-2-phenyl	82–90	62JO4109
4-Dimethylamino-2′-nitroazobenzene	$(NH_4)_2S$–EtOH	2-(4′-dimethylamino)phenyl	(data)	03B3822, 24PC(108)209, 56J1724

Table 2.23. Preparation of Furoxans by Oxidation of α-Dioximes (333 → 335)

Furoxan	Reaction conditions	Yield, %	References
3,4-(7,8-Acenaphtheno)	NaOCl	—	20J1344
3-Anisyl-4-phenyl	NaOCl–NaOH	quantitative	25LA(444)94
3,4-Diaryl	HNO_3	—	30G49
3,4-Dibenzoyl	Ac_2O, heat	—	93G417
Camphor derivatives[a]	KOH–Br_2	(data)	03J514, 27JA514
3-Carboxamido-4-phenyl	N_2O_4	—	68AN200
3,4-Cyclohexeno	NaOCl	76	57JA895
3,4-Dinitrocyclohexeno	liquid N_2O_4	(data)	57JA895
3-Ethyl-4-methyl	NaOCl–NaOH	—	66JA61
3-(*p*-Methoxyphenyl)-4-phenyl	NH_2OH–HCl	(data)	29JA1592
2-Nitrophenanthrene-[9,10-*c*]	HNO_3; EtOH–Cl_2	70–90	58JO1807
Octalin-[2,3-*c*]	NaOCl	60	57JA895
3-Phenyl	N_2O_4	90	08LA(358)36
3,4-Diphenyl	Cl_2 in EtOH or PhH	80	57JA895
3,4-Diphenyl and phenanthreno	$Pb(OAc)_4$	(data)	66LA(700)18
3-Phenyl-4-(*o*-tolyl)	NaOCl	95	29LA(468)202
Steroid [16,17-*c*][b] (various)	NaOCl–NaOH	(data)	68CC77
3,4-Bis-(*N*-substituted)-amino (various)	$K_3Fe(CN)_6$	50–100	68R452

[a] Prepared from β-, γ-, and δ-camphor-quinone dioximes.
[b] Androstane and estrane series.

Table 2.24. Miscellaneous Preparations of Furoxans

Starting material	Reaction conditions	Furoxan formed	Yield, %	References
Phenylacetylene	N_2O_3	3-phenyl	75	21LA(424)107
1-Arylpropenes	HNO_3	3-methyl-4-aryl	—	92CB1956
*Dinitro-olefines	NaN_3–EtOH	3,4-dialkyl	62–75	57JO456
cis-1,2-Dinitrostilbene	NaN_3–EtOH	3,4-diphenyl	86	57JO456
2,3-Dinitrobutane	polyphosphoric acid	3,4-dimethyl	86	65CB1831
1,2-Dinitrocyclohexane	H_2SO_4–polyphosphoric acid	3,4-cyclohexeno	74–94	65CB1831
Nitroacetic ester	H_2SO_4	3,4-dicarboxylic esters	—	69KG175/1
Amphi-chloroglyoxime	N_2O_4–Et_2O, 0°	3-chloro	48	63T143S1
Dichloroglyoxime	90% HNO_3, 25°	3,4-dichloro	86	63T143S1
Chloromethylglyoxime	N_2O_4–Et_2O, 0°	4-chloro-3-methyl	41	63T143S1
p-MeO-C_6H_4-C(NOH)CHMeNO$_2$	HCl	3-methyl-4-*p*-anisyl	—	08LA(358)36
ω-Nitroacetophenone	HNO_3 or H_2SO_4–AcOH	3,4-dibenzoyl	16–52	55JA4333
2,6-Diacetylpyridine	69% HNO_3–AcOH, 50–55°	3,4-di(6-acetylpicolinoyl)	81	63JO3542
Acetone	anhyd. N_2O_4 at 0–5°, then heat to 50°	3,4-diacetyl	93	66TL1727
Cyclopropyl methyl ketone	69% HNO_3–AcOH, 50–55°	bis(cyclopropylcarbonyl)	45	68JO866
Aryl methyl ketones	HNO_3–AcOH–$NaNO_2$	3,4-diacyl (various)	15–82	55JA4233
Acetophenone	HNO_3, 90–100°	3,4-di(benzoylformald-oximino)	5[a]	60JA2220
4-Bromoacetophenone	HNO_3	3,4-di(*p*-bromobenzoyl)	5–10	58JJ808
m-Nitroacetophenone	HNO_3	3,4-di(*m*-nitrobenzoyl)	5–10	58JJ808
2-Acetylpyridine	69% HNO_3–AcOH, 50°	3,4-dipicolinoyl	28	63JO3542

[a] Minor product; major product is dibenzoylfuroxan (cf. Table 2.31).

* *p*-(Propenyl)anisole; see addendum in the Appendix.

Table 2.24. Miscellaneous Preparations of Furoxans—*continued*

Starting material	Reaction conditions	Furoxan formed	Yield, %	References
3-Acetylpyridazine	HNO_3–H_2SO_4, 50°	3,4-bis(3′-pyridazinoyl)	60	68JH379
Methyl 2-thienyl ketone	AcOH–HNO_3–NO_2^-	3,4-dithienoyl	72	67JO1255
2- and 3-Acetylthianaphthene	HNO_3–AcOH, 25°	3,4-di(2- and 3-thianaphthoyl)	ca. 60	58JO1024
Ethyl bromoacetate	$NaNO_2$, -16°	3,4-di(ethoxycarbonyl)	28–48	58JA4333
NC-CH_2CO_2H–CF_3CO_2H	HNO_3 at 40°	3,4-dicyano	38	62T(17)79
Benzenesulphonylacetic acid	HNO_3–AcOH	3,4-di(benzenesulphonyl)	50–65	64J904
$RCOCHN_2$	N_2O_4–$CHCl_3$, -40°	3,4-diacyl	ca. 70	68RC289
R_fCHN_2[b]	Bu_2O, -80°	3,4-di(fluoroalkyl)	20–96	63T131S1
R_fCHN_2[b]	NOCl–$CHCl_2$, -5 to 10°	3,4-di(fluoroalkyl)	11–28[c]	63T137S1
Benzyl bromide	$NaNO_2$, -16°	3,4-diphenyl	20–30	58JA4333
1,2,5-Oxadiazoles	*hv*	3,4-diphenyl	14	69BJ581

[b] Perfluoroalkyldiazomethane.

[c] Corresponding hydroxamyl chloride also formed; the proportion of each product formed is dependent upon the concentration of the reactants and the excess of NOCl. Furoxan formation is favoured by a small excess of NOCl.

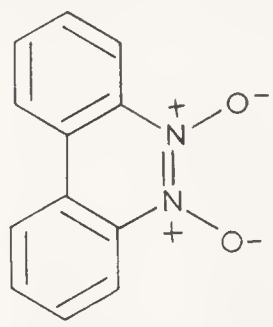
d. Benzofuroxans. Benzofuroxans have been prepared by the oxidation of *o*-quinone dioximes (*336*) (20J1344). *ortho*-Dinitrobenzenes are probably first formed, and then undergo spontaneous cyclization.

iii. Miscellaneous Ring Closures of Nitroso Compounds

This section includes the ring closure of nitroso compounds not previously dealt with and is subdivided according to the ring system formed.

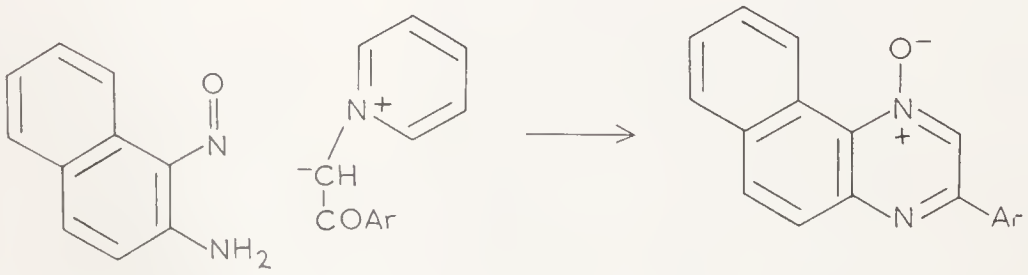
a. Pyridazine and Benzocinnoline N-*Oxides.* Spontaneous cyclization of the bis-nitroso derivative *337* forms the tetrahydropyridazine di-*N*-oxide *338* [65LA(687)236]. A similar type of reaction is probably involved in the reduction of 2,2′-dinitrobiphenyl with phosphine, which yields benzo[*c*]cinnoline 1,2-dioxide (*339*) (65T3285; see also Section II-2Aiia).

(337) (338)



(339)

b. Condensed Pyrazine and Oxazine N-*Oxides.* Pyridinium betaines condense with nitrosonaphthylamines to give benzoquinoxaline *N*-oxides (*340* → *341*) and with nitrosonaphthols to form naphtho-1,4-oxazine-2-thione 4-oxides (*342* → *343*) (62CB1123). In analogous reactions, pteridine 5-oxides of types *346* (R = NH_2) and *346* (R = alkyl) (63JO1197) have been prepared by the routes indicated in structures *344-347*, and *348* (64MI47) was prepared similarly.



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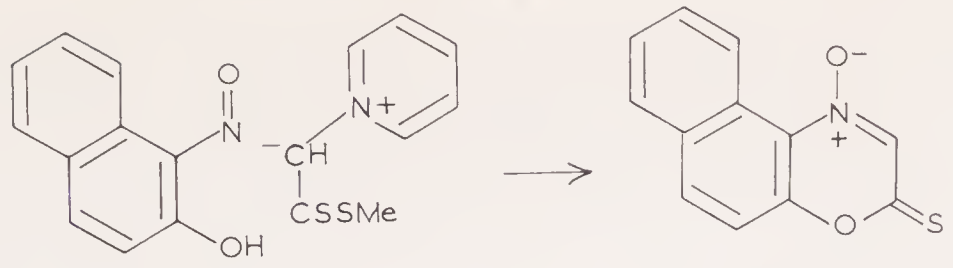

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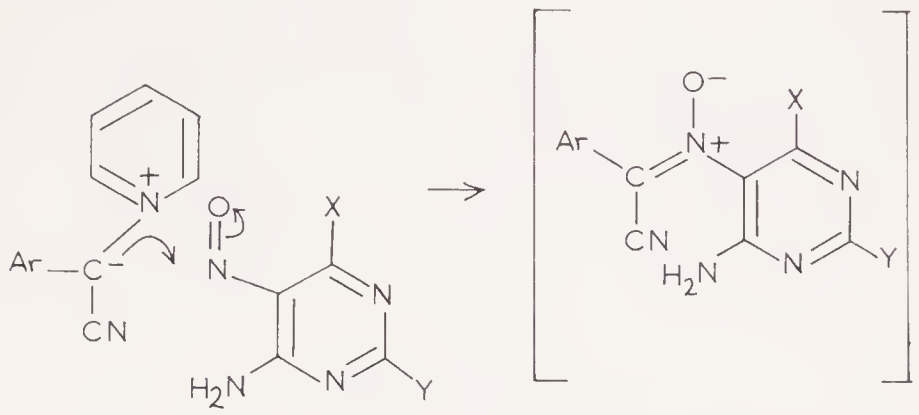

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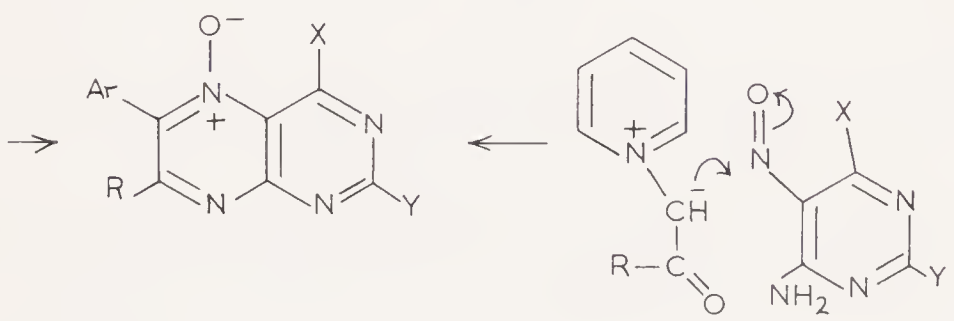
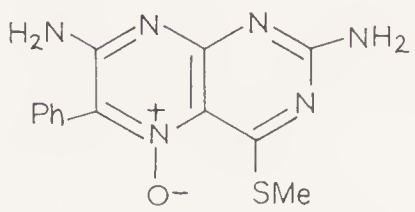


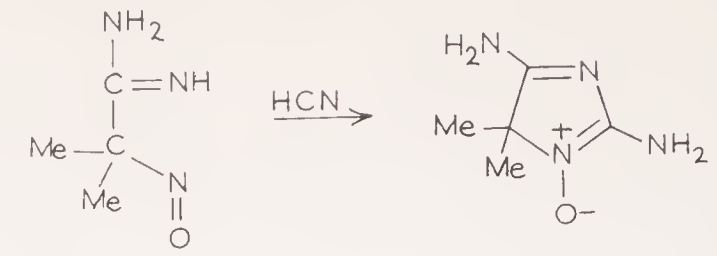
(346) (347)



(348)

c. Imidazole and Benzimidazole N-*Oxides.* Derivatives of imidazole 1-oxide (*350*) (*350* is the most probable tautomeric form) are prepared by the reaction of α-nitrosoamidines with hydrogen cyanide: *349* → *350* (42JO164).

Nitrosobenzene and benzonitrile oxide combine spontaneously to yield 1-hydroxy-2-phenylbenzimidazole 3-oxide: *351* → *352* (63TL785). The reaction is considered to proceed via adduct *353*, which has been isolated at low temperatures. The synthesis has been extended to the preparation of other substituted derivatives [63TL785; cf. 67J(B)911].



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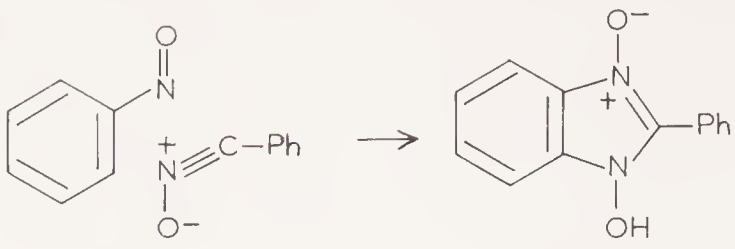

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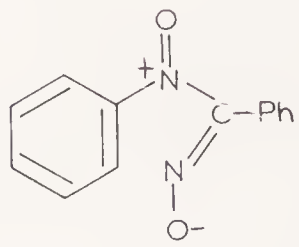
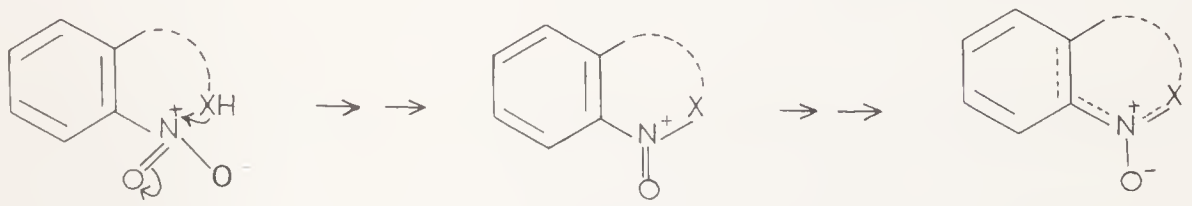


(353)

C. RING CLOSURE OF NITRO COMPOUNDS BY NUCLEOPHILIC ATTACK ON THE NITRO-NITROGEN ATOM

On the basis of the evidence presently available, the reactions described in this section could proceed by a mechanism of the general type *354* → *355* → *356*, i.e. by nucleophilic attack on the nitrogen atom of a nitro group. However, it must be emphasized that other mechanisms, which involve reduction of the nitro group to the nitroso or hydroxyamine stage, are possible, even probable, in some cases. Many reactions of this type are included in a review by Loudon and Tennant (64QR389). The nitro compounds are invariably aromatic and thus the compounds produced are all benzo derivatives. The nucleophilic centre can be an aliphatic (stabilized) carbanion, a reactive aromatic ring, or an amino group. We classify these reactions according to the ring system produced.

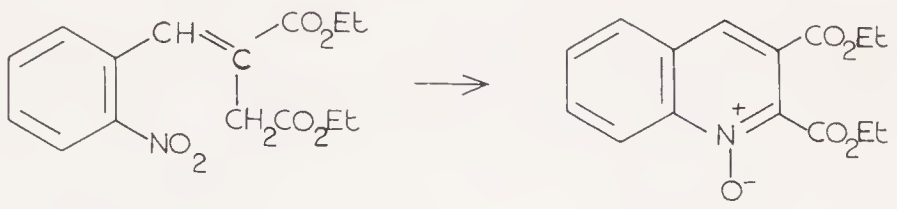


(354) (355) (356)

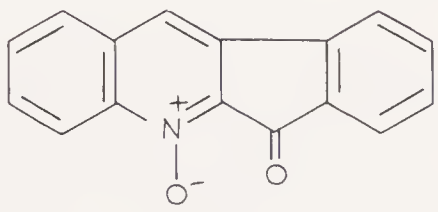
i. Benzo Derivatives of Pyridine

a. Quinoline 1-Oxides. Several successful preparations of quinoline 1-oxide by apparent nucleophilic attack on a nitro-nitrogen atom have been reported. *o*-Nitrobenzylidenemalonic ester (*357*) is cyclized by aqueous

potassium hydroxide to the diethoxycarbonyl *N*-oxide *358*, which under the reaction conditions is hydrolysed and decarboxylated at the α-position (66BJ195). The reaction of *o*-nitrobenzaldehyde with indanone to yield the condensed quinoline oxide *359* is similar (66TL1991). The ring closure of the *o*-nitro-phenyl-ketoester *360* to give *361* has also been effected successfully (64QR389), although attempts to cyclize the somewhat analogous cyano-ketone *362* failed (63JO2890).



(357) (358)



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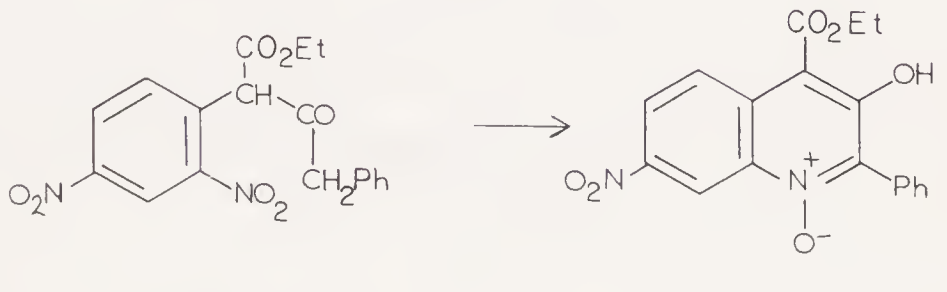

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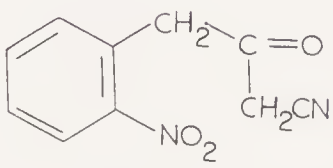
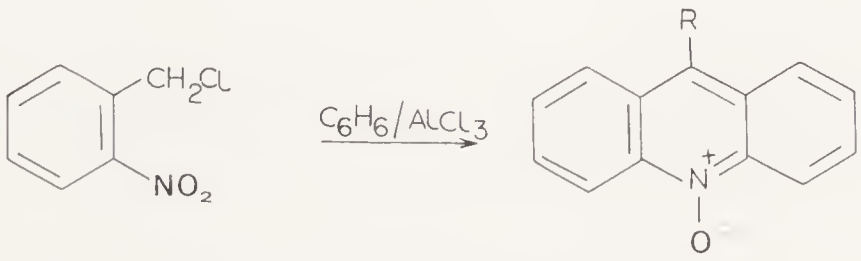
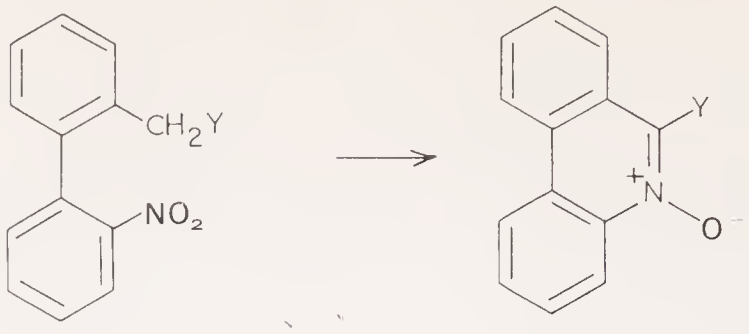


(362)

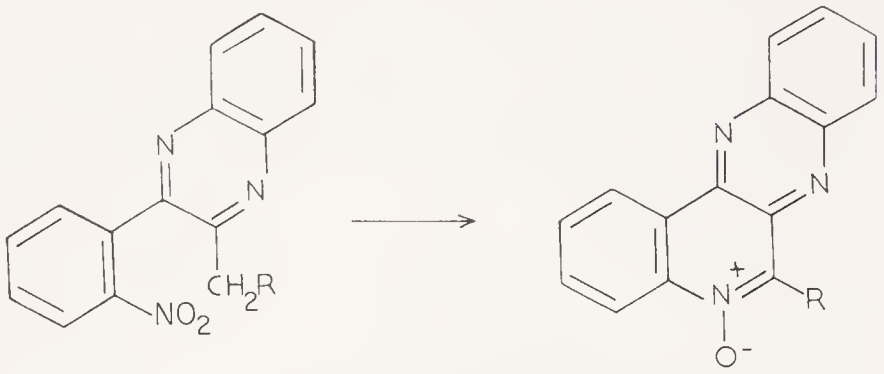
b. Acridine 10-Oxide. Acridine 10-oxide is formed by a Friedel-Crafts type reaction of 2-nitrobenzyl chloride with benzene: *363* → *364* (R = H); this reaction may be related to the preparation of 9-hydroxyacridine 10-oxides (*364*, R = OH) discussed in Section II-2Bia.



(363) (364)



(365) (366)

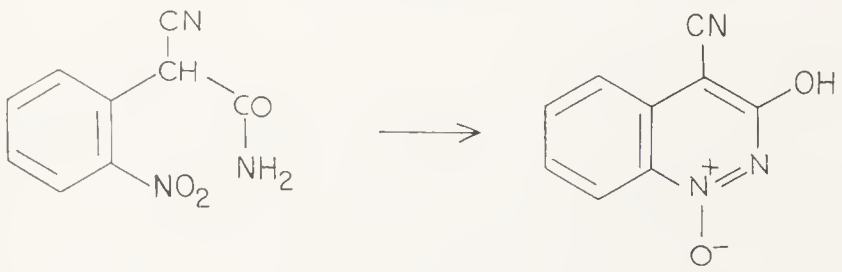


(367) (368)

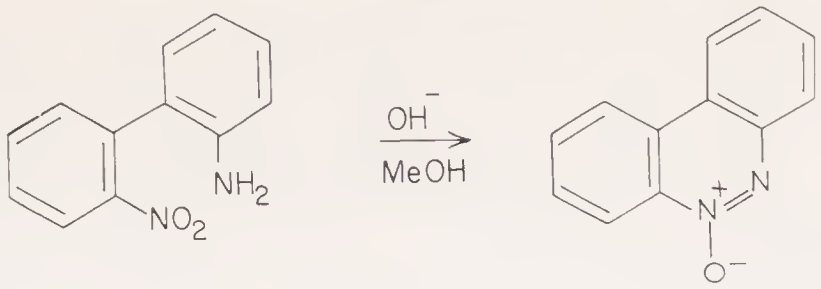
c. Phenanthridine 5-Oxide. Muth and his collaborators prepared phenanthridine 5-oxides (*366*) by the base-catalysed (NaOH–MeOH) cyclization of *o*-nitrobiphenyl derivatives of types *365* (Y = CO_2Me, CN, or $CONH_2$) (57JA6500) and *365* (Y = COPh, SO_2Ph) (60JO736). However, with certain other substituents, ring closure was not observed (58JA465). Analogous transformations of type *367* → *368* to yield quinoxalino-quinoline oxides were also effected successfully (63JO2890).

ii. Benzo Derivatives of the Diazines

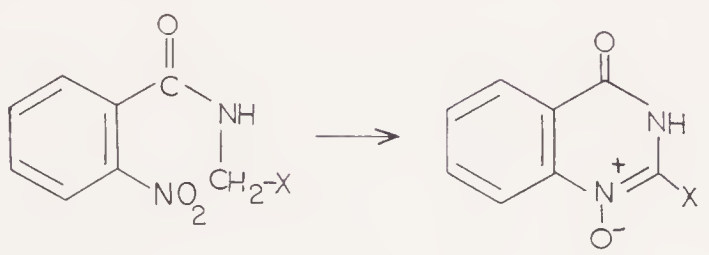
a. Cinnoline N-*Oxides.* The reactions in this section can be formulated as nucleophilic attack by an amino group on a nitro group. The 3-hydroxycinnoline 1-oxide *370* has been prepared by cyclization of the nitro-amide *369* (64QR389). 2-Amino-2′-nitrobiphenyl (*371*) is converted on treatment with alkali into benzo[*c*]cinnoline 1-oxide (*372*) (60JO736); this preparation of cinnoline oxides is general and has been extended to bromo (61J5029), nitro (64J1265), and benzo analogues of *371* [66J(C)890]. Benzocinnoline 1-oxides are also frequently obtained by reduction of 2,2′-dinitrobiphenyls, but here they probably arise via hydroxylamine (or nitroso) intermediates and are considered in Sections II-2Aiia and II-2Biiia.



(369) (370)



(371) (372)

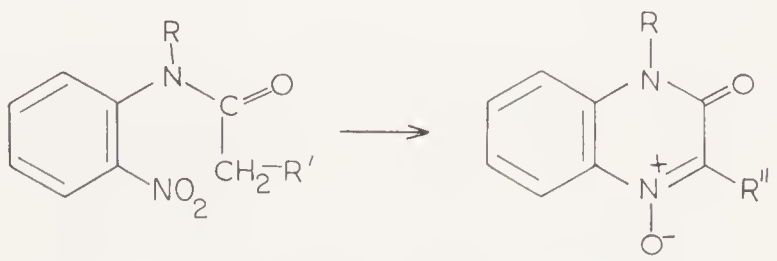


(373) (374)

b. Quinazoline N-*Oxides*. Tennant and Vaughan [66J(C)2287] have shown that substituted *o*-nitrobenzamides of type *373* (X = CN, COPh) are ring closed by sodium ethoxide to 2-ethoxy-4-quinazolinone 1-oxide (*374*; X = OEt). The product probably arises from a subsequent nucleophilic displacement on intermediates of type *374* (X = CN, COPh); such an intermediate can be isolated when X is a benzoyl group. This reaction also succeeds with *N*-substituted analogues of type *373* (69CH194).

c. Quinoxaline N-*Oxides*. Tennant showed (63J2428) that certain *C*-substituted *o*-nitroacetanilides (*375*, R = H) on treatment with alkali give 3-quinoxalinone 1-oxides (*376*). In reactions of this type *β*-ketoanilides lose an acyl group: *375* (R′ = COMe) → *376* (R″ = H); the pyridino derivative *375* ($R' = \overset{+}{N}C_5H_5$) is converted into the amino compound *376* ($R'' = NH_2$). Later it was shown that *N*-alkylacetanilides (*375*, R = Me) cyclize (64J2666), which indicates that the reaction probably involves nucleophilic attack on the nitro group and that an *aci*-nitro compound is not formed. Other examples of this reaction are given in Table 2.25.

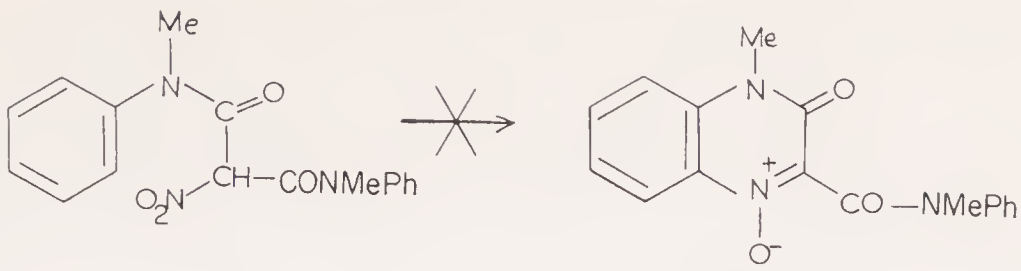
The reaction of nitromalon-bis-*N*-methylanilide (*377*) with sulphuric acid, originally reported to yield *378* (23J1069), actually produces 1-methylisatin 3-oxime (59J2825). However, related isonitroso derivatives have been cyclized to quinoxaline 1-oxides; see Section II-2Bib.



(375) (376)

Table 2.25. Formation of 3-Quinoxalinone 1-Oxides by Cyclization of *o*-Nitroacetanilides (375 → 376)

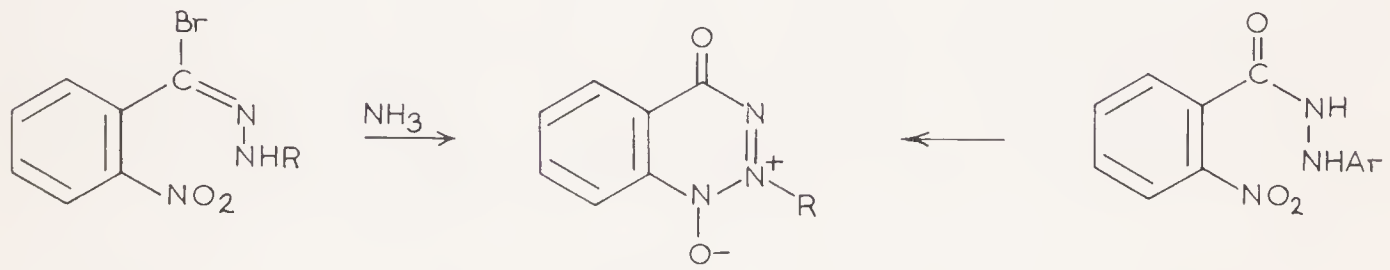
o-Nitroacetanilide o-NO_2-C_6H_3R-NH-CO-CHR′R″			Reagent	3-Quinoxalinone 1-oxide	Yield, %	References
R	R′	R″				
4-H, -OR, -Cl	H	CN	C_5H_5N–1N NaOH	7-*H*(or -alkoxy-, -chloro-)-2-cyano	60–65	64T1107
H	*n*-alkyl	PhCO	2N NaOH–EtOH	2-*n*-alkyl	61–94	66J(C)2285
H	H	Ph, *p*-Cl-C_6H_4	aq. C_5H_5N–KOH	2-(*p*-chlorophenyl) or -phenyl	62–65	65BJ1654
4-H, -OMe, -Cl, -Me	H	CN	"alkaline media"	7-*H*(or -alkoxy-, -chloro-, -methyl-)-2-cyano	—	63IM834
4-H, -OR, -Cl, -5-H, -Cl	H	CN, COR, Ph, *p*-NO_2-C_6H_4	C_5H_5N–20% KOH	2-acyl-, -cyano-, -(*p*-nitrophenyl)-, -phenyl-6- and/or -7-substituted	70–88	65T861
5-OMe	H	Ph	C_5H_5N–20% KOH	6-methoxy-2-phenyl	(data)	68JO201



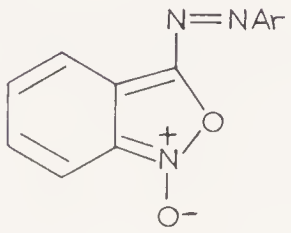
(377) (378)

iii. Benzo Derivatives of Triazine and Oxazine

a. 1,2,3-Benzotriazine 1-Oxides. 1,2,3-Benzotriazin-4-one 1-oxides (*380*) are claimed to result from the elimination of hydrogen halide from bromohydrazones of type *379* (27J323; 30J157; 31J2787; 31J2792; cf. 25J2407) or from the corresponding chloro compounds (30J843). These 1-oxides are also available from the hydrazines (*381*) (35J1005). More recently, Gibson [62T(18)1377] has questioned the formulation of these compounds as triazine derivatives, and has suggested that they are azo-anthranil *N*-oxides (cf. *382*).

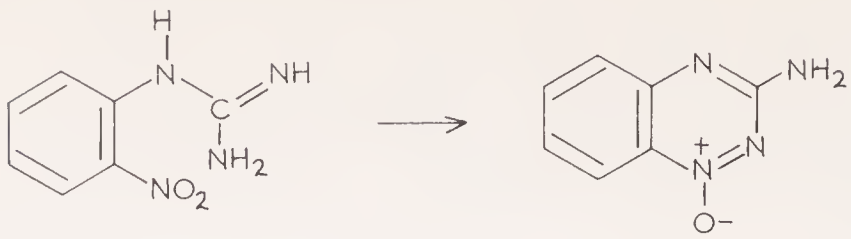


(379) (380) (381)

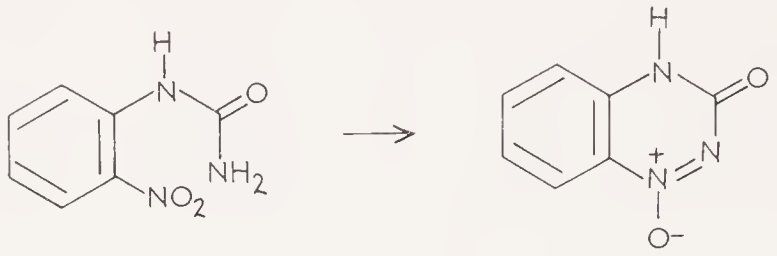


(382)

b. 1,2,4-Benzotriazine 1-Oxides. The base-catalysed cyclization of *o*-nitrophenylguanidines (*383*) to 3-aminobenzo-1,2,4-triazine 1-oxides (*384*) and of *o*-nitrophenylureas (*385*) to the corresponding benzotriazin-3-one 1-oxides (*386*) was discovered by Arndt (13CB3522). Many additional examples of this reaction have been reported, and these often involve an *o*-nitrophenylguanidine which is prepared *in situ* from *o*-nitroaniline and cyanamide. Available data are recorded in Table 2.26. The reaction has also been extended to some heterocyclic analogues: *387* → *388* (57JO654) and *389* → *390* (62JO2504). Compounds of type *387* can be formed *in situ* from an *o*-nitrophenyl azide and phenylacetonitrile [67J(C)1279]. However, attempted preparation of imidazo- and pyrimido-triazine oxides failed (61JO455).



(383) (384)



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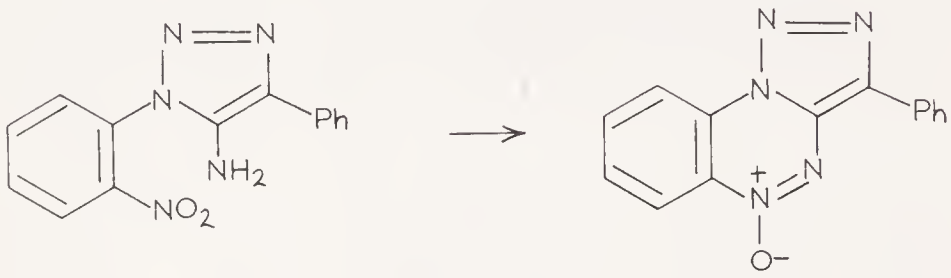
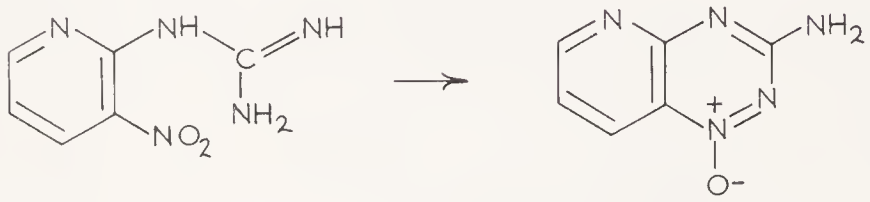
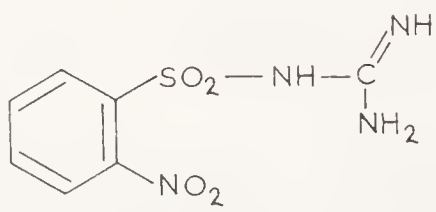


(387) (388)



(389) (390)



(391)

The benzotriazine 1-oxide *384* is also formed by treatment of the sulphonyl guanidine *391* with alkali; sulphur dioxide is eliminated in the reaction (47R689).

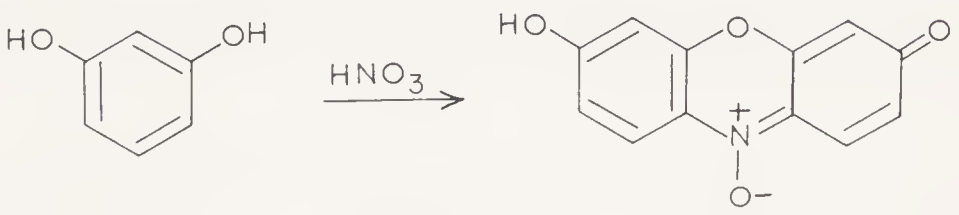
c. Phenoxazine N-*Oxides*. Nitration of resorcinol (*392*) under certain conditions yields resazurin, the structure of which was finally settled as the phenoxazine 10-oxide *393* only after extensive work [71CB613; 72LA(162)273; 84CB1847; 89CB3020; 91CB3366]. The optimum conditions for the preparation of resazurin are discussed in reference 53KM123. The

Table 2.26. Preparation of 1,2,4-Benzotriazine 1-Oxides from *o*-Nitrophenylguanidines (383 → 384) and ureas (385 → 386)

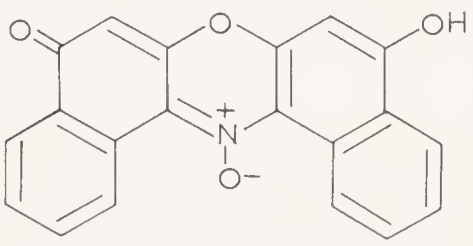
1,2,4-Benzotriazine 1-oxide	Yield, %	References
3-Amino	—	13CB3522, 17CB1248, 50IU91
3-Amino-5-alkoxy and -alkyl	ca. 50	49USP2489352, 57J3186
3-Amino-6-chloro-7-sulphamoyl	12	64R1305
3-Amino-6 (or -7)-mono- and -5,7-di-halogeno	—	49USP2489352
3-Amino-7-nitro	83	68MC946
3-Amino-7-substituted	12–50	49USP2489352, 54JA3551, 57J3186, 59JO813, 64R1305
3-Amino-5,7-disubstituted	ca. 65	54JA3551, 59JO813
7-Carboxy	70	66H651
3-Chloropyrido[2,3-*e*]	—	64USP3137693
3-Hydroxy	—	13CB3522
3-Hydroxy-7-carboxy	—	66H651
3-Hydroxy-7-chloro	85	49USP2489353
3-Mercapto[a]	(data)	17CB1248
3-Substituted-amino	(data)	17CB1248, 62JO185
3-Substituted-amino-7-chloro	30–90	54JA4611

[a] From *o*-nitrophenylthiourea.

reaction mechanism presumably involves nucleophilic attack by one resorcinol molecule on nitroresorcinol. However, the reaction of 2-nitroso-1-naphthol with 2-naphthol yields the dibenzo derivative *394* (68M1915), which resembles some of the reactions in Section II-2Bia.



(392) (393)



(394)

iv. Benzo Derivatives of Azoles

Some of the preparations of isatogen, which are treated in Section II-2Eiia, should probably be classified here.

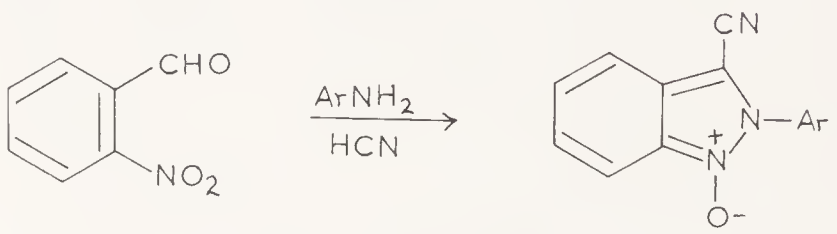
a. Indazole 1-Oxides. 2-Aryl-3-cyanoindazole 1-oxides (*396*) are formed by the reaction of *o*-nitrobenzaldehydes (*395*) with anilines and hydrogen cyanide. The corresponding Schiff's base and a source of cyanide ions or the aldehyde cyanohydrin and the aniline may be alternatively used as starting materials. The reaction, which was first described by Heller and Spielmeyer (25CB834), occurs smoothly and gives good yields; examples are summarized Table 2.27. The reaction can obviously be formulated as ring closure by nucleophilic attack on the nitro-nitrogen atom, but an alternative mechanism needing consideration involves an intermediate nitroso compound, formed as shown in structure *397*.

Table 2.27. Formation of Indazole 1-Oxides from *o*-Nitrobenzaldehydes by Reaction with Anilines and Hydrogen Cyanide (395 → 396)

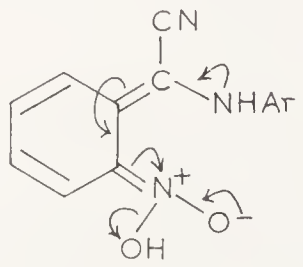
3-Cyanoindazole 1-oxide	Yield, %	References
5-Bromo- and 5-ethoxy-2-phenyl	15	54JA3672
2-(*p*-Ethoxyphenyl)	22	54JA3672
2-(*m*-Halogenophenyl)	—	41SP798
2-(*p*-Halogenophenyl)	ca. 30	25CB834, 41SP798, 54JA3672
2-Phenyl	75	25CB834, 26CB351
2-(*m*-Nitrophenyl)	54	41SP798, 62JO65

2-Arylindazole 1-oxides are also reported to be formed in the reaction of nitro compounds with *o*-nitrophenylacetate ester: *398* → *399* (35BF1016).

o-Nitrobenzalamines (*400*) isomerize in the presence of sodium carbonate to yield 1-hydroxyindazolones (*401*), which are tautomeric with 3-hydroxy-indazole 1-oxides (*402*) (33BF1436; 34BF373; 35BF69). The mechanism of this transformation is obscure.



(395) (396)



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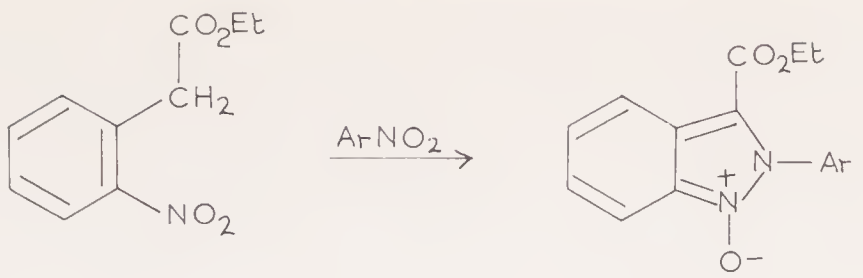

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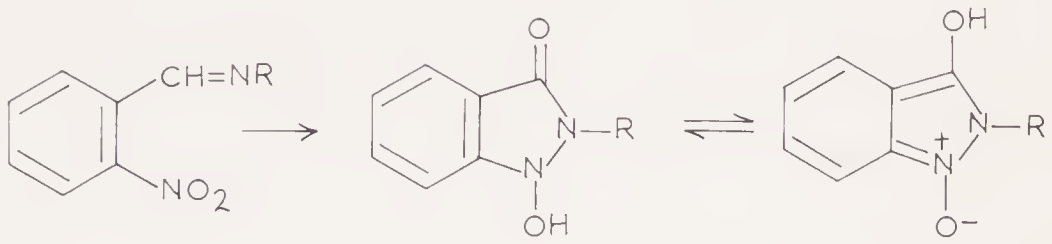
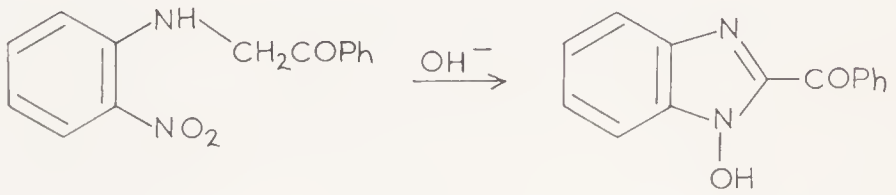
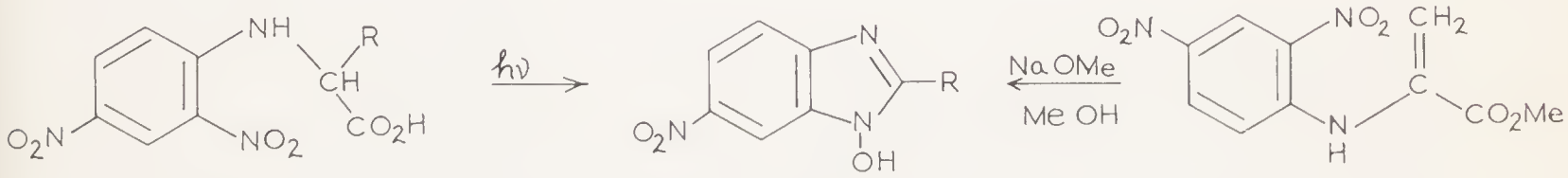


(400) (401) (402)

b. Benzimidazole 1-Oxides. Loudon and Tennant have reported the base-catalysed cyclization of *o*-nitroanilinoacetophenone (*403*) to 1-hydroxybenzimidazole (*404*), which is in tautomeric equilibrium with benzimidazole 1-oxide (see Section III-6Ai) (63J4268). This reaction probably involves nucleophilic attack on the nitro group by the ketone carbanion. A transformation which is similar, at least in a formal if not in a mechanistic sense, is the photolytic conversion of 2,4-dinitrophenyl derivatives of α-amino acids (*405*) into 1-hydroxybenzimidazoles (*406*) [65CH262; 67J(C)1764].* Recently the ring closure *407* → *406* (R = CO_2Me) has been reported; formaldehyde is eliminated in this reaction [66CH301; 67J(C)1750]. Benzimidazole 3-oxides are implicated as intermediates in the cyclization of *o*-nitro-*N*,*N*-dialkylanilines [69J(C)70], and under suitable conditions this reaction gives benzimidazole *N*-oxides in good yield (69CH722). However, the mechanism does *not* involve nucleophilic attack at the nitro group.



(403) (404)



(405) (406) (407)

* See addendum in the Appendix.

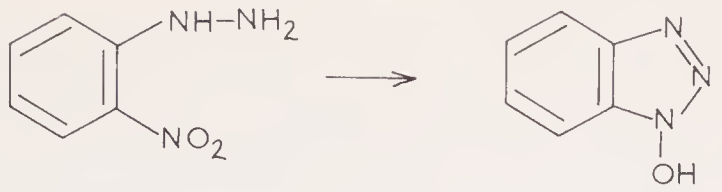
c. Benzotriazole 1-Oxides. The base-catalysed cyclization of *o*-nitrophenylhydrazines (*408*) to yield 1-hydroxybenzotriazoles (*409*), which are tautomeric with benzotriazole 1-oxides (see Section III-6Ai), was discovered by Freund (89CB1663) and by Willgerodt [88PC(37)345] and clarified by Nietzki and Braunschweig [94CB3381; cf. 99PC(60)97]. *N*- and *N'*-Substituted *o*-nitrophenylhydrazines, respectively, undergo reactions *410* → *411* to give 2-substituted and *412* → *413* to give 3-substituted benzotriazole 1-oxides which are not tautomeric. This insensitivity of the reaction to substitution supports its classification as a reaction involving nucleophilic attack on the nitro-nitrogen atom. Examples of these reactions are given in Table 2.28.

The benzotriazole 1-oxide *414* can be obtained from 2,4-dinitrophenylhydrazine and 4-hydroxy-3-methylbutanone (64JO443), presumably via the pyrazoline derivative *415* followed by a reaction essentially of type *412* → *413*.

Table 2.28. Formation of 1,2,3-Benzotriazole 1-Oxides by the Cyclization of *o*-Nitrophenylhydrazines (408 → 409)

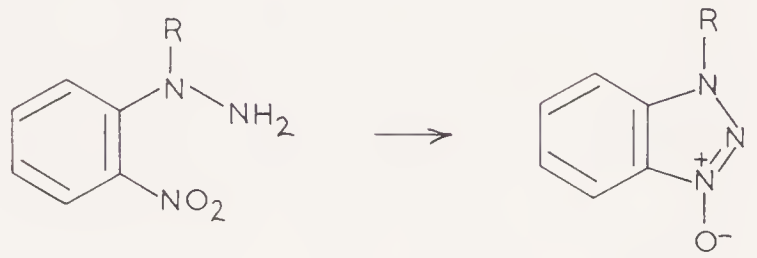
1,2,3-Benzotriazole 1-oxide	References
—	94CB3381, 00LA(311)329
6-Carboxy-5-methoxy-2-phenyl	41H30
4-Chloro-5-methyl	21J1700
Chloro, poly-	69JO359
5-Halogeno	60JO657
4,6-Dihalogeno	60JO657
5-Halogeno-6-methyl	60JO657
5-Halogeno-6-nitro-2-phenyl	59JI417
4-Methyl-6-nitro	23CB1488
5-Methyl-4-nitro[a]	13CB2117
5- (or 7)- and 6-Methyl-4-nitro	21J894, 23J2258
6-Nitro	07PC(76)369
7-Nitro	11LA(370)152
Dinitro-2-aryl	89CB1663, 91PC(43)177, 91PC(44)451
Trinitro-2-aryl	88PC(37)345, 91PC(43)177, 99PC(60)97, 02PC(65)97, 05PC(71)385, 05PC(71)398, 05PC(71)409
2-(*p*-Nitrophenyl)	35G1191
3-(3'-Oxo-butyl and -pentyl)-6-nitro[b]	63JO2326
4,5,6, and 7-H or substituted-2-(*p*-sulphamylphenyl)	64JI845
2-*p*-Tolyl (various)	58JI681

[a] This compound was later suggested to be 7-methyl-6-nitro-1,2,3-benzotriazole 1-oxide (23J2258).
[b] Originally incorrectly formulated as pyrazolines (55IA31).

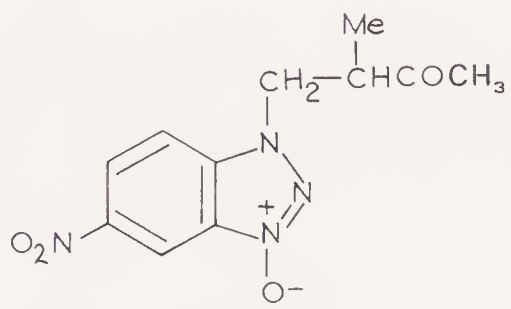


(408) (409)

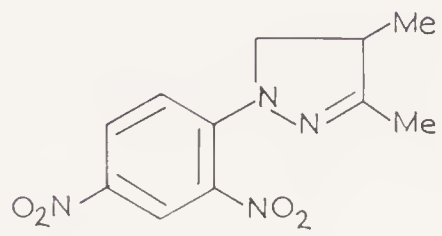
(410) (411)



(412) (413)



(414)



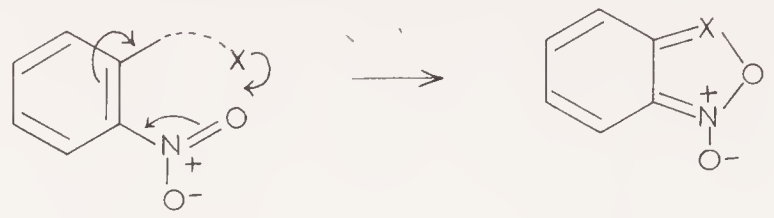
(415)

D. RING CLOSURE OF NITRO COMPOUNDS WITH RETENTION OF BOTH OXYGEN ATOMS

The reactions included in this section all involve ring closure of type *416* → *417*. With one exception, they are limited to the preparation of *N*-oxides with five-membered rings, and the products are necessarily oxazoles or oxadiazoles.

i. 1,2-Oxazine N-*Oxides*

1,2-Benzoxazine 2-oxides of type *419* can be prepared by Michael addition of dihydroresorcinol to α,β-unsaturated nitro compounds, followed by ring closure: *418* → *419* (58CB1344). Compounds of this type are also thought to be intermediates in certain photochemical reactions (69CH125).*



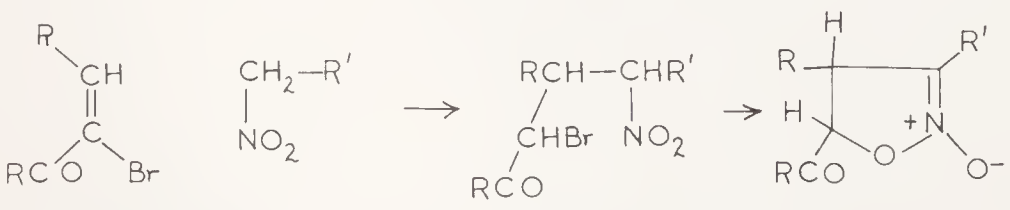
(416) (417)

(418) (419)

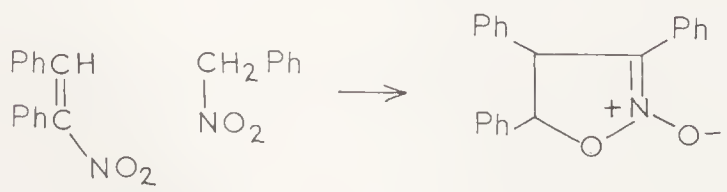
ii. Derivatives of Azoles

a. Isoxazoline 2-Oxides. Kohler and his co-workers showed that α-bromo-α,β-unsaturated ketones (*420*) undergo Michael-type reactions with nitro compounds to give adducts (*421*) which readily cyclize to isoxazoline 2-oxides (*422*). These compounds are, however, very sensitive to acids and bases and frequently react further *in situ* to give ring-opened products. The literature is rather confused because of the ease of these subsequent reactions (24JA503; 24JA1733; 25JA3030; 26JA2425; 28JA221). Unsaturated and saturated nitro compounds also react together: *423* → *424* (24JA2105; 60JO47); however, in this case nitrocyclopropanes can also be produced (cf. 56JO816). For further related work, see references 26JA1770, 35JA2299, 52LA(578)113, and 56JA3412.

The mechanism of the ring closure of 1,3-dinitropropanes has recently been shown to involve an intramolecular nitrite ion displacement from the intermediate mono-anion (69JO984).

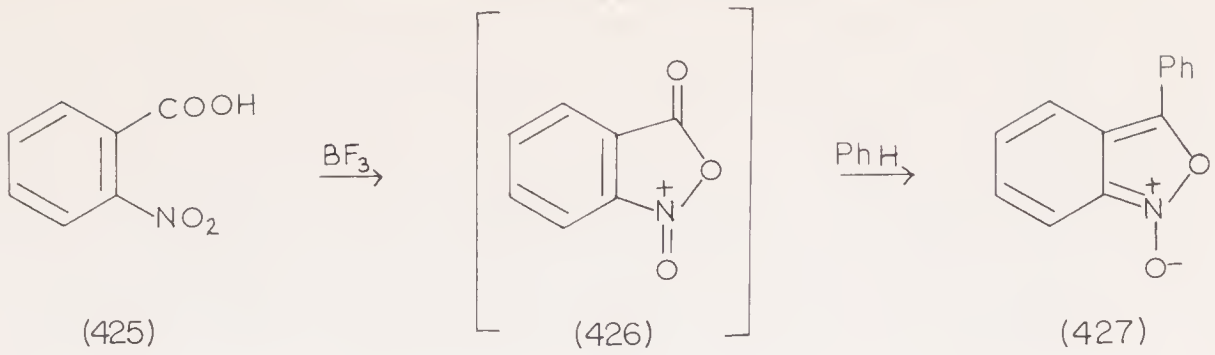


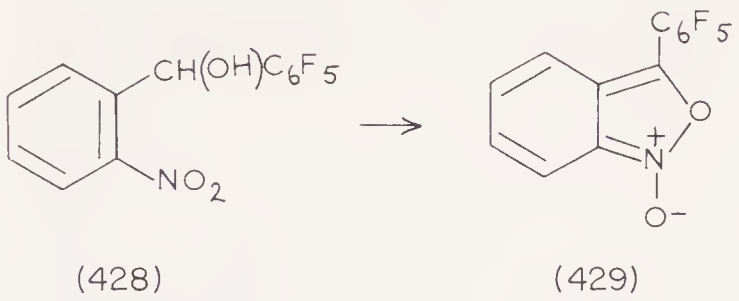
(420) (421) (422)

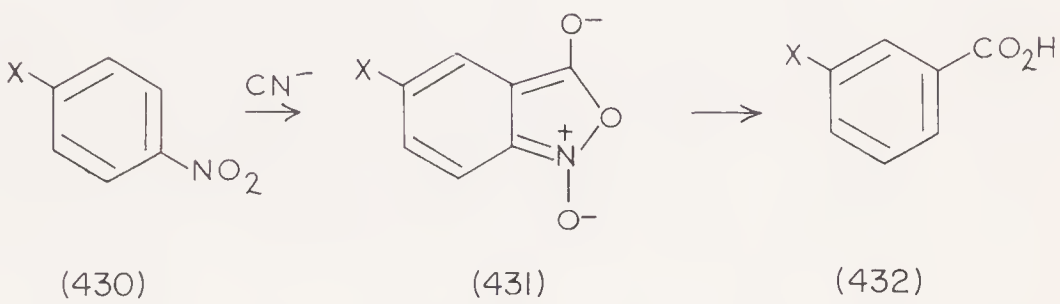


(423) (424)

* See addendum in the Appendix.







b. Anthranil Oxides. 3-Phenylanthranil *N*-oxide can be obtained from *o*-nitrobenzoic acid and benzene by the route shown (*425* → *427*); this reaction involves a reduction stage (59JA962). An analogous reaction is involved in the preparation (*428* → *429*) of the pentafluorophenyl derivative [66J(C)2020].

A series of compounds, the preparation of which is considered in Section II-2Ciiia because they are usually formulated as benzotriazine oxides, has also recently been assigned the anthranil *N*-oxide structure. Intermediates of type *431* are postulated to occur in the von Richter conversion of nitro compounds of type *430* into carboxylic acids (*432*) (60J1318).*

c. Benzo-1,2,5-oxadiazole 2-Oxides (Benzofuroxans). Benzofuroxans (*434*) can be prepared by the pyrolysis of *o*-nitrophenyl azides (*433*) and by the oxidation of *o*-nitroanilines (*435*): in each case a nitrene (*436*) could be an intermediate, but the reactions probably involve participation of the nitro group, see below. References to the preparation of benzofuroxans by these routes are given in Tables 2.29 and 2.30, respectively. The pyrido-furoxan *438* is prepared from the nitropyrido-tetrazole *437* as shown (53JA5298; 56JA423). It should be noted that benzofuroxans were formulated in other ways before structure *434* was established (see Section III-5Ciiib) and many of the earlier references contain incorrect formulations.

The rate of nitrogen elimination from *o*-nitrophenyl azides is correlated by the Hammett equation (60AS1899); the rates are almost independent of

* See addendum in the Appendix.

Table 2.29. Preparation of Benzofuroxans from *o*-Nitrophenyl Azides (433 → 434)

2-Nitrophenyl azide	Reaction conditions	Benzofuroxan formed	References
—	dibutyl phthalate, heat	—	60AS1894, 60AS1899
4-Acetamido	acetic acid, heat 0·5 h	6-acetamido	66J(C)971
4-Acetoxy	toluene, heat 2 h	6-acetoxy	66J(C)971
5-Azido-4-nitro	heat at 80–85°, then P_2O_5 + anhyd. HNO_3	nitrobenzdifuroxan	54JA2233
4-Azido-3,5-dinitro	acetic acid, heat 2 h	nitrobenzdifuroxan	58T(3)113
4,6-Diazido-3,5-dinitro	propionic acid, heat	benztrifuroxan	58T(3)113
3- and 6-Carboxy	sulpholane, 170–180° for 3 min	7- and 4-carboxy	68MC305
4-Carboxy	toluene, heat 0·5 h	6-carboxy	66J(C)971
6-Carboxy-4-methyl	*o*-chlorobenzene, heat 2 h	4-carboxy-6-methyl	66J(B)1004
4- and 5-Chloro	acetic acid, heat	5- and 6-chloro	65J5958
3,6-Dichloro	diethylene glycol, 140° for 1 h	4,7-dichloro	65JA5433
4-Chloro-5-dimethylamino	acetic acid, heat 1 h	6-chloro-5-dimethylamino	66J(C)971
4-Chloro-5-methylamino	acetic acid, reflux 1 h	6-chloro-5-methylamino	68MC305
5-Chloro-4-nitro	acetic acid, heat 0·5 h	5-chloro-6-nitro	58T(3)113
5-Dimethylamino	toluene, heat 1 h	5-dimethylamino	66J(C)971
3- or 5-Ethoxycarbonylamido-4-nitro	xylene, heat 1 h	4- or 6-ethoxycarbonylamido-5-nitro	68T6145
3-Methoxycarbonyl	diglyme, reflux 1 h	7-methoxycarbonyl	68MC305
6-Methoxycarbonyl	xylene, heat 3 h	4-methoxycarbonyl	66J(B)1004
3,6-Dimethyl	diethylene glycol, 140° for 1 h	4,7-dimethyl	65JA5433
3-Methyl-4-nitro	toluene, heat 2 h	7-methyl-6-nitro	66J(B)1011
5-Methyl-4-nitro	acetic acid, heat	5-methyl-6-nitro	66T995
4- and 4,5-Di-nitro	acetic acid, heat	6- and 5,6-dinitro	58T(3)113

Table 2.30. Preparation of Benzofuroxans by Oxidation of *o*-Nitroanilines (435 → 434)

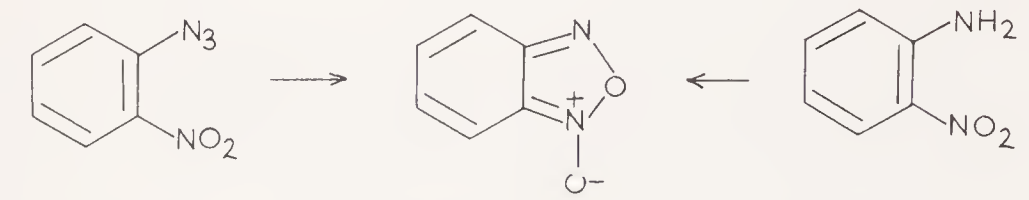
2-Nitroaniline	Oxidizing agent	Benzofuroxan formed	Yield, %	References
5,6-Benzo	$PhI(OAc)_2$	4,5-benzo	ca. 7	58AJ491
5-Bromo	NaOCl	5-bromo	50	62JO3218
3- and 6-Chloro	$PhI(OAc)_2$	7- and 4-chloro	49 and 86	58AJ491
4- and 5-Chloro	NaOCl	6- and 5-chloro	95[a]	54JA2233, 62JO3218
4,5-Dichloro	NaOCl	5,6-dichloro	60	65JA5433
4,6-Dichloro	NaOCl	4,6-dichloro	—	68MC305
5-Chloro-6-methoxy	NaOCl	5-chloro-4-methoxy	10[b]	12J2452, 63JO1656
3- and 6-Methoxy	$PhI(OAc)_2$	7- and 4-methoxy	33 and 2	58AJ491
4-Methoxy	NaOCl	6-methoxy	—	54JA2233
3-Methyl	$PhI(OAc)_2$	7-methyl	10–72[c]	58AJ491
4-Methyl	NaOCl	6-methyl	—	54JA2233
5-Methyl	NaOCl	5-methyl	55–95	12J2452, 13J897, 62JO3218
3,5- and 4,5-Dimethyl	NaOCl	5,7- and 5,6-dimethyl	— and 89	54JA2233, 65JA5433
3- and 6-Nitro	$PhI(OAc)_2$	7- and 4-nitro	93 and 11	58AJ491
4- and 4,6-Dinitro	NaOCl	6- and 4,6-dinitro	—	13J2023

[a] Yield for 5-chlorobenzofuroxan.
[b] 5-Chloro-4-methoxybenzofuroxan obtained in ca. 30% yield using 2,4-dinitroaniline as starting material.
[c] Best yield (72%) in acetone, poorest (10%) in acetonitrile.

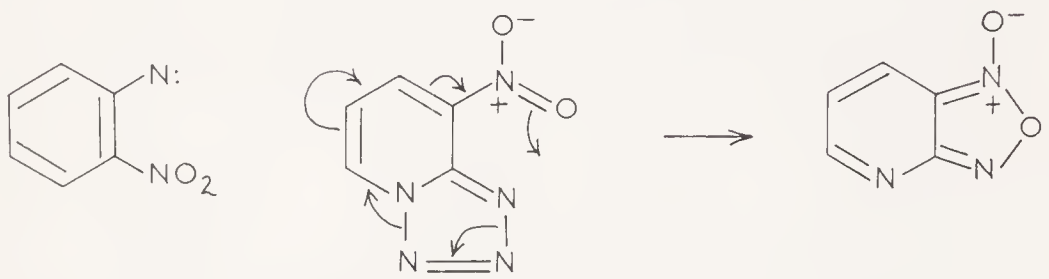
solvent which indicates a cyclic transition-state mechanism [66J(B)489]. Naphtho- and quinolino-furoxans have also been prepared by the pyrolysis of *o*-nitrophenyl azides [68J(B)1516].

The kinetics of the oxidation of *o*-nitroanilines, *435* → *434*, using iodosobenzene diacetate [$PhI(OAc)_2$] have also been investigated (58AJ485). Oxidation with vigorous oxidizing reagents such as hypochlorite sometimes leads to ring substitution as well as to ring closure (12J2452).

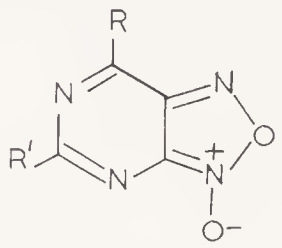
The reaction has been extended to naphtho-furoxans (17J612) and acenaphtho-furoxans (20J1344). Pyrimidino-furoxans (*439*) have been prepared by the reaction of 4-chloro-5-nitropyrimidines with sodium azide (68JO2086).



(433) (434) (435)



(436) (437) (438)



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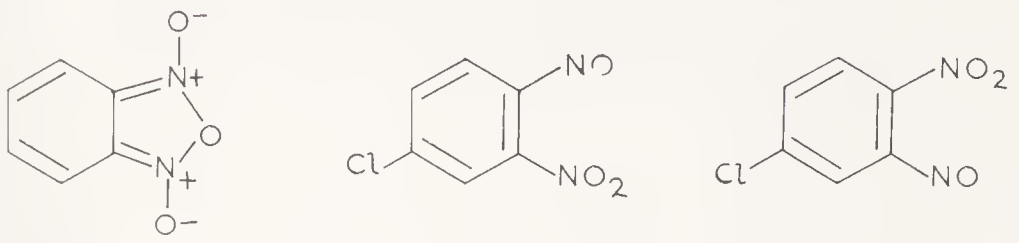


(440) (441) (442)

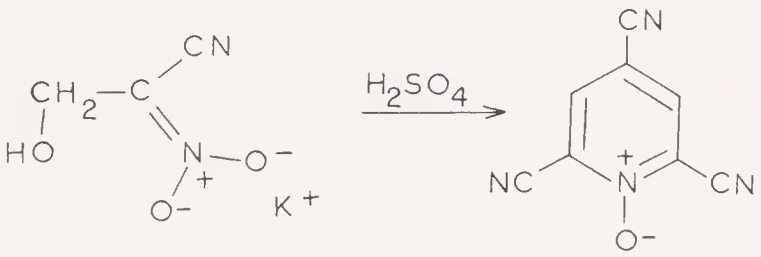
d. Benzo-1,2-5-oxadiazole 2,5-Dioxides. Although benzofurazan 1,3-dioxides (*440*) are evidently unstable at normal temperatures, as demonstrated by the independent existence of compounds *441* and *442*, the fact that *441* and *442* interconvert at higher temperatures indicates the occurrence of intermediates of type *440* (61JO3312).

E. MISCELLANEOUS RING CLOSURES

Included here are a variety of *N*-oxide preparations which do not appear to fit into any of the preceding classifications. In some instances a different species is involved, e.g. a nitrile oxide, in others the reaction mechanism is not clear. The reactions are classified according to the ring system formed.

i. Six-membered Ring Derivatives

a. Pyridine and Quinoline 1-Oxides. 2,4,6-Tricyanopyridine 1-oxide (*444*) has been prepared from salts of α-cyano-β-hydroxyethanenitrolic acid (*443*), and it is reported that the trinitro analogue can be made similarly [66AG(E)846]. Details of the reaction mechanism are still obscure. Quinoline 1-oxides have been suggested as intermediates in the reaction of anthranil with ketones: *445* → *446* [66LA(698)149; cf. 69CB3014].



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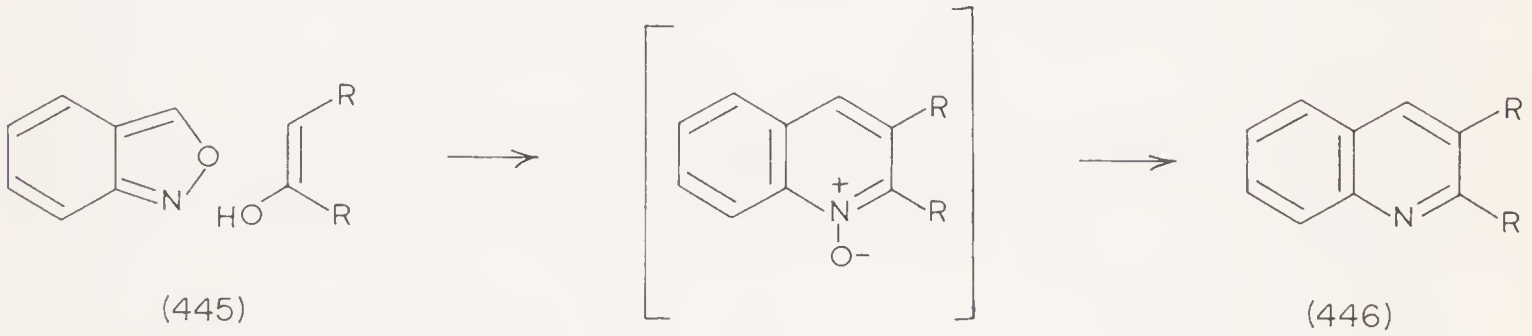

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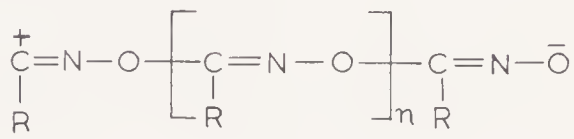

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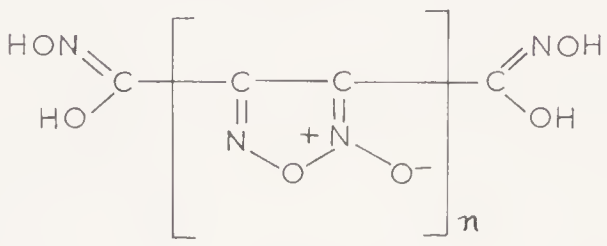
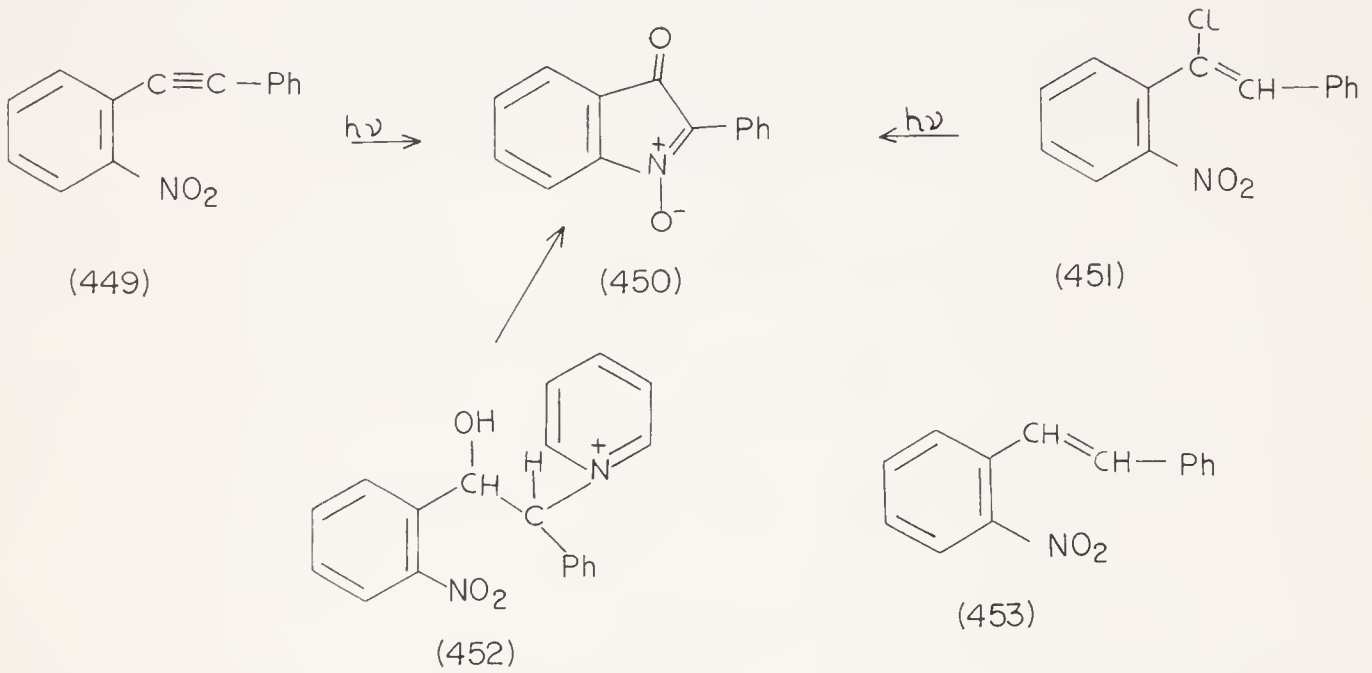


(448)

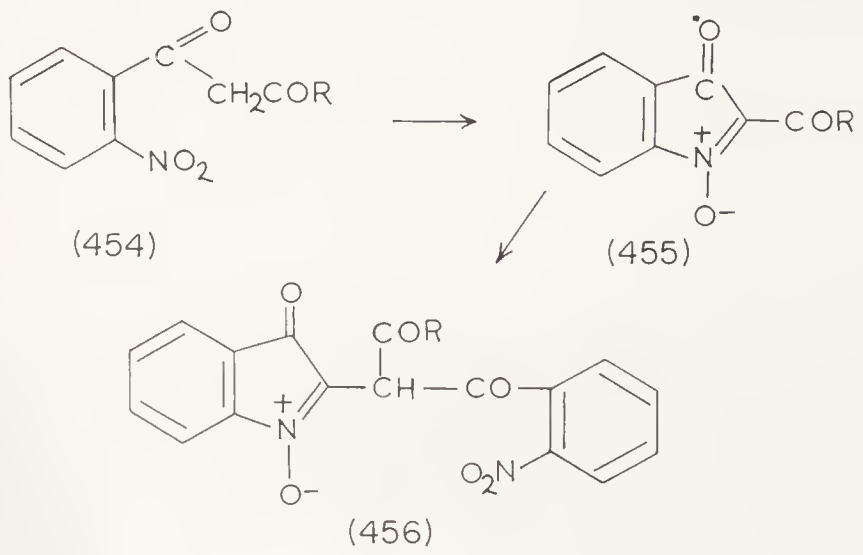
b. 1,3,5-Triazine N-*Oxides.* The preparation of 1,3,5-triazine 1,3,5-trioxides by trimerization of a nitrile oxide is recorded (09CB803; 09CB816); however, these products have more recently been reformulated as polymers of type *447* or *448* [65LA(687)191].

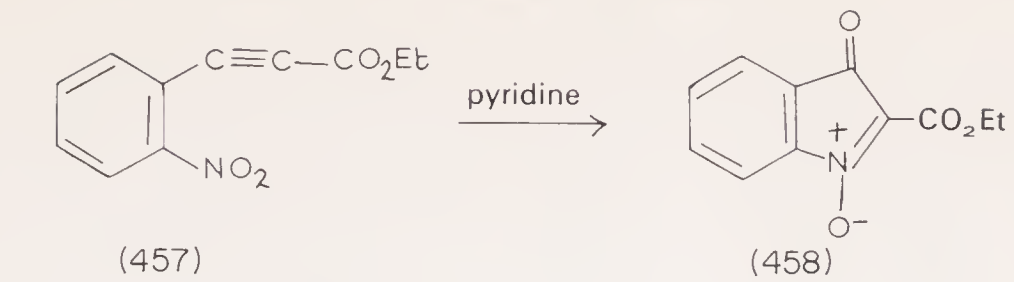
ii. Five-membered Ring Derivatives

a. 3-Indolone N-*oxides* (*Isatogens*). Isatogens (cf. *450*) have been prepared (cf. 38CR193) by photochemical methods and by base-catalysed cyclizations. Irradiation of *o*-nitrotolans (*449*) [13CB3655; 16LA(411)72], *o*-nitro-α-chlorostilbenes (*451*) [16LA(411)72], and the pyridinium cation *452* (52CB376; 53CB1500) leads in each case to isatogens. The ring closure of *o*-nitrotolans to isatogens is also catalysed by nitrosobenzene (37H250). Certain *o*-nitrostilbenes (cf. *453*) form isatogens on irradiation, but the presence of an electron-releasing group in the phenyl ring is required for appreciable yields (55JO1086; cf. 22CB1232).



Isatogens can also be prepared by a variety of non-photochemical methods. These include the base-catalysed transformation of *o*-nitrobenzoylacetone and similar compounds (*454*, R = Me, OMe) into isatogens (*455*), which are usually not isolated as such but condense with another molecule of substrate and undergo further conversion to form *456* [61J5205; 66J(C)1596]. The cyclization of some *o*-nitrophenylacetylenes into isatogens, e.g. *457* → *458*, is not light catalysed [16LA(411)72]. *o*-Nitrobenzaldehydes and 1-benzylpyridinium salts yield isatogens on mild alkali treatment (*459* → *460* → isatogen) (51CB932); the final ring closure is catalysed by light (52CB376).





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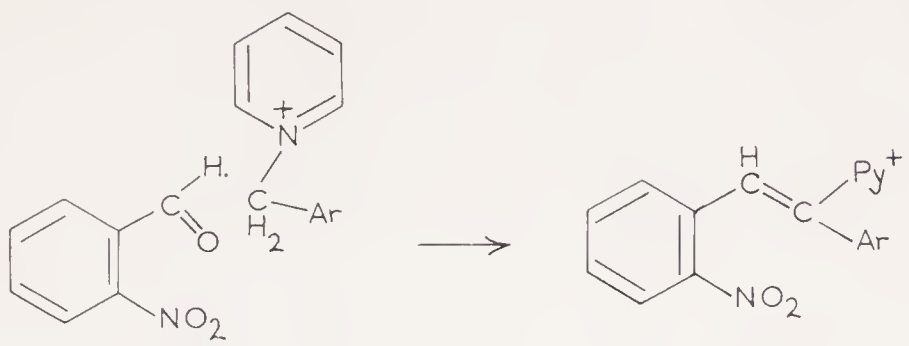
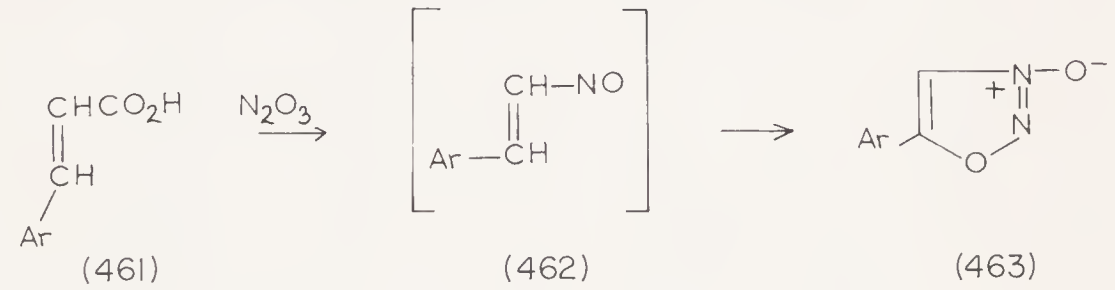


(459) (460)

b. 1,2,3-Oxadiazole 3-Oxides. The reaction of cinnamic acids with nitrogen trioxide is stated to yield 5-aryl-1,2,3-oxadiazole 3-oxides (*463*) by the route shown: *461* → *462* → *463* (59J257).

c. 1,2,4-Oxadiazole 4-Oxides. Wieland (07CB1667; 09CB803) has reported the preparation of diaryl-1,2,4-oxadiazole 4-oxides (*466*) by the spontaneous dimerization of benzonitrile oxides (*465*), which are formed from the hydroxamyl chlorides (*464*), and by the condensation of two molecules of nitroso-oximes (*467*) (06CB1480). The most common mode of dimerization of compounds of type *465* is the formation of furoxans (*468*) (Section II-2Eiid) [69J(C)1901], but the orientation of the dimerization depends on the catalyst concentration and solvent (69G565). 1,2,4-Oxadiazole 4-oxides can be obtained in fair yields (69G565).*



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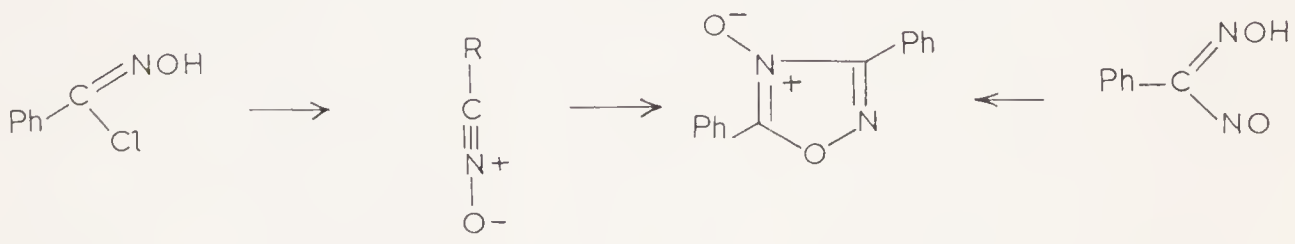


(464) (465) (466) (467)

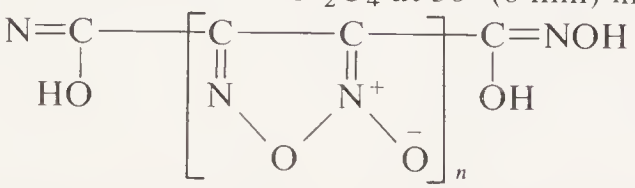
(468) (469)

* See addendum in the Appendix.

Table 2.31. Preparation of Furoxans by Dimerization of Nitrile Oxides (465 → 468)

Nitrile oxide	Reaction conditions	Furoxan formed	Yield, %	References
Alkylnitrile oxide[a]	heat	3,4-dialkyl	84–93	60JA5339
Benzohydroxamic chloride; arylaldoxime	aq. Na_2CO_3–heat, KOH–heat	3,4-diaryl (various)	27–79	99CB1975, 60JO546, 65ME841
Benzoylnitrile oxide[b]	90–100°	3,4-dibenzoyl	—	60JA2220
Mesitonitrile oxide	60–65°, 48 h, ligroin solution	3,4-dimesityl	20	68JO1464
Benzonitrile oxide[c]	See note [c]	3,4-diphenyl	10–82[c]	09CB803, 59JA4237, 60JA5339, 65ME841, 66TL4789
*				
$Ph\text{-}C\equiv CH + O\text{-}N\equiv C\text{-}C\equiv N\text{-}O$	vacuum sublimation	3,4-bis[5-phenyl-isoxazolyl-(3)]	(data)	65LA(687)191
$\overset{-}{O}\text{-}\overset{+}{N}\equiv C\text{-}C\equiv \overset{+}{N}\text{-}\overset{-}{O}$	20°, 60 h, toluene solution	Poly[d]	(data)	65LA(687)191

[a] From phenyl isocyanate and RCH_2NO_2.
[b] From acetophenone and HNO_3.
[c] With phenylnitrolic acid, reaction occurs at 0° (72 h) in 57% yield; with phenyl isocyanate and RCH_2NO_2 upon heating in 82% yield; and with α- or β-benzaldoxime and N_2O_4 at 36° (6 min) in 10% yield.
[d]



* *p*-Chlorobenzonitrile oxide; see addendum in the Appendix.

d. 1,2,5-Oxadiazole 2-Oxides (Furoxans). Of the variety of methods by which furoxans (*468*) can be prepared (cf. 38CR193), the dimerization of nitrile oxides (*465* → *468*) is amongst the most important. Examples of the preparation of furoxans by this general method are collected in Table 2.31. Nitrile oxides normally dimerize so readily that they are difficult to prepare. However, sufficiently sterically hindered nitrile oxides are resistant to dimerization (65JO2809; 67JO2308), although evidence has recently been presented which indicates that even dimesitylfuroxan can be prepared by the dimerization method (68JO1464). Electronic influences on the kinetics of dimerization of benzonitrile oxides have been studied by Dondoni, Mangini, and Ghersetti (66TL4789), who found that electron-accepting substituents facilitate the reaction.* Polymerization of nitrile oxides can also give triazine oxides (Section II-2Eib) or 1,2,4-oxadiazole oxides (Section II-2Eiic).

Styrene reacts with nitrosobenzene to yield two unstable isomeric products which have been formulated as *469* (R = H, R′ = Ph) and *469* (R = Ph, R′ = H) (63TL1361).

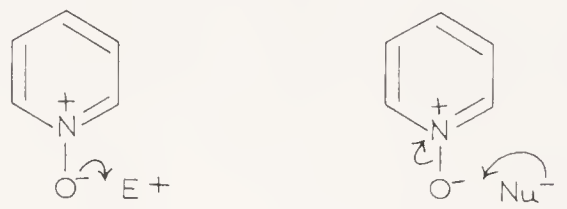
* See addendum in the Appendix.

CHAPTER III

Reactions at *N*-Oxide Rings

In this chapter, the reactions of *N*-oxides which involve attack by a reagent at the *N*-oxide oxygen atom or at ring carbon or nitrogen atoms are considered. Reactions of substituted *N*-oxides are included provided the substituent is not affected by the reaction.

Attack on the *N*-oxide oxygen atom by electrophiles (cf. *1*) and by nucleophiles (cf. *2*) is discussed first. Attention is then given to the numerous reactions which *N*-oxides undergo at ring carbon atoms. Both nucleophiles and electrophiles can attack at carbon atoms *alpha* and *gamma* to the *N*-oxide group because electron displacements of types *3* and *4* are possible.



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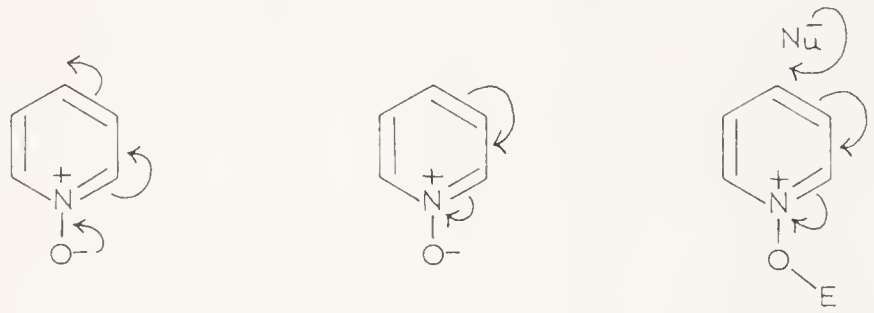

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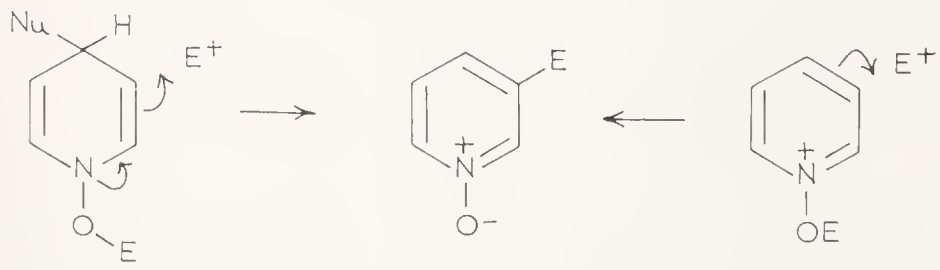


(6) (7) (8)

Many of the reactions involving nucleophilic attack at carbon, and classified as such, require the preliminary reaction of an electrophile at the oxygen atom (cf. *5*). Other reactions appear to involve the rearrangement of an

O-E group, which is also formed by preliminary electrophilic attack at oxygen (cf. *1*), from the nitrogen atom to the α-carbon atom; however, such reactions usually have more complex mechanisms. Several examples of electrophilic attack at the β-position are known which involve reaction with an electrophile (*6* → *7*) after transitory nucleophilic addition. Electrophilic attack at the β-position is also involved in direct reactions of the type illustrated by the sequence *8* → *7*. Reactions at ring carbon atoms are classified according to the mechanism of the step by which the substituent that finally remains attached to the ring is inserted. Hence, a reaction sequence of the type *1* → *5* → *6* → *7* is considered under electrophilic substitutions at carbon, although initial electrophilic attack at oxygen and nucleophilic addition at carbon are also involved. Based on the classification outlined, electrophilic, nucleophilic, and free-radical attack are considered individually, and a short section on miscellaneous reactions including those involving cyclic transition states (e.g., 1,3-dipolar additions) and the formation of charge-transfer complexes concludes the chapter.

Unsubstituted six-membered ring *N*-oxides are not normally capable of tautomerism, but this is not the case with the five-membered ring analogues. For unsubstituted *N*-oxides, we have considered tautomerism under miscellaneous reactions at ring carbon (Section III-5D) or reactions at ring nitrogen (Section III-6Ai) depending on the other ring atom involved. Many substituted *N*-oxides possess potential tautomers in which the substituent is modified in some manner; these tautomeric equilibria are considered under the reactions of the relevant substituents.

1. Reactions of *N*-Oxides with Electrophiles at the *N*-Oxide Oxygen Atom

N-Oxides can react at the oxygen atom with a variety of electrophilic reagents to give adducts (*9* → *10*) which, according to the reagent and reaction conditions, may be stable or react further. If the subsequent reaction(s) involve(s) attack on ring carbon or nitrogen atoms, they are discussed in the section on the appropriate ring reactions (Sections III-3 or III-4). Attack by protons, reactive halides and related compounds, Lewis acids (including metal ions), and other electrophilic reagents are treated in this section.

(9) (10)

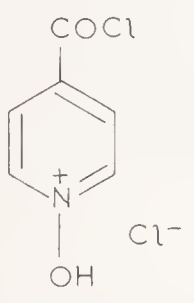
A. REACTIONS OF *N*-OXIDES WITH PROTONS

N-Oxides are weak bases and form salts with strong acids. The *N*-oxide oxygen atom also readily forms hydrogen bonds. In this section, the preparative aspects of salt formation at the *N*-oxide group, quantitative aspects of the base strength of *N*-oxides as measured by the pK_a values of their conjugate acids, and hydrogen bonding are successively discussed.

i. Preparative Aspects of Salt Formation

a. Normal Salts. *N*-Oxides readily form salts, and picrates and picrolonates have frequently been used for the characterization of *N*-oxides. A selection of the data available is summarized in Table 3.01 on the basis of the *N*-oxide ring system concerned. Some *N*-oxides are only stable in the form of salts, e.g. the acid chloride *11* (60USP2945040). *N*-Oxides can be quantitatively analysed by titration with perchloric acid in acetic acid as solvent (56AN528; 62AC1163).

Strong hydrogen bonding often occurs between pyridine 1-oxide cations and the associated anions, especially in the solid state, as is shown by infrared spectral data (63BA111; 64BA383). The structure of 2-carboxypyridine 1-oxide is discussed in Section IV-2Cia.



(11)

(12)

b. Basic Salts. Heteroaromatic *N*-oxides form a number of basic salts of the general type $(Het^+ - O^-)_2 \cdot HX$. These and similar basic salts have been much investigated, especially by Szafran and his co-workers: an indication of the types of compounds which have been studied is given in Table 3.02; for a review, see reference 66WC545. The hydrogen bonds in these derivatives are very strong, as demonstrated by the infrared spectral data. The symmetrically hydrogen-bonded structure *12* has been suggested for the hemihydrobromide of 2-picoline 1-oxide on the basis of infrared spectral data (62J5128) and X-ray studies (63P216). There is evidence for the presence of symmetrical hydrogen bonds in several other *N*-oxide basic salts (63BA111); it has also been suggested on IR spectral evidence that several apparently normal salts have structures of type $(B \cdots H-B)^+ (A \cdots H-A)^-$ (68RC1469).

Table 3.01. *N*-Oxide Salts Formed with Proton Acids

Ring system	Substituents	Salt anions[a]	Spectra	References
Pyridine 1-oxide	—	AsF_6^-, Br^-, Cl^-, $CCl_3CO_2^-$, PF_6^-, phthalate, picrol., SO_4^{2-}, pic.	IR	43JJ78, 49JP177949, 50R468, 56J2404, 59JA156, 62J5128, 63CI607, 64CC2292
	3- and 4-acetyl	picrol.	—	56J2404
	2-, 3-, and 4-alkoxy	Br^-, Cl^-, picrol.	IR	56J2404, 57J4375, 59J3680, 62J5128, 64CC2292, 65CT233
	3- and 4-alkoxycarbonyl	pic., picrol.	—	56J2404, 59J3680
	3-(2-alkoxycarbonyl-vinylene)	pic., picrol.	—	56J2404, 59J3680
	2-alkyl	Br^-, Cl^-, I^-,[b] pic., picrol.	IR, NMR	62J5128, 62JO3856, 65CT233, 63BA169
	3-alkyl[c]	Cl^-, pic.	—	58IZ748, 58J3230, 59J3680, 59JO275
	4-alkyl	picrol.	—	56J2404
	2,4- and 2,6-dialkyl	Br^-, Cl^-, pic., picrol., $C_6H_5CO_2^-$	IR	43JJ78, 62JO1329, 63BA111, 64BA387, 64CC2292, 65CT233
	2,4,6-trialkyl	Cl^-	—	43JJ78
	5- and 6-alkyl-2-amino	Cl^-	—	57J4385
	2,6-dialkyl-4-aryloxy-3,5-diiodo	Cl^-	—	56CT1
	3-alkyl-4-chloro	picrol.	—	56J2404
	2-alkyl-3-hydroxy-4,5-dihydroxymethyl[d]	Cl^-	—	59JO1032
	2- and 4-amino (substituted)	pic., picrol.	—	56J2404, 57J191, 57J4375, 60J3387
	2,5-diamino (substituted)	pic.	—	64R249

[a] Pic. = picrate; picrol. = picrolonate.
[b] Exists only as the dimeric hydriodide, $[Py\text{-}O\text{-}H \cdots O\text{-}Py]^+I^-$.
[c] Nicotine 1′-oxide and 1,1′-dioxide included.
[d] Pyridoxine 1-oxide.

Table 3.01. *N*-Oxide Salts Formed with Proton Acids—*continued*

Ring system	Substituents	Salt anions[a]	Spectra	References
Pyridine 1-oxide, *cont'd.*	2-amino (substituted)-5-nitro	pic.	—	64R249
	4-aryloxy	Cl^-, picrol.	IR	56J2404, 64CC2292
	2- and 4-benzyl	pic., picrol.	—	58J1754
	2- and 3-chloro	pic.	—	62JO1329
	4-chlorocarbonyl	Cl^-	—	60USP2945040
	dimethylenehydrazino, 4-disubstituted	Cl^-	IR	65AN810
	4-hydroxy	pic.	—	52R745
	2-, 3-, and 4-phenyl	pic., picrol.	—	58J1754
	3-piperidino	pic.	—	63J4007
	various	$CCl_3CO_2^-$	IR	64BA383
Quinoline 1-oxide	—	Br^-, I^-, pic.	—	47JJ86
	2-amino	pic.	—	59JJ1063
	3-, 5-, 6-, 7-, and 8-fluoro	pic.	—	63J4007
	2-methyl	various	IR	63BA497, 64BA383, 64BA387
	7-nitro	peroxyphthalate	—	49UK296
	3- and 7-piperidino	pic.	—	63J4007
	2-styryl	Br^-	—	64PC(25)7
	—, 2-methyl, and 2,6-dimethyl	$CHCl_2CO_2^-$, $C_6H_5CO_2^-$, 3,5-dichlorobenzoate, 3,5-dinitrobenzoate	IR	68RC1469
Isoquinoline 2-oxide	—	various	IR	63BA503, 64BA387
	1-amino	pic.	—	59JJ1063
Acridine 10-oxide	—	Br^-, Cl^-, ClO_4^-, I^-, $C_6H_5CO_2^-$	IR	64BA289, 64BA387
Pyridazine 1- and 2-oxide	4-alkoxy	pic.	—	65JJ344
Pyrimidine 1-oxide	—	pic.	—	59J525
	4,6-dimethyl	pic.	—	59J525

Table 3.01. *N*-Oxide Salts Formed with Proton Acids—*continued*

Ring system	Substituents	Salt anions[a]	Spectra	References
Pyrazine 1- and 4-oxide	2-methyl	picrol.	—	59JJ1273
	3-methyl-2-piperidino	SO_4^{2-}	—	64JO1645
Phenazine 5-oxide	—	Cl^-	—	03CB4139
Oxazole 3-oxide	di- and tri-substituted (various)[e]	Cl^-	—	65AP293
Thiazole 3-oxide	2,4-dialkyl	pic., SO_4^{2-}	IR, NMR	64CC2375

[e] Methyl and phenyl substituted.

Table 3.02. *N*-Oxide Basic Salts of the Type $Het^+\text{-}O^- \cdots H^+ \cdots {}^-O\text{-}{}^+Het$

Ring system	Substituents	Anions	Physical measurements	References
Pyridine 1-oxide	—	$CHCl_2CO_2^-$, $CCl_3CO_2^-$	IR	66J(A)439
	2-carboxy	—	IR	69RC309
	2-methyl	Br^-	IR	62J5128
	2,6-dimethyl	ClO_4^-	—	65JO1909
	2-(1-oxido-2-pyridyl)	Br^-, Cl^-, ClO_4^-, $SbCl_6^-$	IR	63SA2132
	2-, 4-, and 2,6-di-methyl, 4-chloro-2,6-dimethyl, 2-methyl-4-methoxy	I^-, ClO_4^-, $SbCl_6^-$	IR	63BA111
Quinoline 1-oxide	—; 2- and 4-methyl	Br^-, ClO_4^-, $SbCl_6^-$, I^- *p*-CH_3-C_6H_4-SO_3^-, 2-$C_{10}H_7SO_3^-$, BF_4^-	IR	63BA497, 66BA509, 66BA621
	2-methyl and 4-methyl	$CCl_3CO_2^-$	IR	64BA383
	—, 2-methyl, and 2,6-dimethyl	2,4,6-trinitrobenzoate	IR	67BA159
Isoquinoline 2-oxide	—	various	IR	63BA503
Acridine 10-oxide	—	Br^-, ClO_4^-, $SbCl_6^-$, I^-, BF_4^-	IR, X-ray	64BA289
Thiazole 3-oxide	2,4-dimethyl	SO_4^{2-}	IR, NMR	64CC2375

Table 3.03. pK_a Values of *N*-Oxide Conjugate Acids

Ring system	Substituents	pK_a values[a]	Method	References
Pyridine 1-oxide	—	0·56, 0·79	UV	55JA4441, 55JJ1546
	2-, 3-, and 4-acetamido	−0·42, 0·99, and 1·59	UV	60J2937
	4-(β-DL-alanyl)	1·15	UV	58JO575
	2-, 3-, and 4-amino	2·67, 1·47,[b] and 3·54[c]	UV	53JJ140, 55JA4441, 57J4375
	4-amino-2-methyl	4·10	UV	59JJ492
	2-*m*-aminophenyl	0·20	UV	60J1511
	2- and 4-*p*-aminophenyl	0·25, 3·92, and 3·64	UV	60J1511
	2-benzamido	−0·44	UV	60J2937
	2-(*N*-benzyl)methylamino	−1·39	UV	60J2937
	4-benzyloxy	1·99	—	57J4375
	2- and 4-benzylthio	−0·23 and 2·09	UV	60J2937
	4-carboxamido-2,6-dimethyl	−0·32	UV	59JJ492
	3-carboxy and *n*-butyl ester	0·09[d] and 0·03	UV	55JA4441
	4-carboxy	−0·48[e]	UV	55JA4441
	4-carboxy (and ethyl ester)-2,6-dimethyl	−0·015 and −0·126	UV	59JJ492
	4-cyano-2- and 2,6-di-methyl	−0·67 and −0·61	UV	59JJ492
	2- and 4-dimethylamino	2·27 and 3·88	pot. titn.	57J4375
	4-dimethylamino-2-methyl	4·37	UV	59JJ492
	2-ethoxy	1·18	—	57JA375
	2- and 4-methoxy	1·23 and 2·04	—	57J4375
	4-methoxy-2-methyl	2·44	—	59JJ492

[a] pK_a values determined in water unless otherwise indicated.
[b] pK_1 = −2·1.
[c] A pK_a value of −6·27 was obtained in sulphuric acid by the ultraviolet method (53JJ140), and a value of 3·65 was obtained in water by potentiometric titration (55JA4441).
[d] pK_2 = 2·73.
[e] pK_2 = 2·86.

Table 3.03. pK_a Values of *N*-Oxide Conjugate Acids—*continued*

Ring system	Substituents	pK_a values[a]	Method	References
Pyridine 1-oxide, *cont'd.*	2-, 3-, and 4-methyl	1·02, 1·08, and 1·29	UV	55JA4441, 59JJ492
	2,6-dimethyl	1·44	UV	59JJ492
	4-(*N*-methyl-acetamido and -benzamido)	1·36 and 1·70	UV	60J2937
	2- and 4-methylamino	2·61 and 3·85	pot. titn.	57J4375
	2-methyl-4-nitro	−0·97	UV	59JJ492
	2,6-dimethyl-4-nitro	−0·86	UV	59JJ492
	4-nitro	−1·7	UV	55JA4441
	2-, 3-, and 4-*m*-nitrophenyl	0·26, 0·47, and 0·58	UV	60J1511
	2- and 4-*p*-nitrophenyl	0·28 and 0·58	UV	60J1511
	2- and 3-phenyl	0·77 and 0·74	UV	60J1511
Quinoline 1-oxide	—	0·70	UV	55JJ1546
	4-amino	−6·55[h]	UV	53JJ140
	2-, 3-, 4-, 5-, and 6-(*p*-dimethylaminophenylazo)	see note [i]	UV	56AA(130)66-O
	*			
Isoquinoline 2-oxide	—	1·01	UV	55JA4441
Pyridazine 1-oxide	3-hydroxy[f,g]	4·1	—	59CT938
Quinazoline 3-oxide	—	1·47	UV	62J5030
	7-chloro	1·49	UV	62J5030
	5-, 6-, 7-, and 8-methoxy	1·20, 0·58, 0·66, and 1·21	UV	62J5030
	7- and 8-methoxy-4-methyl	0·74 and 0·02	UV	62J5030
	4- and 7-methyl	0·06 and 1·00	UV	62J5030
	4,7-dimethyl	0·40	UV	62J5030

[f] A pK_a value of 6·9 was obtained in 50% methanol (59JA6041).
[g] Potentiometric titration; pK_2 = 5·80 (55JA4441).
[h] Determined in sulphuric acid.
[i] Determined in 50% ethanol; pK_a values not given in abstract.
* 8-Hydroxy; see addendum in the Appendix.

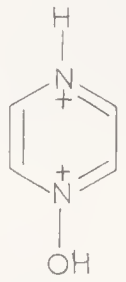
ii. pK_a *Values of* N-*Oxide Conjugate Acids*

The pK_a values for various heterocyclic *N*-oxides are collected in Table 3.03. Inspection shows that, as expected, electron-withdrawing substituents tend to lower the pK_a value and electron-donating substituents tend to increase it. Quantitative aspects are discussed below. Values for potentially tautomeric compounds such as amino- and hydroxy-pyridine 1-oxides have been extensively used as a criterion for the tautomeric structure of these compounds: this work is considered in Chapter IV under the reactions of the particular substituent.

a. Pyridine 1-Oxides. The pK_a values for 3- and 4-substituted pyridine 1-oxides have been shown by Jaffé and Doak (55JA4441) to be correlated by the Hammett equation with ρ equal to 2·09. Thus, the effect of substituents is considerably less for pyridine 1-oxides than for the corresponding pyridines where ρ is 5·71. The strong conjugation of the reaction site with both electron-accepting and electron-withdrawing substituents requires the use of both σ^+ and σ^- values in the Hammett treatment (58JO1790). The pK_a values of 2-substituted pyridine 1-oxides are correlated by σ_p constants (64JA2033).

The acidity function for the protonation of pyridine 1-oxide in sulphuric acid has been investigated. Although the Hammett acidity function serves as a reasonable approximation for the protonation behaviour of *N*-oxides down to H_o of ca. −3 (65T1055), later work [67J(B)1235] has disclosed a significant divergence for stronger acidities and indicates that the amide acidity function, H_A, is a good approximation of the base behaviour. Some pK_a values determined in acetic acid are given in reference 68J(A)905.

b. Other N-*Oxides.* Pyrazine 1-oxides undergo protonation at N-4, as would be expected, but diprotonation evidently also occurs; the ultraviolet spectra of 60% sulphuric acid solutions have been interpreted as evidence for the existence of cations of type *13*. Pyrazine 1,4-dioxides can undergo diprotonation (*14*) [60AA(138)89-P].



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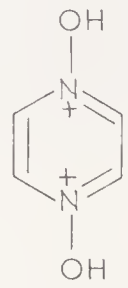


(14)

iii. Hydrogen Bonding

The *N*-oxide oxygen atom readily forms hydrogen bonds, and many examples of both intermolecular and intramolecular hydrogen bonding

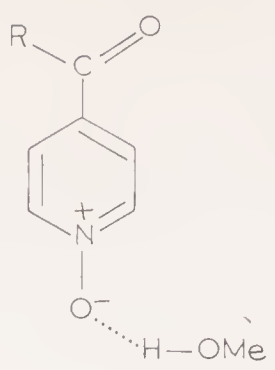
are recorded. Hydrogen bonding is usually detected by infrared and ultraviolet spectroscopy.

a. Intermolecular Hydrogen Bonding. *N*-Oxides are often hygroscopic, probably because of the ease with which they form hydrogen bonds. Sometimes they may be isolated as hydrates, e.g. 6-methylquinoline 1-oxide (59WZ93). Many salts of *N*-oxides, and especially basic salts, are strongly hydrogen bonded, as is discussed in Section III-1Ab.

The infrared spectra of pyridine 1-oxides (57JA2233; 59QR353) and pyrimidine 1-oxides (57JA2233) in chloroform solution disclose the existence of hydrogen bonds between the solute and solvent; the C-H stretching band of chloroform is displaced to lower frequencies and is not adequately compensated by a solvent blank.

Shindo (59CT791) has investigated bonding between pyridine 1-oxide and methanol in carbon tetrachloride solution: the free N^+-O^- stretching vibration at 1265 cm^{-1} is replaced by a new band for the hydrogen-bonded species $N^+-O^- \cdots$ H-OMe at 1244 cm^{-1}. A large number of substituted pyridine 1-oxides were also examined with respect to possible interactions with phenol and methanol in carbon tetrachloride solution; it was found that the methanol OH-stretching frequencies fitted a Hammett-type equation: $\nu\,(cm^{-1}) = 3360 \pm 118\,\sigma$, where σ refers to substituents in the pyridine 1-oxide ring (see also reference 63SA829). The interaction between 4-substituted pyridine 1-oxides and phenol has been investigated by measuring the low frequency shift of the OH-stretching frequency in carbon tetrachloride solution: a correlation with the substituent σ values was found (66I2009). Recently, series of 4-substituted pyridine 1-oxides and 4- and 6-substituted quinoline 1-oxides have been studied for their effect on ν(O–H) for several phenols. ΔH values for the 4-substituted derivatives were found to be correlated by the special σ constant applied to *N*-oxides (cf. Section I-2C), whereas the 6-substituted derivatives correlated better with "normal" σ values (68JA5754). The effect of substituents on methanol–pyridine 1-oxide bonding has also been studied [68J(B)1578].

Shindo (59CT791) also studied the effect of intermolecular hydrogen bonding on the intramolecular electron-donor properties of the *N*-oxide group by examining the shift of the carbonyl stretching frequencies for substituents of the type -CO-X in the pyridine 1-oxide ring on changing the solvent from carbon disulphide to methanol. The results clearly indicate that there is less back-coordination from the *N*-oxide group to the carbonyl substituent in the hydrogen-bonded species (*15*) than in the free molecule (*16*); i.e., the hydrogen-bonded *N*-oxide oxygen atom is a poorer electron donor than the free oxygen. The infrared technique has also been used to compare the strength of the hydrogen bonds formed between methanol and *N*-oxides with those formed between methanol and other bases: correlations with pK_a values are discussed in reference 68J(A)905. Hydrogen bonding can also be demonstrated by NMR chemical shifts [66J(B)1137].



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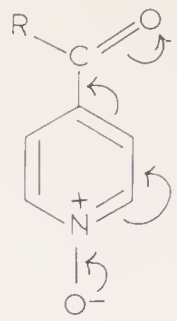

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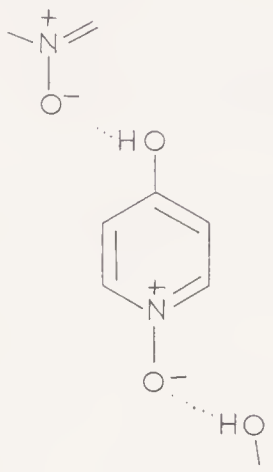

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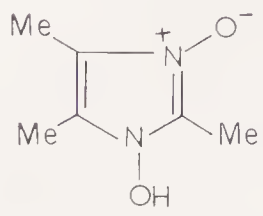


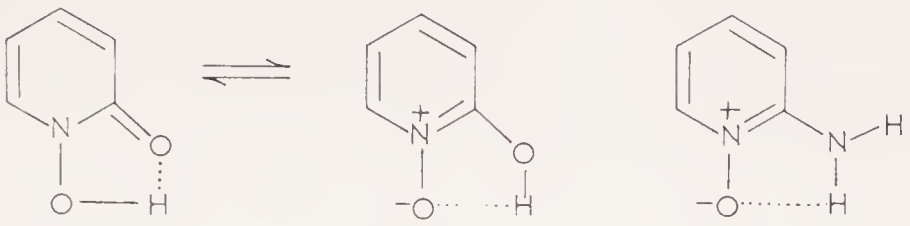
(18)

Bond energy and entropy changes for the formation of hydrogen bonds between quinoline 1-oxide and various phenols were studied using ultraviolet techniques by Kubota (55JJ1540); in the electronically excited state hydrogen bonds tend to be weaker. Studies of the effect of hydrogen bonding on the ultraviolet spectra of pyridine 1-oxide and other heterocyclic *N*-oxides allow determination of ΔH and ΔS values for hydrogen bonds between pyridine and quinoline 1-oxides and phenol and methanol (56SR31); see also references 57JJ785 and 54JJ831. Hydrogen bonding between pyridine 1-oxides and acids or phenols has also been demonstrated by dielectric titration studies [67J(A)48]. Hydrogen bonding between acridine 10-oxide and various proton donors has been investigated by the ultraviolet and fluorescence spectral techniques (58NK916).

4-Hydroxypyridine 1-oxide (*17*) in the solid state has an anomalous infrared spectrum indicating particularly strong intermolecular hydrogen bonding [56ZP(7)123; 57J4375]. 1-Hydroxy-2,4,5-trimethylimidazole 3-oxide (*18*) is also very strongly bonded: in chloroform it forms cyclic trimers and long chain polymers. The spectral characteristics indicate that the hydrogen bond is symmetrical or that the proton moves in a double-minimum potential (68BG630; 69BG164).

b. Intramolecular Hydrogen Bonding. Strong intramolecular hydrogen bonds have been shown to exist in the tautomeric compound 2-hydroxypyridine 1-oxide (*19*⇌*20*) and in 2-aminopyridine 1-oxide (*21*) by infrared spectroscopy [57J4375; 58LA(613)144]. The same applies to 1-hydroxypyrazole 2-oxides (69JO194).

2- and 4-Heptadecylpyridine 1-oxide form monolayers on water by hydrogen bonding of the *N*-oxide group. The effects of silicic acid on these monolayers have been studied [69J(C)823].



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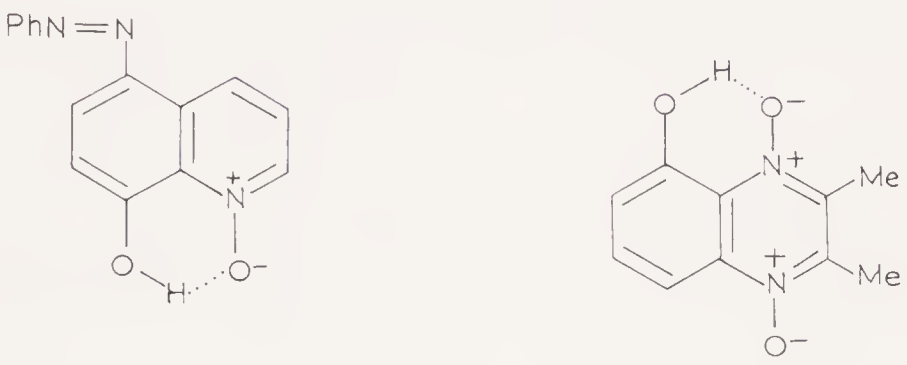

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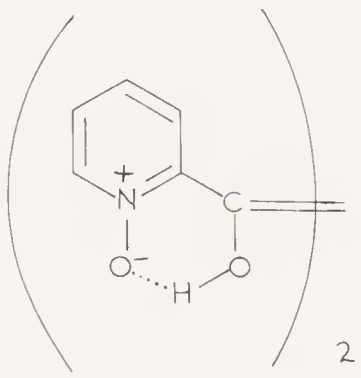


(24)

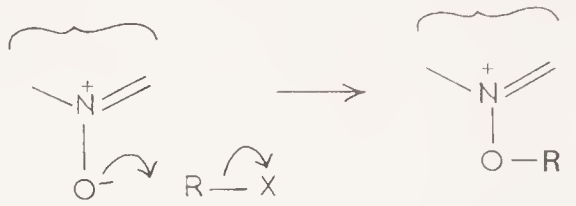
Hydrogen bonding can also occur between an *N*-oxide group and a hydroxyl group in a *peri* position, for example in 8-hydroxyquinoline 1-oxide, its azo derivative *22* (62PI360), and the 5-hydroxyquinoxaline 1,4-dioxide *23* (56J2058). In the azo compound *22*, the interaction is much stronger than in the corresponding 5-azo-8-hydroxyquinoline (56J614). α-Pyridoin 1,1′-dioxide is stabilized as the ene-diol (*24*) hydrogen bonding [58LA(618)152]; the 2-quinolyl analogue has a similar structure for the same reason (61JO1410).

B. ALKYLATION AND ACYLATION OF *N*-OXIDES

i. General Survey

N-Oxides undergo S_{N2} reactions (*25* → *26*) with reactive halides and similar compounds. The quaternary salts (*26*) derived from alkyl halides, sulphonates, etc., can often be isolated, but this is seldom the case for

reactions involving acyl halides. Quaternary derivatives of type *26* are highly reactive, even when R is an alkyl group, and they readily undergo further reactions at either the ring carbon atoms (e.g. *27*→*28*) or the substituents (e.g. *29*→*30*). Reactions which proceed further (without isolation of the quaternary derivative) by attack on either the ring or a substituent are not considered in this section, but are treated under reactions of the ring or relevant substituent.



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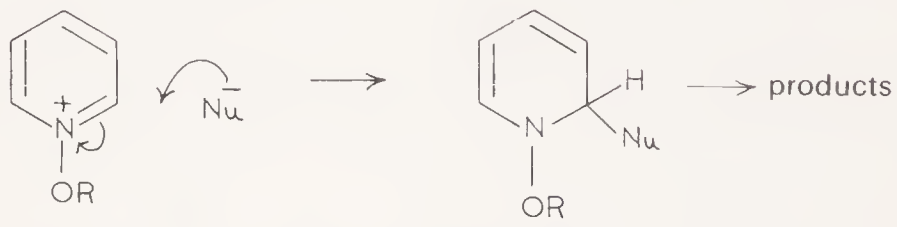

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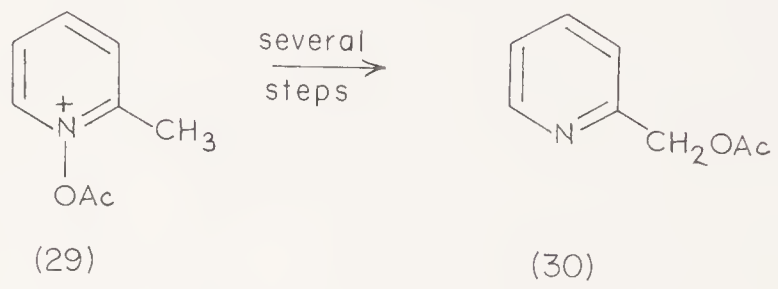

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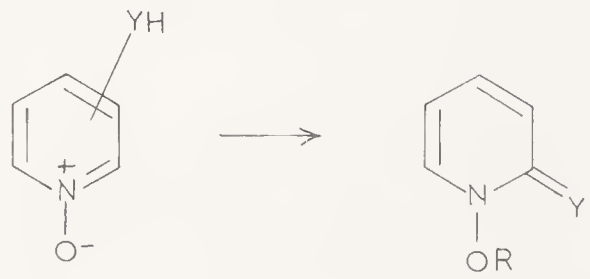

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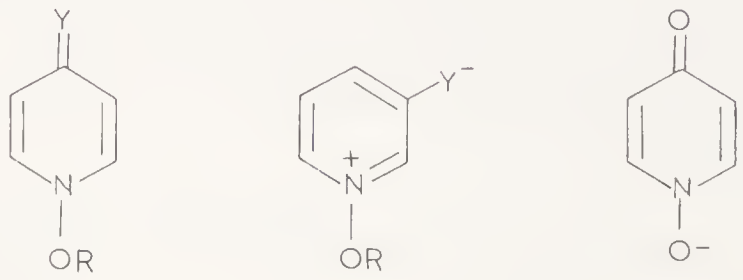


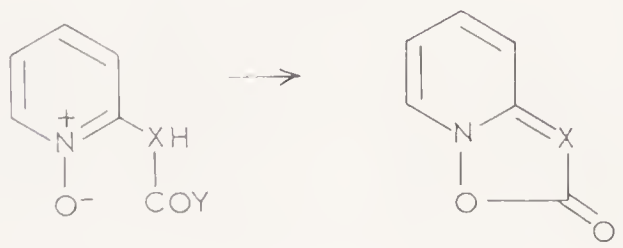
(33) (34) (35)

Substituted heteroaromatic *N*-oxides of the general type *31*, in which the substituent carries a hydrogen on the atom adjacent to the ring (usually

nitrogen or oxygen), can lose a proton from the substituent after acylation or alkylation. If the substituent is in the α- or γ-position, neutral derivatives of the *N*-hydroxypyridone type (cf. *32*, *33*) are formed; with a β-substituent, a zwitterion (cf. *34*) results. Alternatively, the formation of compounds of types *32* and *33* may occur through an anionic derivative of the original substituted *N*-oxide, e.g. *35*. These substituted *N*-oxides (*31*) are all potentially tautomeric. The tautomerism and reactions of the types mentioned are considered under the reactions of the relevant substituents (YH) concerned: amino substituents in Section IV-3Cia, mercapto substituents in Section IV-3Di, and hydroxy substituents in Section IV-3Bia. Alkylation and acylation of α- or γ-hydroxy *N*-oxides and α- or γ-amino *N*-oxides can occur at either the *N*-oxide oxygen atom or the substituent, as is discussed in detail in the sections quoted.

N-Oxides containing an imino group in the ring can also lose a proton from the imino nitrogen atom after acylation or alkylation at the *N*-oxide oxygen. The most important compounds of this type are imidazole and triazole *N*-oxides. Such alkylation and acylation reactions are considered in Section III-6Aiib; the tautomerism of these compounds is discussed in Section III-6Ai.

α- and γ-Benzyloxy and α- and γ-allyloxy *N*-oxides can undergo rearrangement to give *N*-benzyloxy- and *N*-allyloxy-α- and -γ-oxo heterocycles in the presence of acid catalysts. These rearrangements are discussed under the relevant substituents in Section IV-3Biiib. Similarly, certain other alkoxy *N*-oxides are alkylated at the *N*-oxide oxygen with spontaneous loss of the original alkyl group; see Section IV-3Biiic. Cyclizations involving acylation at the *N*-oxide oxygen atom, which are of the general type *36* → *37* (X = N or CR), are also considered under the relevant substituent groups in Sections IV-3Cie and IV-2Cic.



(36) (37)

ii. Formation of N-*Alkoxy Quaternary Salts*

Pyridine 1-oxide and other heterocyclic *N*-oxides form quaternary salts on treatment with alkyl iodides, sulphates, or sulphonates. The reaction is hindered sterically by substituents in the α-position, and hindered electronically by the presence of electron-withdrawing substituents in the β- or γ-positions. These quaternary salts can be conveniently prepared by

Table 3.04. Formation of *N*-Alkoxy Quaternary Salts by *N*-Oxides

Ring system	Substituents	Alkyl group of N^+-OR	Anions[a]	References
Pyridine 1-oxide	—	*n*-Bu, Et, Me	Br^-, $EtSO_4^-$, I^-, TsO^-	43PJ574, 44JJ210, 56J2404, 59CT925, 59CT930, 60CI1482, 63JO1320, 64JO2183, 66J(B)870
	—	*t*-Bu, Me	ClO_4^-, pic.	69T4291
	—	*n*-Bu	SO_3^-	66AG391
	—	*n*-C_9H_{19}, *n*-$C_{10}H_{20}R$[b]	I^-	59JA4004
	—	cyclopentenyl[c]	Br^-	59JA4920
	—	-CH_2-C_6H_4-CH_2- (bis compound)	Br^-	63AS953
	2-, 3-, and 4-alkoxy	Me	I^-, $MeSO_4^-$	43PJ574, 44JJ210, 60JJ1418, 61JJ141
	3,5-dialkoxy	Me	ClO_4^-, $MeSO_4^-$	67J(B)1213
	2-, 3-, and 4-alkyl	Et, Me, CH_2COPh	Br^-, $EtSO_4^-$, I^-, $MeSO_4^-$, TsO^-	43PJ574, 56J2404, 59CT925, 59JA4004, 60CI1482, 60JJ1418, 61JJ141, 63JO1320, 63JO1323, 64JJ287
	2-alkyl-5-cyano-4-hydroxy	Et, Me	$EtSO_4^-$, $MeSO_4^-$	65CT878
	2- and 4-amino, substituted	Me	Br^-, ClO_4^-,[d] I^-, $MeSO_4^-$, pic.,[d] picrol.,[d] TsO^-	43PJ574, 44JJ210, 57J191, 57J4375
	2-aryl, substituted	Me	$MeSO_4^-$, I_3^-	67JO1146
	4-azido	Me	$MeSO_4^-$	60JJ1418, 62CT669

[a] TsO^- = *p*-toluenesulphonate; pic. = picrate; picrol. = picrolonate.
[b] $[C_5H_5N\text{-}O\text{-}(CH_2)_5\text{-}]_2^{2+}2I^-$.
[c] Salt of pyridine 1-oxide and *cis*-3,5-dibromocyclopentene.
[d] Prepared from the TsO^- salt.

Table 3.04. Formation of *N*-Alkoxy Quaternary Salts by *N*-Oxides—*continued*

Ring system	Substituents	Alkyl group of N^+-OR	Anions[a]	References
Pyridine 1-oxide, *cont'd.*	3,5-dibromo	Me	$MeSO_4^-$	61JJ141
	2-, 3-, and 4-carboxylate	Me	$MeSO_4^-$	59CT930, 60JJ1418
	4-chloro	Me	$MeSO_4^-$	60JJ1418, 62CT669
	2-, 3-, and 4-cyano	Me	$MeSO_4^-$	60JJ1418, 61JJ141
	mono-, di-, and tri-methyl	Et	BF_4^-	66CB1769
	2,6-dimethyl	Me	I^-	66J(B)870
	4-nitro	Me	$MeSO_4^-$	60JJ1418, 62CT669
	2- and 4-methyl	Et	Br^-	45JJ18
	*			
Quinoline 1-oxide	—	Et, Me	I^-, $MeSO_4^-$	37CB1270, 58ZO2386, 59CT925, 62SP189, 63CZ535
	—	Et	TsO^-	66JO939
	—	*t*-Bu, Me	ClO_4^-, pic., TsO^-	69T4291
	4-amino	Me	I^-	43PJ574, 44JJ6, 44JJ210
	4-azido	Et, Me	$EtSO_4^-$, I^-, $MeSO_4^-$	62CT669
	4-ethoxy	Me	I^-	44JJ210
	4-hydroxy-2-methyl[e]	Me	$MeSO_4^-$	21CB1067
	6-methoxy	Me	I^-	62JJ1076
	4-, 6-, and 7-methyl	Et, Me	I^-, $MeSO_4^-$	62SP189, 63CZ535
	2- and 4-methyl	Et	BF_4^-	66CB1769
Isoquinoline 2-oxide	—	Me	$MeSO_4^-$, ClO_4^-, pic.	59CT925
Phenanthridine 5-oxide	—	Me	$MeSO_4^-$	60JJ834
Cinnoline 2-oxide	—	Me	ClO_4^-	68J(B)316

[e] 1,4-Dimethoxy-2-methylquinolinium methosulphate.

* 2- and 4-Oximinomethyl; see addendum in the Appendix.

Table 3.04. Formation of *N*-Alkoxy Quaternary Salts by *N*-Oxides—*continued*

Ring system	Substituents	Alkyl group of N^+-OR	Anions[a]	References
Purine 1-oxide	6-amino[f]	Et, Me, $PhCH_2$	Br^-, I^-	65CT1017
	6-amino-9-alkyl	Me, Et, $PhCH_2$	Br^-, I^-	66CI1598
Benzimidazole 1-oxide	2-ethoxycarbonyl-3-methyl	Me	I^-	68CT527
	3-methyl	Me	I^-	64CT783
	2,3-dimethyl	Me	I^-	66CT375
Purine 7-oxide	1,3-dihydro-1,3-dimethyl-2,6-dioxo-8-phenyl[g]	Me	$MeSO_4^-$	64JA4721

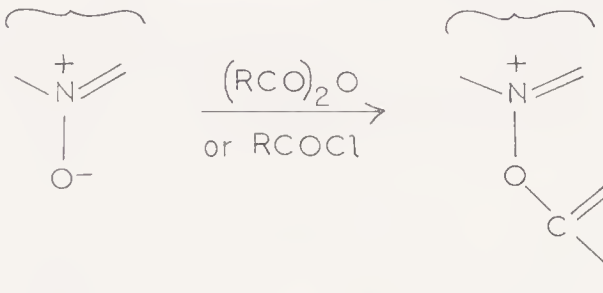
[f] Adenine.
[g] 8-Phenyltheophylline 7-oxide.

heating the *N*-oxide with the theoretical amount of an alkyl *p*-toluenesulphonate: the *N*-alkoxy derivatives can often be isolated as their perchlorates following addition of perchloric acid to the crude reaction mixture (57J4375). Recently triethyloxonium tetrafluoroborate has been shown to form *N*-oxide quaternary salts in good yields (66CB1769). The various quaternary alkyl derivatives that have been prepared are surveyed in Table 3.04.*

2,6-Dimethylpyridine 1-oxide and styrene oxide react in the presence of trifluoroacetic acid to give a quaternary salt of type Py^+-$OCH_2CH(OH)Ph$ $CF_3CO_2^-$ (69TL531).

iii. Formation of N-*Acyloxy Quaternary Salts*

N-Oxides react with a wide variety of acylating agents, and in the majority of cases the reaction probably involves an acylated intermediate of type *39*. However, such intermediates are very reactive and are seldom isolated. In this section only those reactions in which the *O*-acyl derivative (*39*) is isolated are considered; the other reactions involve attack at a ring carbon atom or at a substituent and are discussed in the relevant sections.



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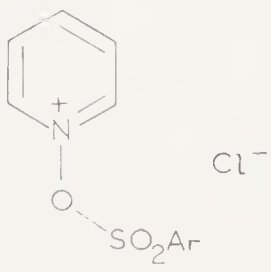
Traynelis and his group (61JO4365) isolated 1-acetoxy-2-methylpyridinium picrate and later (64JA4917) prepared a series of 1-acetoxypyridinium perchlorates. Although other investigators have emphasized the difficulty of working with these compounds (see, e.g., reference 64JO2183), many 1-acyloxypyridinium perchlorates have been reported recently by Muth and Darlak (65JO1909). Parallel work in the quinoline series has been described (60JJ1027; 68JO2762). Adducts with tosyl chloride, which are presumably of structure *40*, have also been reported (61NK616). Pyridine 1-oxide reacts with *N*-sulphinylsulphonamides (RSO_2NSO) and with sulphonylisocyanates (RSO_2NCO) to give products of types *41* and *42*, respectively (65CB1205).



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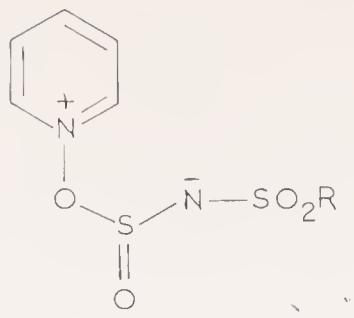
* See addendum in the Appendix.



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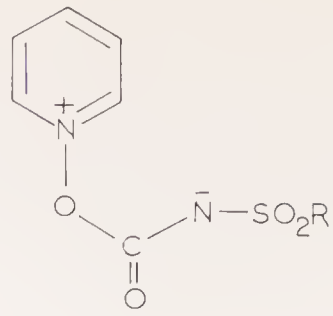

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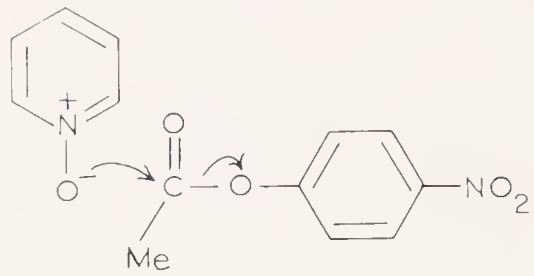


(43)

The rate of pyridine 1-oxide (in common with other hydroxylamine derivatives) catalysed hydrolysis of *p*-nitrophenyl acetate (cf. *43*) appears to be very much more rapid than would be expected by comparison of its pK_a value with those of the other nucleophiles studied (60JA1778).

C. COORDINATION COMPOUNDS OF *N*-OXIDES

The oxygen atom of the *N*-oxide group can form stable coordination compounds with a wide variety of metallic ions and Lewis acids. If a suitable substituent is situated *alpha* or *peri* to the *N*-oxide function, even more stable chelated derivatives are formed; these cases are considered separately.

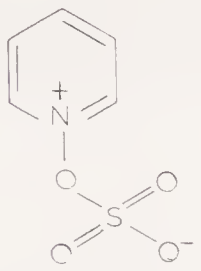
The great majority of the work so far reported has been concerned with pyridine 1-oxides; however, there is every reason to believe that coordination compounds are formed by *N*-oxides generally. The examples known for other ring systems usually involve chelated complexes and are considered under the relevant substituent reactions. The subject has recently been comprehensively reviewed (68CD375).

i. Non-chelated Complexes with Non-metals

No systematic work on complex formation between *N*-oxides and Lewis acids has appeared; however, the available scattered data indicate that stable complexes are formed readily in suitable cases.

Pyridine 1-oxide and sulphur trioxide give an addition compound which is assumed to be *44* (38CB2603), and with sulphurylisocyanate, $SO_2(NCO)_2$, the adduct *45* is formed (64CB852). Stable boron trifluoride adducts of pyridine 1-oxide, its methyl derivative (64CI1259), and quinoline 1-oxide (58JJ1079; 58JJ1083; 62SP189) are known. Solid 1:1 complexes of pyridine

1-oxide with BX_3, where X = H or halogen, have recently been obtained (65JN2111). The reaction between ozone and pyridine 1-oxide in methylene dichloride solution is considered to proceed through the unstable intermediate *46* (57JO1277). Evidence for a weak interaction between pyridine 1-oxide and carbon tetrachloride was obtained from dipole moment measurements (61J2974).*



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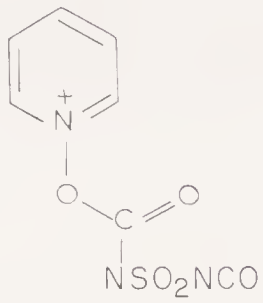

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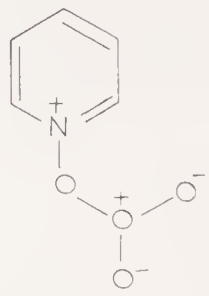


(46)

The *N*-oxide group also appears to interact with halogen molecules, and solid complexes of quinoline 1-oxide and bromine have been obtained by Japanese investigators (47JJ86). Pyridine 1-oxide–iodine complexes have been studied spectrophotometrically (57NK196; 65JA458): the bonding is quite strong, and the equilibrium constants and ΔH values are larger than those for other oxygen–iodine complexes. The authors discuss possible detailed configurations for the complexes, and their conclusions have been confirmed by infrared measurements [67JM(24)378]: the N-O stretching vibration has a considerably lower frequency in the complexes.

ii. Non-chelated Complexes with Metals

Pyridine 1-oxide and its simple substituted derivatives readily form complexes with metal ions. Although it has been stated (61JA3770) that only a single example was reported before 1961, there has certainly been considerable activity in the field since then. Pyridine 1-oxide coordination compounds often precipitate on mixing alcoholic solutions of the *N*-oxide and a metal salt. In other cases their formation is evidenced by changes in some physical property; e.g., their formation can be demonstrated by oscillometric titration (63J2484). The types of complexes formed and the physical measurements that have been made are given in Table 3.05. In these complexes, the pyridine 1-oxide group normally behaves as a monodentate ligand. However, it can also act as a bridging group; in this respect the copper complex $[Cu(PyO)Cl_2]_2$ (*47*) is illustrative (65IC97). In a general discussion of the ligand properties of pyridine 1-oxide, Reedijk concludes that it is a rather strong ligand (69R499).

* See addendum in the Appendix.

Table 3.05. Pyridine 1-Oxide Complexes with Metal Ions*

Complex types	Metals	Other ligands	Substituents in *N*-oxide	Physical measurements[a]	References
$M(PyO)_6X_2$	Co, Cu, Fe, Hg, Mg, Ni, Zn	BF_4^-, Br^-, ClO_4^-, $[Fe_4(CO)_{13}]^{2-}$, I^-, NO_3^-	—; 2-amino; 4-chloro, -methoxy, -nitro	IR, UV, μ, Λ, pK, NMR	59CB2085, 61JA3770, 61JA3773, 62CI651, 62IC285, 63H701, 63SA189, 64J5008, 66IC2009, 69IC550, 69JA1329
	Co, Ni	ClO_4^-	2,3-benzo-4-subst.	IR, μ, Λ, pK	68IC1840
$M(PyO)_4X_2$†	Ba, Cu, Co, Mn, Ni, Zn	Cl^-, ClO_4^-, NO_3^-, NCS^-	—; 2-amino; 5,6-benzo, various	IR, UV, μ, Λ, pK	61JA3770, 61JA3773, 62CI651, 63H701, 63SA189, 66IC615, 69BJ417, 69JA1329
$M(PyO)_3X_2$	Co	Cl^-	—	IR, μ, Λ	61JA3770, 63SA189
$M(PyO)_2X_2$*‡	Co, Cu, Hg, Mn, Ni, Ti, Zn	Br^-, Cl^-, F^-, NCS^-, NO_3^-, R_f[b]	—; 4-bromo, -chloro, -methyl, -nitro; 2,6-di and 2,4,6-tri-methyl	IR, UV, μ, Λ, vis., refl., osc., NMR	61JA3770, 63J2484, 63SA189, 64J5008, 65IC97, 65IC1595, 65JN740, 66BJ58, 66CH601, 66IC615, 66IC1390, 66J(A)1282, 67AJ2403, 67CH297, 67IC946, 68IC1358, 69IC550
$M(PyO)X_2$§	Co, Cu, Hg, Mn, Ni, Zn	acetylacetonate, Br^-, $CH_3CO_2^-$, Cl^-, ClO_4^-; NO_3^-, R_f[b]	—; 3,4- and 5,6-benzo; 4-chloro, -hydroxy, -methyl, -nitro; 2- and 3-methyl; di- and tri-methyl	IR, NMR, μ, Λ, X-ray, pK, osc., refl., vis.	61JA3770, 62CI651, 63J2484, 63SA189, 65IC197, 65JA5350, 65JT504, 66BJ58, 66IC152, 66IC1390, 66IN373, 66JA1399, 67AJ2403, 67BJ1738, 67IC946, 67JA3135, 68IC2035
$M(PyO)X_2 \cdot H_2O$	Co, Ni	Br^-, Cl^-	—	IR, μ, Λ	61JA3770
$M_2(PyO)_2X_4$	Hg	various	—	IR, Λ	69IC550
$M(PyO)_8X_3$	Rare earths	ClO_4^-	—	IR, Λ	67CC189
$M(PyO)_6X_3$	Al, Cr, Fe	ClO_4^-	—	IR, μ, Λ	61JA3770, 61JA3773, 63SA189
$M(PyO)_4X_3$	Y, rare earths	ClO_4^-, NO_3^-, BPh_4^-	—	IR, Λ	68CI770

[a] μ = magnetic susceptibility; Λ = conductivity; X-ray = X-ray diffraction; osc. = oscillometric titration; vis. = visible spectrum; refl. = reflectance spectrum.

[b] R_f = fluoro-alkyl or -aryl.

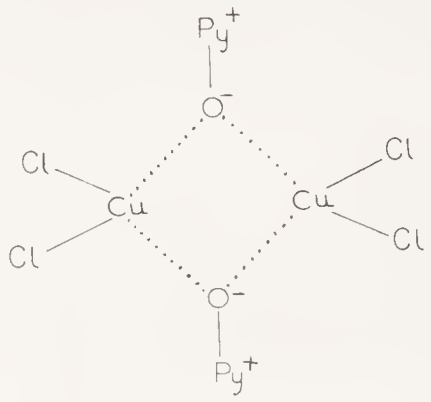
*, †, ‡, § See addenda in the Appendix.

Table 3.05. Pyridine 1-Oxide Complexes with Metal Ions—*continued*

Complex types	Metals	Other ligands	Substituents in *N*-oxide	Physical measurements[a]	References
$M(H_2O)_{6-n}(PyO)_nX_3$	Cr	ClO_4^-	—	UV, vis.	68JA2545
$M(PyO)_8X_4$	Th	ClO_4^-	—	IR, UV	64CC856
$M(PyO)_2X_4$*	Sn, Te, Ti	Br^-, Cl^-, F^-, I^-	—; 2- and 2,6-di-methyl	IR, UV, μ, Λ, NMR, X-ray	61JA3770, 63SA189, 65J3174, 66CH601, 67BJ2463, 67J(A)1813, 69J(A)913
	V	Cl^-	Me, etc.	IR	69JN43
$M(PyO)X_4$	Sn, Te	Cl^-	—	IR, UV, Λ, pK	67BJ2463, 67J(A)1813
$MO(PyO)_6X_2$	Zr	ClO_4^-	—	IR, UV	64CC856
$MO(PyO)_5X_2$	Ti, U, V	Br^-, Cl^-, ClO_4^-	—; 4-chloro, -methoxy, -methyl; 2-methyl	IR, UV, vis.	65CC2685, 65IC1604, 67JN745
$MO(PyO)_4X_2$	V	Cl^-, ClO_4^-	—; 4-methoxy, -methyl	IR, UV	65IC1604
$MO(PyO)_4X_2 \cdot H_2O$	V	Br^-, Cl^-, ClO_4^-, BF_4^-	—; 4-chloro, -methoxy, -methyl; 2- and 2,6-di-methyl	IR, UV, vis.	67JN745
$MO(PyO)_2X_2$	V	Br^-, Cl^-, NCS^-	—; 4-bromo, -chloro, -methoxy, -methyl, -nitro; 2,6-dimethyl	IR, UV, vis.	67JN745
$MO(PyO)_2X_2 \cdot H_2O$	V	Br^-, Cl^-, NCS^-, BF_4^-	—; 4-bromo, -chloro, -methyl, -nitro; 2,6-dimethyl	IR, UV, vis.	65IC1604, 67JN745
$MO(PyO)X_2$	Th, Ti, Zr	ClO_4^-	5,6-benzo	IR	66CC972
M(olefin)$(PyO)X_2$	Pt	Cl^-	— and substituted (various)	IR, UV, NMR	61J2254, 62IC893, 63JA902, 64JA586, 66IC1085, 67IC1096
M(CO)$(PyO)X_2$	Pt	Cl^-	—; 4-alkoxy, -cyano, -nitro	IR, NMR	67JA6500
$MO_2(PyO)_3X_2$	U	Cl^-	—; and 4-substituted	IR, μ, Λ	66JN537
unstated	Ti, Zr	F^-	various	IR	67IC1099, 69JN559

* See addendum in the Appendix.

Pyridine 1-oxide catalyses the alkylation of sodio-malonic esters in benzene solution; this behaviour is attributed to specific solvation of the sodium ions by the *N*-oxide (60JA2895). The heats of reaction of 4-substituted pyridine 1-oxides with the reference acid $VO(acac)_2$ correlate well with *sigma* constants (69JA610). 4-Cyanopyridine 1-oxide complexes resemble those of the parent oxide (69JN1671): for complexes with other substituted pyridines, see reference 69IC1116. The thermal stability of pyridine 1-oxide complexes has been investigated [69J(A)1474].



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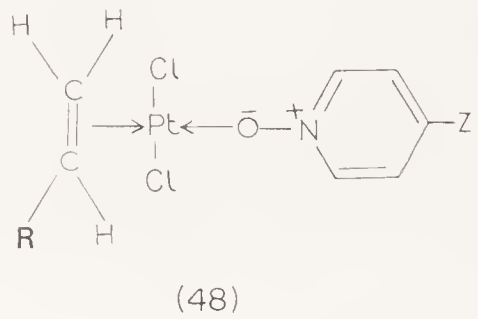

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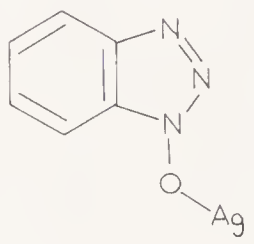


(49)

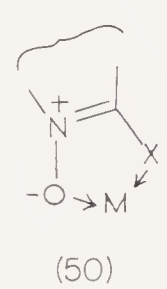
Few quantitative studies have appeared concerning the effect of substituents in the *N*-oxide ring on complex stability. Shupack and Orchin (64JA586) have studied the effects of varying the substituent Z in the 4-position of pyridine 1-oxide and the substituent R in the ethylene in a series of divalent platinum–pyridine 1-oxide–olefin complexes (*48*). The nature of Z has a profound effect on the competition between two olefins for a site on the platinum atom. Evidence for transmission of electronic effects across the platinum atom in compounds of type *48* was also adduced from infrared (63JA902) and NMR spectral data (65IC1393). Herlocker *et al.* (66IC2009) have reported a series of 4-substituted pyridine 1-oxide complexes of the type $[Ni(ONC_5H_4\text{-}X)_4]^{2+}$ and have correlated various infrared band

frequencies with Hammett σ_x values. Back-coordination to the π-system from the metal *d*-orbitals is discussed in detail. Similar work on 4-substituted quinoline 1-oxides has also been reported (68IC1840). For complexes of quinoline 1-oxide itself, see reference 69ZO306.

Very few examples of the formation of non-chelated complexes between metal ions and *N*-oxides other than those of the pyridine or quinoline series have been reported. Early work indicates that isoxazoline 2-oxides form copper complexes (26JA1770). Benzotriazole 1-oxides form silver derivatives, possibly of type *49* (60JO657).

iii. Chelated Complexes

Suitable α-substituted (*50*) or *peri*-substituted *N*-oxides (*51*) are bidentate ligands and form stable coordination compounds. These complexes are discussed under the substituent group involved: α-amino (Section IV-3Cib), α-hydroxy (Section IV-3Bib), α-mercapto (Section IV-3Di), *peri*-hydroxy and *o*-phenanthroline mono-*N*-oxide (Section IV-3Bii), and α-carboxylic acids (Section IV-2Cia). Only the chelate complexes of bis *N*-oxides are considered here.



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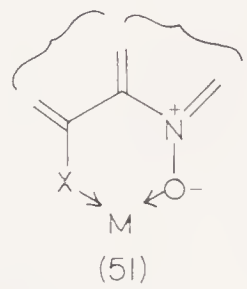

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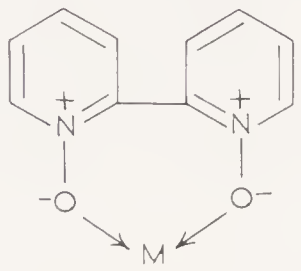

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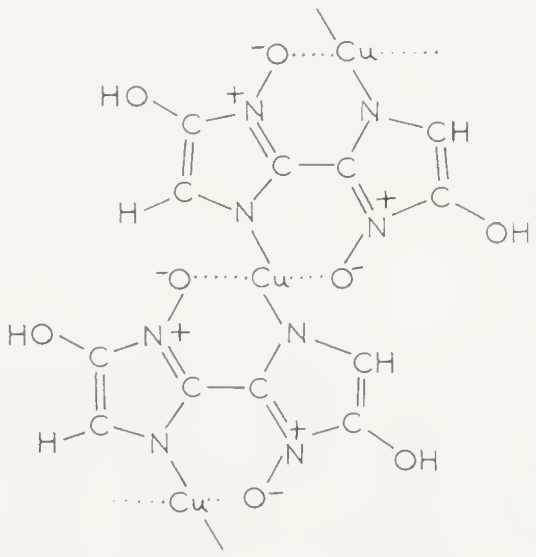


(53)

2,2′-Bipyridyl 1,1′-dioxide is a good bidentate ligand and forms complexes of type *52*, which are somewhat unusual in that they contain a stable seven-membered ring. Specific examples are given in Table 3.06. Complexes of bis(2-pyridyl 1-oxide) disulphide (62USP3027327) and *o*-phenanthroline *N*-oxide are also known (65JO288). Glycosine derivatives also form complexes of this type, e.g. *53* [58LA(615)99; 58LA(615)108]. The interactions of poly-2- and -4-vinylpyridine 1-oxides with monosilicic acid have been studied [68J(B)233; 68J(B)400].

1-Hydroxypyrazole 2-oxides also form stable chelates (69JO194).

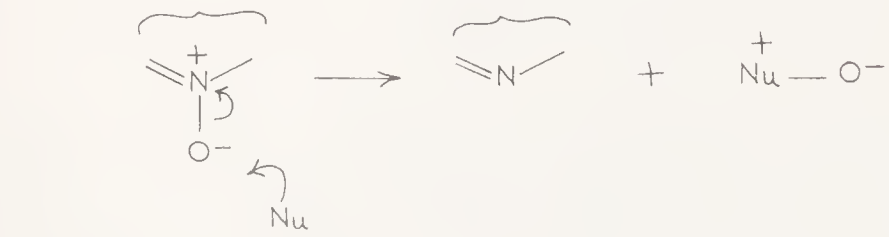
2. Reactions of Heterocyclic *N*-Oxides with Nucleophiles at the *N*-Oxide Oxygen Atom: Reduction

A. REDUCTION MECHANISM AND GENERAL DISCUSSION

The simplest type of reaction between an *N*-oxide and a nucleophile can be represented by the sequence *54* → *55*.

All reductions of *N*-oxides to the corresponding parent heterocycles are considered in this section provided that substituents are neither introduced into the ring nor modified in the course of the reaction; the reactions excluded here are considered as ring and substituent reactions, respectively (note: exceptionally, all catalytic reductions are considered in this section).

Many reactions lead to loss of the *N*-oxide oxygen atom, but those in which the nucleophile is a trivalent phosphorus compound are perhaps the best known. The loss of oxygen may well occur in two stages, even in these phosphorus reactions (*56* → *58*); the electron-donor properties of the *N*-oxide group are called upon in the first stage of the reaction (*56* → *57*), and the second stage involves breakdown of the resulting complex (*57* → *58*).



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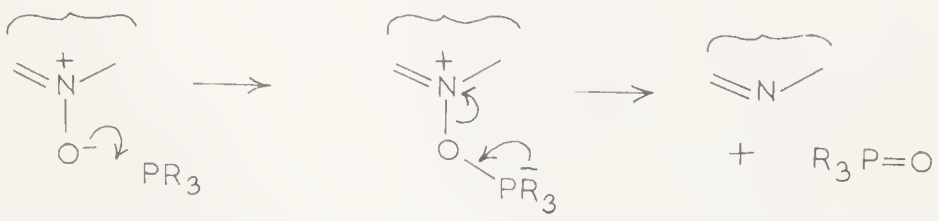
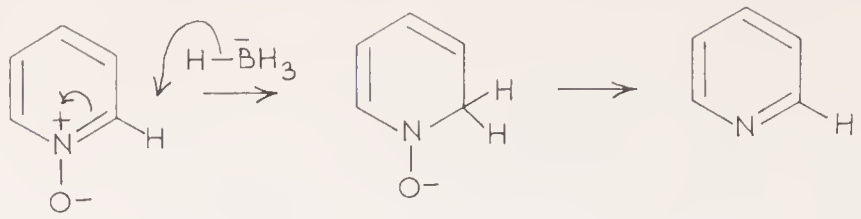


(56) (57) (58)

Table 3.06. Complexes of 2,2′-Bipyridyl 1,1′-Dioxide with Metal Ions

Complex types[a]	Metal(s)	Other ligands	Physical measurements[b]	References
$M(BipyO_2)_4X_3$	rare earths	ClO_4^-	IR, Λ	68JN3017, 69JN1427
$M(BipyO_2)_3X_3$	Al, Co, Cr, Fe, Mn	Br^-, ClO_4^-, I^-, NO_3^-, $(S_2O_8)_2^{3-}$ [c]	IR, UV, μ, Λ	62J1121, 63IC282, 64JN2211
$M(BipyO_2)_3X_2$	Cd, Co, Cu, Hg, Mn, Ni, Zn	Br^-, ClO_4^-, I^-, NO_3^-, $PtCl_4^{2-}$ [d]	IR, UV, μ, Λ	63IC282, 64JN2211
$M(BipyO_2)_2X_2$	Co, Cu, Pb	Cl^-, ClO_4^-, $PtCl_4^{2-}$ [d]	IR, UV, μ, Λ	63IC282, 64JN2211
$M(BipyO_2)X_2$	Cu	Cl^-	IR, UV, μ, Λ	64JN2211
$M(BipyO_2)_2X$	Ag	ClO_4^-	IR, UV, μ, Λ	64JN2211

[a] Water of hydration not indicated.
[b] μ = magnetic susceptibility; Λ = conductivity.
[c] $[Mn(C_{30}H_{24}N_6O_3)](S_2O_8)_{1.5} \cdot 4H_2O$.
[d] $PtCl_4^{2-}$ is equivalent to $2X^-$.

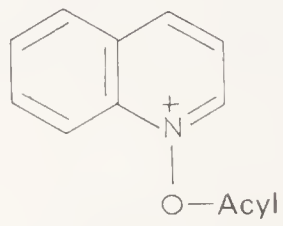


(59) (60) (61)

Although the reduction of pyridine 1-oxide with borohydride probably involves attack on the ring (*59* → *60*) and subsequent elimination (*60* → *61*), and therefore should be formally regarded as a ring reaction, it is included in this section for convenience. Catalytic reductions usually occur at the surface of a solid-phase catalyst. Reductions brought about by dissolving metals presumably involve successive one-electron transfers from the metal to the *N*-oxide.

N-Oxide groups in heteroaromatic *N*-oxides are usually considerably more stable towards reduction than those in aliphatic or alicyclic *N*-oxides. This stability was observed by Ochiai in his early work on pyridine 1-oxide (43JJ307) and numerous examples of this generalization are available: for example, pyridine 1-oxide is unaffected by ferrous hydroxide whereas aliphatic *N*-oxides are slowly reduced by this reagent (38CB2603). Quinoline 1-oxides, however, are significantly more readily reduced than their pyridine analogues (55ZO161), and *N*-oxides containing more than one heteroatom in the ring are reduced rather easily to the corresponding deoxygenated heterocycles: examples are to be found in Sections IIB to IIG. Selectivity in reduction is achieved in suitable cases: thus, phenazine 5,10-dioxides with electron-donating groups in the 2-position yield the 5-mono-oxides, indicating stabilizing interactions between the substituent and the *N*-oxide group in position 5 (64JJ1080).

Hamana and Funagoshi (60JJ1027) have reduced the adducts which pyridine and quinoline 1-oxides form with acetic anhydride, benzoyl chloride, and tosyl chloride. They found that acyl cations of type *62* are readily reduced by sulphur dioxide, stannous chloride, or hydrogen in the presence of Raney nickel, and that the rates of reduction are much faster than those of the parent *N*-oxide.



(62)

Occasionally reduction of the ring occurs without affecting the *N*-oxide group; these reactions are considered in Section III-6Aiii. Finally, furoxans and condensed furoxans are reduced under some conditions to α-dioximes.

For monocyclic furoxans the reducing agent is usually zinc, and for condensed furoxans it is hydroxylamine: these reactions are therefore considered in Sections III-2F and III-2Eii, respectively (see Tables 3.17 and 3.20).

B. CATALYTIC HYDROGENATION

Catalytic hydrogenation has been extensively used in *N*-oxide chemistry. Available data are summarized in Table 3.07; exceptionally, for convenience in discussion and to facilitate comparison, all catalytic reductions are collected in this table, including those in which a substituent is reduced while the *N*-oxide group is unaffected. Most of these reductions have been carried out at atmospheric pressure and at a temperature near 20°; the catalysts most frequently employed have been palladium (usually on a carbon support) and nickel [most often Raney nickel, but frequently "Urushibara nickel", a catalyst prepared from zinc and nickel chloride which can be used at normal temperatures and pressures (54BJ480; 55BJ446)]. With Raney nickel and acetic acid–acetic anhydride as solvent, reduction is very rapid; addition of acetic acid to the reduction mixture is advocated by Japanese investigators for nickel-catalysed reactions [58CT323; 58LA(613)144].

The following generalizations may be drawn from the data summarized in Table 3.07:

(*a*) The *N*-oxide group is readily reduced, unless it is sterically hindered. The resistance of 2,2′-bipyridyl 1,1′-dioxides (62JO640) and 2-arylpyridine 1-oxides (61CC2516) to reduction is attributed to steric hindrance. Hydrogen bonding between the *N*-oxide oxygen atom and an α-substituent also decreases the rate of hydrogenation [58LA(613)144].

(*b*) An azoxy group [$-^{+}N(-O^{-})=N-$] is reduced to an azo group (-N=N-) before the ring *N*-oxide group is attacked.

(*c*) The following groups are reduced less readily than the *N*-oxide group: phenyl, fused benzene rings, heterocyclic rings, $-CO_2H$, $-CO_2R$, -COMe.

(*d*) The following groups are reduced at rates comparable with that of the *N*-oxide group (reduction product in brackets): $-OCH_2Ph$ (-OH, may tautomerize), $-CH_2OAc$ ($-CH_3$), -CH=CH-X ($-CH_2CH_2X$), -Cl (-H), -N=N- (-NH-NH- or $-NH_2$), $-NO_2$ (various products).

In many cases, selectivity can be achieved in the reduction of *N*-oxides containing the functional groups listed under *d* (65NK409; 65NK1328). In all of these cases, palladium catalysts favour reduction of the substituent, and the *N*-oxide group is attacked only on prolonged reaction. In contrast, nickel catalysts favour initial reduction of the *N*-oxide group, and all of the substituents listed under *d* except the nitro group can be left unchanged by choice of suitable reaction conditions. The nitro group is usually reduced simultaneously with the *N*-oxide group; however, if the nitro group is

Table 3.07. Catalytic Reduction of *N*-Oxides

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide	—	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
		Pd-C/EtOH	—	—	84	58J1263
	2-acetoacetylamino	Ni(R)/MeOH	—	—	—	64CT910
	2-acetoxymethyl	Ni(R)	—	(i) 1-oxide, (ii) CH_2OAc	—	65NK409
		Pd-C	—	(i) CH_2OAc, (ii) 1-oxide	—	65NK409
	3- and 4-acyl	Pd-C/EtOH	—	—	70 and 29	58J1263
	2-acylamino	Pd-C	—	—	80	60J2937
	2-acyl-3-carboxy	"catalyst"	—	—	60	60CI402
	4-(β-DL-alanyl)	Pt/H_2O	—	$C_5H_4N \rightarrow C_5H_9N$	(data)	58JO575
	2-alkoxy	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
	4-alkoxy	Ni(R) or Ni(U)	—	—	ca. 85	51JJ1092, 58LA(613)144, 60JJ839
	6-alkoxy-4-aryl-1-benzyloxy-2-oxo	Pd-C	—	1-$PhCH_2O$	—	59J2310
	4-alkoxy-2,6-dimethyl	Pt-Pd/Ac_2O	—	—	—	51JJ156

[a] Resistance of the *N*-oxide group to catalytic reduction is indicated in this column; i.e., no entry indicates reduction of the *N*-oxide group(s) to the parent heterocycle.

[b] Substituents affected *in addition to* or in preference to the *N*-oxide group. The isolable products in stepwise reactions are indicated: $NO_2 \rightarrow NH_2$, Cl or Br → H, $PhCH_2O \rightarrow OH$, $EtO \rightarrow O:$, $OH \rightarrow H$ unless otherwise indicated.

[c] For stepwise reactions, the yields indicate the amount of each product isolated.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Reduction product				
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*	2- and 4-alkoxycarbonyl	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
	2- and 4-alkoxyphenyl-methyl	Pt	—	hetero ring	45–76	64CT588
	2-alkyl	Ni(R)[d]	—	—	17–90	58LA(613)144, 60CB2591, 63CT694
		Pd-C	—	—	68–84	58J1263, 63CT694
	3-alkyl	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
	4-alkyl	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
		Pd-C/EtOH	—	—	82–88	58J1263
	2,6-dialkyl	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
	2,6-dialkyl-3- and -4-amino	Pt	—	—	68	56CT174, 65CT963
	2-alkyl-4-nitro	Pd/AcOH-Ac_2O	—	—	—	47JJ158
		Pd/HCl	1-oxide	4-NO_2	—	47JJ158
		Pd/NaOH	—	4-NO_2 → -N=N-	—	47JJ158
	3-alkyl-4-nitro	Ni(R)/N_2H_4·H_2O	—	4-NO_2	73	64AJ1434

[a] Using methanol as solvent, yields of 17–43% have been reported; with MeOH-AcOH a 90% yield was obtained (63CT694).

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Reduction product				
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*		Ni(W-2R)/EtOH	1-oxide	4-NO_2[e]	(data)	64AJ1434
		Ni(W-2R)/MeOH-AcOH	—	4-NO_2	89	64AJ1434
		Pd/AcOH-Ac_2O	—	4-NO_2	78–100	54JA4184, 56CT174, 57JA3549[f], 64AJ1434
		Pd/H_2O	1-oxide	4-NO_2	94	56CT174
		Pd/HCl	1-oxide	4-NO_2 → NHOH	88	57JA3549
		"catalyst"	—	4-NO_2	—	55JJ292, 58CI1089
	2,5-dialkyl-4-nitro	Pd-C/EtOH	1-oxide	4-NO_2	quant.	55JO1461, 58BF694
	2,6-dialkyl-3-nitro	50% Pd-C	1-oxide	3-NO_2	96–98	65CT963
	2,6-dialkyl-4-nitro	50% Pd-C	1-oxide	4-NO_2	96–98	65CT963
		Pd/H_2O, MeOH, or HCl	1-oxide	4-NO_2[g]	80	56CT174, 62JO1665
		Pd/AcOH-Ac_2O	—	4-NO_2	70	56CT174, 62JO1665
	4-alkylthio	Ni(R)	—	—	—	60JJ1145, 62ZC86
	2-amino	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144

[e] In addition to the 4-aminopyridine 1-oxide, 3,3′-dimethyl-4,4′-azoxypyridine 1,1′-dioxide was obtained.
[f] 4,4′-Dinitro-3,3′-dipicolyl 1,1′-dioxide.
[g] With methanol or hydrochloric acid as solvent, the bis-hydrazo compound is also formed.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Reduction product				
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*		Pd-C/EtOH	—	—	85	58J1263
	4-amino	Ni(R)/MeOH	—	—	98	58CT323, 59CT141
		Pd-C/EtOH or HCl	—	—	77	58CT1263, 59CT141
	2-aryl	5% Pd-alumina	1-oxide	see note [h]	20–25	60J1511
		Pd-C	—	see note [h]	59–87	58J1263, 60J1511
		Pd-C/AcOH	1-oxide	see note [h]	—	61CC2516
	4-aryl	Pd-C/EtOH	—	—	89	58J1263
	2,6-diaryl-4-nitro[i]	Pd	—	4-NO_2	75	62JO640
	4-arylthio	Ni(R)	—	—	—	60JJ1145
	4-arylsulphonyl	Ni(R)	—	—	—	60JJ1145
	4-azo[j]	Ni(R)/MeOH	—	(i) 1-oxide, (ii) N=N → NH-NH	—	60CT649
		Pd/MeOH	1-oxide	N=N → NH-NH	—	60CT649
	4-azoxy[k]	Ni(R)/MeOH	—	(i) azoxy → azo, (ii) 1-oxide, (iii) N=N → NH-NH	—	60CT649

[h] If the aryl group carries a nitro substituent, the nitro group is reduced to an amino group.
[i] 4,4′,4″-Trinitro-bis(2′-pyridyl)pyridine 1,1′,1″-trioxide.
[j] 4,4′-Azopyridine 1,1′-dioxide.
[k] 4,4′-Azoxypyridine 1,1′-dioxide.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Reduction product				
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*		Pd/MeOH	1-oxide	(i) azoxy → azo, (ii) N=N → NH-NH	—	60CT649
	2-benzyloxy	Ni(R)	—	(i) 1-oxide, (ii) $PhCH_2O$	—	65NK409
		Pd-C	1-oxide	2-$PhCH_2O$	69	45JJ1, 49JA67, 51USP2540218, 65NK409
	4-benzyloxy	Ni(R) or Ni(U)/MeOH	—	—	ca. 92	58CT323, 59CT141, 60JJ839
		Ni(R), Cu(R), Co(R), Cu chromite, Ru-C, Pt-C, Rh-C Ni(R) + Pd-C/MeOH	—	4-$PhCH_2O$	—	59CT141, 65NK409
	2-benzyloxy-5-bromo-4-methyl	Pd-C	1-oxide	2-$PhCH_2O$	—	51USP2540218
	4-benzyloxy-3-carboxamido	Ni(R) or Pd-Si	—	4-$PhCH_2O$	50–80	62CB277, 63CB266
	4-benzyloxy-3-carboxy	Pd/AcOH	—	(i) $PhCH_2O$, (ii) 1-oxide	51	60JA3141

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*	2-benzyloxy-6-methyl	Pd/EtOH	1-oxide	2-$PhCH_2O$	72	54JA3168
	4-benzyloxy-2-methyl	"catalyst"	1-oxide	4-$PhCH_2O$	—	48JJ126
	3,5-dibromo	Ni(R)/MeOH	—	—	(data)	61CT414, 65JJ62
	4-bromo-3-carboxamido	Ni(R)/MeOH	—	—	—	63CB266
	3-carboxamido (*N*-substituted)	Pd-C/EtOH	—	—	86	58J1263
	4-carboxamido-, -carboxy-, and -ethoxycarbonyl-vinyl	Pd-C/EtOH	—	(i) 4-CH=CHR′, (ii) 1-oxide	75–83	58J1263
	3-carboxamido-4-halogeno	Ni(R)/MeOH	—	—	—	63CB266
	3-carboxamido-4-methoxy	Pd-Si/MeOH	—	—	40–50	62CB277
	3-carboxamido-4-nitro	Ni(R)/MeOH	—	4-NO_2	—	63CB266
	3-carboxamido- or -ethoxycarbonyl-vinyl	Pd-C/EtOH	—	(i) 3-CH=CHR′, (ii) 1-oxide	58–80	58J1263
	3-carboxy-4-amino (substituted)	Pd-C	—	—	—	61JO122, 64AJ1399
	3-carboxy-4-nitro	Pd-C/NH_4OH	—	4-NO_2	—	61JO122, 63CB266

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*	3-carboxyvinyl	Pd-C/EtOH	—	3-CH=CHCO$_2$H	63	58J1263
	2-chloro	Ni(R)/AcOH-Ac_2O	—	—	—	58LA(613)144
	4-chloro	Ni(R) or Ni(U)	—	—	ca. 88	58CT323, 58LA(613)144, 59CT141, 60JJ839
		Pd-C/EtOH	—	(i) Cl, (ii) 1-oxide	—	58J1263
	4-chloro-3-methyl	Ni(R)/MeOH	—	—	70	64AJ1434
	2- and 2,6-di-chloro-4-nitro	Ni(R)/MeOH	—	4-NO_2	92–99	65JH196
	4-chloro-3-(4-chloro-1-oxido-3-pyridyl)	Pd/HCl	—	—	—	57JA3549
	4-diethylamino	Cu-bronze	—	—	—	44PJ141
	3-ethoxycarbonyl	Pd-C/EtOH	—	—	60	58J1263
	4-ethoxycarbonyl	Pd-C/EtOH	—	(i) 1-oxide, (ii) hetero ring	70	58J1263
	4-ethoxy-2-(4-ethoxy-1-oxido-2-pyridyl)	Ni(R)/EtOH	—	—	33	67J(B)106
	1,2,3,4-tetrahydro-3,3-dimethyl-5-oxo	Pt/EtOH	—	ring C=N	—	59J2105
	2-, 3-, and 4-hydroxy	Ni(R)	—	—	quant.	58CT323, 58LA(613)144, 59CT141

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*	4-hydroxy	Pd/EtOH or HCl	—	—	—	58J1263, 59CT141
	4-hydroxyamino	Pt/HCl	—	4-NHOH → NH_2	—	60G903
	3,6-dihydroxy-2-methyl	Ni(R)/MeOH	—	hetero ring	84	55AS9
	4-hydroxy-2- or 3-methyl-5-nitro	Pd-C/MeOH	—	4-OH, 5-NO_2	—	51JJ789
	4-methoxy-2-(4-methoxy-1-oxido-pyridyl)ethyl	Pt	—	-CH_2CH_2- → CH_3CH_3	87	61JO3796
	4-morpholino	Pd	—	—	—	44PJ141
	3-nitro	Pt	—	3-NO_2	100	60JO1716
	4-nitro	Ni(R)/AcOH-NaOAc	—	4-NO_2	—	52JJ665
		Ni(R)/MeOH	—	4-NO_2[l]	55	52JJ1315, 58CT323
		Ni(R)/AcOH-MeOH-NaOAc	—	4-NO_2[m]	70	52JJ1315
		Ni(R)/AcOH-MeOH	—	4-NO_2	90	58CT323, 59CT141
		Ni(U)/MeOH	—	4-NO_2 → -NHNH-	—	60JJ839
		Ni(U)/MeOH-AcOH	—	4-NO_2	—	60JJ839

[l] Other side products are also obtained.
[m] Reaction carried out at pH 3-4: no side products are formed.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridine 1-oxide, *cont'd.*		Pd-C	—	4-NO_2	—	43JJ79, 56JO1077, 57JA3565
		Pd/MeOH	1-oxide	4-NO_2	—	59CT141
	4-nitro-2-(4-nitro-1-oxido-2-pyridyl)	$NaBH_4$/Pd-C	—	4-NO_2	74	67J(B)106
	2-(*m*- and *p*-nitrophenyl)	Pd/EtOH	1-oxide	*m*- or *p*-NO_2	20–25	60J1511
	4-nitrostyryl	Pd/EtOH	—	4-CH=CH-C_6H_4-NO_2 → 4-CH_2-CH_2-C_6H_4-NH_2	(data)	61JO418
	4-nitro-3-substituted	Ni(R)	—	4-NO_2	85	62J2379, 65MC296
		"catalyst"	—	4-NO_2	"poor"	58CI1089
	2-styryl	Ni(R)/MeOH	—	(i) 1-oxide, (ii) 2-CH=CHPh	—	60CT649, 65NK1328
		Pd-C	—	(i) 2-CH=CHPh, (ii) 1-oxide	45	58J1263, 60CT649, 65NK1328
	4-styryl	Ni(R), Cu(R), Co(R), Cu chromite, Ru-C	—	(i) 1-oxide, (ii) 4-CH=CHPh	—	65NK409
		Pd-C/EtOH	—	(i) 4-CH=CHPh, (ii) 1-oxide	89	58J1263, 65NK409

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Quinoline 1-oxide	—	Ni(R) or Ni(U)	—	—	ca. 80	59CT145, 60JJ839
	2-acetamido-4-cyano-3-phenyl	Pd/AcOH	—	—	—	60J3466
	3-alkyl- and -alkoxy-4-nitro	Pd-C/EtOH	see note [n]	4-NO_2	15	68CT839
	8-alkyl-4-nitro	Pd-C/EtOH	—	4-NO_2 → 4-NHOH	80	68CT839
	4-alkylthio	Ni(R)	—	—	—	62ZC86, 68JJ672
	4-amino	Ni(R)/MeOH	—	—	74	59CT145
		Pd-C	—	—	—	43PJ574
	4-amino-3-nitro	Pd/EtOH-HCl	—	(i) 3-NO_2, (ii) 1-oxide	—	47JJ141
	4-benzylamino	Ni(R)	—	(i) 1-oxide, (ii) 4-$PhCH_2O$	69	59CT145
	3,6-dibromo	Ni(R)/MeOH	—	—	(data)	61CT414, 65JJ62
	3-bromo-4-nitro	Pd-C/EtOH	—	3-Br	41	68CT839
	4-chloro	Ni(R)/MeOH	—	—	90	59CT145
	4-chloro-2-cyano	Pd-C	—	1-oxide	—	63JJ348
	6-chloro-3-ethoxycarbonyl-8-fluoro-4-nitro	Pd-C/EtOH	—	4-NO_2 → 4-NHOH	84	68CT839
	4-chloro-2-hydroxy	Ni(R)	—	—	47	68JJ656
	4-chloro-2-methyl-8-nitro	Pd/MeOH-HCl	—	4-Cl, 8-NO_2	—	51JJ1078

[n] 4-Amino-3-methylquinoline 1-oxide (17%) and 4-amino-3-methoxyquinoline 1-oxide (62%) are also obtained.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Catalyst/solvent	Reduction product		Yield, %[c]	References
Ring system	Substituents		*N*-Oxide unaffected[a]	Substituents affected[b]		
Quinoline 1-oxide, *cont'd.*	4-chloro-2-phenyl	Pd	—	4-Cl	—	65JJ66
	3-(diethoxycarbonyl-methyl)-4-nitro	$Pd/CHCl_3$	—	—	25	64JO3381
	4-hydrazo[o]	Pd-C	—	4-NHNH- → NH_2	—	43PJ574
	2-hydroxy	Ni(R)/MeOH	—	—	83	59CT149
	4-hydroxy	Ni(R)	—	see note [p]	ca. 85	52JJ1317, 59CT145
	8-hydroxy	Ni(R)	—	—	—	52ZO1224
	4-hydroxy-2-methyl	Pd-C	—	6-Cl	—	60J3470
	4-hydroxy-3-nitro	Pd/Ac_2O	—	3-NO_2 → NHAc	—	52JJ767
	4-mercapto (and sodium salt)	Ni(R)	1-oxide	see note [q]	—	60JJ1145
	4-methoxy	Ni(R)	—	see note [r]	61–93	52JJ1317, 59CT145
	3-nitro	Pd/Et_2O	—	3-NO_2	see note [s]	58JJ584
		Pd/Et_2O-$NaHCO_3$	1-oxide	3-NO_2 → NHOH	—	58JJ584
		Pd/various solvents	—	(i) NO_2 → NHOH → NH_2, (ii) 1-oxide	25–65	58JJ584

[o] Bis compound.
[p] Reduction of the 1-oxide group occurs at 40–55°, but at 160–240° side reactions occur including reduction of the benzo ring.
[q] The 4-SNa derivative leads to a dimeric product.
[r] Reduction of the 1-oxide group occurs at 40–50°; above 140° reduction of the benzo ring is also observed.
[s] About one-half of the oxide remains.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Reduction product				
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Quinoline 1-oxide, *cont'd.*	4-nitro	$(HCO_2)_2Ni$/MeOH-paraffin	—	4-NO_2, benzo ring	70	52JJ1317
		Ni(R)/MeOH	—	4-NO_2	32	52JJ1317
		Ni(R)/MeOH-AcOH	—	4-NO_2	79	58CT323, 59CT145
		Pd	—	4-NO_2 → -NHNH-	—	43PJ574, 44JJ206
		"catalyst"/acid	see note [t]	(i) 4-NO_2 → NHOH → NH_2 (ii) 1-oxide	—	44JJ206
		"catalyst"/neutral	1-oxide	4-NO_2 → -NHNH-[o]	—	44JJ206
		"catalyst"/alkali	1-oxide	4-NO_2 → OEt	—	44JJ206
	5-nitro	Pd-C/EtOH	1-oxide	5-NO_2 → 5-NHOH	33	68CT839
	4,6-dinitro	"catalyst"/acid	—	4,6-diNO_2	—	45JJ(5/6A)3
		"catalyst"/neutral	1-oxide	4,6-diNO_2	—	45JJ(5/6A)3
	4-nitro-2-phenyl	Pd-C	—	4-NO_2	—	66JJ59
	2-styryl	Ni(R), Pd-C, or Pt	—	(i) 2-CH=CHPh, (ii) 1-oxide	—	64PC(25)7, 65NK1328
	2-vinyl	Ni(R)/EtOH	—	(i) $CH=CH_2$, (ii) 1-oxide	—	65PC(28)82

[t] Reduction of the *N*-oxide not complete; a mixture of 4-amino-quinoline and -quinoline 1-oxide is obtained.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Isoquinoline 2-oxide	1-benzyl	Pd	—	—	—	68AI9
	1-hydroxy	Ni(R)	—	—	(data)	62CT51
	5-nitro	Pd/alc.	see note [v]	5-NO_2[v]	80	45JJ(4A)17, 53JJ666
		Pd/HCl-alc.	—	5-NO_2[u]	—	45JJ(4A)17, 53JJ666[u]
Phenanthridine 5-oxide	—	Ni(R)	—	—	—	60JJ834
Benzo[*f*]quinoline 1-oxide	—	Pd/AcOH-Ac_2O	—	—	—	52JJ985
1*H*-Pyrazolo[4,3-*c*]-pyridine 5-oxide	3-hydroxy	Ni(R)/MeOH	—	—	55	65AJ379
	3-hydroxy-1-methyl	Ni(R)/MeOH	—	—	99	65AJ379
	3-hydroxy-1-phenyl	Ni(R)/NaOH	—	—	65	65AJ379
*						
1,6-Naphthyridine 1,6-dioxide	—	Ni(R)/MeOH	1-oxide (in part)	—	(data)	69CT1045
Pyridazine 1-oxide	6-acetamino-3-methoxy-4-nitro	10% Pd-C/AcOH	—	4-NO_2 → -NHNH-[o]	—	63CT1157
	3- and 4-alkoxy	Pd-C	—	—	—	62JJ244
	3-alkoxy-6-amino-5-nitro	20% Pd-C/5% HCl	—	5-NO_2 → NHOH	—	63CT1157
	3-alkoxy-6-chloro	Pd-C	1-oxide	6-Cl	(data)	61JJ1048, 62CT989, 62JJ244

[u] Some concomitant reduction of the hetero ring has been reported.
[v] Reduction of the 2-oxide group is not complete.
* 1,6-Naphthyridine 1- or 6-oxide; see addendum in the Appendix.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material		Catalyst/solvent	Reduction product		Yield, %[c]	References
Ring system	Substituents		*N*-Oxide unaffected[a]	Substituents affected[b]		
Pyridazine 1-oxide, *cont'd.*	4-alkoxy-3,6-dichloro	Pd-C/MeOH-NH_4OH	1-oxide	3,6-diCl	85	63CT83
	5-alkoxy-3,4-dichloro	Pd-C/MeOH-HCl	—	3,4-diCl	85	68CT142
	5-alkoxy-3,6-dichloro	Pd-C/MeOH-HCl	—	3,6-diCl	93	63CT83
	3-alkoxy-4-chloro-6-hydroxy[w]	Pd-C/MeOH	—	4-Cl	48	63CT1073
	3-alkoxy-6-methyl-4-nitro	Pd/Ac_2O	—	4-NO_2	—	63CT29
	3-alkoxy-4-nitro	Ni(R)	—	4-NO_2	83	60JJ712, 61JJ554
		Pd-C/alcohol	1-oxide	4-NO_2	86	60JJ712, 61JJ554
		Pd-C	—	4-NO_2	—	55JJ966, 61JJ708
	3-alkoxy-6-nitro	Ni(R)	—	6-NO_2	—	60JJ712, 61JJ554
		Pd-C	1-oxide	6-NO_2	—	60JJ712, 61JJ554
	6-alkylaminomethyl-3-hydroxy	Pd-C	—	—	95	67CT1172
	6-carboxy-4-chloro-3-hydroxy	Pd/NaOH	1-oxide	4-Cl	—	63CT1511
	3-carboxy-4-nitro	Ni(R)	—	4-NO_2	—	65CR51
	4-chloro-3-hydroxy	Pd-C/NaOH	1-oxide	4-Cl	—	63CT1511
	4-chloro-6-hydroxy-iminomethyl	Pd/MeOH	1-oxide	4-Cl, CH=NOH → CH_2NH_2	—	63CT1511
	3-chloro-4- and -5-methyl	Pd-C/NH_3-MeOH	1-oxide	3-Cl	(data)	63CT35

[w] 1-Hydroxy-6-pyridazinone.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridazine 1-oxide, *cont'd.*	3-chloro-6-methyl	Pd-C/NH_4OH	1-oxide	3-Cl	70–75	61CT1017, 61JJ1817, 63CT29
	3-chloro-6-methyl-4-nitro	Pd/MeOH	—	3-Cl, 4-NO_2	—	63CT29
	3-chloro-6-phenyl	Pd-C/NH_4OH	1-oxide	3-Cl	(data)	63CT1522
	6-chloro-3-phenyl	Pd-C/NH_4OH	1-oxide	6-Cl	(data)	63CT1522
	2,5,6-trimethyl-3-oxo[z]	Pd/H_2O	—	—	—	63CT721
	3-methyl	Pd-C	—	—	—	61JJ1817
	3-methyl-5-nitro	Pd/MeOH	1-oxide	5-NO_2	50	63CT29
	3,6-dimethyl-4-nitro	Pd-C	1-oxide	4-NO_2	82	63CT337
	5,6-dimethyl-3- or -4-nitro	Ni(R), Pd-C	—	4-NO_2	83	63CT726
	4- and 4,6-di-morpholinomethyl-3-hydroxy	Pd-C	—	—	95	67CT1733
	3-oxo[z]	Pd-C	—	—	—	62JJ244
	3-nitro	Pd-C/MeOH	—	(i) 3-NO_2→ NHOH→ NH_2, (ii) 1-oxide	76	63CT342
		Pd-C/HCl	—	3-NO_2	31	63CT342

[z] 3-Pyridazinone 1-oxide.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Pyridazine 1-oxide, *cont'd.*	4-nitro	Ni(R)/AcOH	—	4-NO_2	59	63CT83
		Pd-C/MeOH	1-oxide	4-NO_2	44	63CT83
	5-nitro	Ni(R)/EtOH-AcOH	—	5-NO_2	—	63CT1157
		Pd-C/HCl	—	5-NO_2	—	63CT342, 63CT1157
		15% Pd-C/AcOH	—	5-NO_2→-NAc[o]	—	63CT1157
	4-nitro-2,5-disubstituted	Ni(R)	—	4-NO_2	70–90	62JJ253
		Pd-C	1-oxide	4-NO_2	—	62JJ253
Cinnoline 1-oxide	4-chloro	Pd-C/EtOH-OH^-	—	4-Cl	62	64CT619
	3-chloro-5,6,7,8-tetrahydro	Pd-C	1-oxide	3-Cl	(data)	63CT1527
	4-nitro	Ni(R)	—	4-NO_2	75	63CT268
Cinnoline 2-oxide	4-chloro	Pd-C/EtOH	—	(i) 4-Cl, (ii) 2-oxide	(i) 31, (ii) 19	64CT619
	5-nitro	Pt	—	(i) 2-oxide, NO_2, (ii) N=N	(i) 5, (ii) 36	63CT1326, 66CT816
	6-nitro	Pd-C	2-oxide	6-NO_2	70	63CT1326, 66CT816
		Pt	—	(i) 6-NO_2, (ii) 2-oxide	(i) 35, (ii) 55	63CT1326
	8-nitro	Pd-C	2-oxide	8-NO_2	—	63CT1326, 66CT816

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Cinnoline 2-oxide, *cont'd.*		Pt	—	(i) NO_2, (ii) 2-oxide	(i) 33, (ii) 49	63CT1326
Cinnoline 1,2-dioxide	—	Pd-C	—	—	84	67CT1088
Benzo[*c*]cinnoline 5-oxide	3,8-bis(trifluoro-methyl)	Pt/EtOH	—	—	quant.	52JA1297
Benzo[*c*]cinnoline 6-oxide	3-amino	Ni(R)	—	—	—	56JO651
	2-nitro	Ni(R)	—	2-NO_2	80	45J824
	4-nitro	"catalyst"	—	4-NO_2	—	64J1265
Benzo[*c*]cinnoline 5,6-dioxide	—	Pt/EtOAc	3,8-bis(trifluoro-methyl)	—	(data)	52JA1297
Pyrimidine 1-oxide	6-amino-1-benzyl-oxy-2-oxo[aa]	Pd-C/EtOH	—	1-$PhCH_2O$	61	65M169
	4-amino-1-benzyl-oxy-2-oxo	Pd-C/EtOH	—	1-$PhCH_2O$	77	65M169
	4-benzyloxy-6- and 2,6-di-methyl	Ni(R)	—	—	ca. 90	59CT158
		Pd-C/MeOH	—	(i) 4-$PhCH_2O$, (ii) 1-oxide	64–80	59CT158
	4-hydroxy-6- and 2,6-di-methyl	Pd-C/MeOH	—	—	80	59CT158
	4-methoxy-6-methyl	Ni(R)/MeOH	—	—	90	59CT158
	6-methyl-4-piperidino	Ni(R)/MeOH	—	—	—	59CT505

[aa] Cytosine derivative.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield %[c]	References
Quinazoline 1-oxide	4-alkoxy	Ni(R)	—	—	—	59CT152
	4-alkoxy-2-hydroxy	Ni(R)/MeOH	—	—	—	59CT149
		Pd-C	1-oxide	—	—	59CT149
	2-amino-4-hydroxy[bb]	Ni(R)	—	—	—	63CI1559
	4-benzyloxy	Ni(R)	—	(i) oxide, (ii) 4-$PhCH_2O$	—	59JJ831
		Pd-C/MeOH	—	(i) 4-$PhCH_2O$, (ii) 1-oxide	—	59JJ831
	4-benzyloxy-2-hydroxy	Ni(R)/MeOH	—	(i) 4-$PhCH_2O$, (ii) 1-oxide	70	59CT149
	4-isopropyl	Ni(R)/MeOH	—	—	73	64CT43
	4-hydroxy[bb]	Ni(R)	—	—	72	64CT43
Quinazoline 3-oxide	—	Ni(R)	—	(i) 3-oxide, (ii) C=N[cc]	—	61CT635
		Pd-C	—	hetero ring[dd]	—	57JJ507
	6,7-dimethyl-2-dimethylamino-methyl-4-phenyl	Ni(R)	—	(i) 3-oxide, (ii) C=N[cc]	—	60JA475
		Pd	—	—	—	60JA475
Purine 1-oxide	9-alkyl-6-amino	Ni(R)	—	—	64–74	65CT1017
	6-amino	Ni(R)	—	—	—	59JO2035

[bb] 4-Quinazolinone 1-oxide.
[cc] Product is a 3,4-dihydro derivative.
[dd] Product is a 1,2,3,4-tetrahydroquinazoline.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Purine 1-oxide, *cont'd.*	6-amino-2-mercapto	Ni(R)/NaOH	—	2-SH	—	63JO2560
	6-amino-2-methyl	Ni(R)	—	—	—	60JA1148
	6-amino-9-substituted[ee]	Ni(R)	—	—	"high"	59JA1734
	6-hydroxy	Ni(R)	1-oxide	—	—	59JO2019, 59JO2035
		PtO_2	—	—	—	59JO2019
	6-methyl	Ni(R)/H_2O	—	—	83	62JO567
Purine 3-oxide	6-amino-7-methyl	Ni(R)/NH_4OH	—	—	85	59JO2035
	6-mercapto	Ni(R)/NH_4OH	—	6-SH	ca. 100	65MC190
	2,6-dioxo	Ni(R)/H_2O	—	—	—	65JO408
8-Azapurine 1-oxide	6-amino	Ni(R)	—	—	see note[ff]	60JA3189
8-Azapurine 3-oxide	2,6-dihydroxy	PtO_2	—	—	—	65JO408
Pteridine 1-oxide	2,4-dihydroxy-6,7-dimethyl	PtO_2/H_2O	—	—	(data)	65JO408
Pyrazine 1-oxide	3-chloro-6-methyl	Pd-C/NH_4OH	—	3-Cl	—	62JJ249
	4-diethylamino	Cu-bronze	—	—	—	44PJ141
Pyrido[1,2-*a*]pyrazine 2-oxide	1,5-dibromo	Pt	—	1-Br→H	—	67J(C)2391
Quinoxaline 1-oxide		Ni(R)	—	—	—	67JJ942
	2-amino-3-hydroxy[gg]	Ni(R)/NH(Et)Me	—	—	—	63CI1559
	4-nitro	Ni(R)	—	4-NO_2	75	64CT1090

[ee] Adenosine mono- and di-phosphate.
[ff] 8-Azaadenine is the major product.
[gg] 2-Amino-3-quinoxalinone 1-oxide.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Quinoxaline 1-oxide, *cont'd.*	2-hydroxy	Ni(R)	—	—	—	62ZO2967
	3-phenyl	Ni(R)	—	—	—	62JJ1093
Quinoxaline 1,4-dioxide	—	Ni(R)	1-oxide	—	—	62ZO2967
	2-amino	Ni(R)	—	—	—	63ZO1544
	2-ethoxycarbonyl	Ni(R)	—	—	—	58ZO1378
Phenazine *N*-oxide	—	Pd-C	—	—	—	65CR51
	2-chloro	Ru-C	—	—	—	65CR51
	1,7-dinitro	Pd-C	—	1,7-diNO_2	—	58CT77
1,2,4-Benzotriazine 1-oxide	3-amino-7-chloro	Ni(R)/EtOH[hh]	—	—	43	54JA3551
	6- and 7-chloro	Ni(R)	—	—	—	49USP2489351
	7-methoxy	Ni(R)	—	—	—	49USP2489351
	5- and 7-methyl	Ni(R)	—	—	—	49USP2489351
2-Azapurine 1-oxide	6-amino	Ni(R)	1-oxide	—	—	60JA3189
2-Azaquinolizinium bromide 2-oxide	3-methyl	Pt/MeOH	—	hetero rings[ii]	—	66JO941
Δ^1-Pyrroline 1-oxide	2-azo-5,5-dimethyl	Ni(R)	—	2-azo→NH_2	(data)	65J1224
Isopyrazole 1,2-dioxide	3,5,5-trimethyl	Pt	—	(i) 2-oxide, (ii) C=C→3,4-dihydro, (iii) 1-oxide	50	62JO1309

[hh] Reaction carried out under 45 p.s.i. of hydrogen.
[ii] 3-Methyl-2-azaquinolizidine formed.

Table 3.07. Catalytic Reduction of *N*-Oxides—*continued*

Starting material			Reduction product			
Ring system	Substituents	Catalyst/solvent	*N*-Oxide unaffected[a]	Substituents affected[b]	Yield, %[c]	References
Imidazole 1-oxide	1-ethoxy	Ni(R)	—	1-OEt→H	(data)	64CT282
	1-ethoxy-5- or -6-nitro	Ni(R)	—	1-EtO, 5- or 6-NO_2	(data)	64CT282
	3-hydroxy-2,4,5-trisubstituted	Ni(R)	—	3-OH	70–94	65AP293
* Benzimidazole 1-oxide	3-hydroxy-2-phenyl	Ni(R) or Pt	—	3-OH	—	63TL785
	3-substituted	Ni(R)/MeOH	—	—	—	63CT1375
Furoxan	dialkyl	Ni(R)	—	=N-O-NO=→ glyoxime	(data)	60JA5339
	3-(4)-carboxamido-4-(3)-phenyl	Pd/EtOH	—	=N-O-NO=→ glyoxime	—	68AN200
3*H*-1,4-Benzodiazepine 4-oxide	7-chloro-2-hydrazino-5-phenyl	Ni(R)/MeOH	—	—	89	68J(C)1103
	7-chloro-2-methylamino-5-phenyl	Ni(R)/dioxane	—	—	quant.	61JO1111
		Pt/AcOH	—	$C=\overset{+}{N}\text{-}O^{-}\rightarrow$ CHNH[jj]	63	61JO1111
	7-chloro-5-phenyl	Ni(R)	—	—	—	61JO4936
		Pt	—	$C=\overset{+}{N}\text{-}O^{-}\rightarrow$ CH-NOH	—	61JO4936

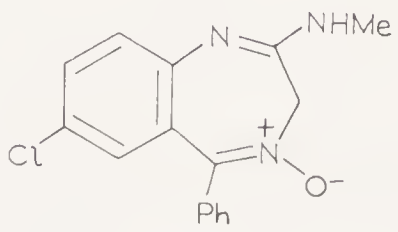
[jj] The 4,5-dihydro derivative is obtained.
* Imidazole 3-oxide; see addendum in the Appendix.

somewhat hindered, as in 3-methoxy-4-nitropyridazine 1-oxide, it may be unaffected by the nickel-catalysed hydrogenation (60JJ712). As might be expected, the nature of the products resulting from reduction of the nitro group is highly dependent on the p*H* of the reaction mixture: in acid solution the reduction usually proceeds directly to the amino compound, whereas in neutral or alkaline solutions intermediate products may be isolated (44JJ206).

Palladium-catalysed reduction of 4-nitroquinoline 1-oxide in ethanol solution gives a product which was originally formulated as 4,4′-hydrazoquinoline 1,1′-dioxide (44JJ206), but was later shown to be 4-hydroxyaminoquinoline 1-oxide (57CT310).

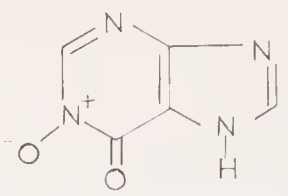
Katritzky and Monro (58J1263) investigated the palladium-catalysed hydrogenation of numerous substituted pyridine 1-oxides under standard conditions, and reached conclusions similar to those given above: semi-quantitative data are contained in this paper. German investigators have reported similar results (63CB266).

There is limited evidence (65NK409) that the selectivities of Raney cobalt, Raney copper, copper chromite, and ruthenium catalysts are similar to that of nickel, while platinum and rhodium show behaviour which is intermediate (ca. midway) between that of palladium and the nickel-type catalysts. However, other workers have reported that attempted reduction of various quinoline 1-oxides with Raney cobalt and Raney copper was not successful (59CT145). Hydrogenation of the benzodiazepine *N*-oxide *63* in the presence of nickel leads to selective reduction of the *N*-oxide group, but if a platinum catalyst is used the carbon–nitrogen double bond [i.e. $\diagdown C{=}N^{+}(-O^{-})\diagup$] is also reduced (61JO1111). Attempted reduction of 4-picoline 1-oxide using hydrazine and Raney nickel was not successful (58JO575).



(63)

(64) (65)



(66)

The N-O bond in cyclic hydroxamic acids (e.g. *64*⇌*65*) is very resistant to reduction in the presence of palladium, but it can be hydrogenolysed smoothly over a nickel catalyst (59CT149). On the other hand, hypoxanthine 1-oxide (*66*) is resistant to reduction with Raney nickel, but can be reduced over platinum (59JO2019).

Catalytic reduction of sulphur-containing compounds may be difficult because of catalyst poisoning. Thus, although 4-phenylthio- and 4-phenylsulphonyl-pyridine 1-oxides were reduced smoothly over a nickel catalyst to the corresponding pyridines, reduction of the 4-ethylthio analogue stopped after about one-half of the theoretical amount of hydrogen had been taken up, and 4-mercaptoquinoline 1-oxide was not reduced under these conditions (60JJ1145).

C. REDUCTION WITH COMPLEX HYDRIDES

As already indicated, the reactions included in this section probably all involve nucleophilic attack on carbon (*59*→*60*→*61*) rather than direct nucleophilic attack at the *N*-oxide oxygen atom. However, they are included in this section for convenience. Examples of reductions which have been effected with complex metal hydrides are collected in Table 3.08.

Pyridine 1-oxide is smoothly deoxygenated by sodium borohydride with aluminium trichloride in diglyme at 25°; at 75° further reduction to dihydropyridine occurs (56JA2582). In aqueous solution, pyridine 1-oxides are apparently not attacked by sodium borohydride (cf. 63CT694). The reactions of quinoline 1-oxides with ethanolic sodium borohydride can be complex; thus, 4-nitroquinoline 1-oxide yields 4-nitroquinoline together with quinoline 1-oxide (presumably formed by nucleophilic displacement of NO_2^-) and 4-hydroxyaminoquinoline 1-oxide (65CT1103). Lithium trimethoxyaluminohydride reduces 4-picoline 1-oxide to 4-picoline (65JA5614).

Lithium aluminium hydride reduction of isoquinoline 2-oxide and phenanthridine 5-oxide yields the same dihydro derivatives as are obtained in similar reductions of the parent bases (60H265). Lithium aluminium hydride has been used frequently to deoxygenate the benzocinnoline *N*-oxides (see Table 3.08). Yields are good, often better than with stannous chloride, but halogen substituents are frequently lost during the reaction.

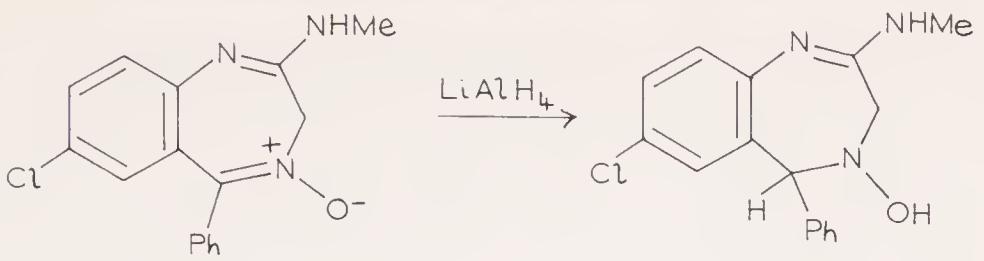
Table 3.08. Deoxygenation of *N*-Oxides with Complex Metal Hydrides

Ring system	Reagent	Substituents unaffected	Substituents reduced in addition to the *N*-oxide group	Remarks, % yield	References
Pyridine 1-oxide	$NaBH_4$-$AlCl_3$ in diglyme	—	—	Good yield at 25°	56JA2582
	KBH_4	1,2,3,4-tetrahydro-3,3-dimethyl	5-oxo	1,5-dihydroxy compd. formed in good yield	59J2105
Quinoline 1-oxide	$NaBH_4$	—	see note [a]	64–71	65CT1103
	$NaBH_4$	Cl	—	69	65CT1103
	$NaBH_4$	3- or 8-alkyl, 8-fluoro, 3-methoxy	$4\text{-}NO_2 \rightarrow NHOH$	39–95	68CT839
	$NaBH_4$	—	$3\text{-}Br \rightarrow H$, $4\text{-}NO_2 \rightarrow NHOH$	27	68CT839
	$NaBH_4$	—	$4\text{-}NO_2 \rightarrow NHOH$	63	68CT839
Isoquinoline 2-oxide	$LiAlH_4$	—	see note [b]	—	60H265
Phenanthridine 5-oxide	$LiAlH_4$	—	see note [b]	(data)	60H265
Benzo[*c*]cinnoline *N*-oxide	$LiAlH_4$	2-bromo	$4\text{-}Br \rightarrow H$	—	61J5029
	$LiAlH_4$	2-bromo	—	93	61J5029
	$LiAlH_4$	3-methyl	$1\text{-}Br \rightarrow H$	—	61J5029
Naphtho[1,2-*c*]-cinnoline *N*-oxide	$LiAlH_4$	—	—	90–95	60J3646

[a] Tetrahydroquinoline (11 %) was also obtained.
[b] A dihydro derivative is formed; see text.

Table 3.08. Deoxygenation of *N*-Oxides with Complex Metal Hydrides—*continued*

Ring system	Reagent	Substituents unaffected	Substituents reduced in addition to the *N*-oxide group	Remarks, % yield	References
Benzo[*f*]naphtho-[2,1-*c*]cinnoline *N*-oxide	$LiAlH_4$	—	—	—	59J3025
Benzo[*h*]naphtho-[1,2-*c*]cinnoline *N*-oxide	$LiAlH_4$	—	—	—	59J3025
Dibenzo-1,4,5-thiadiazine 1,4,5-trioxide	$LiAlH_4$	$-SO_2-$	—	92	57JA4382, 57JA5583
Isopyrazole 1,2-dioxide	$LiAlH_4$	3,5,5-trimethyl	$C=C \rightarrow CH_2CH_2$	—	62JO1309
Benzimidazole 1-oxide	$NaBH_4$	3-methyl	—	—	66CT375
	$NaBH_4$	2,3-dimethyl	—	(data)	66CT1219
1,4-Benzodiazepine 4-oxide	$LiAlH_4$	7-chloro-2-methylamino-5-phenyl-3*H*	$=C=N- \rightarrow =CHNH-$	*N*-oxide reduced to *N*-OH; 85% yield	61JO1111
	$LiAlH_4$	7-chloro-1,3-dihydro-5-phenyl	$=C=N-$, $=C=O$	*N*-oxide reduced to *N*-OH	63JO2150



(67) (68)

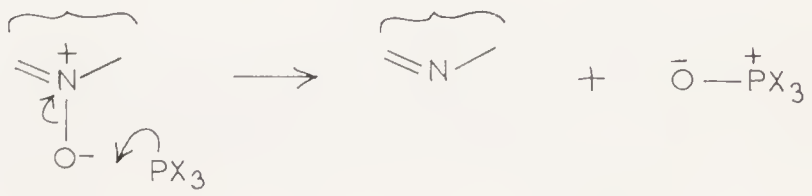
(69) (70)

(71) (72)

Reduction of the benzodiazepine *N*-oxide *67* with lithium aluminium hydride yields a product (*68*) different from that obtained using other reducing agents (61JO1111; cf. 63JO2150; 63JO2459). Boyer and Ellzey (60JA2525) showed that furoxans and benzofuroxans are reduced by borohydride to dioximes (*69* → *70*), but lithium aluminium hydride reduction of furoxans leads to ring cleavage with production of two primary amines (57CB2124; 67JO1255). Pyrroline 1-oxides (*71*) are reduced by borohydrides to 1-hydroxypyrrolidines (*72*) (59J2094; 59J2116).

D. REDUCTION WITH TRIVALENT PHOSPHORUS COMPOUNDS

Trivalent phosphorus compounds are particularly useful reducing agents for heterocyclic *N*-oxides because of their selectivity. Apparently, the first reported example of this reaction is the reduction of 3-cyano-2-phenylindazole 1-oxide with phosphorus trichloride (26CB351). Phosphite esters, substituted phosphines, and phosphorus trihalides have since become important reagents from a preparative standpoint because substituents which are easily reduced, such as nitro groups, are unaffected. Examples of *N*-oxides which have been reduced by these reagents are collected in Tables 3.09–3.12. The mechanisms of these reactions, although simple at first sight (cf. *73* → *74*), are considerably more complicated, at least in some cases, and can involve radical-chain reactions (see below).



(73) (74)

The ease with which trivalent phosphorus compounds reduce any particular *N*-oxide decreases in the order: $PCl_3 > PhPCl_2 > Ph_2PCl \gg (PhO)_3P > (EtO)_3P \gg Ph_3P > Bu_3P > Et_2PhP$. From this series it is apparent that reduction is retarded by electron-releasing groups attached to the phosphorus atom, and that, at least to some extent, electron donation from the *N*-oxide oxygen atom to the phosphorus atom is significant in the transition state [58AA(134)42-N; 62QR208]. This acceptance of electrons could precede electron donation (cf. *56–58*) or be a concerted process. In the pyridine series, electron-donor substituents in the ring increase the reaction rate (64J2319), but the opposite situation appears to exist in the furoxan series (64CB575).

In certain cases, phosphorus pentachloride can deoxygenate an *N*-oxide, e.g. in the isoxazoline 2-oxide (24JA2105; 26JA1770) and furoxan series [08LA(358)36]. Possibly, dissociation of the phosphorus pentachloride to chlorine and phosphorus trichloride precedes the reduction, which is then effected by the trichloride.

i. Trialkyl and Triaryl Phosphite Esters

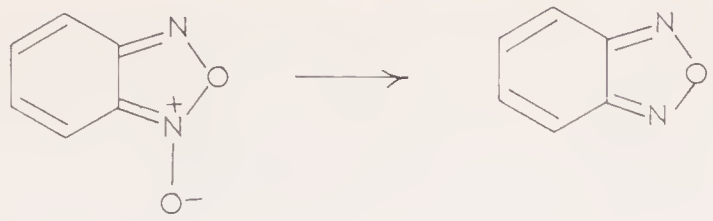
Triethyl phosphite has been used extensively for deoxygenation of *N*-oxides (cf. Table 3.09), and good yields have been reported for a variety of ring systems and substituents. Benzotrifuroxan is reduced to benzotrifurazan, which forms a complex with the corresponding trialkyl phosphate [67J(C)2105]. Benzo[*c*]cinnoline 5-oxide is reduced by triethyl phosphite under forcing conditions (5 h at 160°); this compound is not reduced by phosphorus trichloride under normal conditions (65J4831). The reaction mechanism has been investigated by Emerson and Rees (60P418; 62J1917), who found that in diethylene glycol–diethyl ether the reaction proceeds rapidly at room temperature. The presence of both solvent peroxides and gaseous oxygen is required for rapid reaction, hence they proposed a free-radical chain mechanism. An interesting side reaction is the conversion of 2-nitropyridine 1-oxide by triethyl phosphite into diethyl 2-pyridylphosphonate: a 4-nitro group is not affected [69J(C)1314].

Triphenyl phosphite is a considerably less effective deoxygenating agent than are the phosphorus trihalides, and more vigorous conditions are required for reaction (55JJ139). However, the lower general reactivity towards other functional groups as compared with that of the phosphorus trihalides is sometimes advantageous.

ii. Trialkyl- and Triaryl-phosphines

Available data on these reactions are summarized in Table 3.10.

Tri-*n*-butylphosphine can effect deoxygenation of benzofuroxans (*75* → *76*) (61JO4684), but no reaction was observed with furoxans (61JO4684) or pyridine 1-oxide (56AG473).



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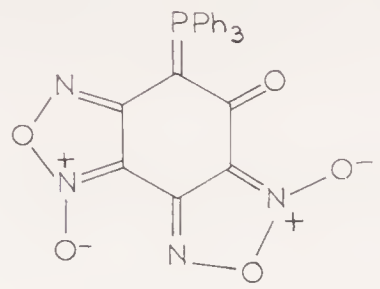


(77)

Triphenylphosphine was first reported to deoxygenate aliphatic amine oxides but not react with pyridine or quinoline 1-oxides (56AG473); however, it was later found that these heteroaromatic *N*-oxides are also reduced but a higher temperature is required (ethylene glycol). A kinetic study indicated that the reaction with 4-nitropyridine 1-oxide [58AA(134)42-N] was second order, but no heterocyclic products were isolated (59JA1483). Triphenylphosphine also deoxygenates Δ^1-pyrroline 1-oxides, and, for these compounds at least, triphenyl-arsine, -stibine, and -bismuthine are less effective reducing reagents (62CC181). Benzotrisfuroxan is converted by triphenylphosphine into the phosphoro-organic compound *77* (66CH664).*

iii. Phosphorus Tribromide and Trichloride

Reductions of *N*-oxides with phosphorus trihalides (Table 3.11) are carried out in chloroform or ethyl acetate or without solvent, and the reaction mixture is usually kept at 70–80° for a few hours. Phosphorus tribromide requires more vigorous conditions but sometimes gives better results than the trichloride (55JJ135). The effect of varying the solvent and reaction conditions has been studied (55JJ121). Yields are generally good, and although hydroxy and amino compounds often give poor yields, these can be improved by acetylation of the functional group (55JJ130).

Side reactions are rare; however, with phosphorus trichloride, 4-nitropyridine 1-oxide is partially converted into 4-chloropyridine (54CT247), and 4-nitroquinoline 1-oxide yields 4-chloro- and 2,4-dichloro-quinoline together with 4-chloroquinoline 1-oxide and 4-chloro-2-quinolone (51JJ1088; 55JJ127). Good results can be obtained in both of these cases by using phosphorus tribromide and short reaction times. With phosphorus tribromide under more vigorous conditions, a 4-nitro group is replaced by bromine simultaneously with the deoxygenation (66CC1765). Reaction of quinoxaline 1-oxide with phosphorus tribromide gives 2-bromoquinoxaline

* See addendum in the Appendix.

Table 3.09. Deoxygenation of *N*-Oxides with Phosphite Esters

Ring system	Phosphite ester	Substituents	Yield, %	References
Pyridine 1-oxide	$P(OEt)_3$, $P(OPh)_3$	—	67–84	55JJ139, 60P418
	$P(OPh)_3$	4-amino	40	55JJ139
	$P(OPh)_3$	4-hydroxy	20	55JJ139
	$P(OEt)_3$	4-methoxy	70	60P418
	$P(OEt)_3$	4-nitro	10	60P418
Quinoline 1-oxide	$P(OPh)_3$	—	71	55JJ139
	$P(OPh)_3$	4-amino or -hydroxy	21 or 13	55JJ139
Benzo[*c*]cinnoline 1,2-dioxide	$P(OEt)_3$	—	86	65J4831
Oxazole 3-oxide	$P(OPh)_3$	4-acyl-2-aryl-5-methyl	47	68J(C)1397
Furoxan	$P(OEt)_3$	—	19	65J4831, 68MC305
	$P(O\text{-alkyl})_3$[a]	4,5-dialkyl, -diaryl, -dicarboxamido, -dicarboxylate, -dicyano	40–94	62JO3651, 64CB575
	$P(OEt)_3$	5-carboxy, -dimethylamino, -methyl, -nitro; 4-methoxy	—	68MC305
Benzofuroxan	$P(OEt)_3$	5-chloro	60	65J5958

[a] Alkyl = methyl, ethyl, and octyl.

Table 3.10. Deoxygenation of *N*-Oxides with Phosphines

Ring system	Phosphine	Substituents	Yield, %	References
Pyridine 1-oxide	PPh_3	—	89	59JA1483
	PPh_3	4-methoxy	62	59JA1483
	PPh_3	2-methyl	51	59JA1483
	PPh_3	4-methyl	93	59JA1483
Quinoline 1-oxide	PPh_3	—	89	59JA1483
Isoquinoline 2-oxide	PPh_3	3,4-dihydro	47	58CB1488
Naphtho[1,2-*e*]-1,2,4-triazine *N*-oxide	PPh_3	3-oxo	75	64TL641
Δ^1-Pyrroline 1-oxide	PPh_3	2,4,4-trimethyl	75	62CC181
	PPh_3	methyl and phenyl derivatives of 5,5-dimethyl	22–53	68AJ2483
Furoxan	PPh_3	4,5-dicarboxylate	45	64CB575
	$P(n\text{-}Bu)_3$	4,5-diphenyl	82	64CB575
Benzofuroxan*	PMe_3	5-dimethylamino	55	66J(C)971

* See addendum in the Appendix.

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides

Ring system	Phosphorus trihalide	Substituents		Yield, %	References
		Unaffected	Affected		
Pyridine 1-oxide	PCl_3	—	—	48–90[a]	51JJ263, 55JJ121, 57JA3565
	PCl_3	—	$N(O)Me_2 \rightarrow NMe_2$	—	65R785
	PBr_3, PCl_3	—	4-$NO_2 \rightarrow$4-Cl(Br)	50	54CT247, 67J(B)106
	PCl_3	3- and 4-alkoxy	—	58, good	55JJ130, 57R58
	PCl_3	6-alkoxy-2-alkyl	—	30–94	59JA2537
	PCl_3	4-alkoxy-2-alkyl and 4-aryloxy-2-alkyl	—	57–84	60JJ875
	PCl_3	4-alkoxy-2-halogeno	—	—	61BA561
	PCl_3	3,5-dialkoxy-2,6-dinitro	—	64	67J(B)1213
	PCl_3	2-, 3-, and 4-alkyl	—	34–48, good	51JJ1385, 61JO122, 63CT694
	PCl_3	2,4- and 2,6-dialkyl	—	good	51JJ1385, 65CT233, 65RC709
	PBr_3, PCl_3	2,5-dialkyl	4-$NO_2 \rightarrow$4-Cl(Br)	70–75	56J771, 57JO936
	PCl_3	2,6-dialkyl-4-halogeno	—	100	62JO1665
	PBr_3	2-alkyl-4-hydroxy	—	56	54CT147
	PCl_3	2-alkyl-4-hydroxy-3- and 3,5-di-nitro	—	ca. 88	51JJ789, 54JJ666
	PCl_3	2- and 3-alkyl-4-iodo	—	60–90	61JJ1206
	PCl_3	2,5- and 2,6-dialkyl-4-iodo	—	60–90	61JJ1206
	PBr_3, PCl_3	2- and 3-alkyl-4-nitro	—	65–79	54CT147, 54JA4184, 55JJ279, 60J4953, 61JO3796
	PCl_3	2,5-dialkyl-4-nitro	—	—	68RC1873
	PCl_3	4,6-dialkyl-2-nitro	—	—	57JA3565

[a] Yield depends on reaction time and temperature.

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides —*continued*

Ring system	Phosphorus trihalide	Substituents		Yield, %	References
		Unaffected	Affected		
Pyridine 1-oxide, *cont'd.*	PCl_3	3,5-di- and 2,3,5,6-tetra-alkyl-4-nitro	—	(data)	60J4953
	PCl_3	4-allyloxy	—	(data)	66CB368
	PCl_3	4-amino (and substituted-amino)	—	—	51JJ263, 55JJ130
	PCl_3	3-amino-2,6-dimethyl-4-nitro	—	82	65RC601
	PCl_3	2-amino-(and substituted-amino)-5-nitro	—	—	64R249
	PCl_3	2- and 3-amino-(and substituted-amino)-4-nitro	—	ca. 89	61BA561, 64RC777
	PCl_3	2-aryl	4-NO_2→4-Cl	—	66JJ59
	PCl_3	2- and 4-aryl	—	90–94	58J1754
	PCl_3	4-aryl-2- and 3-halogeno	—	—	64J2175
	PCl_3	4-benzyloxy	—	77	67J(B)106
	PCl_3	3-carboxy	—	—	59CB2266
	PCl_3	2-cyano	—	—	60JJ1519
	PCl_3	3-ethoxycarbonyl-5-nitro	—	70	65CT113
	PBr_3, PCl_3	3-halogeno	4-NO_2→4-Br(Cl)[b]	72–76	62RC417, 64RC777
	PCl_3	3,4,5-trihalogeno	—	74	62CB1104
	PCl_3	3,5-dihalogeno-4-hydroxy	—	(data)	52JJ274
	PBr_3, PCl_3	2-halogeno-4-nitro	see note [c]	71–88	62RC417
	PBr_3, PCl_3	3-hydroxy	2-NO_2→2-Br(Cl)	(data)	59R644
	PCl_3	4-hydroxy	—	54	51JJ263, 55JJ130

[b] On deoxygenation with PCl_3, the 4-nitro group of the 3-bromo, -chloro, -fluoro, and -iodo compounds is replaced by a chloro group. Treatment with PBr_3 leads to replacement of the 4-nitro group in the 3-bromo and -chloro compounds; however, in the case of the 3-iodo compound, 3-iodo-4-nitropyridine is obtained in 85% yield.

[c] For 2-iodo-4-nitropyridine 1-oxide, a mixture of 2-chloro-(or -bromo)-4-nitropyridine and the corresponding iodo compound is obtained.

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides—*continued*

Ring system	Phosphorus trihalide	Substituents		Yield, %	References
		Unaffected	Affected		
Pyridine 1-oxide, *cont'd.*	PCl_3	4-hydroxy-3,5-dinitro	—	(data)	52JJ274
	PCl_3	3-methyl-4-nitro	3-Me→3-H, 4-NO_2→4-Cl	—	66J(C)1816
	PCl_3	3-nitro	—	—	60JO1716
	PCl_3	4-nitro	—	65–70[d]	51JJ263, 54CT247, 55JJ123, 61JO122, 62CB1098, 64J2319
	PCl_3	2-phenyl	4-NO_2→4-Cl	—	66JJ59
	PCl_3	3- and 4-phenylazoxy	—	—	65AN435
	PCl_3	2-(2′-pyridyl)-4,4′-dinitro[e]	see note [e]	—	55JJ733, 54NK682
	PBr_3, PCl_3	2-(2-pyridyl)-4-substituted	—	54–77	58JA2745, 62JO640
Quinoline 1-oxide	PBr_3, PCl_3	—	—	30–100[a]	51JJ263, 51JJ1385, 55JJ121, 55JJ135
	PCl_3	6-alkoxy-4-alkyl	—	—	51JJ263
	PCl_3	2-alkyl	4-OH→4-Cl	—	21CB1067
	PCl_3	3-alkyl	4-NO_2→4-Cl	—	64JO3381
	PCl_3	3-alkyl-4-amino	—	25[f]	64JO3381
	PCl_3	4-alkyl-8-nitro	—	87	55JJ33
	PCl_3	4-amino	—	45	51JJ263
	PCl_3	8-bromo	—	—	53JJ823
	PCl_3	8-bromo-6-methyl	—	(data)	55JJ490
	PCl_3	6-bromo-5-nitro	—	96	51JJ263
	PBr_3	2-bromo-4-nitro	—	(data)	68JJ656

[d] The product (58% yield) is reported as 4-chloropyridine in reference 54CT247; a mixture of 4-nitro- and 4-chloro-pyridine has also been reported (55JJ123).

[e] 1- and 1,1′-Di-oxide. If reaction is carried out in a sealed tube, 4,4′-dichloro-2,2′-bipyridyl is formed.

[f] The intermediate 4-amino compound, obtained by hydrogenation over Pd-C, was not isolated; yield based on the 4-nitro compound.

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides—*continued*

Ring system	Phosphorus trihalide	Substituents: Unaffected	Substituents: Affected	Yield, %	References
Quinoline 1-oxide, *cont'd.*	PCl_3	4-chloro	—	30	51JJ263
	PCl_3	4-chloro	2-CN→2-$CONH_2$	—	63JJ348
	PCl_3	2-deutero	—	85	68CT1696
	PCl_3	4-hydroxy	—	36	51JJ263
	PBr_3, PCl_3	4-nitro	—	82[g]	51JJ263, 51JJ1088, 55JJ135, 56JJ1337
	PCl_3	4-thiocyanato	—	69	61JJ1151
	PCl_3	4-styryl	—	—	63JJ342
Isoquinoline 2-oxide	PCl_3	—	—	—	51JJ1385
	PCl_3	—	3-CO_2H→3-COCl	—	58JO900
	PCl_3	5-amino	—	—	53JJ666
	PCl_3	1-benzyl	—	—	68AI9
Acridine 10-oxide	PCl_3	—	9-NO_2→9-Cl	—	60J3367
Phenanthridine 5-oxide	PBr_3	—	—	—	60JJ834
1,6-Naphthyridine 6-oxide	PCl_3	5-methyl	—	(data)	58CT263
1,6-Naphthyridine 1,6-dioxide	PCl_3	—	—	(data)	69CT1045
1,6,7-Triazanaphthalene *N*-oxide	PCl_3	5-hydroxy-8-methyl	—	91	63J6073
Pyrroline[2,3-*c*]quinoline 1-oxide	PCl_3	6-carboxy-4-methyl-5-oxo	—	53	64JO3381
Pyridazine 1-oxide	PCl_3	3-alkoxy-4-chloro-6-substituted	—	(data)	63CT29, 63CT1157
	PCl_3	4-azido	—	70	63CT1059

[g] If the reaction with PBr_3 is allowed to proceed at 15° for 15 min, the deoxygenated nitro compound is obtained in good yield; if it is carried out at 100° for one hour, 4-bromoquinoline is formed (51JJ1088).

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides—*continued*

Ring system	Phosphorus trihalide	Substituents		Yield, %	References
		Unaffected	Affected		
Cinnoline 1- and 2-oxide	PCl_3	—	—	40	67CT1088
Cinnoline 1,2-dioxide	PCl_3	—	—	—	67CT1088
Phthalazine 3-oxide	PBr_3	1,4-diaryl	—	—	67JJ940
o-Phenanthroline 1-oxide	PCl_3	—	4-NO_2→4-Cl	64	65JO288
Pyrimidine 1-oxide	PCl_3	alkoxy and alkyl (various)	—	—	55CT175
Quinazoline 1-oxide	PCl_3	6-chloro-2-methyl-4-phenyl	—	—	60JA475
	PCl_3	4-ethoxy	—	37	59CT152
Quinazoline 3-oxide	PCl_3	—	—	—	61CT635
	PCl_3	6-chloro-2-formyl-4-phenyl	—	62	68J(C)1103
	PCl_3	6-chloro-1,2-dihydro-2,2-dimethyl-4-phenyl	—	53	65JO3957
	PCl_3	6-chloro-2-hydroxy-4-phenyl[h]	—	—	62JO4424
	PCl_3	6-chloro-2-methyl-4-phenyl	—	92	60JA475
	PCl_3	4-methyl	—	—	57JJ514
	PCl_3	4-methyl-3-phenyl	—	—	65CB1049
Quinazoline 1,3-dioxide	PCl_3	—	see note[i]	—	64J2319
Quinoxaline 1-oxide	PCl_3	3,6-dialkyl-1-methoxy-2-oxo	—	—	69CT851
	PBr_3	—	—	—	67JJ942
Quinoxaline 1,4-dioxide	PCl_3	2-amino (substitued)	see note[j]	—	60J3387
	PCl_3	3-phenyl	—	—	62JJ1093
Phenazine 5-oxide	PCl_3	—	—	—	64J2319
	PCl_3	1,7- and 3,7-dinitro	—	—	58CT77
Phenazine 5,10-dioxide	PCl_3	—	see note[k]	—	64J2319

[h] Exists as a 2-quinazolinone derivative.
[i] Deoxygenation occurs stepwise.
[j] Partial deoxygenation occurs giving the 1-oxide.
[k] 2-Chloro-1-methylbenzimidazole is also formed.
* Thiazolo[3,2-*a*]pyrazinium bromide 2-oxide; see addendum in the Appendix.

Table 3.11. Deoxygenation of *N*-Oxides with Phosphorus Trihalides—*continued*

Ring system	Phosphorus trihalide	Substituents		Yield, %	References
		Unaffected	Affected		
s-Triazine 1-oxide	PCl_3	2-amino-4-methyl-6-phenyl	—	—	63JO1816
Dibenzo-1,4,5-thiadiazine 1,1,5-trioxide	PBr_3	$-SO_2-$	—	—	57JA5583
Pyrazole 2-oxide	PCl_3	3,4,4,5-tetramethyl	—	(data)	66CB618
Imidazole 1-oxide	PCl_3	2,4,5-triphenyl	3-HO → 3-H	—	65AP293
Imidazole 1- and 3-oxide	PCl_3	2,5-dimethyl-4-phenyl	—	—	65TL1565
Indazole 1-oxide	PCl_3	3-cyano-2-phenyl	—	—	26CB351
Benzimidazole 1-oxide	PCl_3	—	—	(data)	62AJ792
	PCl_3	3-methyl	—	(data)[k]	64CT783
	PCl_3	2,3-dimethyl	—	(data)	66CT1219
Purine 9-oxide	PCl_3	1,3,8-trimethyl-2,4-dioxo-1,2,3,4-tetrahydro[l]	—	—	64ZC454
1*H*-1,4-Benzodiazepine *N*-oxide	PCl_3	7-chloro-2,3-dihydro-5-phenyl	—	—	63JO2459
2*H*-1,4-Benzodiazepine 4-oxide	PCl_3	7-chloro-1,3-dihydro-2-oxo-5-phenyl	—	—	62JO562
3*H*-1,4-Benzodiazepine 4-oxide	PCl_3	2-amino-5-phenyl-7-substituted	—	78	61JO4488, 64MC235
	PCl_3	7-chloro-5-phenyl	—	—	61JO4936

[l] 8-Methyltheophylline 9-oxide.

Table 3.12. Deoxygenation of *N*-Oxides with Phosphorus and Iodine

Ring system	Substituents	Reagent	Yield, %	References
Pyridine 1-oxide	2-hydroxy-5-nitro[a]	$P + I_2 + AcOH$	see note [a]	49JA70
Quinoline 1-oxide	4-hydroxy-2-methyl	$HI + P$	—	21CB1067
Isoquinoline 2-oxide	3-alkyl-1-hydroxy	$P + I_2 + AcOH$	32	63JO2215
Pyrazine 1-oxide	2-hydroxy-3,6-diisobutyl	$P + I_2 + AcOH$	(data)	64J1507
Pyrazine 1,4-dioxide	3,6-dihydroxy-2,5-diisobutyl	$P + I_2 + AcOH$	—	63CC165
1,2,3-Benzotriazine 1-oxide	1-methyl	$HI + P$	—	28J193
1,2,4-Benzotriazine 1-oxide	3-amino-5-, -6-, or -7-substituted	$P + I_2 + AcOH$	ca. 49	49USP2489351, 54JA3551
Thiazole 3-oxide	2-mercapto-4-methyl-5-phenyl	$HI + P$	72	64CB2165

[a] A 1-hydroxy-2-pyridone; 5-nitro group reduced to 5-amino; reaction product not isolated.

as a by-product (67JJ942). α-Halogen atoms are exchanged: for example, 2-bromo-4-nitropyridine 1-oxide and phosphorus trichloride give 2-chloro-4-nitropyridine, but use of the tribromide gives the expected 2-bromo compound (62RC417). 1-Acyloxy-4-quinolones are reduced by phosphorus trihalides to 4-quinolones (52JJ767).

The phosphorus trihalide reductions are inhibited by traces of hydrochloric acid. If the acid is removed by addition of a base such as 2,6-lutidine, the reactions are found to be first order in phosphorus trichloride and second order in 4-nitropyridine 1-oxide or phenazine 5-oxide with respect to time, but not with respect to concentration. The detailed mechanism remains in doubt (64J2319).

iv. Phosphorus and Iodine

A mixture of phosphorus and iodine has been used successfully for the reduction of quinoline, pyrazine, benzotriazine, and other heterocyclic *N*-oxides (see Table 3.12). The reaction is usually carried out in refluxing acetic acid as solvent; the structure of the products formed can be influenced by the presence of acetic anhydride (63CC165).

E. REDUCTION WITH OTHER NON-METALS

i. Sulphur Compounds

In general, heteroaromatic *N*-oxides are not reduced by either sulphur dioxide or sodium sulphite. A variety of quinoline and isoquinoline *N*-oxides as well as 4-methylpyrimidine 1-oxide were reported by Ochiai and Sai (45JJ72) to be unaffected by these reagents; later attempts to reduce other *N*-oxides, e.g. quinazoline 1-oxide, also failed (59CT152). This behaviour of the heteroaromatic *N*-oxides is in contrast to that of the saturated *N*-oxides which are readily reduced, and because of this selectivity these reagents have been used to prepare nicotine 1-oxide (58J3230; 59JO275) and quinine 1-oxide (47JJ101; 48JJ109) from the corresponding *N*,*N*′-dioxides. In some cases the site of *N*-oxidation can be established on the basis of the selectivity of these reducing agents; for example, it has been shown that the oxygen atom in the mono-*N*-oxide formed by hydrogen peroxide oxidation of the alkaloid quitenine is situated on the nitrogen atom in the quinuclidine nucleus and not on that in the quinoline ring system (47JJ248; 59CT744).

However, a number of cases are known where sulphur dioxide or sulphite ion does effect reductive removal of the heteroaromatic *N*-oxide oxygen atom, particularly under vigorous conditions; see Table 3.13. Reaction temperatures are generally high, and the yields are often poor in the pyridine and quinoline series. Daniher and Hackley (66JO4267) have recently shown that pyridine 1-oxide and many of its substituted derivatives can be reduced

Table 3.13. Deoxygenation of *N*-Oxides with Sulphur Dioxide or Sulphite Ions

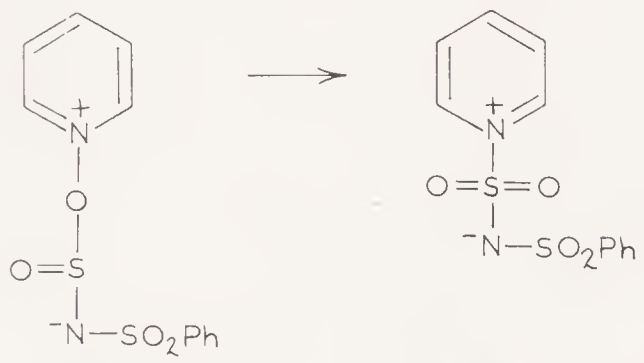
Substituent	Substituents		Reagent	Reaction conditions	References
	Unaffected	Affected			
Pyridine 1-oxide	2,6-dimethyl	4-Cl → 4-SO_3H	SO_3^{2-}	180°	62JO1665
	2,6-dimethyl	4-NO_2 → 4-NH_2[a]	HSO_3^-, SO_3^{2-}	—	62JO1665
	2-, 3-, and 4-(1-oxido-2-, -3-, and -4-pyridyl)[b]	—	SO_2	—	56JJ858
Quinoline 1-oxide	2-amino-3-phenyl	—	SO_2	100°	38CB2226
	2-phenyl	—	SO_2	—	54RS2351
Benzo[*h*]quinoline 1-oxide	—	—	SO_2	—	51JJ1288
Quinazoline 1-oxide	4-isopropyl or -methoxy	—	HSO_3^-	—	64CT43
Quinoxaline 4-oxide	2-phenyl	—	HSO_3^-, SO_2	—	62JJ1093, 64CT43
Phenazine 5-oxide	1,6-dihydroxy	—	HSO_3^-	—	65B176
Pyrazole 2-oxide	1-hydroxy-4,5-dimethyl-3-phenyl	—	HSO_3^-	—	66JH544
Imidazole 3-oxide	2,4,5-trimethyl	1-OH → 1-H	HSO_3^-	—	64JO1620
Benzimidazole 1-oxide	2,3-dimethyl	—	HSO_3^-, SO_2	ca. 20°	66CT1219

[a] 4-Amino-2,6-lutidine-3-sulphonic acid is also formed.
[b] 4,4′-Bipyridyl 1,1′-dioxide most easily reduced; 3,3′-bipyridyl 1,1′-dioxide most resistant to reduction.

by passing a slow stream of sulphur dioxide through a dioxane solution of the *N*-oxide.

Sodium dithionite ($Na_2S_2O_4$) and sodium thiosulphate ($Na_2S_2O_3$) have been used as reducing agents in several instances (see Table 3.14). These reagents appear to have some advantages in the case of water-soluble *N*-oxides. 4-Oxopyrazole 1,2-dioxides are reduced by dithionite to 1,4-dihydroxypyrazoles (67TL4917).

(78) (79)



(80) (81)

Many other types of sulphur compounds reduce *N*-oxides to the parent bases. Thus, pyridine 1-oxide and its 2- and 4-methyl derivatives are deoxygenated by sulphur, *n*-butyl mercaptan, thiophenol, thiourea, and benzothiazole-2-thione; however, the reduction is not effected by thiophene (62JO477). Carbon disulphide reduces the aliphatic *N*-oxide group in 2-dimethylaminopyridine *N*,*N*′-dioxide, but leaves the 1-oxide group unaffected (*78* → *79*) (65R785). Other sulphur-containing reagents which have been used as reducing agents in isolated cases are summarized in Table 3.15. The isomerization of the adduct *80* into *81* (65CB1205) must also be considered as a type of deoxygenation reaction.*

ii. Amines and Related Compounds

Examples of the reduction of *N*-oxides by amines and other nitrogen-containing compounds are collected in Table 3.16. Many of these deoxygenation reactions were observed during attempted nucleophilic displacement of halogen atoms on aromatic *N*-oxides. Frequently concomitant reduction of the *N*-oxide group and replacement of the halogen atoms occur. Presumably, at least some of these reactions involve transfer of oxygen from the *N*-oxide group to the nitrogen atom of the amine. However, it has been reported that pyridine 1-oxide remained unchanged after being heated at 140° for 40 h with benzylamine, diphenylamine, or pyrrole (62JO477).

* See addendum in the Appendix.

Table 3.14. Deoxygenation of *N*-Oxides with Dithionite Ions

Ring system	Substituents unaffected	Remarks (% yield)	References
Pyridine 1-oxide	2,6-dimethyl	4-NO_2 → 4-NH_2(65)[a]	62JO1665
Quinoline 1-oxide	8-alkoxy and -hydroxy	4-NO_2 → 4-NH_2	44JJ206
1,7-Naphthyridine 7-oxide	3-carboxy-4-hydroxy	(data)	56LA(599)233
Quinazoline 3-oxide	4-hydroxy-2-methyl and -phenyl	(ca. 47)	60J2157
Quinoxaline 1-oxide	2-acyl-, -amino-, -benzyl-3,4-dihydro-3-oxo	—	63J2428
	4-alkyl-2-aryl-6-halogeno-3,4-dihydro-3-oxo	—	65BJ1654
	4-alkyl-(or H)-2-carboxamido (substituted)-3,4-dihydro-3-oxo	(72–98)	60J3384
	2-aryl-6,7-dichloro-3-hydroxy	—	65BJ1654
	2- and 3-carboxy	(— and 84)	55ZO161
	3,4-dihydro-6-methoxy-4-methyl-3-oxo-2-phenyl	(quant.)	68JO201
Quinoxaline 1,4-dioxide	2,3-diaryl	(92)	66JO4067
	2-carboxy	—	55ZO161
Phenazine 10-mono- and 5,10-di-oxide	2-carboxy	—	52AN519
Pteridine 8-oxide	2-amino-4-oxo-6-phenyl	(75)	68JA2424
1,2,4-Benzotriazine 1-oxide	3-benzoyl	(60–80)	67J(C)2658
Naphtho[1,2-*e*]-1,2,4-triazine 4-oxide	—	see note [c]	64TL641
Pyrido[2,3-*c*]-1,3,5-triazine 1-oxide	3-amino	-NO=N- → -NH-NH-	62JO2504
1,2,3-Triazolo[5,1-*c*]-1,2,4-benzotriazine 5-oxide	3-phenyl	-NO=N- → -NH-NH-	67J(C)1279
Pyrazole 1,2-dioxide	3,5-disubstituted	4-C=O → 4-OH, ·NO·NO· → ·NOH·N:	69JO187

[a] 4-Amino-2,6-lutidine-3-sulphonic acid also formed.
[b] A mixture of 4-aminoquinoline and the 1-oxide obtained.
[c] Unstable dihydro compound formed.

Table 3.15. Deoxygenation of *N*-Oxides by Other Sulphur-containing Reagents

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected		
Pyridine 1-oxide	S, BuSH, BuS^-, PhSH, NH_2-CS-NH_2, 2-mercaptobenzothiazole	—	—	—	59AA(135)76-O, 62JO477
	S-NH_3	—	4-NO_2 → 4-NH_2	—	55JJ620
	$(NH_4)_2S$	2,6-dimethyl	4-NO_2 → 4,4′-hydrazo	75	65RC709
	diaryl disulphides (various)	—	—	quant.	68TL3791
	p-nitrobenzenesulphinyl chloride	—; 2-methyl	—	(data)	66BJ1306, 67BJ1420
	benzenesulphinyl chloride	2-methyl	—	(data)	66BJ1306
	$SOCl_2$	3-carboxy	—	—	59CB2266, 62JO3856
	$S_2O_3^{2-}$	—	4-NO_2 → 4-$NHSO_2H$	—	43JJ186
	PhSCl, SCl_2	—; 4-chloro, -methyl, -nitro; 2-methyl	—	ca. 80	55CT230
	P_2S_5	—	-CH_2CONH_2 → -CH_2CSNH_2	—	57JO984
	Me_2SO	methyl	—	40–92	69TL1015
Quinoline 1-oxide	PhSCl	—; 4-nitro	—	75–90	55CT230
	$(NH_4)_2S$	4-nitro and 1-oxide	4-NO_2 → 4,4′-hydrazo → 4-NH_2	—	44JJ206
	Me_2SO	2-methyl	—	55	69TL1015
Isoquinoline 2-oxide	Me_2SO	—	—	95	69TL1015
Quinoxaline 1-oxide	thiourea	—	2-Cl → 2-$SC(NH_2)_2^+$	—	69KG940
Phenazine 5-oxide	benzenesulphinic acid	2-chloro [a]	7-H → 7-SO_2Ph	—	62J4438
3*H*-1,4-Benzodiazepine 4-oxide	$SOCl_2$	4-hydroxy	—	—	61JO1111

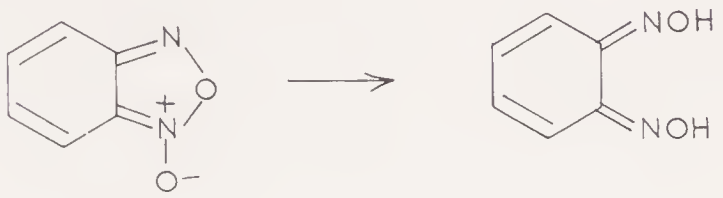
[a] If $PhSO_2H$ is in large excess, 2,7-diphenylsulphonylphenazine is obtained as a second product.

Table 3.16. Deoxygenation of *N*-Oxides by Amines and Related Compounds

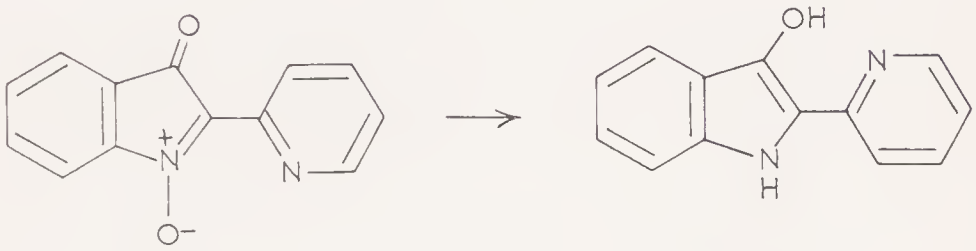
Reagent	Ring system	Other substituents affected	Remarks (% yield)	References
Hydroxylamine	phenazine 5,10-dioxide	—	—	46G239
Hydroxylamine	furoxan[a]	H, 3-CO_2H	(72, —)	58JO1807, 68MC305
Hydroxylamine	furoxan	H; 5-Cl; 4,5-C_4H_4	—	68MC305
Aniline	pyridine 1-oxide	4-Cl → 4-NHPh	(6)	56J2404
Aniline	phenazine 5-oxide	—	—	52JA971
Ethylamine	1-hydroxyimidazole	—	—	19CB43
2-Amino-5-diethylaminopentane	quinoline 1-oxide	4-Cl → 4-Et_2N	(67)	46JJ60
1-(3-Aminopropyl)piperidine	phenazine 5,10-dioxide	—	—	56J2550
p-Dimethylaminobenzaldehyde	pyridine 1-oxide	4-Me → 4-CH=CH-C_6H_4-$NMe_2(p)$[b]	—	58JO201
Morpholine	pyridine 1-oxide	4-(*p*-Me-C_6H_4-) → 4-morpholino	—	44PJ141
Morpholine, piperidine	quinoline 1-oxide	4-NO_2 → 4-morpholino, 4-piperidino	—	46JJ170
Morpholine	phenazine 5- and 5,10-di-oxide	Cl → morpholino	(data)	69BJ506
Hydrazine	pyridine 1-oxide	4-NO_2 → 4-NH_2	—	61BA561
Hydrazine	quinoline 1-oxide	—	Cu catalyst	60JJ1573
Hydrazine	quinoline 1-oxide	2-Cl → 2-$NHNH_2$	—	61JJ1743
Hydrazine	benzo[*c*]cinnoline 5- and 5,6-di-oxide	—	Ni(R) catalyst (88–97)	58JO1504
Hydrazine	quinazoline 4-oxide	see note [c]	—	67JJ942
Hydrazine	pyrazine 1-oxide	—	(65)	49J126S
Hydrazine	quinoxaline 1-oxide	2-Cl → 2-N_2H_3	—	69KG940
Phenylhydrazine	quinoline 1-oxide	—	17–70	68CT839
Phenylhydrazine	quinoline 1-oxide	3-Br → H	27	68CT839
Phenylhydrazine	1-hydroxyimidazole	—	—	19CB43
sym-Diphenylhydrazine	pyridine 1-oxide	—	"good"	59AA(135)76-O, 62JO477

[a] Furoxan derived from 9,10-dinitrosophenanthrene; reduction product is the corresponding 9,10-dihydroxyimino compound.
[b] Deoxygenation is a side reaction in the preparation of styryl derivatives.
[c] Hetero ring hydrogenated; dimerization occurs with excess hydrazine.

A convenient test for *N*-oxides is the production of a blue colour when they are gently heated with dimethylaniline and hydrochloric acid; this test was devised by Coats and Katritzky (59JO1836). The colour is due to the formation of crystal violet by an oxidative dealkylation involving formaldehyde; the same reaction is observed with many inorganic oxidizing agents, and with some other organic compounds, including nitro compounds. The test has been found to be rather general for *N*-oxides (61JO3802; 61R1066; 62R604; 63JO2215; 64JA38).



(82) (83)



(84) (85)

Condensed furoxans have been reduced to *o*-benzoquinone dioximes by hydroxylamine (cf. *82* → *83*) (Table 3.17), but it is not clear whether or not an exchange of the nitrogen atoms occurs in this reaction. Phenylhydrazine converts 2-(α-pyridyl)isatogen (*84*) into the indoxyl *85* (65J1706).

iii. Hydrogen Halides

Pyridine 1-oxides do not generally liberate iodine from hydrogen iodide, in contrast to most aliphatic amine oxides (43PJ307; 43PJ574). However, some exceptions are known, e.g. 2-ethoxypyridine 1-oxide (49J2091) and 1-(1-oxido-2-pyridylmethyl)pyridinium iodide (60CT692). Quinoxaline 1,4-dioxides (43J322), 2,9-diazaphenanthrene 9-oxides (53J350), 1,3,4-trihydroxy-2-pyridone [83PC(27)257], and the pyrazine derivative aspergillic acid (47JB321) liberate iodine from acidified potassium iodide. Attention is drawn to a claim that saturated *N*-oxides liberate iodine from hydrogen iodide only by virtue of adsorbed hydrogen peroxide (54AP326).

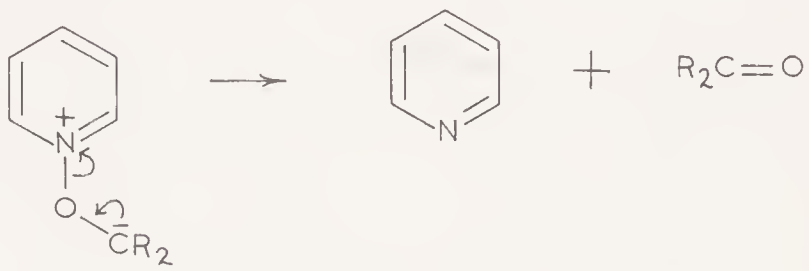
Table 3.17. Reduction of Benzofuroxans to *o*-Benzoquinone Dioximes (82 → 83)

Furoxan	Reducing agent	References
5-Chlorobenzofuroxan	NH_2OH–NaOH–EtOH	13J897
Benzofuroxan	NH_2OH–NaOH–EtOH	99LA(307)28, 12J2452
Naphthofuroxan	NH_2OH–NaOH–EtOH	17J612

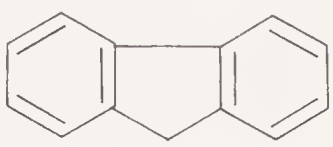
There are isolated examples of the deoxygenation of heterocyclic *N*-oxides by the other hydrogen halides. Thus, at 160° the reaction of 4-nitropyridine 1-oxide with hydrobromic acid gives 3,5-dibromo-4-pyridone (51JJ591), and 4-nitro-2,6-lutidine 1-oxide yields 4-bromo-2,6-lutidine (62JO1665). Certain quinoxaline *N*-oxides [49J2579; 66J(C)157] and triazole *N*-oxides (99G277) have been reduced by hydrochloric acid.

iv. Carbon-containing Compounds

a. Carbenes. Dichlorocarbene, generated by the usual methods, smoothly deoxygenates pyridine 1-oxide. Probably an adduct of type *86* is formed, which subsequently decomposes as shown (*86* → *87*) (63JO2460). Fluorene carbene (*88*), prepared from 9-diazofluorene, has been used to effect deoxygenation of several *N*-oxides in the pyridine series (64JO1744; 66T35).



(86) (87)



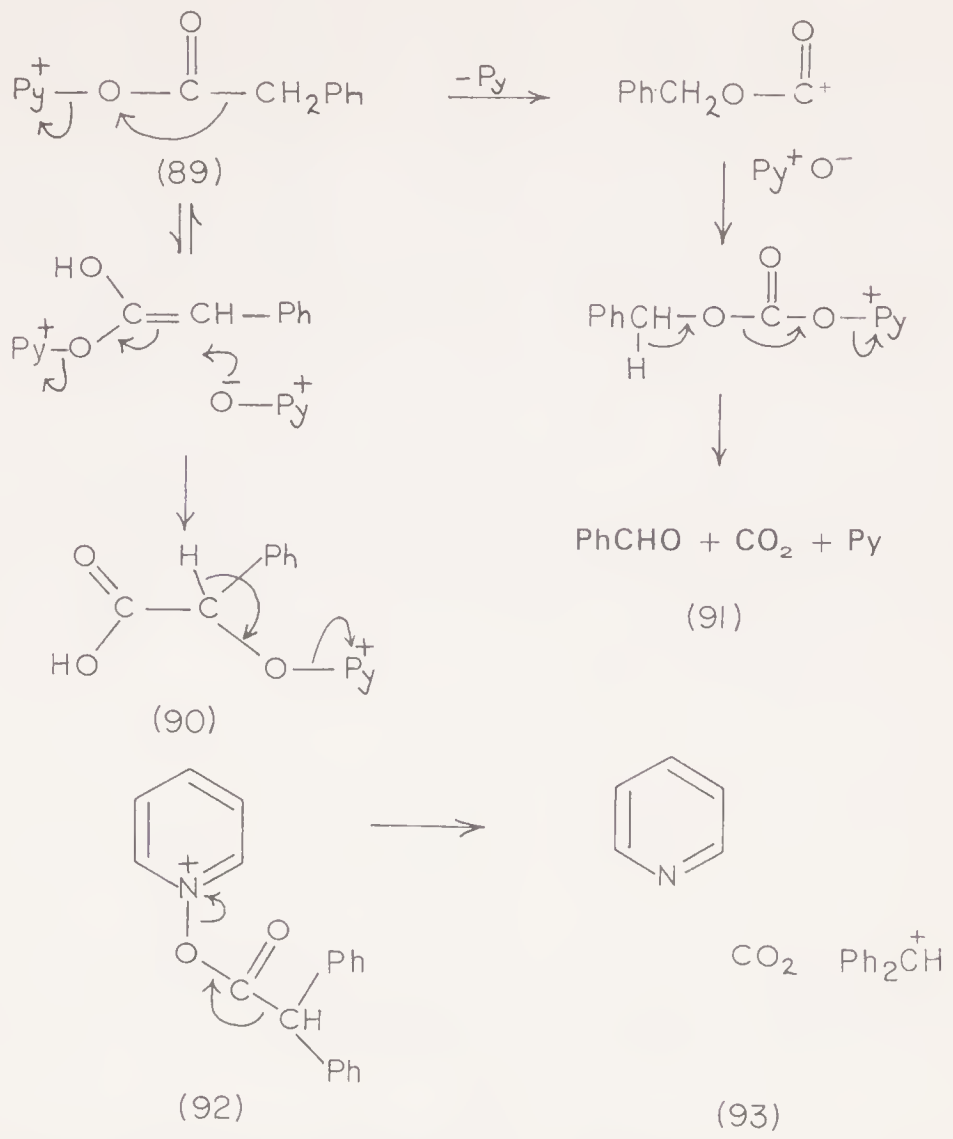
(88)

A similar reaction was observed with the carbene derived from 1-methyl-3-diazooxindole (64JO3577). Isocyanides, which may be considered a special type of carbene, are oxidized by pyridine 1-oxides to isocyanates; this reaction is catalysed by halogens (67JO1939).

b. Miscellaneous Carbon Compounds. Alkyl halides can deoxygenate *N*-oxides; they react to form a quaternary derivative (Section III-1Bii) which subsequently decomposes to an aldehyde and the parent heterocycle (see Section IV-4Ai). Some of the reactions discussed here undoubtedly involve processes of this type.

Pyridine 1-oxide can be deoxygenated by heating with phenylacetic acid: the reaction has been carefully studied by Rüchardt and Krätz (66TL5915) who originally suggested the mechanism illustrated in the conversion of *89* into *90*. However, Cohen *et al.* (65TL237; 67JA4968) believe that this reaction occurs by a mechanism of the type shown in the scheme *89* → *91*, which would explain the production of both benzaldehyde and phenylglyoxalic acid in the reaction of α-bromophenylacetic acid with pyridine 1-oxide. Koenig (67TL2751) has reached essentially similar conclusions.

This mechanism is supported by the smooth oxidative decarboxylation of α-halogeno acids, $RCHBrCO_2H \rightarrow RCHO$, by pyridine 1-oxide which has been suggested as a degradative procedure (66JO3058).



Diphenylacetic anhydride causes deoxygenation of pyridine 1-oxide according to the scheme *92* → *93* (65TL233; 65TL237). For similar work with phenylacetic anhydride and diphenylketene, see reference 65TL3127.* Pyridine 1-oxide is also deoxygenated by aldehydes (58JA915), benzylic alcohols (66CT663), and epoxides (66NK975). 4-Nitropyridine 1-oxide gives 4-benzylaminopyridine and 4-pyridone on reaction with benzyl alcohol and alkali (66CT731). 4-Nitroquinoline 1-oxide has been shown to be partially deoxygenated to 4-nitroquinoline by free radicals generated from azodiisobutyronitrile (65JJ66); see also Section III-5A.

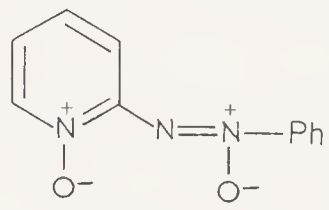
Reactions of Grignard reagents with *N*-oxides (Section III-4Fii) often lead to some simple deoxygenated products, and sometimes these products are obtained exclusively (54RS2351).

F. REDUCTION WITH DISSOLVING METALS AND METAL IONS

The reduction of *N*-oxides by dissolving metals has been a popular technique. The most commonly used reagents and conditions are summarized

* See addendum in the Appendix.

in Table 3.18, and examples of these reactions are recorded in Table 3.19. As may be seen from the data in Table 3.19, the following substituents are usually unaffected in dissolving metal reductions: alkyl, -Cl, -OH, -OR, -SR, $-NH_2$, and $-NR_2$. Almost without exception nitro groups are simultaneously reduced and nearly always to amino groups; cyano groups are sometimes hydrolysed to an amide, and bromine atoms are occasionally lost. Carbon–carbon double bonds are usually unaffected, but there are exceptions [52AJ387; 61T(14)151]. In a few cases, dissolving metals or metal ions reduce a substituent without affecting the *N*-oxide group. For example, stannous chloride reduces the azoxy compound *94* to 2-phenylhydrazinopyridine 1-oxide (55G1148) and certain nitrophenanthridine 5-oxides to the amino *N*-oxides (50J703). Little is known of the relative reducibility of *N*-oxides towards reagents of this type, but phenylpyridine 1-oxides are reduced less readily by ferrous hydroxide than are their quinoline analogues (56RS2782). Heterocyclic *N*-oxides may be quantitatively determined by titanometric titration (59AC561).



(94)

A rather different reaction type is the reductive conversion of furoxans into α-dioximes (Table 3.20), cf. *69* → *70*.

G. MISCELLANEOUS REDUCTIONS*

i. Electrolytic Reduction

a. Preparative Aspects. Little work has been done on the preparative aspects of electrolytic reduction of *N*-oxides. Ochiai *et al.* (45JJ429) found that 4-nitroquinoline 1-oxide is reduced to 1,2,3,4-tetrahydroquinoline or 4-aminoquinoline, depending on the nature of the cathode employed. Under similar conditions 4-nitropyridine 1-oxide gives 4,4′-azobipyridine 1,1′-dioxide, indicating that the rings and *N*-oxide groups of pyridine 1-oxides are more resistant to electrolytic reduction than are those of quinoline 1-oxides. Adenine 1-oxide has been electrolytically reduced in good yield (60JA3193). Recently good yields were obtained by reduction at a mercury cathode (68CB4179); the technique has also been applied to benzotriazole 1-oxides (68AS2879).

b. Polarographic Reduction Potentials. More work has been done on the measurement of polarographic reduction potentials. The early Japanese investigators (43PJ307) found that pyridine 1-oxide derivatives are reduced

* See addendum in the Appendix.

Table 3.18. Reagents and Typical Reaction Conditions for the Deoxygenation of *N*-Oxides by Dissolving Metals (and Metal Ions of Lower Valency)

Reagent	Typical reaction conditions	Representative reference
Iron–acetic acid	Iron powder is added to a suspension of the *N*-oxide in hot glacial AcOH; keep at 100° ca. 2 h.	50R468, 55CT227, 62JO1665
Zinc–acetic acid	A solution of the *N*-oxide in AcOH is heated ca. 1 h with zinc dust.	56BC(63)124, 60J3470
Zinc–aqueous ammonium chloride	A suspension of the *N*-oxide, zinc dust, and NH_4Cl in H_2O stirred at 20° for 17 h.	49USP2489357, 59JO813
Zinc–acetic acid–hydrochloric acid	Zinc dust is added to a refluxing solution of the *N*-oxide in AcOH–HCl; heat under reflux ca. 1 h.	60J3462
Zinc–sodium hydroxide	A solution of the *N*-oxide in 3N NaOH and zinc dust heated ca. 3 h at 100°.	52R1145, 62CB1098
Ferrous sulphate–ammonium hydroxide	Concentrated NH_4OH is added to an aqueous solution of the *N*-oxide and $FeSO_4$; heat under reflux 1 h.	61RC463
Ferrous hydroxide	Aqueous $FeSO_4$ is added to a solution of the *N*-oxide in EtOH–20% KOH and the mixture kept at 20° for 4 days.	61BA561, cf. 56RS2512, 56RS2782
Titanium trichloride	Dilute HCl solution of $TiCl_3$ added to an aqueous solution of the *N*-oxide in an inert atmosphere; reaction often complete in 5 min at room temperature.	59AC561, 66M1558
Stannous chloride–hydrochloric acid	An aqueous ethanol solution of $SnCl_2 \cdot 2H_2O$, HCl, and the *N*-oxide warmed on a water bath ca. 0·5 h.	59JO813, 64J1265

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected[a]		
Pyridine 1-oxide	Fe-AcOH	—	2,4,6-tri-CN → 2,4,6-tri-CO_2Me	60	66AG846
	Fe-AcOH	—	4-NO_2 → 4-NH_2	—	51R581
	Fe-AcOH	3-amino	—	—	54JO2008
	Fe-AcOH	3-amino-5-methyl	4-NO_2 → 4-NH_2	90	66RC1457
	Fe-AcOH	2- and 4-(*p*-aminostyryl)	—	50–70	61G991, 61T(14)151
	Fe-AcOH	3-amino-2,6-dimethyl	4-NO_2 → 4-NH_2	89	65RC601
	Fe-AcOH	2-aryl[b]	4-NO_2 → 4-NH_2	41	58JA2745
	Fe-AcOH	2-bromo	—	—	58R340
	Fe-AcOH	4-bromo	—	(data)	51R581
	Fe-AcOH	2,6-dibromo	—	—	58R340
	Fe-AcOH	2- and 2,6-di-bromo-3-hydroxy	—	—	66RC405
	Fe-AcOH	2-bromo	4-NO_2 → 4-NH_2	95–100	51R591
	Fe-AcOH	3-bromo	4-NO_2 → 4-NH_2	29–80	50R468, 59JO1008, 62RC1465
	Fe-AcOH	2,6-dibromo	4-NO_2 → 4-NH_2	100	58R340
	Fe-AcOH	3,5-dibromo	4-NO_2 → 4-NH_2	(data)	53R296
	Fe-AcOH	5-bromo-3-methoxy	2-NO_2 → 2-NH_2	90–95	55R1171
	Fe-AcOH	3-carboxy	—	—	61JJ1748
	Fe-AcOH	4-chloro	—	"good"	51R581, 60TU24
	Fe-AcOH	3,4-dichloro	—	—	55R59
	Fe-AcOH	2,4,6-trichloro-3,5-diethoxy	—	—	57R261

[a] Substituents affected in addition to *N*-oxide group.
[b] 4,4′-Dinitro-2,2′-bipyridine 1,1′-dioxide.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected[a]		
Pyridine 1-oxide, *cont'd.*	Fe-AcOH	5-chloro-2-(2,4,5-trichlorophenylthio)	—	90	61R1066
	Fe-AcOH	4-chloro-2-methyl	—	ca. 78	59WZ187, 60PC(11)22
	Fe-AcOH	4-chloro-2,6-dimethyl	—	12	62JO1665
	Fe-AcOH	4-chloro-2,3,6-trimethyl	—	ca. 100	59J1312
	Fe-AcOH	4-ethoxy	—	(data)	51R581
	Fe-AcOH	3,5-diethoxy-2,6-dimethyl	—	—	57R261
	Fe-AcOH	2- and 3-ethoxy	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	(data)	51R591
	Fe-AcOH	2-ethyl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	89	59ZO915
	Fe-AcOH	5-ethyl-2-methyl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	72	55JO1461
	Fe-AcOH	4-ethylthio-2-methyl	—	72	59WZ187
	Fe-AcOH	3-hydroxy	$2\text{-}NO_2 \rightarrow 2\text{-}NH_2$	—	59R644
	Fe-AcOH	2- or 3-methoxy	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	85–100	55R1160
	Fe-AcOH	3,5-dimethoxy	$2\text{-}NO_2 \rightarrow 2\text{-}NH_2$	—	55R1171
	Fe-AcOH	2,4,6-trimethyl	—	72	61J5556
	Fe-AcOH	2-methyl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	95–100	51R591
	Fe-AcOH	3-methyl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	"poor"	55JJ292, 58CI1089, 66CC1765
	Fe-AcOH	2,6-dimethyl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	76, 55	54CT131, 67R655
	Fe-AcOH	3-(1-methyl-2-pyrrolo)[c]	—	—	58J3230
	Fe-AcOH	$2\text{-}CH_2\text{-}\overset{+}{N}C_5H_5I^-$	—	58	63CT694
	Fe-AcOH	3-styryl	$4\text{-}NO_2 \rightarrow 4\text{-}NH_2$	(data)	61JO418
	$Fe(OH)_2$	4-alkoxy-2-halogeno	—	—	61BA561

[c] Nicotine 1-oxide.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Pyridine 1-oxide, *cont'd.*	$FeSO_4$-NH_4OH	—	2-CN → 2-$CONH_2$, 4-NO_2 → 4-NH_2	(data)	61RC463
	$FeSO_4$-NH_4OH	3-fluoro	4-NO_2 → 4-NH_2	85	64RC777
	$FeSO_4$-NH_4OH	2-halogeno-4-methoxy[d]	—	73–83	61RC475
	Sn-HCl	2-amino	—	(data)	49J133S
	Sn-HCl	2,6-dimethyl	4-NO_2 → 4-NH_2[e]	80	65RC709
	$SnCl_2$-HCl	6-chloro	2-N=NO-Ph → 2-NHNHPh	—	55G1508
	$SnCl_2$-HCl	2-hydroxy	—	(data)	48J1864
	$SnCl_2$-HCl	2-hydroxy-6-(2-amino-2-carboxyethyl)	—	58	68JO2118
	$SnCl_2$-HCl	2-methyl	4-NO_2 → 4,4′-azo[f] + 4-NH_2	—	47JJ158
	$TiCl_3$-HCl	—	—	quant.	59AC561
	$TiCl_3$-HCl	2-mercapto[g]	—	quant.	59AC561
	$TiCl_3$-HCl	2,6-dimethyl	—	quant.	59AC561
	Zn-AcOH	4-aryloxy-3,5-diiodo-2,6-dimethyl	—	65	56CT1
	Zn-HCl	see note [h]	CH=CH → CH_2CH_2	—	52AJ387
	Zn-HCl	3-(1-methyl-2-piperidyl)[i]	—	—	58IZ788

[d] Halogeno = Br, Cl, I.
[e] 4,4′-Hydrazo-2,6-lutidine 1,1′-dioxide also formed.
[f] 4,4′-Azobis(2-picoline) 1,1′-dioxide.
[g] Sodium and zinc salts of 2-pyridinethiol 1-oxide and bis(2-pyridyl 1-oxide) disulphide.
[h] *N*-Oxide of the pyridine ring in the alkaloid canthinone.
[i] *N*-Methylanabasine *ar*-*N*-oxide or *al*-di-*N*-oxide.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Pyridine 1-oxide, *cont'd.*	Zn-H_2SO_4	4-alkoxy-3-methyl	—	75–85	61AP292
	Zn-EtOH	3-hydroxy-4,5-dihydroxymethyl-2-methyl[j]	—	40	59JO1032
	Zn-NaOH	—	4-NO_2 → 4-azo[k]	—	52R1145
	$ZnCl_2$-HCl	2,6-dimethyl	4-NO_2 → 4-NH_2	—	65RC709
Quinoline 1-oxide	Fe-AcOH	2-amino-4-cyano-3-phenyl	—	(data)	60J3466
	Fe-AcOH	2- and 4-(aminostyryl)	—	60 and —	63G1093
	Fe-AcOH	2-(2-arylvinyl)[l]	—	—	60G1179
	Fe-AcOH	4-methoxy-6-methyl	—	ca. 78	59WZ93, 60AF1029
	Fe-AcOH	—	4-NO_2 → 4-NH_2	66–75	55CT227
	Fe-HCl	3-hydroxy	6-NO_2 → 6-NH_2	(data)	60CT126
	$Fe(OH)_2$	2-mesityl and -phenyl	—	—	54RS2351
	Fe-AcOH	2-chloro	4-NO_2 → 4-NH_2	(data)	68JJ656
	$SnCl_2$	4-chloro-2-methyl	—	—	61ZC84
	$SnCl_2$-HCl	—	4-NO_2 → 4-NH_2; 4-NO_2 → 4,4′-NHNH-	—	43PJ574, 44JJ206
	Zn	see note[m]	4-NO_2 → 4,4′-NHNH-	—	44JJ206
	Zn-AcOH	—	see note[n]	—	53JO1755
	Zn-AcOH	3-carboxy-6-chloro-4-hydroxy-2-methyl	—	—	60J3470

[j] Hydrochloride.
[k] 4,4′-Azopyridine.
[l] 1,2-Bis(α-quinolyl)ethylene *N*,*N*′-dioxide.
[m] A mixture of products including both the *N*-oxide and the deoxygenated compound results.
[n] 1,2,3,4-Tetrahydro-1-hydroxyquinoline.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Quinoline 1-oxide, *cont'd.*	Zn-AcOH	—	4-NO_2 → 4,4′-NHNH-	—	43PJ574
	Zn-AcOH-HCl	4-carboxy-2-hydroxy[o]	3-CO_2H → H	—	60J3462
	Zn-HCl	4-hydroxy- or methoxy-2-oxo-1,2-dihydro	(1-MeO → H)	—	53CB957
	Zn-HCl	4-hydroxy-2-methyl	—	—	22JA1573
	Zn-H_2SO_4	2-alkyl	—	ca. 56	60CB2591
	Zn-NH_4OH	2-amino-3-carboxamido	—	—	53JO1755, 55J203
	Zn-NaOH	2-amino	3-$CONH_2$ → 3-CO_2H	—	53JO1755
Isoquinoline 2-oxide	Zn-AcOH	1-aryl-4-ethyl-6,7-dimethoxy	—	—	50JA1118
	Na-EtOH	3,4-dihydro	(ring reduced)[p]	53	58CB1488
Acridine 10-oxide	Fe-AcOH	octahydro	—	—	65RO947
	Zn-EtOH	3-bromo-9-hydroxy	3-Br → H, 6-NO_2 → 6-NH_2	see note[q]	60BF693
Phenanthridine 5-oxide	Zn-HCl	—	—	—	57JA6500
4,9-Diazapyrene 4,9-dioxide	Fe-AcOH	5,10-dimethyl	—	46	60J2553
4,5,9,10-Tetraazapyrene di-*N*-oxide	$SnCl_2$-HCl	—	—	(data)	64J6090
Pyridazino[4,3-*f*:5,6-*f*′]-diquinoline 1-oxide	Zn-NaOH-EtOH	—	—	(data)	65J799
Benzo[*c*]cinnoline 6-oxide	Na-Hg/EtOH	3-amino	—	68	56JO651

[o] 1,2-Dihydro-1-hydroxy-2-oxoquinoline-3,4-dicarboxylic acid.
[p] Tetrahydroisoquinoline obtained.
[q] 6-Aminoacridone (45–50%) and 6-amino-3-bromoacridone (37%) formed.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Benzo[*c*]cinnoline 6-oxide, *cont'd.*	$SnCl_2$-HCl	—	2-, 3-, or 4-NO_2 → 2-, 3-, or 4-NH_2	45–75	45J824, 56JO651
	$SnCl_2$-HCl	1- or 4-bromo	—	(data)	61J5029, 64J1265
	$SnCl_2$-HCl	1-bromo-3-methyl	—	(data)	61J5029
	Zn-AcOH	3-amino	—	—	56JO651
Benzo[*c*]cinnoline 5,6-dioxide	$SnCl_2$-HCl	—	2-NO_2 → 2-NH_2	68–90	62J2454
Naphtho[1,2-*c*]- and -[2,1-*c*]cinnoline *N*-oxide	$SnCl_2$	—	—	40–55	60J3646
Benzo-naphthocinnoline *N*-oxide[r]	$SnCl_2$	—	—	(data)	59J3025, 60J3646
	Zn-EtOH	—	—	(data)	65T3285
Quinazoline 3-oxide	Fe-AcOH	4-methyl-3-phenyl	—	—	65CB1049
	Fe-$FeSO_4$	2- and 4-amino	—	—	57JJ510
	Fe-$FeSO_4$	4-methyl	—	—	57JJ514
	$Fe(OH)_2$	2,4-dihydroxy	—	55	44G3
	Na-Hg	4-hydroxy	N=C-OH → $NHCH_2$	5–25	44G3
Purine 3-oxide	Ni(R)-NH_3	6-Cl, -Br, -I, -SO_3H, -OMe, -OH	—	—	69JO2157
Pyrazine 1-oxide	Zn-AcOH	3,6-di-*s*-butyl-2-hydroxy	5-Br → 5-OH	see note[s]	47JB321, 47JB341
Pyrazine 1,4-dioxide	Zn-AcOH	2,3,5,6-tetraphenyl	—	80	30G899

[r] *N*-Oxides of benzo[*f*]naphtho[1, 2-*c*]-, benzo[*f*]naphtho[2,1-*c*]-, and benzo[*h*]naphtho[1,2-*c*]-cinnoline.
[s] 5-Bromoaspergillic acid yields a diketopiperazine on reduction.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Pyrazolo-pyrimidine 5-oxide	Zn-HCl	2-phenyl-4,6-dioxo	—	17	67JH325
Pyrazolo-pyrimidine 6-oxide	Zn-HCl	1-methyl-5,7-dioxo	—	44	66JO2491
Quinoxaline 1-oxide	Zn-AcOH	3,4-dihydro-2-hydroxy-3-oxo-7-substituted	—	—	64T1107
Quinoxaline 4-oxide	Zn-AcOH	3-cyano-1,2-dihydro-2-oxo	—	—	64J2666
Phenazine 5-oxide	Fe-AcOH	—	—	87–100	60UK86
	Fe-HCl	—	1- or 3-NO_2 → 1- or 3-NH_2	—	55UK249
	$SnCl_2$-HCl	—	2,8-diNO_2 → 2,8-diNH_2	(data)	55AN1031
	$SnCl_2$-HCl	1-, 2-, or 3-chloro	7-NO_2 → 7-NH_2	—	56CT117
	$SnCl_2$-HCl	2,7-disubstituted[t]	—	(data)	11LA(382)82
	Zn-AcOH	1-bromo-2-methoxy and 4-bromo-1-methoxy	—	(data)	59CT581
	Zn-AcOH	1,8-dimethoxy	—	—	57CT81
	Zn-H_2O	—	—	57	59ZO228
	Zn-H_2O	7-chloro-1-methoxy-4-methyl	—	51	59ZO228
	Zn-H_2O	2,7-disubstituted[u]	—	—	60ZO1661
	Zn-NaOH	—	—	70	66J(B)260
Phenazine 5,10-dioxide	Fe-AcOH	—	—	—	38ZO151
	Zn-NaOH	—	—	—	66J(B)260
1,2,4-Benzotriazine *N*-oxide	Fe-AcOH	3-amino-5,6-benzo	—	—	57G446

[t] Substituents: 2,7-dibromo, -dichloro, -diiodo, -dimethyl.
[u] Various derivatives; quaternary salts were reduced.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected[a]		
1,2,4-Benzotriazine *N*-oxide, *cont'd.*	Sn-HCl	3-amino and substituted-amino	see note [v]	—	13CB3522, 17CB1248, 59JO813
	Zn-AcOH	3-amino	—	87	62JO185
	Zn-NH_4Cl	3-chloro, -hydroxy, -dimethylamino	—	(data)	59JO813, 49USP2489357
1,4-Benzoxazine 4-oxide	Zn-AcOH	3-hydroxy[w]	—	—	60AS1214
	Zn-AcOH	2,3-dihydroxy[x]	—	57	60AS504
	Zn-HCl	2,3-dihydroxy[x]	—	—	59SU252, 60AS499
Phenoxazine 10-oxide	$SnCl_2$	3-hydroxy[y]	7-oxo → 7-OH	—	89CB3020
	$TiCl_3$	7-hydroxy	3-oxo → 3-OH	—	66M1558
Pyrrolenine 1-oxide	Zn-AcOH	2,3,5-triphenyl	see note [z]	—	34JA2774
Δ^1-Pyrroline 1-oxide	Sn-HCl or Zn-AcOH	2,4,4-trimethyl	—	(data)	59J2094
	Zn-NH_4Cl	methyl, phenyl	(2,2′-dimerization)	(data)	68AJ2497
Pyrazole 2-oxide	Zn-AcOH	4,5-dimethyl-3-phenyl	1-OH → 1-H	—	66JH544
Pyrazole 1,2-dioxide	Zn-AcOH	3,5-disubstituted	4-C=O → OH, 1-N^+—O^- → NH	35–85	69JO187
Indazole *N*-oxide	Zn-AcOH	3-cyano-2-phenyl	—	—	25CB834

[v] The 1,2-dihydro compound is formed, but very easily aromatizes.

[w] 1,4-Benzoxazin-3-one.

[x] More correctly named 2,4-dihydroxy-1,4-benzoxazin-3-one; the glucoside reacts analogously.

[y] Resazurin; reduction product is 3,7-dihydroxyphenoxazine.

[z] For the 2,3,5-triphenyl compound the deoxidation is reported to proceed in quantitative yield. For the 2,3,5-triphenyl-2-methoxy compound, the reaction probably involves 1,3-addition of hydrogen to the C=N^+—O^- system, followed by 1,4-elimination of methanol to give the 1-hydroxypyrrole, which is further reduced by addition of hydrogen and subsequent elimination of water to give the oxygen-free pyrrole.

Table 3.19. Deoxygenation of *N*-Oxides with Dissolving Metals (and Metal Ions of Lower Valency)—*continued*

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected[a]		
Indazole *N*-oxide, *cont'd.*	$SnCl_2$-HCl	1,2-*endo*-2′-arylimino-2,3-dihydro-3-keto	—	—	31J2787
	Zn-EtOH	2-aryl-3-ethoxycarbonyl	—	—	35BF1016
Imidazoline 1-oxide	Zn-AcOH	2,3,5-triaryl	—	(data)	31CB1816
	Zn-HCl	4,5-dimethyl-2-phenyl	3-OH → H	—	45G216
Purine 7-oxide	$SnCl_2$-HCl	2,6-diamino-8-phenyl	—	—	57MI138
1,2,3-Triazole 1-oxide	$SnCl_2$-HCl	5-methyl-2-phenyl	4-PhNHNH → 4-NH_2	—	42G399
Oxazole 3-oxide	Zn-AcOH	4-acyl-2-aryl-5-methyl	—	—	68J(C)1397
	Zn-AcOH	4-acyl-5-methyl-2-phenyl	—	58	65CI1340
	Zn-AcOH	2,4,5-triphenyl	—	—	30PC(127)292
4,5-Benzisoxazole 1-oxide	Fe-AcOH	3-phenyl	see note [aa]	—	59JA962
Benzotriazole 1-oxide	$SnCl_2$-HCl	2-aryl and -$(CH_2)_2$aryl	—	(data)	99CB3256, O3CB3822, 56J1724, 62AG155
1,2,4-Oxadiazole 4-oxide*	Zn-AcOH	3,5-diphenyl	—	—	O6CB1480
Furoxan	Zn-AcOH	4-(or 3-) carboxamido-3-(or 4-)phenyl	—	—	68AN200
Dibenzo-1,4,5-thiadiazepine 4-oxide	Sn	—	—	(data)	66J(B)255
Dibenzo-1,4,5-thiadiazacyclohepta-2,4,6-triene 1,1,4-trioxide	Zn-AcOH	—	—	64–87[bb]	57JA4382, 57JA5583

[aa] *o*-Aminobenzophenone is obtained.
[bb] Yield is dependent on the stereochemistry of the molecule.
* See addendum in the Appendix.

Table 3.20. Reduction of Furoxans to α-Dioximes

Furoxan substituents			
3-	4-	Reducing agent	References
Alkyl	alkyl	H_2/Ni(R)	60JA5339
Carboxamido	phenyl	H_2/Ni(R)	68AN200
Methyl	dimethoxyphenyl	AcOH	92CB1956
Phenyl	methoxyphenyl	Zn–EtOH–AcOH	25LA(444)94
Phenyl	*o*-, *m*-tolyl	Zn–EtOH–AcOH	29LA(468)202

at lower potentials than is dimethylaniline *N*-oxide, which is a reflection of the fact that the former compounds are more resistant to reduction. References to work on the determination of polarographic reduction potentials are given in Table 3.21, and a selection of the actual values is given in Table 3.22.

Russian workers (56ZO1740) who measured the values for pyridine, quinoline, acridine, quinoxaline, and phenazine *N*-oxides concluded that the ease of reduction of an *N*-oxide group increases as the number of condensed rings and/or the number of nitrogen atoms in the molecule increases. Reduction potentials tend to vary in the same sense as the dipole moment : the lower the dipole moment, the less back-coordination there is and the less tightly held is the *N*-oxide oxygen atom; consequently it is more easily reduced

Table 3.21. Bibliography of Half-wave Reduction Potentials

Ring system	References
Pyridine 1-oxides	43PJ307, 53G1051, 53G1059, 62BJ1549, 62J1923, 65ZC310, 66BJ2057, 67BJ245, 67TT745
Pyridine alkaloids	60IZ938
Quinoline 1-oxides	57AL62, 67CT1112, 67TT745, 68CT839
Acridine 10-oxides	58ZO2693, 60ZO3480
Pyridazine *N*-oxides	68TL1855
Benzocinnoline *N*-oxides	52JA4122,[a] 62J1923, 66BJ2057
Purine *N*-oxides	60JA3193, 65CZ4210
Pyrazine 1- and 1,4-di-oxides	68JJ1170
Quinoxaline *N*-oxides	55AN251, 62J1923, 66BJ2057
Phenazine *N*-oxides	53AL796, 58ZO2693, 62J1923
Benzophenazine *N*-oxides	55AL78, 55AL179
Phenoxazine 10-oxides	45NA(155)401
Benzotriazole 1-oxides	68AS2879
5,6-Benzo-1,3-diazepine 3-oxides	67AP250

[a] The reliability of these data has been questioned ; see reference 62J1923.

Table 3.22. Half-wave Reduction Potentials of Some Selected *N*-Oxides[a]

Ring system	Substituents	$-E_{1/2}$, V	pH	References
Pyridine 1-oxide	—	1·2786	3·5	43PJ307
	—	1·281	5·0	66BJ2057
	—	1·41, 1·73	7·0	62J1923
	3-amino	1·280	5·0	66BJ2057
	4-amino	1·416	5·0	66BJ2057
	3-bromo	1·040	5·0	66BJ2057
	4-bromo	1·094	5·0	66BJ2057
	4-carboxy	0·862	5·0	66BJ2057
		1·21, 1·39, 1·76	7·0	62J1923
	3-chloro	1·071	5·0	66BJ2057
	4-chloro	1·174	5·0	66BJ2057
	3-cyano	0·943	5·0	66BJ2057
	4-cyano	0·857	5·0	66BJ2057
	3-ethoxycarbonyl	0·992	5·0	66BJ2057
	3-fluoro	1·144	5·0	66BJ2057
	4-hydroxyamino	1·434	5·0	66BJ2057
	3-methoxy	1·168	5·0	66BJ2057
	4-methoxy	1·56	7·0	62J1923
	3-methyl	1·272	5·0	66BJ2057
	4-methyl	1·357	5·0	66BJ2057
	2,3,6-trimethyl	1·3924	3·5	43PJ307
	4-nitro	1·6622	3·5	43PJ307
		0·25, 1·53	7·0	62J1923
	4-phenoxy	1·2820	3·5	43PJ307
3,4-Benzocinnoline 5-oxide	—	0·69	7·0	62J1923
3,4-Benzocinnoline 5,6-dioxide	—	0·60, 1·36	7·0	62J1923
Quinoxaline 1-oxide	—	0·52, 0·68, 1·52	7·0	62J1923
Quinoxaline 1,4-dioxide	—	0·52, 0·68, 1·53	7·0	62J1923
Phenazine 5-oxide	—	0·19, 0·36, 1·26	7·0	62J1923
Phenazine 5,10-dioxide	—	0·23, 0·36, 1·27	7·0	62J1923
Dimethylaniline *N*-oxide	—	0·7047	3·5	43PJ307

[a] Measured against a saturated calomel electrode at 25°.

(58ZO2693). Half-wave potentials of the first reduction wave correlate reasonably well with the energy of the lowest unoccupied molecular orbital (67BB230).

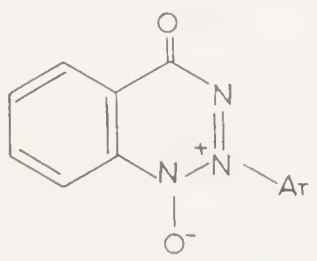
The effect of substituents on polarographic reduction potentials has been studied, especially by Emerson and Rees (62J1917) and by Kubota and

Miyazaki (66BJ2057); the latter investigators showed a correlation between the half-wave reduction potentials and the substituent σ-constants. Reduction is hindered by a methoxy group and facilitated by a carboxyl group, as would be expected. Several polarographic waves are often obtained. In general *N*,*N*-dioxides, e.g. quinoxaline 1,4-dioxides, are not reduced more easily than the corresponding mono-*N*-oxides.

ii. Thermal and "Oxidative" Deoxygenation

Some *N*-oxides are deoxygenated on mild heating in various solvents. An isolated example of the simple deoxygenation of a quinoline 1-oxide by acetic anhydride is known (65JJ66). Several phenazine 5,10-dioxides are converted into mono-*N*-oxides on recrystallization from acetic acid (56JO1034); others can be deoxygenated by heating them in acetic anhydride (53CT66; 54CT25; 61JJ861) or in acetic anhydride–dimethylamine (55CT365). Loss of the *N*-oxide oxygen atom from a naphthotriazine *N*-oxide (64TL641) and from benzotriazine *N*-oxides of type *95* on refluxing in ethanol has been reported (27J323; 30J157; 30J843; 31J2792) [Note: compounds formulated as *95* may be anthranil oxides, see Section II-2Ciiib].

Many *N*-oxides are converted into the parent bases if they are heated more strongly, either alone or in the presence of various solid catalysts. Simply heating pyridine 1-oxide at 220° gives some pyridine; the deoxygenation is catalysed by copper or zinc powder. 4-Ethoxypyridine 1-oxide reacts similarly, but the 4-nitro compound is thermally stable. Analogous results were obtained in the quinoline series (47JJ53). More recently, ferrous oxalate and granulated lead have been used to promote deoxygenation; several pyridine 1-oxides have been reduced in reasonable yields using these catalysts (61CC2134). Deoxygenation of *N*-oxides by heat alone has been reported in the following series: 3,4-dihydroisoquinoline 2-oxides (*96*) (the corresponding isoquinolines are formed) (58CB1488), acridine 10-oxides (60AR105; 60BF693), 4-oxoquinazoline 1-oxides [66J(C)2287], phenazine 5- and 5,10-di-oxides (38J479; 55AN1031), pyrroline 1-oxide (68AJ2521), and various hydroxamic acids (64G590). In other cases deoxygenation has been effected by heating the *N*-oxide with the catalyst indicated: quinoxaline 1,4-dioxide with aluminium chloride (the mono-*N*-oxide was obtained) (56J2058), phenazine 5-oxide with iron powder (58J4492), and benzimidazole *N*-oxides with zinc (87CB1874; 64JO153).



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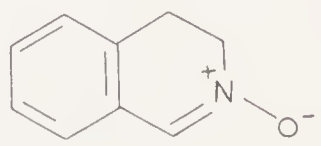


(96)

"Oxidative deoxygenatations" have been reported, that is deoxygenation reactions which occur on treatment of an *N*-oxide with an oxidizing agent. Hydrogen peroxide has been shown to deoxygenate benzo[*a*]phenazine 12-oxide (51JA4958) and benzimidazole 1-oxide [59AK(14)419]. Similarly, peracetic acid causes loss of the *N*-oxide oxygen from 2-hydroxyquinoline 1-oxide (64CT345), and peroxytrifluoroacetic acid effects the same reaction with certain polychloropyridine 1-oxides [68J(C)1537]. Attempts to oxidize substituents, e.g. hydroxymethyl groups, on pyridine 1-oxide with selenium dioxide usually causes loss of the *N*-oxide oxygen (58JJ957).

Several cases in which deoxygenation occurs under strongly acidic conditions, usually in the presence of nitric acid, may possibly be examples of related reactions. If 4-nitropyridine 1-oxide is heated with potassium nitrate and sulphuric acid at 165°, some 4-nitropyridine is produced: it was concluded that deoxygenation is actually caused by nitrogen dioxide (47JJ56). It has since been shown that 4-nitropyridine 1-oxide is also deoxygenated by nitrosylsulphuric acid, nitric acid–sulphuric acid mixtures, or nitric oxide, and that 4-nitropyridine can be prepared from pyridine 1-oxide in one step (62CB1098). Partial deoxygenation is often observed with nitration reactions carried out at high temperatures (see Section III-2Gii), or on heating the *N*-oxide with sulphuric acid above 270° (59R586; 60J3462). Sulphuric acid and trace amounts of selenium dioxide effect deoxygenation of pyridine 1-oxide at 200° (52JJ1643).

iii. Photochemical Deoxygenation

Many photochemical transformations of *N*-oxides are known, of which deoxygenation is but one; other reactions of this type are discussed in Section III-5B. Photochemical deoxygenation of pyridine 1-oxides has been extensively investigated by Hata. In the vapour phase, pyridine 1-oxide is converted smoothly into pyridine; a remarkable dependence of the quantum yield of pyridine on the reaction temperature was observed [62JT(36)2072]. 3-Picoline 1-oxide in the vapour phase reacts similarly to pyridine 1-oxide (61BJ1444); deoxygenation of 2-picoline 1-oxide occurs on irradiation with 2537 Å light, but with 3261 Å light 2-pyridylmethanol is the main product (61BJ1440) (see also Section III-5Bi). Moreover, Sigwalt and his colleagues have found that photolysis of pyridine 1-oxide in benzene solution gives high quantum yields of phenol, which they ascribe to the intermediate formation of atomic oxygen (67CH979) (the other products formed are discussed in Section III-5Bi); however, in ethanol solution the reaction is more complex (see Section III-5Bi).*

Photolysis of pyridazine 1-oxide in the presence of benzene or cyclohexane produces pyridazine together with phenol or cyclohexanol; with toluene as solvent a mixture of cresols is obtained (68CT767). Benzocinnoline 5-oxide is also smoothly deoxygenated photochemically (68BJ1664),

* See addendum in the Appendix.

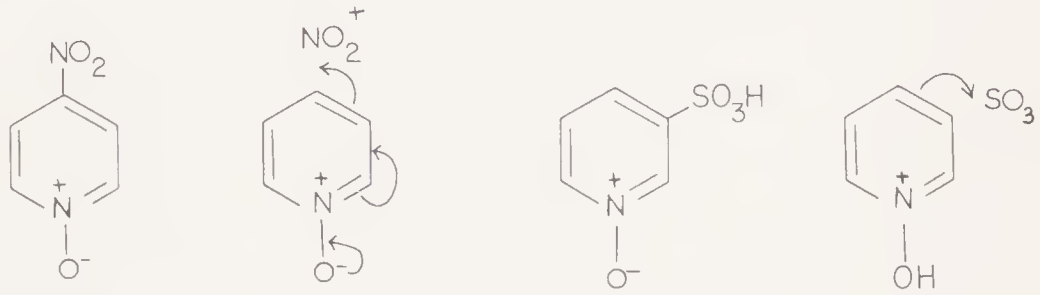
and Brown and Levin have shown that many purine *N*-oxides can be thus deoxygenated (62FE372; 63MC825; 64B880).

3. Electrophilic Attack on Ring Carbon Atoms

The electrophilic substitution of pyridine and quinoline 1-oxides has been extensively investigated; other heterocyclic *N*-oxides have been less well studied. Nitration, acid-catalysed hydrogen exchange, sulphonation, halogenation, mercuration, and other related reactions are included in this section, which is prefaced by a general discussion of orientation and mechanism.

A. ORIENTATION AND MECHANISM

The facile nitration of pyridine 1-oxide in the 4-position (*97*) was discovered by Ochiai (42PJ561; 43JJ79), and independently by den Hertog (50R468), both of whom correctly reasoned that the *N*-oxide oxygen atom would release electrons to the 4-position thereby promoting the reaction (cf. *98*). However, the fact that sulphonation of pyridine 1-oxide under some conditions gives a good yield of the 3-sulphonic acid (*99*) (55JA2902) had to be explained. It was early postulated that this difference in orientation is a reflection of the fact that nitration occurs on the free base (*98*), whereas sulphonation involves the conjugate acid (*100*); e.g. reference 61MIa. Recently, good evidence has been obtained that electrophilic reactions in strongly acidic media yield γ-substituted products when the free base is attacked, and β-substituted derivatives when reaction proceeds through the conjugate acid.



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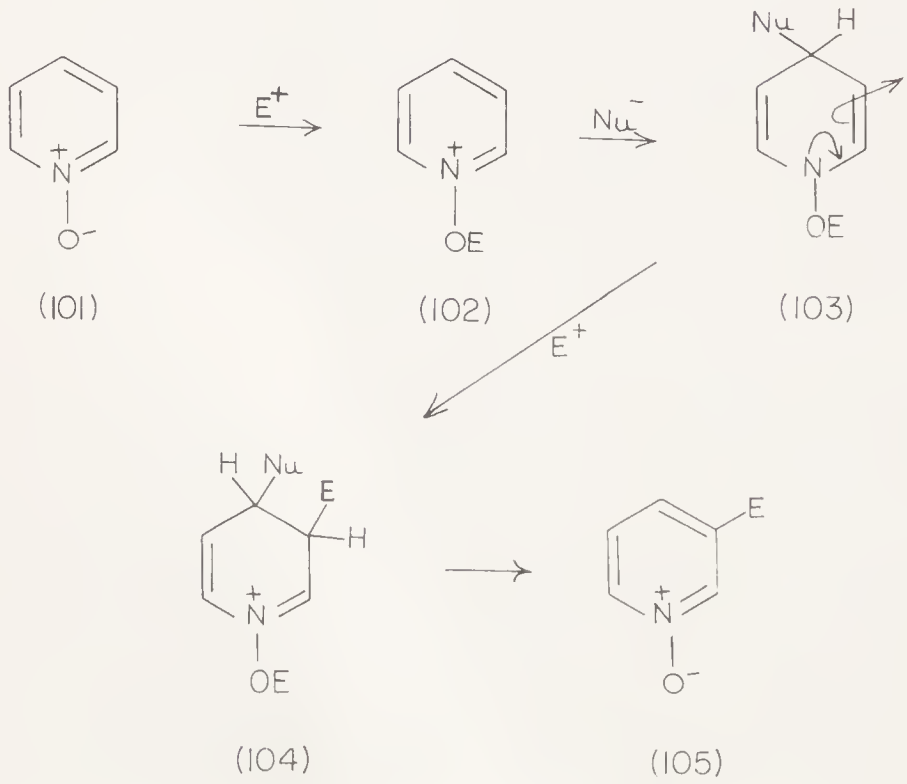
As is discussed in detail under the individual reactions, nitration at the γ-position involves the free base; if nitration is directed to the β-position by activating substituents, or if the γ-position is occupied, the conjugate acid is involved. However, this simple and satisfying interpretation has recently been challenged by the Exeter group, who find that the pre-exponential Arrhenius parameters do not agree well with the proposed mechanism of nitration on the free base. They have suggested various alternative mechanisms, but the situation is not yet clear [68J(B)316]. Acid-catalysed hydrogen

exchange normally occurs in the β-position on the conjugate acid, but if this exchange is directed to the γ-position, the free base is the reactive species. Halogenation of rings carrying an *N*-oxide group requires rather vigorous reaction conditions; however, conditions which lead to substitution in the α- and γ-positions do not give β-isomers and *vice versa*, again suggesting that the free base undergoes substitution *alpha* or *gamma* to the *N*-oxide group and the conjugate acid *beta* to this group. Sulphonation, which succeeds only under forcing conditions and gives a β-substitution product, is considered to take place on the conjugate acid. Mercuration usually occurs on the free base at a position *alpha* to the *N*-oxide group.

The above generalizations although they were originally formulated principally by reference to pyridine 1-oxide, also apply to benzo derivatives such as quinoline and acridine oxides and to pyridazine 1-oxide and its benzo derivative cinnoline 1-oxide (but not to pyrimidine or pyrazine *N*-oxides). However, for the benzo derivatives, nitration on the conjugate acid species generally occurs in the benzo ring rather than at the β-position of the heterocyclic ring. The strong orienting effect of the *N*-oxide group is also seen in compounds such as phenazine 5-oxide, where substitution is found to occur in the benzene ring.

In addition to the simple electrophilic substitution so far discussed, β-substitution may occur by a more complex mechanism involving massive electrophilic attack at oxygen, γ-(or α-)nucleophilic attack, and finally β-electrophilic attack (*101* → *105*). Such reaction paths have been observed for both nitration and bromination and are discussed in detail under those sections. β-Substitution can be achieved in benzo *N*-oxides by such means.



B. NITRATION BY DIRECT ATTACK OF NITRONIUM IONS

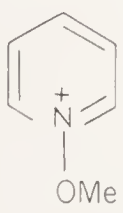
i. Pyridine 1-Oxides

a. Nitration in the γ-Position. The direct influence of the *N*-oxide group on the γ-position is very strong, and pyridine 1-oxides normally give 4-nitro derivatives. To overcome this influence, a hydroxy or dialkylamino group, or two alkoxy groups, is required.

As first shown by Ochiai (43JJ79) and later, independently, by den Hertog and Overhoff (50R468), pyridine 1-oxide is converted into 4-nitro-pyridine 1-oxide in 80–90% yield on heating with concentrated sulphuric acid and fuming nitric acid at 100°. Many substituted 4-nitro-pyridine 1-oxides have been similarly prepared (see Table 3.23). As discussed in Section III-2Gii, deoxygenation often occurs concomitantly with nitration, e.g. in the nitration of 3-bromopyridine 1-oxide (60J4953). If electron-withdrawing substituents are present in the pyridine 1-oxide ring, nitration frequently does not occur, thus 3-cyano- and 3-carboxy-pyridine 1-oxide (46JJ21) and 2-carboxy-5-methoxycarbonylpyridine 1-oxide (60JO565) are resistant to nitration. Attempted nitration of nicotine 1-oxide (58J3230) and dipyridylalkane *N,N′*-dioxides also failed. Phenylpyridine 1-oxides undergo nitration exclusively in the benzene ring (see Section IV-2Aii).

Moodie, Schofield, and Williamson (64CI1577) showed that nitration of the 1-methoxypyridium ion (*106*) gives only a very low yield of 4-nitropyridine 1-oxide; this product is probably formed by initial demethylation of the substrate. The partial rate factor for the nitration of pyridine 1-oxide, that is the rate of nitration as compared to that of one position in benzene (one-sixth the total rate), was estimated to be ca. 10^{-4} by these authors.

Detailed rate studies by the Exeter and Norwich groups of the nitration of pyridine 1-oxide and its 2,6-dimethyl, 3,5-dimethyl, and 2,6-dichloro derivatives over the acidity range 80–98% sulphuric acid confirm the fact that nitration occurs on the free base. Comparison of the kinetic rates of these reactions with the rates for the analogous benzene compounds also shows that substitution of a CH group in a benzene ring by an N^+-O^- group reduces the rate of reaction at the *para*-position by a factor of ca. 10^{-4} [66J(B)870; 67J(B)1213]; see, however, Section III-3A.



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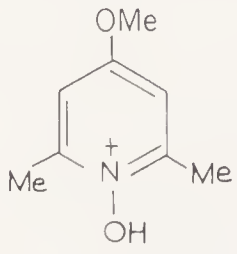

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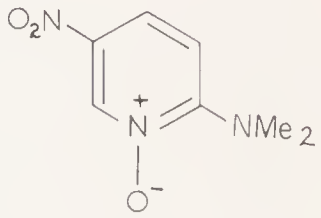

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b. Nitration in the β-Position. If the 4-position of pyridine 1-oxide is occupied by a substituent, nitration usually fails; for example, 4-methoxy-,

Table 3.23. Nitration of Pyridine 1-Oxides in Sulphuric Acid

Substituents	Position of nitration	Yield, %	Temperature, °C	References
—	4	54–90	90–130[a]	43JJ79, 45JJ(5/6A)1, 45JJ73, 47JJ79, 47JJ157, 50R468, 60TU24, 62CB1098, 62JO1665, 62RC539
2-Alkoxy	4	55–60	75–90	51R591, 55R1160
3-Alkoxy	4	70–80	75–85	51R591, 55R1160, 55R1171
2-Alkyl	4	49–90	80–100	43JJ79, 51R591, 54JA3167, 59ZO915, 62RC539
3-Alkyl	4	35–60	90–100[b]	54JA3167, 54JA4184, 54JO1633, 55JJ292, 60J4953, 66J(C)1816
2,3- and 2,5-Dialkyl	4	40–87	90–110	55JO1461, 56J771, 57JO936, 58BF694, 61J5556, 67R655, 68RC1873
2,6-Dialkyl	4	87	100	54CT131, 62JO1665, 62RC539
3,5-Dialkyl	4	46	90–100	60J4953
2,3,6-Tri- and 2,3,5,6-tetra-alkyl	4	55–60	90–100	59J1312, 60J4953, 61J5556
*3-, 5-, and 6-Alkyl-2-chloro	4	—	90	57JA3565
2-Alkyl-3-halogeno	4	65	65	67RC279
2,3:5,6-Dibenzo	4	77	—	65RO947
2-Carboxy	4	45	120–135	59CB155, 61PC(13)58
3-Fluoro-2,6-dimethyl	4	64	60	65RC601
2-Halogeno	4	50–69	90	51R591, 56JO1077, 57JA3565, 59JA2674, 62RC539, 64MC296

[a] The yield has been reported to decrease above 140° (47JJ157); use of H_2SO_4–SO_3 gives a better yield than concentrated H_2SO_4 (43JJ79). A small amount of the 2-nitro compound has been reported to form in addition to the 4-nitro derivative (47JJ79).

[b] Potassium nitrate–sulphuric acid has been used as the nitration mixture.

* 6-Alkyl-2-bromo-3-hydroxy; see addendum in the Appendix.

Table 3.23. Nitration of Pyridine 1-Oxides in Sulphuric Acid—*continued*

Substituents	Position of nitration	Yield, %	Temperature, °C	References
3-Halogeno	4	40–90, 120–130	—	46JJ21, 50R468, 55R1171, 59JO1008, 62RC539, 64RC777, 65J2096
2,6-Dihalogeno	4	79–90	80–90	58R340, 59R408, 65JH196
3,5-Dihalogeno	4	90–95	90	53R296, 55R1171
2-(1-Oxido-2-pyridyl)	4-mono and 4,4′-di	see note [c]	100	56NK682, 67J(B)106[c]
2- and 2,6-Di-(1-oxido-2-pyridyl)	4, 4′, 4‴	ca. 22	—	55JJ731, 62JO640

[c] Nitration was carried out on the crude oxidation mixture which contained both the mono- and di-*N*-oxides of 2,2′-bipyridyl.

2,4-dimethyl-, and 2,4,6-trimethyl-pyridine 1-oxides resist direct nitration [45JJ6; 67J(B)1213]. However, if the ring is sufficiently activated, substitution occurs at the 3-position, as was first demonstrated for 4-hydroxypyridine 1-oxide (50JJ145; 52JJ274) and its 2-methyl derivative (3,5-dinitro compounds were also formed) (50JJ142; 51JJ789). Later, β-nitro derivatives of 2,6-di- and 2,4,6-tri-methoxypyridine and 4-methoxy-2,6-dimethylpyridine 1-oxides were prepared [67J(B)1213], and it was shown kinetically that these reactions involve nitration of the conjugate acids (cf. *107*). Nitration of 4-hydroxypyridine 1-oxide occurs so readily that it can be effected by the nitrous acid (or its decomposition products) produced in the preparation of 4-hydroxypyridine 1-oxide from the 4-nitro analogue (see Section IV-3Ciib).

2-Hydroxypyridine 1-oxide (1-hydroxy-2-pyridone) undergoes nitration in the 5-position (49JA70) or in both the 3- and 5-positions (56R1259); in contrast, 2-methoxypyridine 1-oxide reacts in the 4-position (55R1160). 2-Dimethylaminopyridine 1-oxide (64R249) and the corresponding *N*,1-dioxide (65R785) yield the 5-nitro 1-oxide *108* on nitration; the second reaction involves deoxygenation of an aliphatic *N*-oxide which probably precedes the electrophilic substitution.

c. Nitration in the α-Position. The nitration of pyridine 1-oxide in sulphuric acid, which yields mainly 4-nitropyridine 1-oxide, was shown by Ochiai *et al.* (47JJ79) to give also a small quantity of 2-nitropyridine: this is considered to arise from the occurrence of some α-nitration followed by deoxygenation of the 2-nitropyridine 1-oxide thus formed. If the 4-position is sterically hindered, α-nitration can become predominant. Thus, the nitration of 3-*t*-butylpyridine 1-oxide yields 5 (or 3)-*t*-butyl-2-nitropyridine; the 1-oxide group is again lost in the reaction (60J4953). If sufficiently strong electron-donating groups are present in the 3- or 3,5-position(s), nitration also occurs at the α-position. Thus, 3-dimethylaminopyridine 1-oxide gives a mixture of 2- and 6-nitro derivatives [70J(B)ip1], and 3-hydroxypyridine 1-oxide was shown by Polish investigators to undergo nitration at the 2-position (59R644). 3,5-Diethoxypyridine 1-oxide reacts with nitronium ions to yield first the 2-mono- and then the 2,6-di-nitro derivative (53R296). 3,5-Dimethoxy- and 5-bromo-3-methoxy-pyridine 1-oxide also undergo nitration at the 2-position (55R1171); it has been shown kinetically that nitration of the former compound occurs on the conjugate acid [67J(B)1213].

ii. Other Six-membered Heterocyclic N-*Oxides*

a. Quinoline 1-oxides. Quinoline 1-oxides undergo nitration by mixed acids in the 4-, 5-, or 8-positions; nitration occasionally occurs in the 6-position, but rarely elsewhere. Available data are summarized in Table 3.24. The following factors favour substitution in the benzenoid ring: the presence

Table 3.24. Nitration of Quinoline 1-Oxides in Sulphuric Acid

Substituents	Position of nitration	Yield, %	Temperature, °C	Reagent[a]	References
—	4, 8, and 5	see note [b]	see note [b]	H_2SO_4–HNO_3 or KNO_3	43JJ280, 44PJ599, 45JJ(5/6A)1, 45JJ73, 47JJ157, 50JJ384, 57CM388, 68J(B)316
2-Amino	3	70–80	—	HNO_3–AcOH	47JJ141
Benzo[*f*]	7 and 10	see note [c]	—	—	52JJ985
Benzo[*h*]	7, 9 and 10	—	40–115	KNO_3–H_2SO_4	51JJ1291
6-*n*- and 6-*t*-Butyl	4	20, 56	90	KNO_3–H_2SO_4	69CT544
6-Carboxy	4	70	100	—	60JJ339
6-*n*- and 6-Cyclohexyl	4	6, 8	90	KNO_3–H_2SO_4	69CT544
3-Fluoro	4	96·5	90	KNO_3–H_2SO_4	68CT1742
2-Halogeno	4	66–71	70	KNO_3–H_2SO_4	68JJ656
3-Halogeno	5, 8, and 4	see note [d]	see note [d]	—	50JJ376
3- and 5-Halogeno	4	—	—	—	67CT1
6-Halogeno	4 or 5	see note [e]	see note [e]	—	48JJ209, 51JJ727, 66CT319
7-Halogeno	4	ca. 90	—	—	46JJ60, 48JJ209
8-Halogeno	5	—	—	—	48JJ209
2-Hydroxy	6 and 6, 8	see note [f]	—	—	59CT273, 61JJ1601
4-Hydroxy	3	see note [g]	70–80	HNO_3–Ac_2O	52JJ767
8-Hydroxy	5 (?)	70	ca. 20	HNO_3–AcOH	54J570
4-Hydroxy-2-methyl	3	—	—	—	21CB1067

[a] A mixture of concentrated nitric acid–sulphuric acid unless otherwise specified.

[b] At 0–20°, 8- (major product) and 5-isomers are formed; at 60–100° the 4-isomer is the main product; above 120° deoxygenated 5- and 8-isomers are obtained.

[c] 7-Nitro derivative is the major product, only a trace of the 10-isomer being formed.

[d] At 20°, 5- (major product) and 8-nitro compounds are formed; at 60–70° the 4-isomer is the major product; above 120–130° deoxygenated 4-, 5-, and 8-mono-nitrated and 3,8-dinitrated products are obtained.

[e] At low temperatures the 5-isomer is obtained, at high temperatures the 4-isomer (51JJ727).

[f] A 25% yield of the 6,8-dinitro derivative was obtained using nitric acid–acetic acid (59CT273).

[g] Obtained as the 1-acetoxy derivative.

* 2,3-Tetramethylene and 5-, 6-, or 7-tritio; see addenda in the Appendix.

Table 3.24. Nitration of Quinoline 1-Oxides in Sulphuric Acid—*continued*

Substituents	Position of nitration	Yield, %	Temperature, °C	Reagent[a]	References
4-Methoxy	6 and 8	—	5–7	see note [h]	45JJ(3A)5
4-Methoxy	7 and 6	see note [i]	5–6	—	47JJ144
6-Methoxy	5	56	40	KNO_3–H_2SO_4	45JJ(3A)5, 48JJ209, 51JJ727, 66CT319
2-Methyl	4	70	70	—	45JJ(3A)4, 59EGP16921, 61ZC84
2-Methyl	5 and 8	—	see note [j]	KNO_3–H_2SO_4	51JJ1078
3-, 5- and 8-Methyl	4	—	—	—	67CT1
4-Methyl	8	see note [k]	—	—	45JJ(3A)4, 55JJ33
6-Methyl	4 and 5	see note [e,l]	—	—	45JJ(3A)4, 48JJ209, 51JJ727, 59WZ93, 60AF1029, 66CT319
2-Methyl-5- and -8-nitro	4	46 and 69	25	$NaNO_3$–H_2SO_4	51JJ1078
2-Methyl, substituted[m]	4	—	—	—	60JJ339, 64CT1495
4-Nitro	8 and 6	—	—	—	44PJ599
4-Nitro	5	—	0–20	—	50JJ384
5- and 6-Nitro	4	—	—	—	44PJ599, 48JJ209, 50JJ384, 51JJ727
8-Nitro	4 and 6	—	—	HNO_3–P_2O_5	44PJ599, 50JJ384
4, 6-Dinitro	8	—	—	HNO_3–P_2O_5	44PJ599
2-(1-oxido-2-quinolyl)	4,4′	21	80–90	—	66JH170
2-Phenyl	4	—	—	—	66JJ59
Pyrido[2, 3-*d*][n]	4	—	—	—	61JJ1323
Pyrido[2, 3-*f*]	4	(data)	85–90	—	65JO288
6-Sulphonic acid	4	32–36	—	—	60JJ339
"Mixed coal-tar bases"	—	—	—	—	50JJ265

[h] No reaction occurred with nitric acid–acetic acid at 25°.

[i] The 7-isomer is the major product; 4-methoxycarbostyril is formed as a by-product.

[j] Below 50° only 5- and 8-nitro derivatives obtained; at 50–100° the 4-, 5-, and 8-mono-nitro derivatives are formed; above 100° deoxygenated products are obtained.

[k] Starting material was recovered from the reaction mixture in 47% yield.

[l] The 4-isomer has been reported to be formed in 21% yield together with some of the 5-isomer; other investigators (59WZ93, 60AF1029) report only the 4-isomer to be formed (52 and 80% yields).

[m] Chloromethyl, 2-hydroxyethyl (55% yield), hydroxymethyl (35% yield), and (*N*-morpholino)methyl.

[n] 1-Methyl-3-hydroxy-4, 7-phenanthroline 7-oxide.

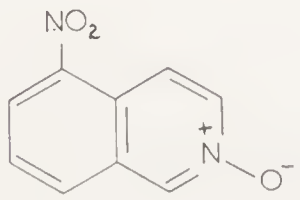
of a substituent in the 4-position, an electron-donating substituent such as a methoxy or halogeno group in the benzenoid ring, a reaction medium of high acidity, and a low reaction temperature. Conditions which favour substitution at the 4-position are: an electron-withdrawing substituent such as a nitro group in the benzene ring, a reaction medium of low acidity, and a high reaction temperature. Recent work has shown that the effect of the acidity of the reaction medium is far more important than the temperature: a high concentration of sulphuric acid favours reaction at the 6-position and lower concentrations favour reaction at the 4-position (66CT319). A substituent in the 4-position appears to offer some steric hindrance to reaction at the 5-position, and substitution may then occur at the 6- or 8-positions. Very strong activation is prerequisite to substitution in the 2- or 3-position of the hetero ring; e.g., 4-aminoquinoline 1-oxide yields the 3-nitro derivative (47JJ141), and the 4-hydroxy analogue behaves similarly (52JJ767).

These generalizations concerning the orientation of substitution are most simply rationalized if reaction at the 4-position occurs on the free base and those in the benzene ring involve the conjugate acid. This pattern was proved kinetically by the Exeter group who demonstrated that the increase in the rate of nitration with increasing acidity was much less for the 4-position than for the 5- or 8-position [68J(B)316]. Presumably the temperature effect (see especially references 50JJ376 and 50JJ384) depends on the variation of the pK and H_0 values, and hence the free base concentration, with temperature.

At high temperatures (>ca. 120°), deoxygenation accompanies nitration and 5- and 8-nitroquinolines are obtained (cf. 50JJ376; 50JJ384; 51JJ1078); see also Section III-2Gii.

b. Isoquinoline and Acridine N-*Oxides.* Nitration of isoquinoline 2-oxide affords the 5-nitro derivative *109* (45JJ17); it was later claimed (53JJ666) that a trace of 8-nitroisoquinoline 2-oxide is also formed, but other investigators have been unable to obtain this derivative (57J2521). The kinetics of the nitration of isoquinoline 2-oxide have been investigated by Schofield *et al.* [64CI1577; 66J(B)870]; they also showed that the 2-methoxyisoquinolinium ion reacts at about the same rate as the *N*-oxide, which provides good evidence that nitration of the latter involves the conjugate acid.

Acridine 10-oxide undergoes nitration at 0° to yield the 9-nitro derivative (*110*) (60J3367).



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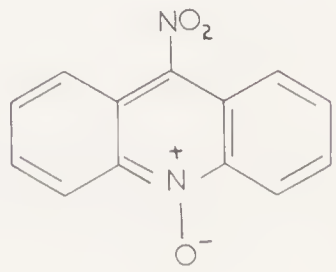

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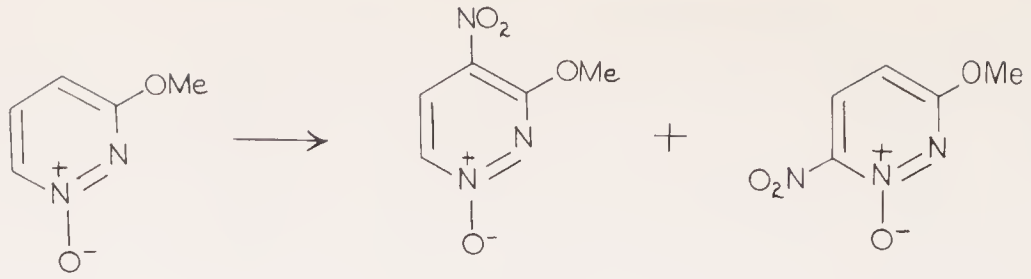

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c. Pyridazine N-*Oxides.* Pyridazine *N*-oxides are readily nitrated by fuming nitric acid–sulphuric acid at temperatures ranging from 10–140° depending on the substitution. In most cases, substitution of the nitro group occurs at the position *para* to the *N*-oxide group (Table 3.25); if this position is occupied as it is in 4-methylpyridazine 1-oxide (63CT35), the reaction often fails. However, nitration can occur in other positions: 3-methoxypyridazine 1-oxide (*111*) yields both the 4- (*112*) and 6-nitro derivatives (*113*), together with 3-methoxy-6-nitropyridazine (61JJ554). Earlier workers (60CT550) obtained only the 4-nitro (*112*) and 4,6-dinitro compounds. 3-Methoxy-4-methylpyridazine 1-oxide undergoes nitration exclusively in

Table 3.25. Nitration of Pyridazine 1-Oxides in Sulphuric Acid

Pyridazine 1-oxide	Position of nitration	Temperature, °C	Yield, %	References
—	4	105–110	8[a]	62JJ253
3-Acylamino-6-alkoxy	5	10	72–83	63CT1157
3,6-Dialkoxy	4	10[b]	—	55JJ966, 61CT149
6-Alkyl-3-halogeno	4	—	(data)	64JP22970
3-Chloro-6-methyl	4	85–100	ca. 46	62JJ253, 63CT29
3-Chloro- or -methoxy-5,6-dimethyl	4	20–70	66–86	63CT726
3-Ethoxy	4	—	22	61JJ708
3-Methoxy	4[c] and 6	—	—	60JJ712
3-Methoxy-4-methyl	6	—	—	62JJ1005
3-Methoxy-6-methyl	4	50–60	ca. 80	62JJ253, 63CT29
3-Methyl and 3,4-dimethyl	4 and 6[d]	50–90	9–30	63CT726
6-Methyl	4	90–100	ca. 55	62JJ253, 63CT29
3,6-Dimethyl	4	70–100	54–83[e]	61CT149, 62JJ253
Naphtho[1,2-*e*]	4	—	85–90	65JO288

[a] Starting material recovered, 50%.

[b] Reaction time is 1–2 days.

[c] Deoxygenated; isolated as a 1:1 compound of 3-methoxy-4-nitropyridazine and the starting material.

[d] Reaction occurs at the 6-position if the 4-position is occupied.

[e] Yields of 54 and 55% were reported at 60–65° (62JJ253) and at 90–100° (61CT149); an 83% yield was reported at 70° (62JJ253).

the 6-position (62JJ1005), and the 6-acylamino-3-alkoxy derivative reacts in the 4-position (63CT1157). 3-Hydroxypyridazine 1-oxide and its 5- and 6-methyl derivatives are nitrated in the 4-position, while the 4-methyl analogues react in the 6-position; 3-methoxy-5-methylpyridazine 1-oxide gives a mixture of the 4- and 6-nitration products (69CT756).

d. Cinnoline and Benzocinnoline N-*Oxides.* Cinnoline 1-oxide (*114*) yields mainly the 4-nitro compound on nitration with mixed acids, but at low temperatures a small amount of the 5-nitro analogue can be obtained as a by-product. Both of these mono-nitro derivatives give the 4,5-dinitro compound on further nitration (63CT268; 64CT1090).* Nitration of 3-methyl-4-phenylcinnoline 1-oxide leads to a mixture of four mono-nitro compounds of unknown structure (47J1649). Additional examples of the nitration of substituted cinnoline 1-oxides are given in Table 3.26.

Table 3.26. Nitration of Cinnoline *N*-Oxides Using Nitric Acid–Sulphuric Acid

Cinnoline *N*-oxide	Position of nitration	Temperature, °C	Yield, %	References
1-Oxide				
—	4	130–140	22	62CT643, 63CT83
6-Acylamino-3-methoxy	4	25	72–83	63CT1157
6-Chloro-3-hydroxy	4	50	53	62CT933
6-Chloro-3-methoxy	4	50	65	62CT933
3-Methoxy	4 and 4, 6	50–55	(data)	60CT550
	4[a] and 6[b]	—	—	61JJ554
	4	20	(data)	63CT1527
3-Methoxy-4-nitro	4, 6	70–75	—	60CT550
5-Methyl	4	100	low	63CT35
2-Oxide				
—	5, 6, and 8	80	(data)	68J(B)316

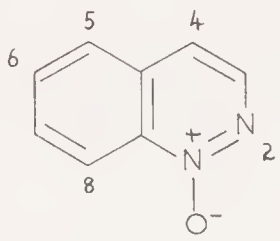
[a] Isolated from the reaction mixture as a molecular compound with 3-methoxycinnoline 1-oxide.

[b] Oxygenated and deoxygenated; see text.

Cinnoline 2-oxide (cf. *114*) affords a mixture of the 5-, 6-, and 8-mono-nitro derivatives on nitration with mixed acids (63CT1326). Suzuki and co-workers (66CT816) have shown that the proportion of the isomers obtained is very dependent on the nitration conditions: high sulphuric acid concentrations and low reaction temperatures favour nitration at the 5- and 8-positions, whereas low acidity and high temperatures greatly increase the amount of the 6-nitro compound. This observation clearly indicates that the 5- and 8-nitro compounds are produced by nitration of the conjugate acid, and that the 6-nitro derivative arises by nitration of the free base. This conclusion was recently confirmed by the Exeter group who found that

* See also reference 69CB4177.

the 2-methoxycinnolinium cation undergoes nitration in the 6- and 8-positions and has a rate profile in agreement with that for the analogous nitration of cinnoline 2-oxide; the nitration of cinnoline 2-oxide in the 6-position shows a rate profile which increases much less rapidly with increasing acidity [68J(B)316].



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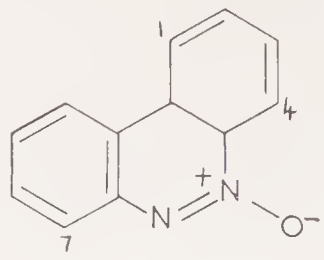

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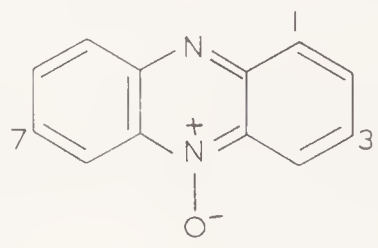
Benzo[*c*]cinnoline 5-oxide undergoes mono-nitration by mixed acids in the 1-, 4-, and 7-positions (cf. *115*); the nitration of some alkyl derivatives has also been described (62J2454; 62J4384). These findings clarified earlier work on the nitration of benzo[*c*]cinnoline 5-oxide (45J824; 56JO651). With nitric acid alone, 2-nitrobenzo[*c*]cinnoline 6-oxide is the major nitration product (62J2454).

e. Pyrimidine, Pyrazine, and Triazine N-*Oxides.* Attempted nitration of pyrimidine 1-oxide has not been successful (59J525). The 1-mono- and 1,4-di-oxides of pyrazine as well as their 2- and 2,5-di-methyl derivatives are resistant to nitration (58JO1603), as are various quinoxaline *N*-oxides (56J2058; 58CT566).



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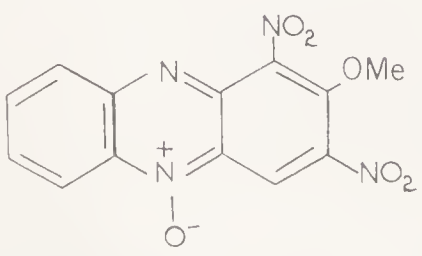

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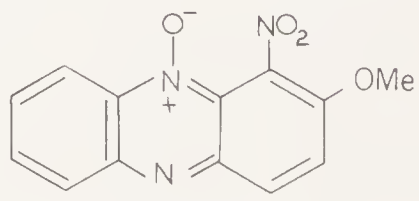

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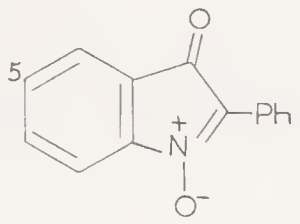
Nitration of phenazine 5-oxide (*116*) yields a mixture of 3-nitro- (major product) and 1-nitro-phenazine 5-oxides (54CT283; 55AN1031; 55UK249); further reaction affords the 1,7- and 3,7-dinitro derivatives (58CT77).

The isomeric 2-methoxyphenazine 5- and 10-oxides yield the nitration products *117* and *118*, respectively (54CT283). Other substituted phenazine *N*-oxides have been nitrated (56CT117; 61JJ861). In general, the phenazine *N*-oxides are nitrated under milder conditions than are the parent phenazines.

For nitration reactions in the 1,2,4-benzotriazine *N*-oxide series, see reference 57J3186.

iii. N-*Oxides with Five- and Seven-membered Rings*

2-Phenylisatogen (*119*) undergoes nitration in the 5-position on treatment with mixed acids at 20° (66JO65), and data are available on the nitration of 1-ethoxybenzimidazoles (64CT282). Benzofuroxans (*120*) are readily nitrated; most frequently substitution occurs in the 4(or 7)-position, but substituent effects can direct the reaction to the 5(or 6)-position. Examples are given in Table 3.27.



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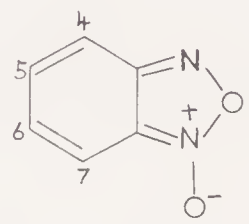

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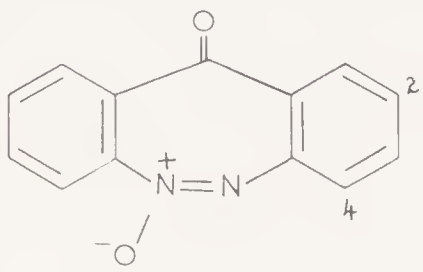

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Table 3.27. Nitration of Benzofuroxans

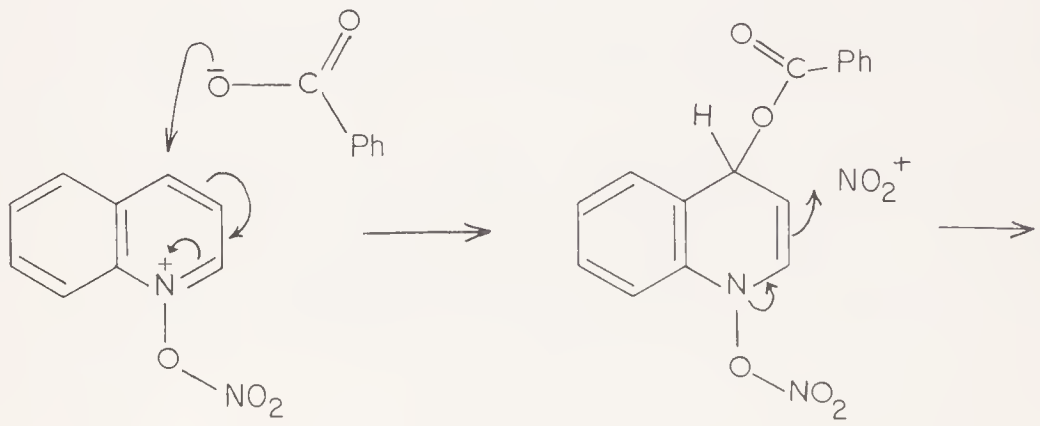
Benzofuroxan	Position of nitration	Yield, %	Reagent	References
—	4	—	—	68MC305
5-Anilino	4	—	H_2SO_4–HNO_3, O°	68J(B)334
4-Chloro	7	70	H_2SO_4–$NaNO_3$, 60°	66J(B)1004
5-Chloro	4	—	H_2SO_4–KNO_3, O°	62RR691, 65J5958, 68J(B)334
	—	—	H_2SO_4–HNO_3, O°	68MC305
5, 6-Dichloro	4	—	—	68MC305
5-Methoxy	4	—	H_2SO_4–HNO_3, O°	68J(B)334
4-Methyl	7	—	H_2SO_4–KNO_3, O°	62RR691
5-Methyl	4	—	H_2SO_4–KNO_3, O°	62RR691, 68J(B)334, 68MC305
5-Nitro	7	50	fuming HNO_3, O°	58T(3)113

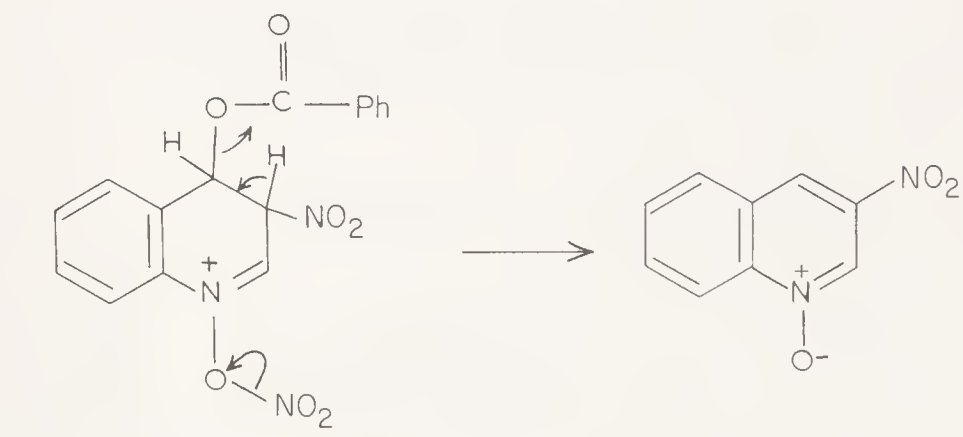
Nitration of the dibenzodiazepinone *N*-oxide *121* occurs successively at the 2- and 4-positions (67AJ723): this orientation is comparable to that reported for azoxybenzene.

C. NITRATION *beta* TO THE *N*-OXIDE GROUP WITH BENZOYL NITRATE AND RELATED REAGENTS

In 1957, Ochiai and Kaneko (57CT56) reported that quinoline 1-oxide could be nitrated with benzoyl nitrate to give 3-nitroquinoline 1-oxide. The benzoyl nitrate can be prepared *in situ* from benzoyl chloride and silver nitrate (59CT267) or potassium nitrate (62SP189), and tosyl or acetyl chloride can replace the benzoyl chloride (59CT267). This reaction has since been extended to pyridine, pyridazine, and cinnoline *N*-oxides (Table 3.28); in each case substitution occurs *beta* to the *N*-oxide group.

Ochiai proposed (57CT56) the mechanism shown in scheme *122* → *125* for the *beta* nitration of quinoline 1-oxide with benzoyl nitrate, and presumably similar mechanisms are involved for the other ring systems. The use





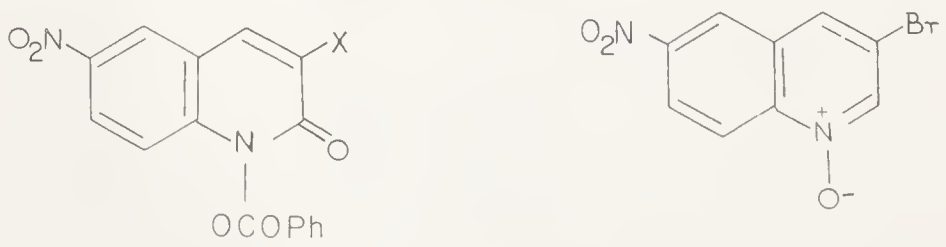


Table 3.28. Nitration *beta* to the *N*-oxide Group Using Benzoyl Nitrate and Related Reagents

Substrate		Reagent	Substituents in products (% yield)	References
Ring system	Substituents			
Pyridine 1-oxide	—	$BzONO_2$	3-nitro 1-oxide (9–10) and 3,5-dinitro 1-oxide (9–10)	57CT56, 60CT28
	3-ethoxycarbonyl	p-NO_2-C_6H_4-CO_2NO_2	3-nitro 1-oxide (50)	65CT112
Quinoline 1-oxide	—	$AcONO_2$[a]	3-nitro 1-oxide (21–32); 6-nitro 1-oxide (1–4); and 3,6-dinitro 1-oxide (6–10)	57CT56, 59CT267
	—	$BzONO_2$	3-nitro 1-oxide (0–50)[b] and 1-benzyloxy-1,2-dihydro-3,6-dinitro-2-oxo (8–51)[b]	57CT56, 59CT191, 59CT267
	—	$TsONO_2$	3-nitro 1-oxide (12) and 1-tosyloxy-1,2-dihydro-3,6-dinitro-2-oxo (3)	59CT267
	3-bromo	$BzONO_2$	3-bromo-6-nitro	59CT195
	4-halogeno	$BzONO_2$	1-benzoyloxy-3-halogeno-4-hydroxybetaine	60CT284
	5- and 7-methoxy	$BzCl + AgNO_3$	3-nitro-5- or -7-methoxy 1-oxide	62JJ773
	2-methyl	$BzONO_2$[c]	2-benzoyloxymethyl; 2-cyano-3-nitro[d]; and 2-methyl-3-nitro 1-oxide	57CT313, 59CT540
	4-methyl	$BzONO_2$	3-benzoyloxy-4-methyl	58JJ1079
	6-methyl	$BzONO_2$	6-methyl-3-nitro and 1-benzoyloxy-1,2-dihydro-6-methyl-3-nitro-2-oxo	59CT195

[a] If excess $AcONO_2$ is used, 1-acetoxy-3,6-dinitrocarbostyril is formed (59CT267). In another report, 4-hydroxy-3,6,8-trinitroquinoline is described as a reaction product (57CT56).

[b] The yield depends upon the ratio of $BzONO_2$ to *N*-oxide.

[c] Excess $BzONO_2$; if theoretical amount used, 2-cyano-3-nitroquinoline not obtained.

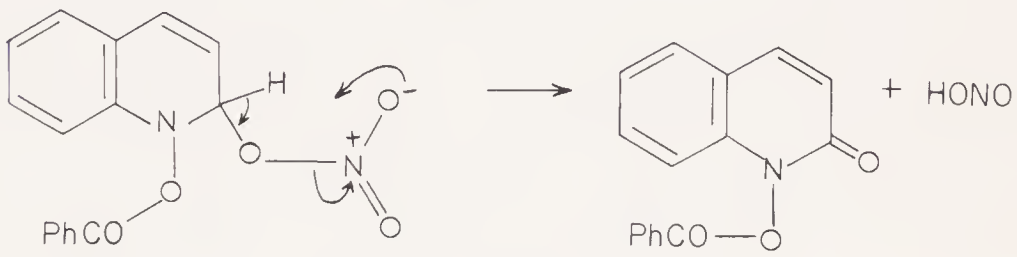
[d] Originally incorrectly formulated.

Table 3.28. Nitration *beta* to the *N*-oxide Group Using Benzoyl Nitrate and Related Reagents—*continued*

Substrate				
Ring system	Substituents	Reagent	Substituents in products (% yield)	References
	2,4-dimethyl	$BzONO_2$	3-benzoyloxy-2,4-dimethyl; 2-benzoyloxymethyl-4-methyl; and 2-cyano-4-methyl[d]	58JJ1079
	2-methyl-3-nitro	$BzONO_2$	2-cyano-3-nitro[d]	57CT313, 59CT540
	6-methyl-3-nitro	$BzONO_2$	1-benzoyloxy-1,2-dihydro-6-methyl-3-nitro-2-oxo	59CT195
	3-nitro	$AcONO_2$	1-acetoxy-1,2-dihydro-3,6-dinitro-2-oxo	59CT267
	3-nitro	$BzONO_2$	1-benzoyloxy-1,2-dihydro-3,6-dinitro-2-oxo (83)	59CT191
	5- and 7-nitro	$BzONO_2$	1-benzoyloxy-1,2-dihydro-3,5-(or 3,7)-dinitro-2-oxo	59CT191
	6-nitro	$BzONO_2$	1-benzoyloxy-1,2-dihydro-3,6-dinitro-2-oxo (90)	59CT191
	5- and 7-tosyloxy	$BzCl + AgNO_3$	3-nitro-5- and -7-tosyloxy 1-oxide[e]	62JJ773
Pyridazine 1-oxide	—	$AcONO_2$	3-nitro 1-oxide (17) and 5-nitro 1-oxide (0·8)	63JJ342
	—	$BzONO_2$	3-nitro 1-oxide (33) and 5-nitro 1-oxide (0·8)	63CT342
	3-methoxy	$BzONO_2$	5-nitro 1-oxide (25)	64CT228
	3-methyl	$BzONO_2$	5-nitro 1-oxide (12)	64CT228
	3,6-dimethyl	$BzONO_2$	5-nitro 1-oxide (11)	64CT228
Cinnoline 1-oxide	—	$BzONO_2$	3-nitro 1-oxide (71)	63CT268, 64CT1090

[e] Further reaction with benzoyl chloride gives the 1-benzoyloxycarbostyrils.

of *p*-nitrobenzoyl chloride and silver nitrate with pyridine 1-oxide leads to the formation of some 3-mono- and 3,5-di-nitro-pyridine 1-oxide (60CT28). In the case of quinoline 1-oxide, further reaction can lead to introduction of a nitro group at the 6-position and conversion of the *N*-oxide into the 1-benzoyloxy-2-oxo derivative (*126*, X = NO_2) (59CT191; 59CT195). If the 3-position is blocked, nitration occurs only in the 6-position; for example, 3-bromoquinoline 1-oxide yields *127*, which on further reaction is converted into *126* (X = Br) (59CT195). Similarly, 3,6-dinitroquinoline 1-oxide gives *126* (X = NO_2) (59CT267). Reactions at the 2-position probably involve addition of a nitrate ion, followed by the elimination of nitrous acid (*128* → *129*); see also Section III-4Civd. Ochiai's mechanism is supported by the reactions which occur on attempted nitration of 4-halogenoquinoline 1-oxides with benzoyl nitrate: the resultant 1-benzoyloxy-3-halogeno-4-quinolones are probably formed by the mechanism shown (*130* → *131*). The adduct *132* formed by 2-ethoxyquinoline 1-oxide loses the elements of ethyl nitrate yielding the 2-quinolone *133* (60CT284).



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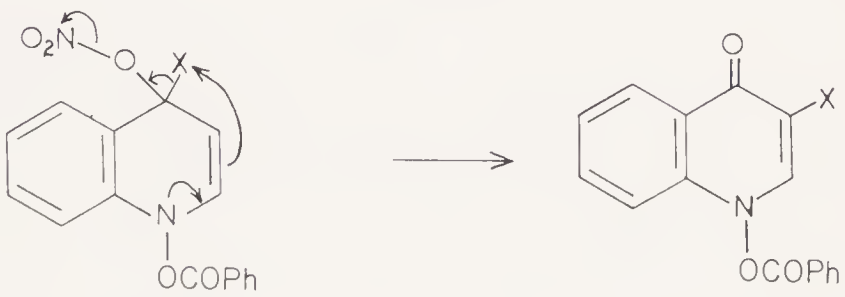

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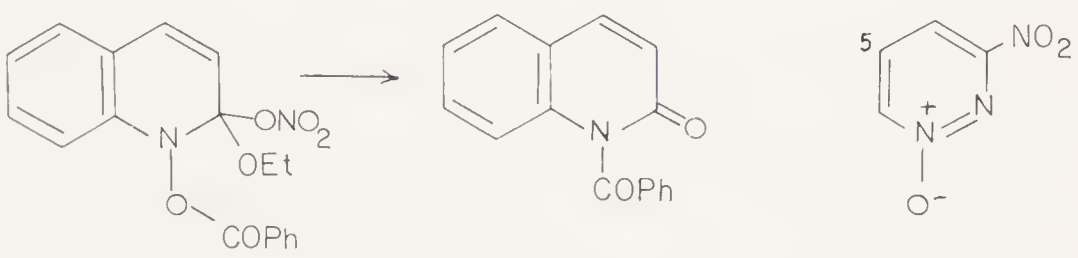
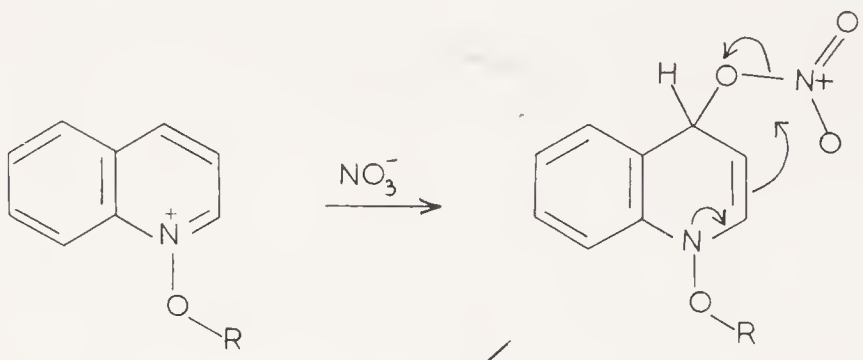


(132) (133) (134)

Pyridazine 1-oxide reacts with benzoyl nitrate to yield 3-nitropyridazine 1-oxide (*134*) together with a small amount of the 5-nitro isomer (63CT342). Nitration of 3-substituted pyridazine 1-oxides by the same methods gives

reasonable yields of the corresponding 5-nitro compounds (64CT228). 3,6-Dimethoxypyridazine 1-oxide undergoes a reaction of the type shown in the equation *132* → *133* (64CT228).

Introduction of a nitro group in the 3-position of quinoline 1-oxide has also been achieved by treatment of either the 1-methoxyquinolinium ion or the quinoline 1-oxide–boron trifluoride complex with a metallic nitrate under neutral conditions; the reaction probably proceeds by the sequence *135* → *138* (62CT349). This reaction has been extended to substituted quinoline 1-oxides (62SP189). However, nitration of the quinoline 1-oxide –boron trifluoride complex with benzoyl nitrate gives 4-nitroquinoline 1-oxide, possibly via intermediate formation of the nitronium salt NO_2^+ $PhCO_2BF_3^-$ and quinoline 1-oxide (58JJ1079).



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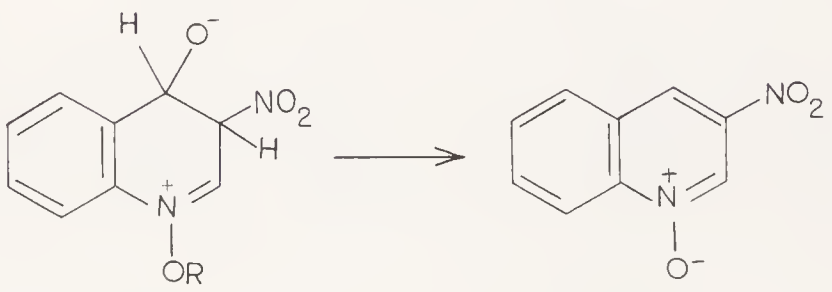

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D. ELECTROPHILIC HALOGENATION

i. Direct Halogenation of Pyridine 1-Oxides

Halogenation of pyridine 1-oxide does not proceed easily: for example, no reaction occurs with bromine and an iron catalyst at 110° (55JA2902). However, using bromine, 90% sulphuric acid, and silver sulphate, den Hertog and his co-workers (61TL32) obtained a mixture of 4- (7%) and 2-bromopyridine 1-oxide (3%). 2-Bromopyridine 1-oxide reacts further under these conditions giving the 2,4- and 2,6-dibromo derivatives [62T(18)227].

Bromination of pyridine 1-oxide in 65% oleum was found by the Dutch

group [62T(18)227] to give a moderate yield of mono-, di-, and tri-bromopyridine 1-oxides. 3-Bromopyridine 1-oxide is the major mono-bromination product; trace amounts of the 2- and 4-bromo compounds are also obtained. 2,5- and 3,4-Dibromopyridine 1-oxide are formed together with a small amount of the corresponding 2,3-dibromo isomer. Bromination of 2-bromopyridine 1-oxide in 65% oleum gives 2,3- and 2,5-dibromopyridine 1-oxide.

In 90% aqueous sulphuric acid, bromination probably occurs on the free base, and consequently substitution occurs in the 2- and 4-positions. When the reactions are conducted in 65% oleum, pyridine 1-oxide probably reacts either in the protonated form or as the sulphur trioxide adduct, which would explain the predominance of *beta* substitution.

In contrast to the unsubstituted compounds, heterocyclic *N*-oxides carrying hydroxyl or amino substituents are readily halogenated. Bromination of 4-hydroxypyridine 1-oxide yields the 3-mono- or 3,5-di-bromo derivative (51JJ213; 52JJ274; cf. 52R745); the corresponding iodo (51JJ213) and chloro compounds (55R59) have also been prepared. Similarly, bromination of 2-hydroxypyridine 1-oxide gives the 3-mono- (49JA70) or 3,5-di-bromo derivative (56R1259). Bromination of 3-hydroxypyridine 1-oxide occurs successively at the 2-, 6-, and 4-positions under quite mild conditions (66RC405); however, iodination gives preferentially the 4,6-diiodo derivative, although under forcing conditions a third iodine atom is introduced, probably at the 2-position (66RC1875).*

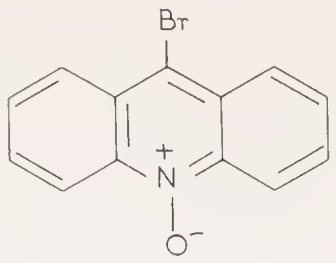
Alkoxy groups also have an activating effect: 3,5-diethoxypyridine 1-oxide reacts with sulphuryl chloride to give successively the 2,6-di- and 2,4,6-tri-chloro derivatives (57R261).

ii. Direct Halogenation of Other N-*Oxides*

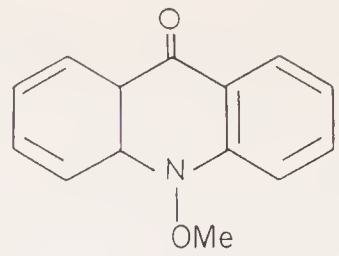
The perbromide of quinoline 1-oxide was found by Ochiai and Okamoto to give 4-bromoquinoline 1-oxide in 32% yield on shaking with bromine and water at 20° (47JJ87). 4-Amino- (47JJ246) and 4-hydroxy-quinoline 1-oxide (51JJ213) undergo bromination in the 3-position under mild conditions. However, 4-methoxyquinoline 1-oxide is resistant to bromination (47JJ246). Acridine 10-oxide gives the 9-bromo derivative (*139*) in good yield if the reaction is carried out in acetic acid solution (60J3367). 10-Methoxyacridone (*140*) is reported to yield 4-chloroacridone (*141*) on treatment with hydrochloric acid (39CB1071). 9-Hydroxyacridine 10-oxide also undergoes bromination (57CB60).

3-Hydroxypyridazine 1-oxide is readily brominated at the 4- and 6-positions (67CT1411), and 5-hydroxypyridazine 1-oxides are also substituted at the same positions (68JJ479). 5-Methoxybenzofuroxan undergoes bromination in the 4-position (69MC505). *N*-Hydroxyuracils are readily iodinated and brominated in the 5-position (68M847).

* See addendum in the Appendix.



(139)



(140)

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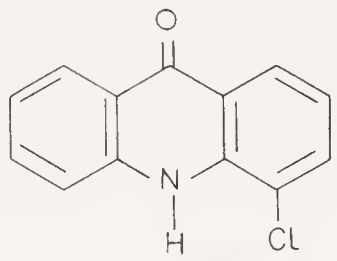

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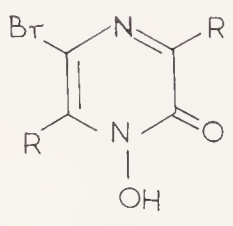

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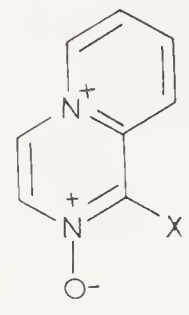
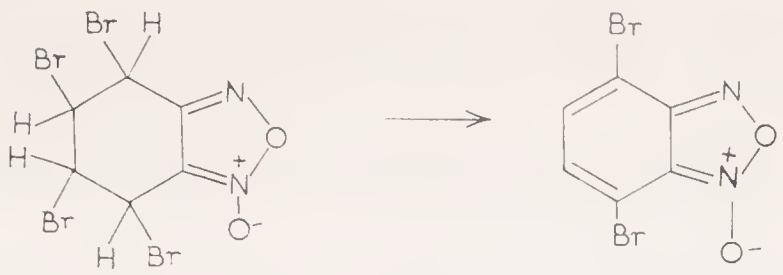


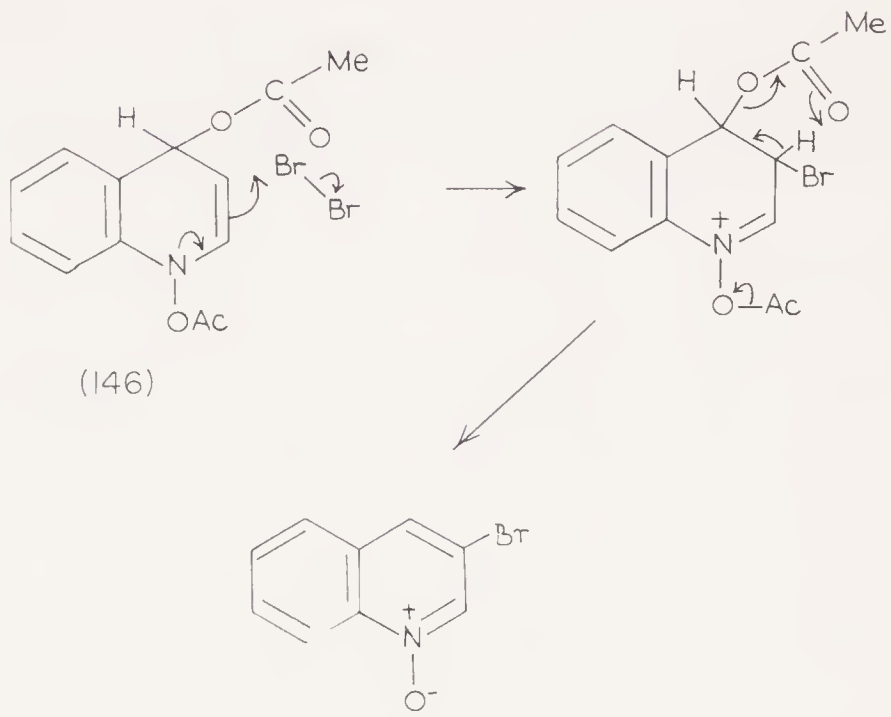
(143)

The only pyrazine *N*-oxides which have been halogenated are cyclic hydroxamic acids of the aspergillic acid group, which react readily with bromine to yield products of type *142* (47JB321; 47JB341). A quinoxaline 1,4-dioxide has been reported to undergo bromination in the benzene ring [60AA(138)14-P]. The surprisingly facile reaction of the pyridino-pyrazinium *N*-oxide cation *143* (X = H) with bromine to give *143* (X = Br) has been described [67J(C)2391]. Phenazine 5-oxide could not itself be brominated, but 1-, 2-, and 3-methoxyphenazine 5-oxide are smoothly brominated *ortho* or *para* to the methoxy group (59CT581).

1-Ethoxybenzimidazole undergoes chlorination in the benzene ring (64CT282). Bromination of benzofuroxan gives a tetrabromo addition compound (*144*) which eliminates two molecules of hydrogen bromide; the product was originally tentatively formulated as the 4,6-dibromo derivative (31J3308), but later was shown to be 4,7-dibromobenzofuroxan (*145*) (61ZN413). Substituted 3-hydroxypyridazine 1-oxides are also easily halogenated in the position expected (69CT756).



(144) (145)



(146) (147)

iii. Bromination beta *to an* N-*Oxide Group Following a Nucleophilic Addition Reaction*

Hamana and Yamazaki have reported that pyridine 1-oxide is converted on heating with bromine and acetic anhydride–sodium acetate into 3,5-dibromopyridine 1-oxide (61CT414; 65JJ62). Quinoline 1-oxide and various substituted derivatives also undergo bromination in the 3-position; 4-bromoisoquinoline 2-oxide can be prepared similarly. In the case of quinoline 1-oxide, if the reaction is allowed to proceed further, bromination also occurs in the 6-position. The mechanism proposed, which is shown in the scheme *146* → *147*, is analogous to that for the nitration of *N*-oxides in the *β*-position (see Section III-3C). The reported conversion of 2-methyl-4-nitroquinoline 1-oxide into 3-chloro-2-methyl-4-nitroquinoline 1-oxide by phosphorus oxychloride is possibly also a reaction of the same general type (61ZC84).

E. OTHER ELECTROPHILIC REACTIONS

i. Acid-catalysed Hydrogen Exchange

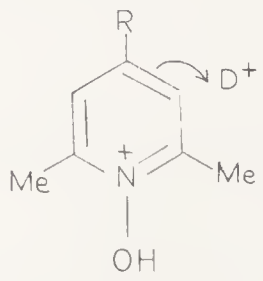
a. Pyridine 1-Oxides. 2,6-Dimethyl- and 2,4,6-trimethyl-pyridine 1-oxide undergo acid-catalysed hydrogen exchange at the 3- and 5-positions under

forcing conditions (200–260°; 55–100% D_2SO_4). Rate profiles and entropies of activation indicate that the conjugate acids are undergoing substitution (cf. *148*). The $\rangle N^+–OH$ group appears to be slightly more deactivating than the $\rangle N^+–H$ group towards reaction in the *meta* position [64CI1576; 67J(B)1222].

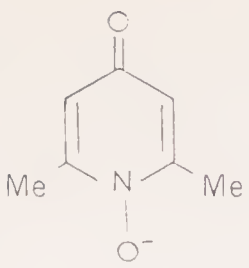
The kinetics of exchange of 4-aminopyridine 1-oxide at 107° over the acidity range $H_o = 0$ to -8 demonstrate that the first conjugate acid is the reactive species; comparisons with *para*-substituted anilines indicated that for $\rangle N^+–OH$ the $\sigma_m^+ = 1{\cdot}99$ (cf. σ_m^+ for $\rangle N^+–H$ is 1·82) [68J(B)864]. 1-hydroxy-2,6-dimethyl-4-pyridone undergoes exchange in the 3- and 5-positions; as the acidity is increased the reactive species is successively the anion *149*, the neutral molecule *150*, and the cation *151*. A Hammett treatment then yields σ_m^+ values of 2·1 to 2·3 for the protonated *N*-oxide group, and σ_m^+ of 0·8 for the neutral *N*-oxide group [68J(B)866].

3,5-Dimethylpyridine 1-oxide undergoes acid-catalysed hydrogen exchange at the 2-, 4-, and 6-positions, and kinetic data show that these reactions involve the free base (cf. *152*). Hydrogen atoms in the 2- and 6-positions of 3,5-dimethoxypyridine 1-oxide exchange; substitution on the free base predominates at acidities less than $H_o - 3{\cdot}5$, but at stronger acidities the conjugate acid reacts [67J(B)1222]. Attempts to induce acid-catalysed exchange of the ring hydrogens in 3-hydroxypyridine 1-oxide failed (67CT1411).

b. Quinoline 1-Oxides. From a semi-quantitative study of the acid-catalysed hydrogen-deuterium exchange in quinoline 1-oxide, Kawazoe and Ohnishi (67CT826) determined that the reactivity order is $8 > 5,6 > 7 > 3$: reaction does not occur at the 2- and 4-positions. The kinetics of hydrogen exchange of quinoline 1-oxide (at the 8- followed by the 5- and 6-positions), isoquinoline 2-oxide (at the 5- and 8-positions) and 6-methylquinoline 1-oxide (at the 5- and 8-positions) show that these compounds all react as their conjugate acids [70J(B)ip2].



(148)



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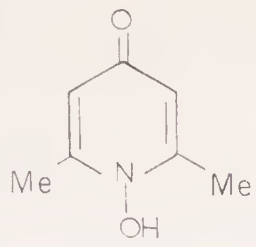

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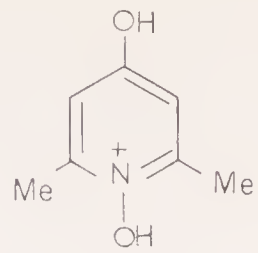

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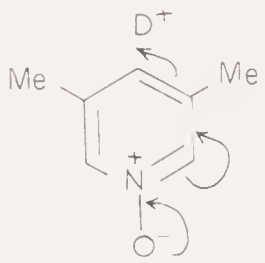

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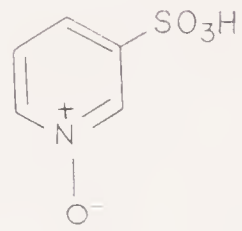


(153)

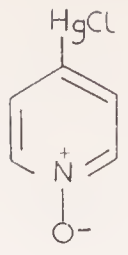
ii. Sulphonation

In contrast to the relatively mild conditions required for nitration, the sulphonation of pyridine 1-oxide requires 20% oleum, mercuric sulphate as catalyst, and a temperature of 230°; the 3-sulphonic acid (*153*) is formed (55JA2902). 2,6-Dimethylpyridine 1-oxide yields the corresponding 3-sulphonic acid under similar conditions (62JO1329). Attempted chlorosulphonation was unsuccessful (55JA2902).

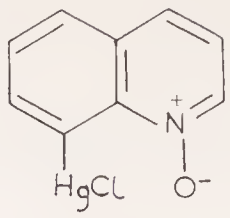
A more detailed investigation of the sulphonation of pyridine 1-oxide by van Ammers and den Hertog (59R586) disclosed that ca. 45% of the 3-sulphonic acid of pyridine 1-oxide is produced, together with small amounts of the corresponding 2- (1%) and 4-sulphonic acids (2%). Although no kinetic results are available, the reaction almost certainly occurs on the conjugate acid.

iii. Mercuration

The reaction of pyridine 1-oxide with mercuric acetate–acetic acid was originally erroneously reported to give, after treatment with sodium chloride, the 4-chloromercuri derivative *154* (53JJ823). van Ammers and den Hertog (58R340; 62R124) proved that under these conditions 2-mono- and 2,6-di-chloromercuripyridine 1-oxide are the major products obtained, together with a small amount of the 3-analogue. However, the Dutch investigators showed that mercuration with mercuric sulphate, chloride, or bromide also yields some 3- and 4-mercuripyridine 1-oxide, although 2-substitution always predominates. 4-Hydroxypyridine 1-oxide undergoes mercuration in the 3-position (51JJ213), but this reaction fails with nicotine 1-oxide (58J3230).



(154)

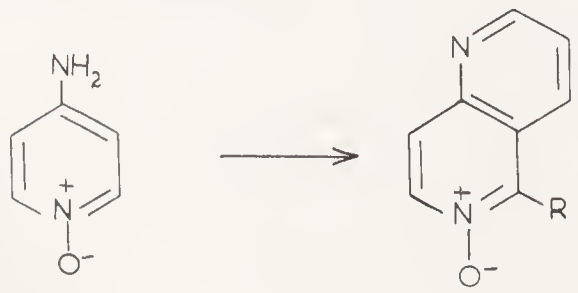


(155)

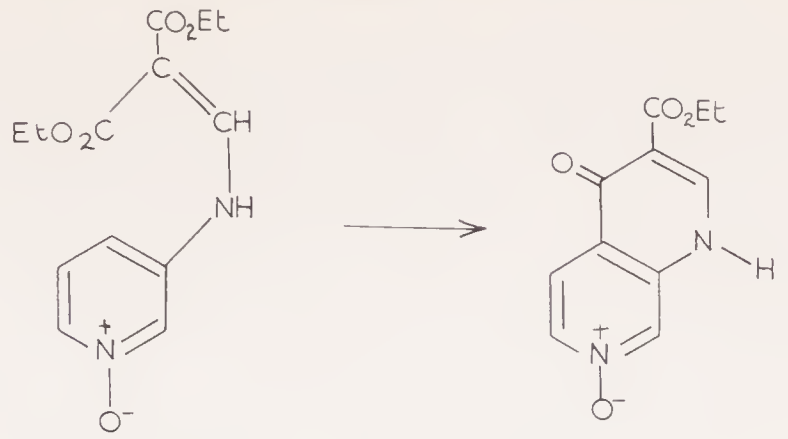
Quinoline 1-oxide yields the 8-mercuri derivative (*155*), and 4-bromo- and 6-methyl-quinoline 1-oxide react similarly. 8-Bromoquinoline 1-oxide, which has the 8-position occupied, is reported to undergo mercuration in the 4-position (53JJ823; 55JJ490). This preferential 8-orientation has been explained in terms of preliminary coordination of the mercury atom at the *N*-oxide oxygen atom (55CT105). Recently, reinvestigation has shown that small amounts of the 3-, 5-, 6-, and 7-isomers are formed in the mercuration of quinoline 1-oxide in acetic acid or perchloric acid: mercuration in the absence of solvent by mercuric sulphate yields in addition some 2- and 4-substitution, i.e. all possible isomers are formed, but the overall **yield** is poor (69CT906).

iv. Ring Closure onto an N-*Oxide Ring*

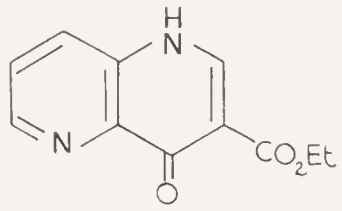
Relatively few examples are known of electrophilic ring closures involving carbon atoms of the hetero ring of a heteroaromatic *N*-oxide. In such reactions, ring positions *gamma* to the *N*-oxide group are generally preferentially substituted. Kato and his co-workers (56CT178) showed that 4-aminopyridine 1-oxide (*156*) undergoes the Skraup reaction to give 1,6-naphthyridine 6-oxide (cf. *157*, R = H). The product from the analogous reaction with 4-amino-2-picoline 1-oxide was later shown to be *157* (R = Me) (58CT263). 3-(2,2-Diethoxycarbonylethyleneamino)pyridine 1-oxide also cyclizes analogously (*158* → *159*); it is of interest that the corresponding compound *without* the *N*-oxide group also cyclizes, but substitution then occurs at the 2-position to yield *160* (54JO2008). The Fischer indole synthesis succeeds with the 4-hydrazinopyridine 1-oxide *161* (*161* → *162*) (65AN810). Both the ring closure shown in scheme *163* → *164* and the analogous reaction for the corresponding pyridine are known (66T35); curiously the orientation appears to favour substitution in the α-position in both cases. Several failures have been reported for reactions of this general type [60AP(293)92; 60JO2242].



(156) (157)



(158) (159)



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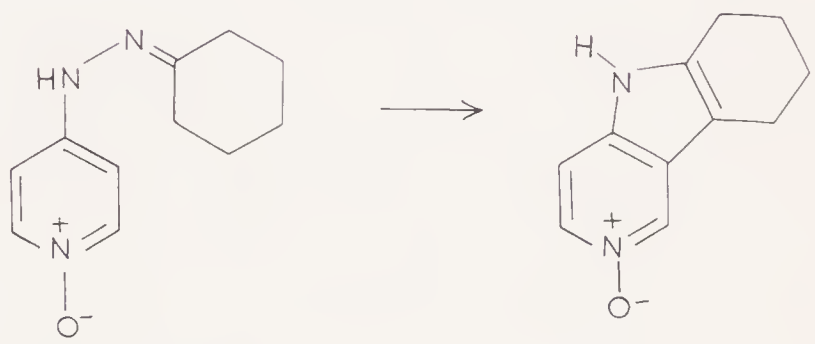
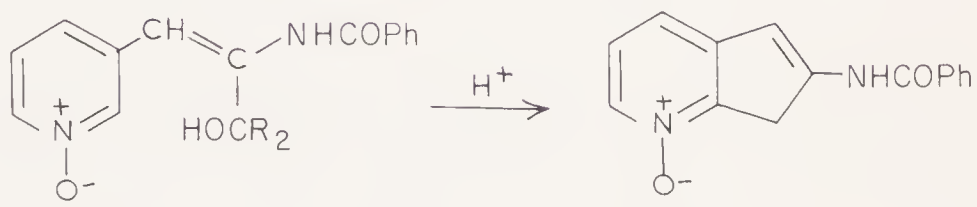


(161) (162)



(163) (164)

v. Oxidation

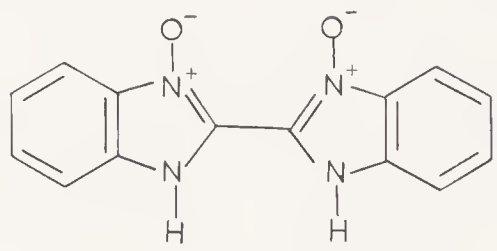
The ozonolysis of 3-methylisoquinoline 2-oxide to phthalic acid (64JA38) and of 3,4-diphenylfuroxan to benzoic acid (27JA514) are known. These reactions are included in the present section because here ozone is acting as an electrophile; however, in other reactions with *N*-oxides, ozone behaves as a nucleophile (Section III-4Civa).

Certain other miscellaneous oxidations of *N*-oxides are included in this section that may involve electrophilic attack, although in several cases free radicals could well be involved. 4-Quinazolinone 1-oxides are converted into *o*-nitrobenzamides (cf. *165* → *166*) by peracetic acid (65JJ507). 3-Quinoxalinone 1-oxides yield 1-hydroxy-2,3-quinoxalinediones (68KG545).

Cyclic nitrones are oxidized to hydroxamic acid derivatives under mild conditions with ferric chloride if an α-hydrogen atom is present [66J(C)1477]; however, periodate oxidation of 5,5-disubstituted pyrroline 1-oxides yields nitroso compounds, *167* → *168* [66J(C)412]. 1-Hydroxyindoles autoxidize to isatogens and other products (67AN1205). Benzimidazole *N*-oxide undergoes oxidative coupling with oxygen to yield bimolecular products of type *169* [58LA(615)99]. The formation of pyrazole 1-oxides has been considered to be the first step in the oxidative cleavage of pyrazoles [56AA(130)22-O]. 2-Arylindazole 1-oxides (*170*) undergo oxidative cleavage to give products of type *171* (26CB351; 54JA3672; 62JO65).

(165) (166)

(167) (168)



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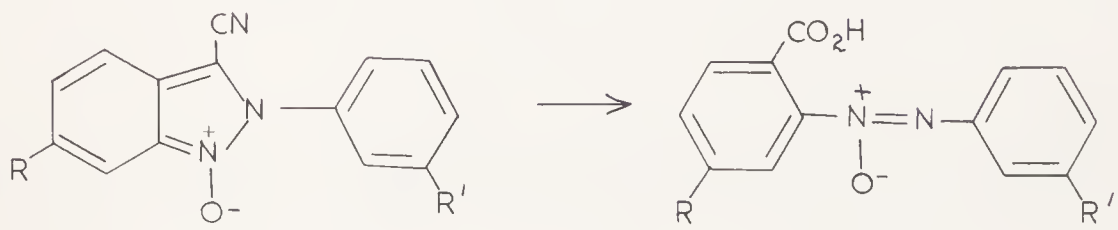
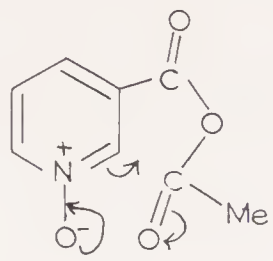


(170) (171)

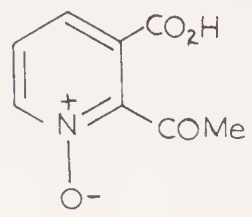
vi. Miscellaneous Reactions Involving Electrophilic Attack

Friedel-Crafts reactions on either pyridine 1-oxide (44JA2902) or the activated 3-methoxypyridine 1-oxide have not been successful (55JA2902). However, 3-carboxypyridine 1-oxide reacts with acetic and propionic anhydrides to yield *173* and *175*, respectively (60CI402; 61J5216); presumably the reactions are of an intramolecular Friedel-Crafts type on intermediate

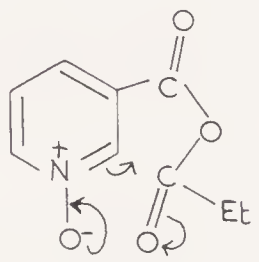
mixed anhydrides (*172* → *173*; *174* → *175*), although the orientation is curious. Decarboxylation, and subsequent rearrangement to 2-pyridone (cf. Section III-4Ciia), is the only reaction observed on heating 2- or 4-carboxypyridine 1-oxide with acetic anhydride.



(172)



(173)



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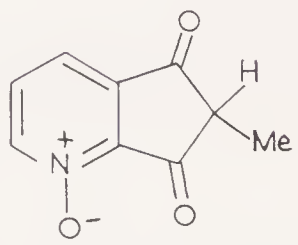

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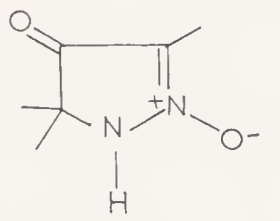

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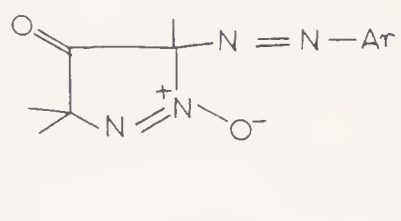
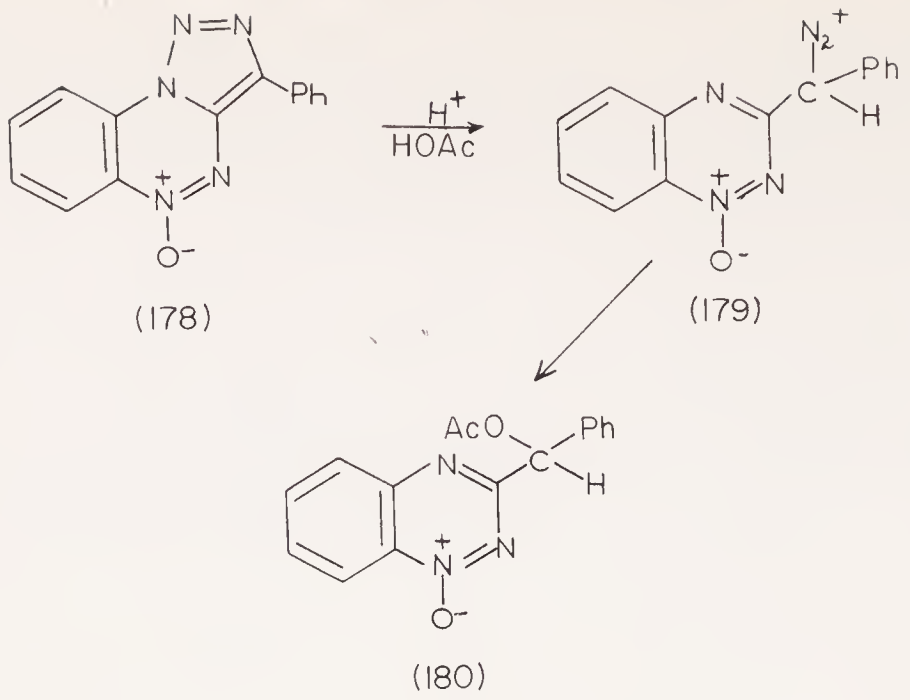


(177)

3-Hydroxypyridine 1-oxide does not undergo azo coupling, even with diazotized picramide (55JA2902). However, azo-coupling reactions do succeed with certain pyrazole *N*-oxides (*176* → *177*) (62JO2881) and with 8-hydroxyquinoline 1-oxide; in the latter case substitution occurs *para* to the hydroxy group (56J614).

Nitrosation of *N*-hydroxyuracil derivatives has been accomplished (65JO408; 67JO3689). 3-Hydroxypyridazine 1-oxide undergoes Mannich reactions at the 6-position (67CT1172), or if this is blocked, at the 4-position (67CT1733). 5-Hydroxypyridazine 1-oxide also undergoes Mannich reactions, first at the 6-position, then at the 4-position (68CT142). For Mannich reactions of these hydroxypyridazine 1-oxides with primary amines, see reference 68CT939.

The acid-catalysed conversion of triazolo-benzotriazine oxides of type *178* into acetoxybenzylbenzotriazine *N*-oxides (*180*) is probably initiated by protonation at the phenyl-substituted triazole carbon atom, followed by ring opening to a diazonium salt (*179*) [67J(C)2658].



4. Reactions of Nucleophilic Reagents at the Ring Carbon Atoms of Heterocyclic *N*-Oxides

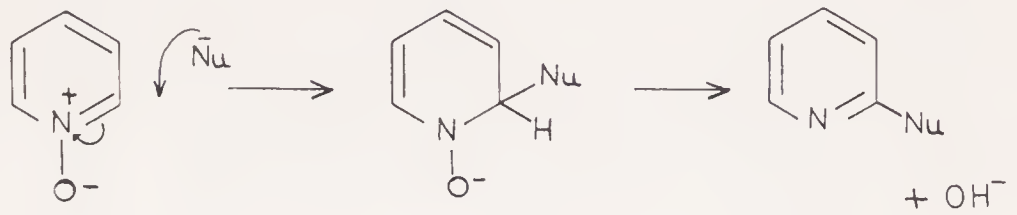
A. GENERAL SURVEY

Electrons are pulled towards the positively charged nitrogen atom in heterocyclic *N*-oxides, consequently they can undergo nucleophilic attack in positions *alpha* and *gamma* to the *N*-oxide group (*181* → *182*). In nearly all of these reactions, the *N*-oxide group is then lost giving the substituted heterocycle (*182* → *183*) (for exceptional cases where the *N*-oxide function is retained, see Section III-4Civ). There is evidence for the intermediate formation of Meisenheimer complexes in these reactions. For example, 4-nitropyridine 1-oxide forms deeply coloured complexes with amines and phenols (62CB1098); for a discussion of the related charge-transfer spectra, see reference 67JJ1309. Nitrobenzofuroxans form complexes of this type which have been isolated (see Section III-4Cia).*

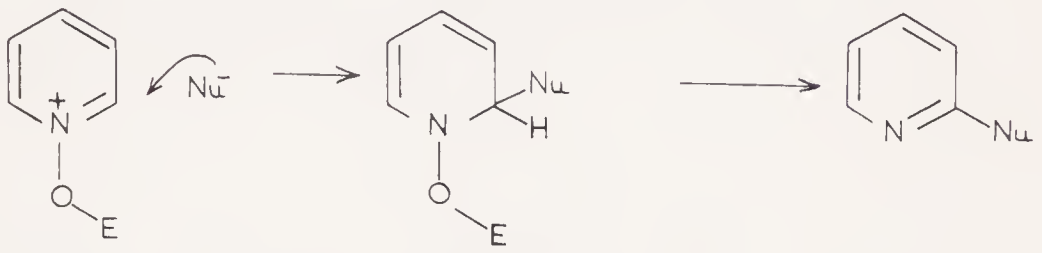
Usually only the strongest nucleophiles, such as the carbanions derived from organometallic reagents, can attack an unactivated ring carrying an *N*-oxide group. Many more examples are known of nucleophilic attack when the *N*-oxide has previously added an electrophile at the *N*-oxide oxygen atom (*184* → *185*). The most frequent next step is again the formation of an α- or γ-substituted heterocycle (cf. *185* → *186*), but alternatively ring opening (with or without reclosure) or another type of rearrangement can occur. Addition products which have been isolated (e.g. *187* from the reaction of pyridine 1-oxide with phenylmagnesium bromide) sometimes show surprising stability and are versatile reaction intermediates as well (67JO3788). These reactions generally occur preferentially at the α-position, but if this is blocked the γ-position is attacked. If positions on the heterocyclic ring are not open, reaction can sometimes occur on a fused benzenoid

* See addendum in the Appendix.

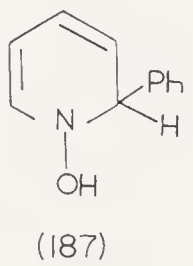
ring; various examples are known in the benzimidazole *N*-oxide series (cf. *188* → *190*) (66CT1219). 3-Hydroxypurine-2,4-diones react with a variety of nucleophiles to give 8-substituted purine-2,4-diones; reaction occurs in the fused imidazole ring with loss of the *N*-hydroxy group (69TL785).



(181) (182) (183)



(184) (185) (186)



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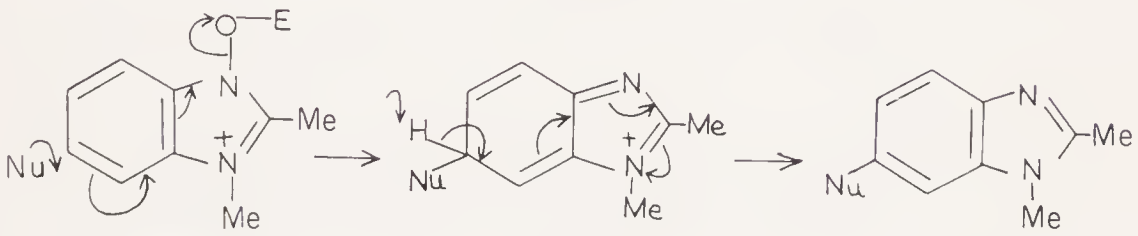


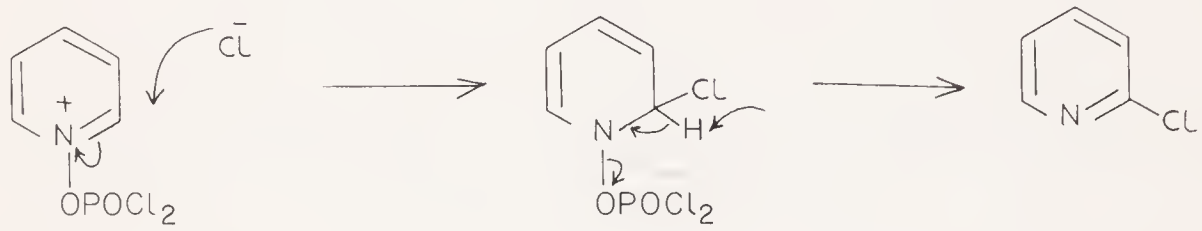
(188) (189) (190)

In the following sections, these reactions are classified according to the type of bond which is formed in the initial attack at the ring carbon atom by the nucleophile. Separate sections are devoted to reactions in which ring carbon atoms are bonded to halogen, oxygen, sulphur, nitrogen, and carbon atoms. However, nucleophilic attack on ring hydrogen atoms is considered in Section III-6Bi.

B. FORMATION OF A CARBON-HALOGEN BOND BY NUCLEOPHILIC ATTACK

α- and γ-Chloro heterocycles are formed from heterocyclic *N*-oxides by the action of phosphorus oxychloride, phosphorus pentachloride, or sulphuryl chloride (SO_2Cl_2); of these reagents, phosphorus oxychloride is

the most frequently used. Isolated examples of the use of tosyl chloride are known (51NK509) but this reagent also gives several other types of products (see Section III-4Ciiib). In typical reactions of this type the *N*-oxide and sulphuryl chloride are heated at 110° for 2 h; with phosphorus oxychloride, temperatures ranging from 40° to the boiling point of the mixture (reflux) and times of 0·5–5 h have been used, sometimes with chloroform as solvent. The mechanism of the reaction with phosphorus oxychloride and the other reagents is almost certainly of the type illustrated for the conversion of pyridine 1-oxide into 2-chloropyridine in scheme *191* → *193* (cf. 49NK393), although other suggestions have been made (41BS86).

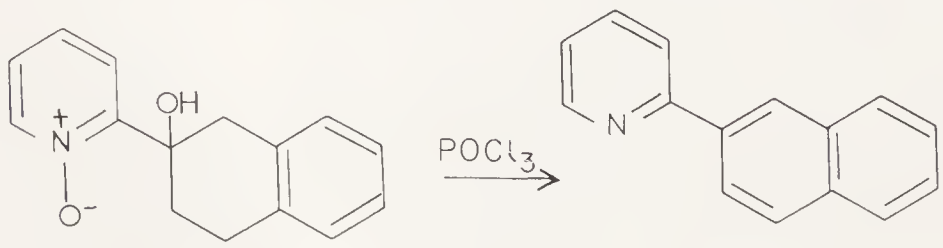


(191) (192) (193)

i. Pyridine and Quinoline 1-Oxides

Examples of the use of this reaction to prepare halogenopyridines from pyridine 1-oxides are collected in Table 3.29. The reaction product is usually a mixture of mono-halogenated compounds in which a chlorine atom is introduced into one of the available α- or γ-positions. Often the yields of the various isomers are comparable, but no sound generalization can be made as to the directive effects of substituents on the basis of the data presently available.

This reaction has been used extensively for the preparation of α- and γ-chloroquinolines; see Table 3.30. Bachman and Cooper (44JO302) found that 2- and 4-chloroquinolines are produced in comparable amounts; this ratio is affected by the substituents already present, but not by the reaction conditions. Very few examples are known in which the reaction fails; exceptionally, the tetralinylpyridine 1-oxide *194* yields not the expected 4- and 6-chloro derivatives, but undergoes internal oxidation-reduction to form 2-(2-naphthyl)pyridine (*195*) (62JO964).



(194) (195)

Table 3.29. Conversion of Pyridine 1-Oxides into Chloro-(or Bromo-)-pyridines with Loss of the *N*-Oxide Group

Substituents	Reagent	Position of halogen introduced (% yield)	References
—	PCl_5	4	49NK393
	SO_2Cl_2	2 and 4[a]	26CB1848,[a] 38CB2385, 40BS133, 49NK393[a]
4,5-Diacetoxy	$POCl_3$	6 (36)	63J4600
4-Alkoxycarbonyl	$POCl_3$	2	57CF369
5- and 4,5-Di-alkoxycarbonyl-2-alkyl	$POCl_3$, PCl_5	6 (data)[b]	61JJ182, 63J1841
4-Alkoxy-2-carboxamido	$POCl_3 + PCl_5$	2, 4 (33)[c]	56JA214
2-Alkyl	$POCl_3$	4	54CT137, 55JJ1239
3-Alkyl	$POCl_3$	2, 4, and 6	57CT78
	SO_2Cl_2	2	63AG169
2,6-Dialkyl	$POCl_3$	4 (75)	51JJ217, 54CT131, 55JJ1236
3-Alkyl-4-cyano	$POCl_3$	2 and 6 (data)	62JA3393
2,6-Dialkyl-3- and -4-nitro	$POCl_3$	4[d]	45JJ(3A)6
2-Aryl	$POCl_3$	4 (5–43) and 6 (29–35)	53CC457
2-Arylazo and -arylazoxy	$POCl_3$	6 (data)[e]	55G1508
3-Bromo	SO_2Cl_2	2, 4, and 6 (data)	51R578
3,5-Dibromo	SO_2Cl_2	2 and 4 (data)	57R261
3- and 4-Carboxamido	$POCl_3 + PCl_5$	2[c]	54JO1633, 61JJ1204
3-Carboxy	$POCl_3 + PCl_5$	2 (data)[f]	54JO1633, 59CB2266
2-Chloro	$POCl_3$	6 (91)	61JJ574
4-Chloro	SO_2Cl_2	2 (20–30)	55R59

[a] Only 4-chloropyridine reported to be formed.
[b] 2-Chloromethyl derivative also formed.
[c] Carboxamido → cyano.
[d] 4-Nitro → 4-chloro.
[e] Chlorination of phenyl group (*para* to azo group) also occurs.
[f] 3-Carboxy → 3-carboxylic acid chloride.

Table 3.29. Conversion of Pyridine 1-Oxides into Chloro-(or Bromo-)-pyridines with Loss of the *N*-Oxide Group—*continued*

Substituents	Reagent	Position of halogen introduced (% yield)	References
3,4-Dichloro	SO_2Cl_2	2 (50–60) and 6 (low)[g]	55R59
2,3,4,5-Tetrachloro	SO_2Cl_2	6 (92)	66CB698
3-Chloromethyl	$POCl_3$	2	62H1860
4-Chloro-3-nitro	$POCl_3$	2 (55) and 6	64CT866
3-Chloro- and -cyano-methyl	$POCl_3$	2 (37) and 6 (14)[h]	59JA740, 62H1860[h]
4-Hydroxy	$POBr_3$	3, 4, 5[i]	52R745
3-Nitro	$POCl_3$	2 (30) and 6 (8)[h]	60CT28[h], 60JO1716
4-Nitro	aq. HBr	3, 5[j]	51R581
	$POCl_3$	4 and 2, 4[d]	45JJ70
	SO_2Cl_2	2, 4[d]	50R468
3,5-Dinitro	$POCl_3 + PCl_5$	2 (data)	60CT28

[g] A small amount of 3,4-dichloro-2-hydroxypyridine also formed.
[h] Only 2-chloro compound reported to be formed.
[i] 4-Hydroxy → 4-bromo.
[j] 4-Nitro → 4-hydroxy.

Table 3.30. Conversion of Quinoline 1-Oxides into Halogenoquinolines with Loss of the *N*-Oxide Group

Substituents	Reagents	Position of halogens introduced	References
—	$POCl_3$	2 and 4	46JA1229
—	SO_2Cl_2	2 and 4[a]	26CB1848,[a] 36CB1113, 38CB578, 44JO302
4-Acyl	$POCl_3$	2	68AI1
6-Alkoxy	SO_2Cl_2	2 and 4	44JO302
6-Alkoxy-2-aryl	$POCl_3$	4	44JA621
6-Alkoxy-4-(1-hydroxymethyl)	$POCl_3$	2	58CT273
4-Alkoxy-7-nitro	$POCl_3$	2	47JJ144
4-Alkylcarbonyl-6-methoxy[i]	$POCl_3$	2	62AI11, 62AI29
2-Alkyl	SO_2Cl_2	4	41BS86
2-Alkyl-4-nitro	$POCl_3$	4, 7	60EGP20182
4-Amino	$POCl_3$	2	57CT310
2-Aryl	$POCl_3$	4	51BS82, 54RS2351
Benzo[*f*]	SO_2Cl_2	2 and 4	44JO302
4-Carboxy	$POCl_3$, $SOCl_2$, SO_2Cl_2	2[b]	48JJ123, 51BS82
6-Chloro	$POCl_3$	2 and 4	44JO302
2-Hydroxy	$POCl_3$	2, 4[c]	59CT273
4-(1-Hydroxyalkyl)	$POCl_3$	2	58CT208,[d] 59CT744
4-(1-Hydroxyalkyl)-6-methoxy[e]	$POCl_3$	2[e]	51JJ260, 54JJ1315
4-Hydroxyamino	$POCl_3$	2[f]	57CT310

[a] Only the 4-chloro derivative reported to be formed.
[b] 4-Carboxy → 4-carboxylic acid chloride.
[c] Hydroxy → chloro.
[d] Dihydrocinchonine *ar*-*N*-oxide.
[e] Quinine and dihydroquinine *ar*-*N*-oxide.
[f] 4-Hydroxyamino → 4-amino.

Table 3.30. Conversion of Quinoline 1-Oxides into Halogenoquinolines with Loss of the *N*-Oxide Group—*continued*

Substituents	Reagents	Position of halogens introduced	References
4-Hydroxy-3-nitro	$POCl_3$	2[c]	52JJ767
11*H*-Indeno[1,2-*b*]	$POCl_3$	4	61JO3812
4-Nitro	$POCl_3$	2, 4[g]	43JJ280
	$POBr_3$	2 and 2, 4[g]	56JJ1337
5- and 8-Nitro	SO_2Cl_2	2	43JJ280
5- and 6-Nitro	$POCl_3$, SO_2Cl_2	2, 3, and 4[h]	44JO302, 47JA303, 66JJ1090
4,6-Di-and 4,6,8-tri-nitro	$POCl_3$	2[e]	44PJ599
2-(1-Oxido-2-quinolyl)	$POCl_3$	4, 4′	66JH170
2-Phenyl	$POCl_3$	4	66JJ59
4-Styryl	$POCl_3$	2	63JJ342

[g] 4-Nitro → 4-chloro.
[h] Yields reported: 2-Cl, 30%; 3-Cl, 20%; 4-Cl, 10% (47JA303).
[i] Dihydroquininone *ar*-*N*-oxide.

Certain substituents are affected by the reaction conditions. Nitro groups in the 4-position of pyridine and quinoline 1-oxides are replaced by chloro groups during the course of the reaction with phosphorus oxychloride (43JJ280; 45JJ70; see also footnotes to Table 3.30); however, mild treatment with phosphorus oxybromide successfully converts 4-nitroquinoline 1-oxide into 2-bromo-4-nitroquinoline (56JJ1337). 2-Hydroxyquinoline 1-oxide (1-hydroxy-2-quinolone) is converted into 2,4-dichloroquinoline by phosphorus oxychloride (59CT273), and α- and γ-hydroxyl groups in the pyridine (55R59) and isoquinoline *N*-oxides (58JA3443) are also simultaneously replaced by chlorine. However, in other cases where hydroxyl groups are replaced, the *N*-oxide function can simply be lost *without* the addition of another hydrogen atom to the ring (see Section IV-3Bic). 4-Methoxypyridine 1-oxides are also generally converted into 4-chloro compounds (56JA214), however an exception is known in the quinoline series (47JJ144). Amide groups are dehydrated to cyano groups (54JO1633; 56JA214) and a 4-hydroxyamino group is converted into an amino group (57CT310). Side-chain hydroxyl groups can be protected by acetylation (63J4600).

Chlorine substitution in the ring sometimes occurs at other than the α- or γ-positions. 2,4-Dibromoquinoline 1-oxide is converted by phosphorus oxychloride into 2,4-dibromo 6-chloroquinoline (57CM388). 6-Nitroquinoline 1-oxide is reported to give 3-chloro-6-nitroquinoline (20% yield) together with the 2- and 4-chloro analogues (44JO302), and quinoline 1-oxide itself was reported to yield a tetrachloroquinoline, the structure of which was not determined (38CB578). Another side reaction is the formation of traces of chloromethyl compounds from methylpyridine 1-oxides: this has been reported for the 2-methyl- (55JJ1239), 2,6-dimethyl- (55JJ1236), and 2-methyl-4,5-dimethoxycarbonyl derivatives (61JJ182). The mechanism of the formation of these chloromethyl by-products is discussed in Section IV-2Biia.

ii. Other Condensed Pyridine and Pyridazine N-*Oxides*

Examples of the conversion of these heterocyclic *N*-oxides into the corresponding chloro-heterocycles are given in Table 3.31. Isoquinoline 2-oxides give 1-chloroisoquinolines in good yield. Phenanthridine 5-oxides with a free 6-position yield 6-chlorophenanthridines; however, 6-phenylphenanthridine 5-oxide gives a 2-chloro derivative (*196*, R = Ph), and the 6-methyl analogue forms a mixture of 2-chloro-6-methyl- (*196*, R = Me) and 6-chloromethyl-phenanthridine (50J703). The reaction proceeds normally with pyridazine, cinnoline, phenanthroline, naphthyridine, and imidazo[4,5-*c*]pyridine *N*-oxides (Table 3.31), but in the purine series a failure has been reported (64JO2611).

Table 3.31. Conversion of Other *N*-Oxides into Chloro-heterocycles with Loss of the *N*-Oxide Group[a]

Ring system	Substituents	Reagent	Position of chlorine atoms introduced (Yield, %)	References
Isoquinoline 2-oxide	—	$POCl_3$	1 (ca. 60)	26CB1848, 47JA1939, 54CT109, 54CT111, 57JO514
	4-bromo	$POCl_3$	1 (data)	54CT72
	1-hydroxy	$POCl_3$	1, 4 (43)[b]	58JA3443
	5-nitro	$POCl_3$	1	61WZ1
Acridine 10-oxide	—	$POCl_3$	5	50MI144
Phenanthridine 5-oxide	—	$POCl_3$	9	50J703
	6-methyl and -phenyl[c]	$POCl_3$	3	50J703
1,7-Phenanthroline 7-oxide	—	SO_2Cl_2	8	45J375
1,5-Naphthyridine 1-oxide	—	$POCl_3$	2	54J1879
1,5-Napthyridine 1,5-dioxide	—	$POCl_3$	2, 6	54J1879
	—	PCl_5	2, 4	67JO241
1,6-Naphthyridine 1,6-dioxide	—	$POCl_3$	2, 5 and 2, 8	69CT1045
1*H*-Imidazo[4,5-*c*]pyridine 5-oxide	—	$POCl_3$	2 (43)	64CT866
	3-glycosyl	$POCl_3$	2 (59)	64JO2611
Pyridazine 1-oxide	3-alkoxy-6-methylcarbamoyl	$POCl_3$	4 (data)	63CT1157
	3-alkoxy	$POCl_3$	6 (data)	59CT938
	3,6-dialkoxy	$POCl_3$	4 (72)	60CT368
	3,6-dimethyl	$POCl_3$	4 (28)	63CT337, 62JJ1208
Cinnoline 1-oxide	—	$POCl_3$	4 (data)	63CT268, 64CT1090

[a] Pyridine 1-oxides (Table 3.29) and quinoline 1-oxides (Table 3.30) are listed in separate tables.
[b] 1-Hydroxy → 1-chloro.
[c] 6-Chloromethylphenanthridine also formed.

Table 3.31. Conversion of Other *N*-Oxides into Chloro-heterocycles with Loss of the *N*-Oxide Group[a]—*continued*

Ring system	Substituents	Reagent	Position of chlorine atoms introduced (Yield, %)	References
	3-alkoxy-5,6,7,8-tetrahydro	$POCl_3$	4 (data)	63CT1527
	3-phenyl	$POCl_3$	4 (data)	66MC670
Cinnoline 2-oxide	3-phenyl	$POCl_3$	4 (data)	66MC670
Phthalazine 3-oxide	1-phenyl	$POCl_3$, SO_2Cl_2	4	66JJ576
Quinazoline 1-oxide	4-alkoxy	$POCl_3$, SO_2Cl_2	2 (55–63)	59JJ699, 64CT43
	4-isopropyl	$POCl_3$, SO_2Cl_2	2 (63)	64CT43
Pyrazine 1-oxide	—	$POCl_3$	2 and 6	61AA(140)28-Q, 63JO1682, 67JJ942
	3-alkoxy-6-alkyl	$POCl_3$	4 (data)	63CT29
	3-amino	$POCl_3$	2	63G339
	2- and 3-carboxamido	$POCl_3$	5[d]	61G1431, 61JJ1475, 63G339
	3-chloro	$POCl_3$	5	61G1431
	3-chloro-2,5-dimethyl	$POCl_3$	6	48J1859
	3,5-dichloro	$POCl_3$	2	66F805
	2,5-dimethyl	$POCl_3$	6	47J1183, 61AA(140)28-Q
	2,5-dimethyl-3-dimethylamino	$POCl_3$	6 (37)	64JO1645
	2-phenyl-3-methoxy	$POCl_3$	6 (88)	56JA4071
	2,3-diphenyl	$POCl_3$	6	56J1885
Pyrazine 1,4-dioxide	—	$POCl_3$	2 and 2, 6	61AA(140)28-Q, 61G1431, 63JO1682
	—	$PhSO_2Cl$	2	67KG183
	2-methyl	$POCl_3$	3 and 3, 5[e]	61AA(140)28-Q
	2,5-dimethyl	$POCl_3$	3, 6	47J1183

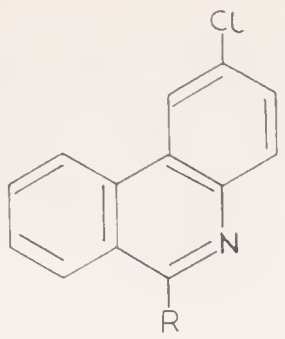
[d] 2-(or 3)-$CONH_2$ → 2-(or 3)-CN.

[e] 2-Methylpyrazine 1,4-dioxide has also been reported to give a mixture of a dichloromethylpyrazine and a chloromethylpyrazine 1-oxide (63JO1682).

Table 3.31. Conversion of Other *N*-Oxides into Chloro-heterocycles with Loss of the *N*-Oxide Group[a]—*continued*

Ring system	Substituents	Reagent	Position of chlorine atoms introduced (Yield, %)	References
Quinoxaline 1-oxide	—	$POCl_3$	2	53J2816
	—	$PhSO_2Cl$	2	67KG724
	3-ethoxycarbonyl	$POCl_3$	2	55ZO161
	3-ethoxy-2-methyl	HCl	6	49J2579
	2,3-dimethyl	AcCl	3[f]	66JO2613
	3-phenyl	AcCl; SO_2Cl_2	3[g], 2	62JJ1093, 66JO2613
Quinoxaline 1,4-dioxide	—	$POCl_3$	2, 3	53J2816, 62ZO2967
	—	$PhSO_2Cl$	2	67KG724
Phenazine 5-oxide	—	$POCl_3$	2	54ZO485
Phenazine 5,10-dioxide	—	$POCl_3$	2, 6	54ZO485
5,6-Benzoquinoxaline 1-oxide	—	$POCl_3$	2[h]	53J2816
Benzimidazole 3-oxide	1-methyl	$POCl_3$, SO_2Cl_2, TsOCl	2 (90, data)	64CT783

[f] 3-Chloromethyl derivative formed.
[g] 3-Chloro-2-phenyl derivative formed.
[h] Another isomer is also formed.



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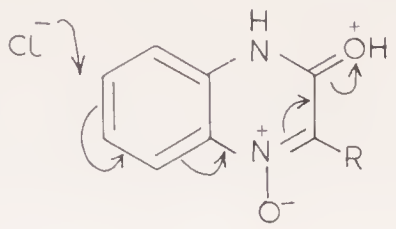


(197)

iii. Pyrazine, Quinoxaline, and Phenazine N-*Oxides*

Chloro derivatives of these heterocyclic systems have been prepared by nucleophilic attack on the corresponding *N*-oxide and are listed in Table 3.31.

Although many pyrazine 1-oxides yield 2- and 6-chloropyrazines with phosphorus oxychloride, 3- or 5-chloro derivatives are sometimes produced (Table 3.31). The orientation appears to depend on the substituent type (63G339): a 3-amino group favours chlorination at the 2-position, whereas a 3-carboxamido group leads to reaction at the 5-position (5-chloro-3-cyanopyrazine is formed). Moreover, pyrazine 1,4-dioxide gives 2,6-dichloropyrazine (61G1431; 63JO1682). The reason that chlorination occurs *beta* to the *N*-oxide group, and the mechanism of the reaction, remains obscure. Methylpyrazine 1-oxides also yield products arising from side-chain chlorination (63JO1682); cf. Section IV-2Biia.

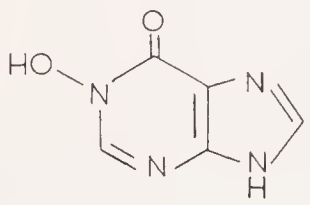
Quinoxaline 1-oxide gives a mixture of 2- and 6-chloroquinoxaline on treatment with phosphorus oxychloride, sulphuryl chloride, or acetyl chloride (67JJ942). With phosphorus oxychloride 2,3-disubstituted quinoxaline 1-oxides form 6-chloro derivatives, but the yields are poor [66J(C)157]. Certain 3-quinoxalinone 1-oxides give 6-chloro-3-quinoxalinones with aqueous hydrochloric acid or acetyl chloride (49J2579; 65BJ1654; 65BJ1659), and it has been suggested that these reactions are initiated by nucleophilic attack, as shown in structure *197*. A more recent paper by Habib and his co-workers (66JO2613) reports that the oxygen function at C-3 controls the nucleophilic attack by chlorine at C-6. In the absence of the oxygen function, treatment of the quinoxaline *N*-oxide with hydrochloric acid or acetyl chloride has no effect unless there is hydrogen or a methyl group in the 2- or 3-position.

Phenazine 5,10-dioxide reacts with phosphorus oxychloride to give 2,6-dichlorophenazine (54ZO485).

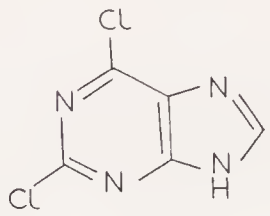
iv. Other Heteroaromatic N-*Oxides*

The purine derivative *198* is converted into 2,6-dichloropurine (*199*) by phosphorus oxychloride (67BJ639). 1,2-Dimethylbenzimidazole 3-oxide on treatment with phosphorus oxychloride gives the 6-chloro compound *200* (66CT1219); this reaction probably involves a mechanism of the type

shown in structure *201*. The 2-cyano analogue reacts similarly (68CT527). The conversion of the 3-ethoxycarbonylindazole 1-oxide *202* into the chloroindazole *203* by heating under reflux with hydrochloric acid (35BF1016) presumably involves nucleophilic attack by chloride ions and decarboxylation following preliminary ester hydrolysis.



(198)



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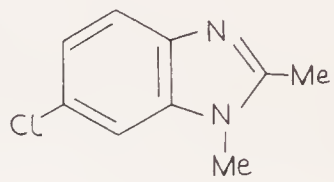

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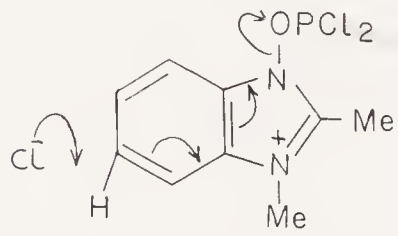

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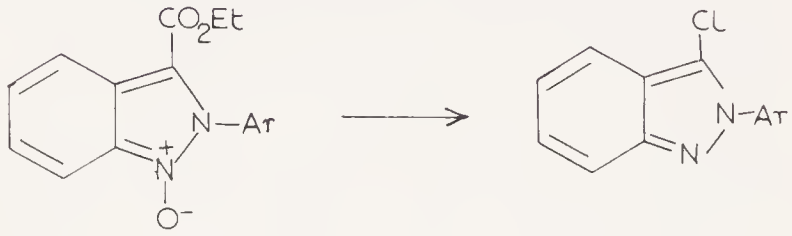
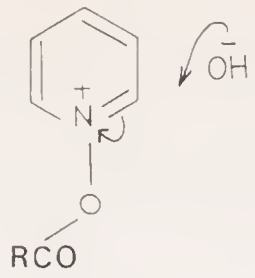


(202) (203)

C. FORMATION OF A CARBON-OXYGEN BOND BY NUCLEOPHILIC ATTACK

Heteroaromatic *N*-oxides in which the ring contains at least two hetero atoms are often susceptible to nucleophilic attack by hydroxide (or alkoxide) ions under basic conditions, or by water (or alcohols) under acid catalysis. These reactions may proceed further either with or without ring cleavage; each of these reaction paths is considered separately.

Hydroxide ions readily attack pyridine and benzopyridine 1-oxides in the presence of acid chlorides, and the first step of the reaction is of the general type shown in structure *204*. The reactions between *N*-oxides and acid anhydrides, in which carboxylate ions attack the *O*-acylated species (*205*), are related. Two further reaction types yield β-acyloxy and β-sulphonyloxy derivatives: both are considered to involve rearrangements of the acyloxy or sulphonyloxy radical from the heterocyclic nitrogen atom to the β-carbon.



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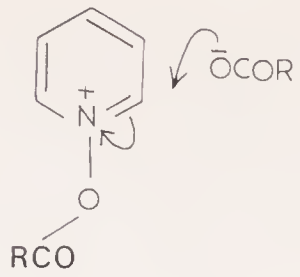

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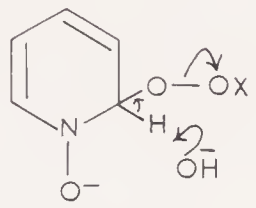
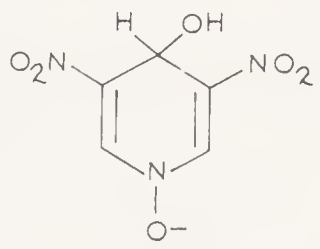


(206)

All the reactions mentioned so far result in loss of the *N*-oxide group. However, if the nucleophile is an oxidizing agent, a reaction of the type illustrated in structure *206* can occur, in which case the *N*-oxide function is retained. Reactions of this type are discussed in Section III-4Civ.

i. Water or Hydroxide Ions

a. Without Ring Cleavage. The *N*-oxides of pyridines and benzopyridines are not usually attacked by water or hydroxide ions. Sufficiently strong activation by substituents, however, can increase their susceptibility, and 3,5-dinitropyridine 1-oxide (60CT28) probably forms Meisenheimer-type complexes (*207*) in alkali. Quaternary *N*-oxide derivatives usually undergo reactions of a different type with alkali, see Section IV-4Ai, but certain quaternary acridine *N*-oxide derivatives do form stable pseudo-bases, e.g. *208* gives *209* (39CB1071).



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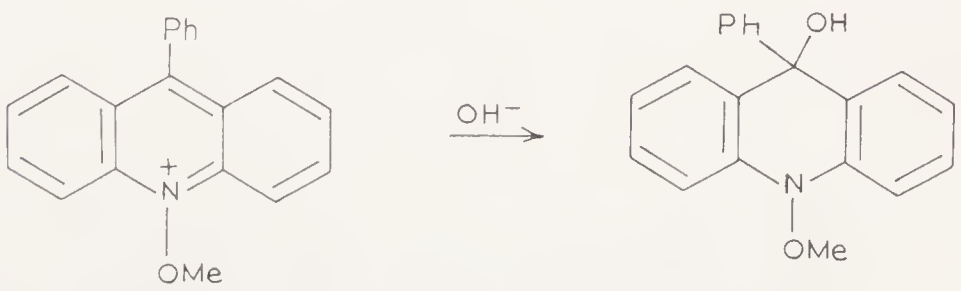

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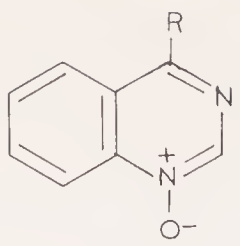

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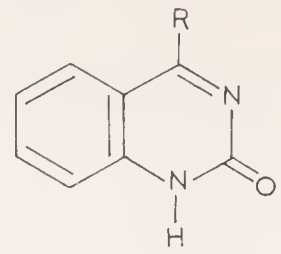

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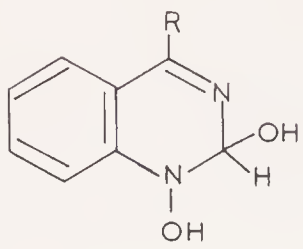

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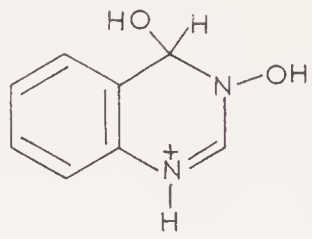

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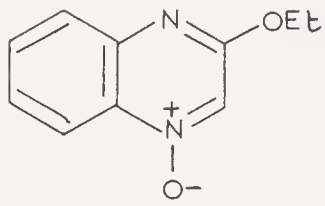

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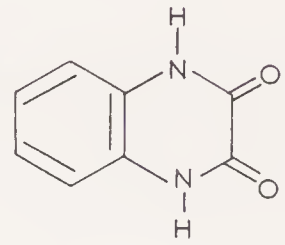

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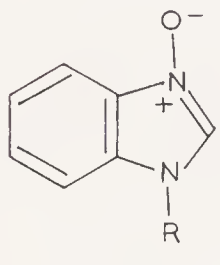

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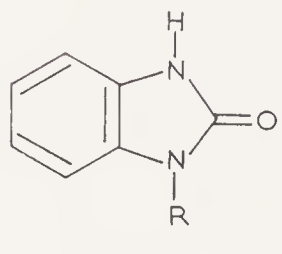

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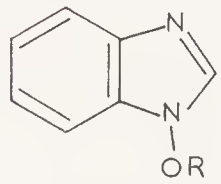

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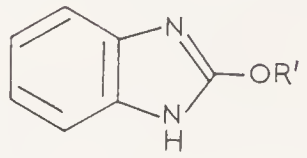

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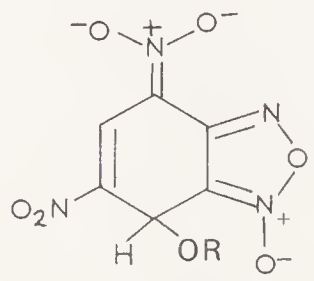


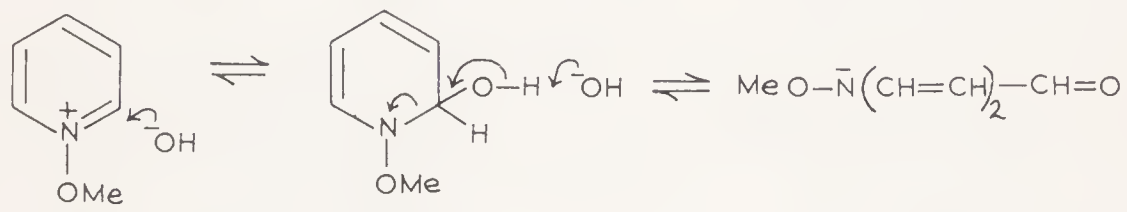
(220)

Benzazine *N*-oxides are much more frequently attacked by aqueous alkali; thus, 4-phenylphthalazine 2-oxide yields 4-phenyl-3-phthalazinone (66JJ576), and quinazoline 1-oxides are converted into 2-quinazolinones

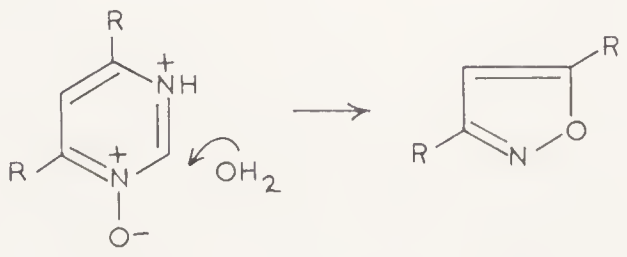
(*210* → *211*) (64CT43). These reactions probably occur via covalently hydrated intermediates of type *212* (64MI111). Several quinazoline 3-oxides which are not substituted in the 4-position have been reported to form stable covalently hydrated cations of structure type *213* in weakly acidic solution: this behaviour is similar to that of the parent quinazolines (62J5030). 3-Ethoxyquinoxaline 1-oxide (*214*) is converted by aqueous hydrochloric acid into 2,3-quinoxalinedione (*215*) (48J519), and analogous reactions have been described for other quinoxaline *N*-oxides (61J1246; 64J2666). On treatment of quinoxaline 1-oxide with sodium methoxide some 2-methoxyquinoxaline is formed (67JJ942).

Benzimidazole *N*-oxides are converted into benzimidazolones under rather mild conditions: for example, *216* (R = H, Me) yields *217* (R = H) (10CB3012) and *217* (R = Me) (64CT783) on refluxing in acetone or chloroform.* 1-Alkoxybenzimidazoles (*218*) yield 2-alkoxy derivatives (*219*) simply on boiling in alcohol (64CT282) or on standing with sodium alkoxides in the cold (63CT375); on treatment with sodium hydroxide they yield benzimidazolone (66CT375). 4,6-Dinitrobenzofuroxan forms Meisenheimer-type complexes *220* (R = H) (65JO2407; 65JO2452) and *220* (R = Me) with sodium methoxide (65J5414). Some of these complexes have recently been obtained as crystalline solids and their structures proved by NMR spectroscopy (68MC305).

b. With Ring Cleavage. Ring opening is generally considered to occur readily only with *N*-oxides in which the ring contains two or more hetero atoms in a *beta* relationship. However, Eisenthal and Katritzky (65T2205) found that the familiar reaction of 1-methoxypyridinium salts with alkali to give an aldehyde and pyridine (cf. Section IV-4Ai) is preceded by a rapid, reversible opening of the ring (*221* ⇌ *222* ⇌ *223*); 1-*t*-butoxypyridinium cations react similarly (69Tip1). Many more examples of ring-opening reactions with relatively simple compounds are likely to be discovered.

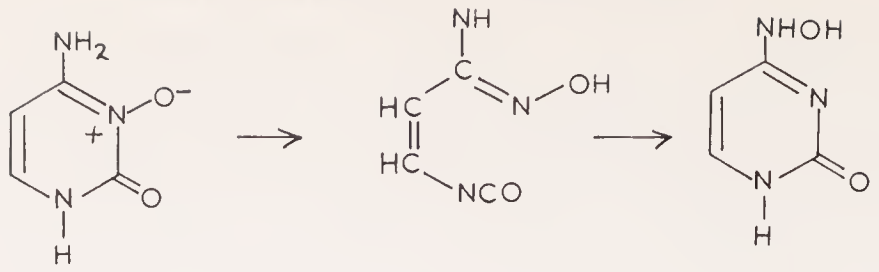


(221) (222) (223)



(224) (225)

* See addendum in the Appendix.



(226) (227) (228)

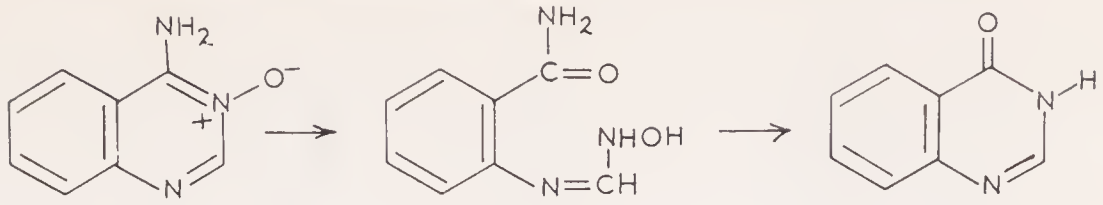
(229)

Numerous examples of ring fission are known in the chemistry of pyrimidine and condensed pyrimidine *N*-oxides. Simple pyrimidine 1-oxides are converted into isoxazoles by acid hydrolysis; attack by a water molecule on the cation results in ring opening and reclosure as shown: *224* → *225* (67JO3593). Cytosine 3-oxide (*226*) undergoes ring opening on acid treatment, probably to form an isocyanate intermediate (*227*); the ring then recloses to yield the hydroxyamino derivative *228* (65JO2766). On reaction with acetic anhydride, 5-fluorocytosine 3-oxide also yields a rearranged product (*229*) (68M847).

Quinazoline 3-oxide (61CT635) and its 4-phenyl derivative (61JO4936) are hydrolysed by alkali yielding oximes: *230* → *231*. Similar ring cleavage occurs readily with 1-alkyl-3-oxidoquinazolinium iodides (*232* → *233*), where the 4-substituent can be hydrogen (57JJ507), a methyl group (57JJ514), or an amino group (57JJ510). An interesting example is the conversion of 4-aminoquinazoline 3-oxide (*234*) into 4-quinazolinone (*236*) by hydrochloric acid (57JJ510); this reaction probably involves the ring-opened intermediate *235*.

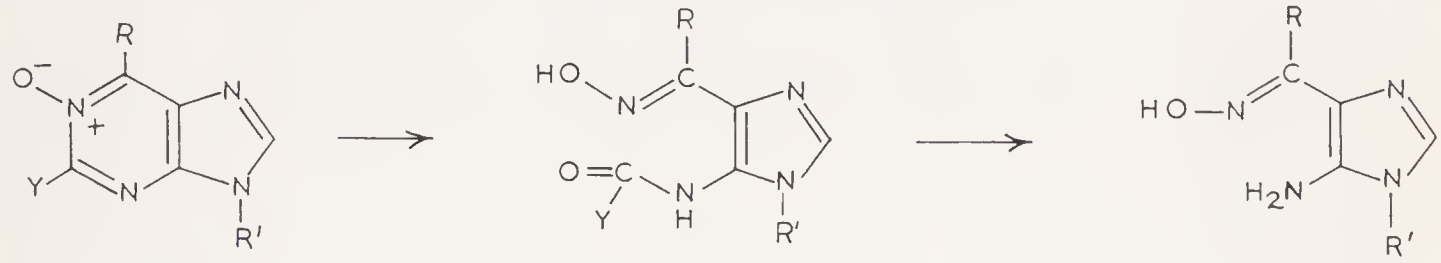
(230) (231)

(232) (233)

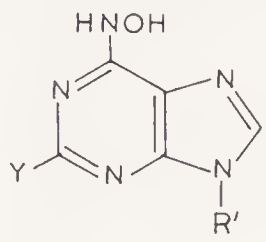


(234) (235) (236)

The facile hydrolytic ring-opening reactions of purine 1-oxides (*237* → *239*), which have been studied by Brown and others, are summarized in Table 3.32. Where R = NH_2, the intermediate *238* sometimes recloses to give a hydroxyaminopurine (*240*) (67JO1151). In another example of the Dimroth-type rearrangement in the purine series, i.e. *241* → *243*, it was found possible to isolate intermediate *242* (66CI1967). The ring opening of the thiazolopyrimidine *244* to give the oxadiazolylthiazole *245* (65MC190) is of a similar type. The transformation *246* → *247* (57MI138) involves opening of the five-membered ring in a purine 7-oxide.



(237) (238) (239)



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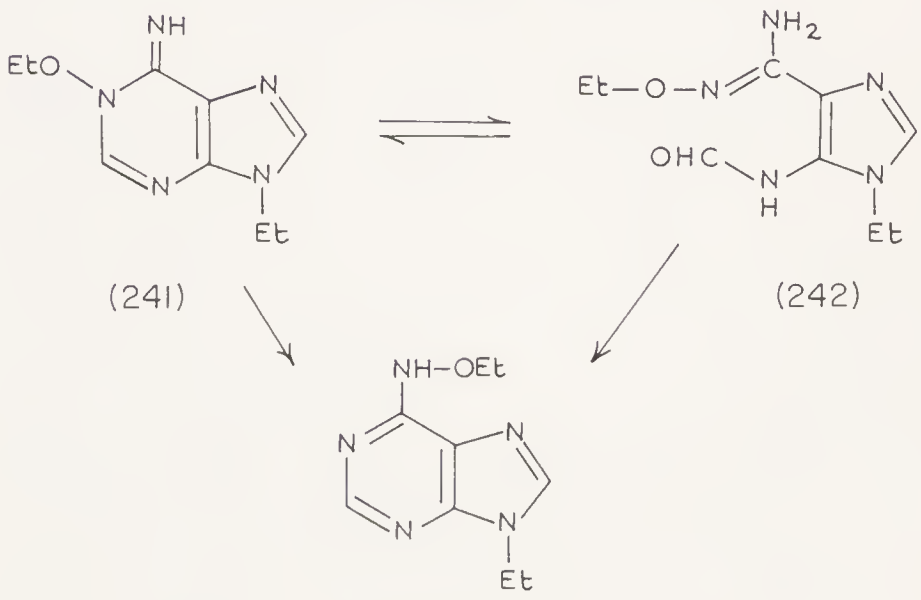
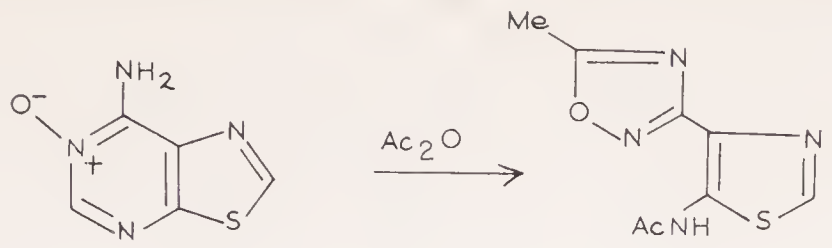


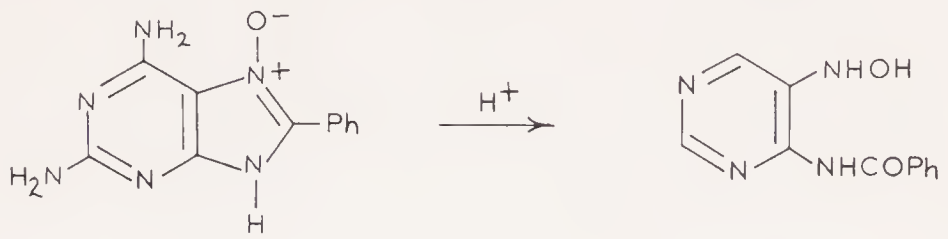
(241) (242) (243)

Table 3.32. Hydrolytic Ring-opening Reactions of Purine *N*-Oxides and Related Compounds (237 → 239)

Ring system	Substituents	Reagent	Hydrolysis product	References
Purine 1-oxide	6-amino	HCl	4-aminoimidazole-5-carboxamidoxime	58JA2759, 59JA1734, 60JA3189, 60MI111
	6-amino-2-oxo	HCl	4-aminoimidazole-5-carboxamidoxime + 6-hydroxyamino-2-oxopurine	67JO1151
	6-amino-2-oxo	Ac_2O	3-[5′-(4′-acetamido)imidazolyl]-5-methyl-1,2,4-oxadiazole	67JO1151
	6-amino-9-ribosyl	HCl	4-aminoimidazole-5-carboxamidoxime	58JA2759, 59JA1734
	6-amino-9-ribosyl or -9-phosphoribosyl	NaOH	5-amino-1-ribosyl- or -9-phosphoribosyl-imidazole-4-carboxamidoxime	59JA1734
	6-methyl	HCl	4-acetyl-5-aminoimidazole	60JA3189, 62JO567
Purine 7-oxide	2,6-diamino-8-phenyl	dil. AcOH	2,4,6-triamino-5-hydroxyamino-pyrimidine	57MI138
8-Azapurine 1-oxide	6-amino	HCl	4-amino-1,2,3-triazole-5-carboxamidoxime	60JA3189
Thiazolo[5,4-*d*]pyrimidine 6-oxide	7-amino	Ac_2O	3-[5-(4-acetamido)thiazolyl]-5-methyl-1,2,4-oxadiazole	65MC190



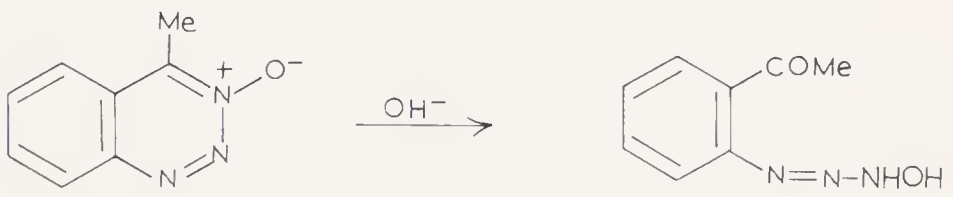
(244) (245)



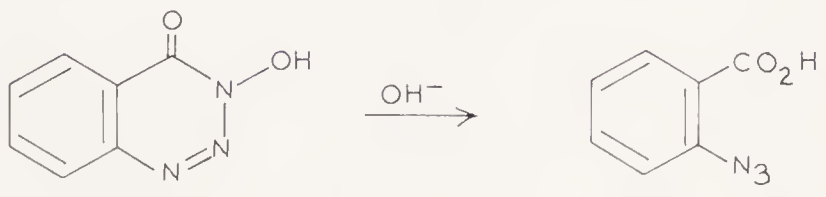
(246) (247)

For ring-opening reactions with pteridine *N*-oxides, see reference 65AG(E)1075.

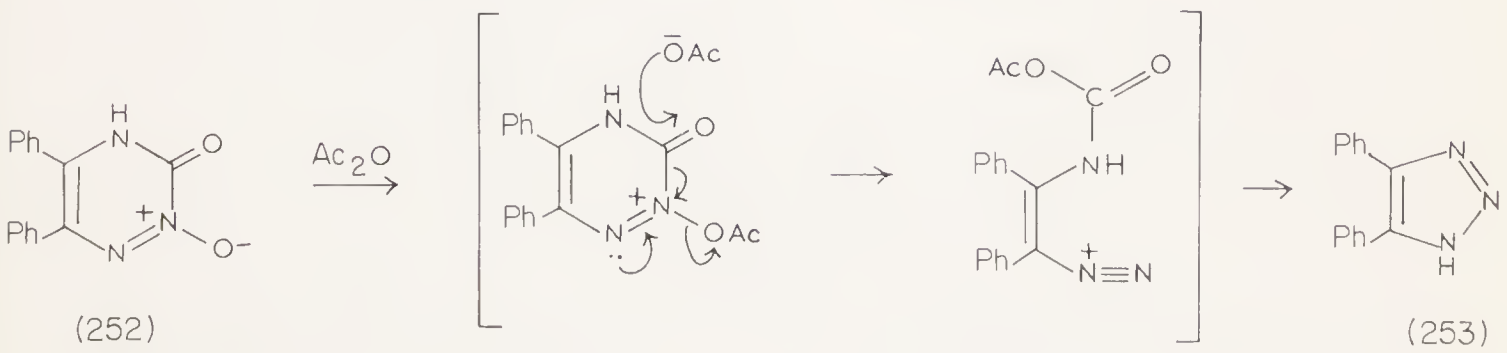
Triazine *N*-oxides are prone to ring fission. 4-Substituted benzo-1,2,3-triazine 3-oxides (*248*) are converted by alkali into 1-acyl-2-hydroxyamino-azobenzene (*249*) (27CB1736), whereas 3-hydroxybenzo-1,2,3-triazin-4-one (*250*) yields *o*-azidobenzoic acid (*251*) [25PC(111)36; 60J2157]. 1,2,4-Triazine *N*-oxides are converted into triazoles by ring contraction, as has been reported for 1,2,4-triazin-3-one 2-oxides (*252* → *253*) (66JO3914), 3-amino-1,2,4-triazine 2-oxides (*254* → *255*) [however, this compound gives an open-chain derivative (*256*) with acetic anhydride] (66JO3917), and benzo-1,2,4-triazine 1-oxides (*257* → *260*) (60G1113; 62JO185; cf. 62JO2504). The mechanisms indicated are speculative.



(248) (249)



(250) (251)



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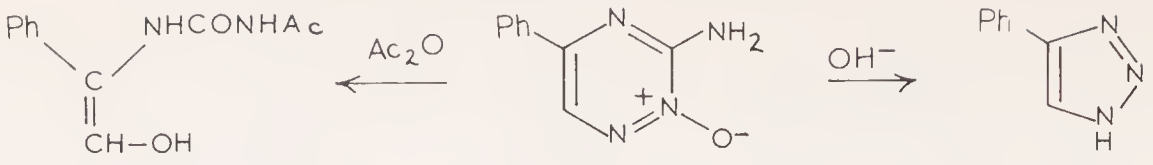
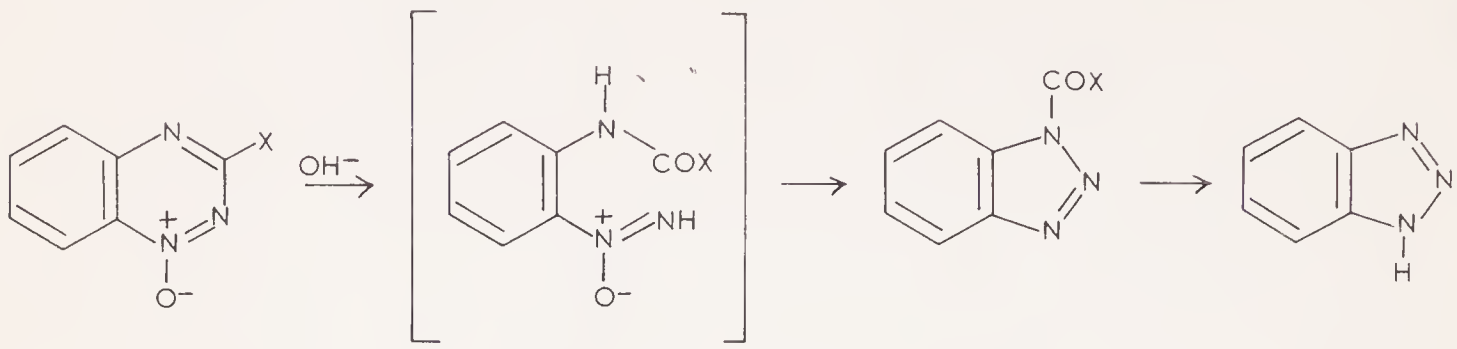


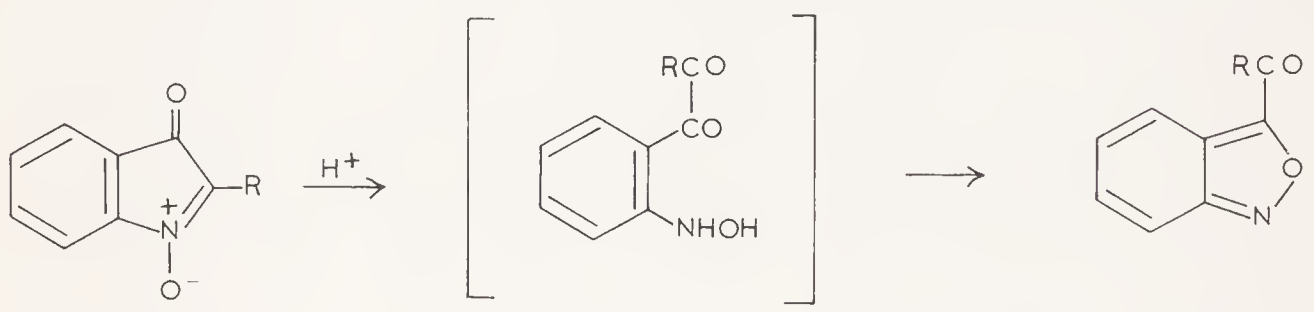
(256) (254) (255)



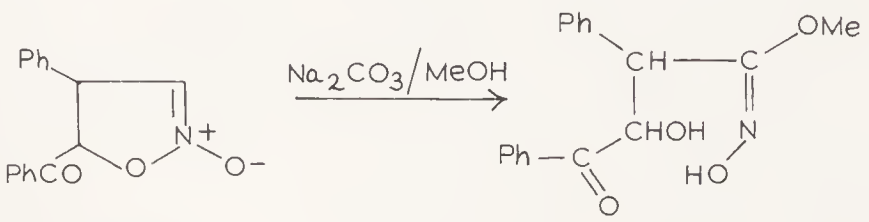
(257) (258) (259) (260)

A variety of *N*-oxides with five-membered rings also undergo hydrolytic ring fission. Isatogens (*261*) are transformed into anthranils (*263*) via open-chain intermediates (*262*) (60P70; 65JO1104) [earlier formulations of the products are incorrect (19CB1; 39H140)]. Isoxazoline 2-oxides are cleaved to give oximes (*264* → *265*) (28JA221; cf. 24JA503), whereas thiazole 3-oxides (e.g. *266*) break down completely on treatment with alkali (47JJ34). In the presence of alkali 1,2,3-oxadiazole 3-oxides undergo ring fission to give α-hydroxy-carbonyl compounds (*267* → *268*) (59J257), and 1,2,4-oxadiazole 4-oxides are also cleaved: *269* → *270* (07CB1667).*

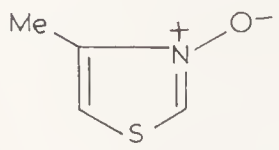
The hydrolytic opening of seven-membered *N*-oxide rings is illustrated by the sequence *271* → *272* (61JO4936; 62JO562; cf. 65JO1311).



(261) (262) (263)

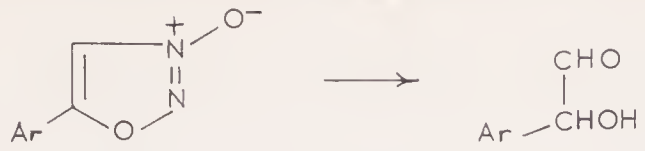


(264) (265)



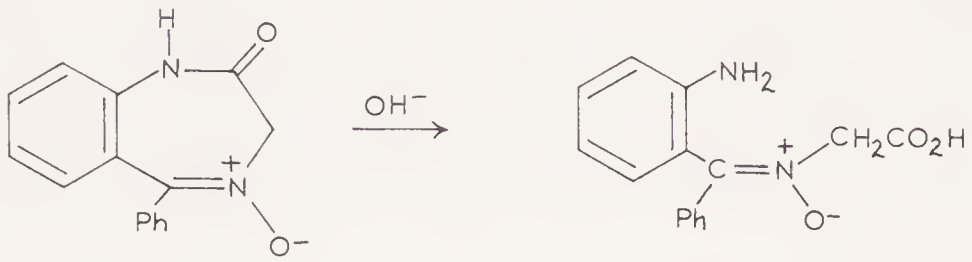
(266)

* See addendum in the Appendix.



(267) (268)

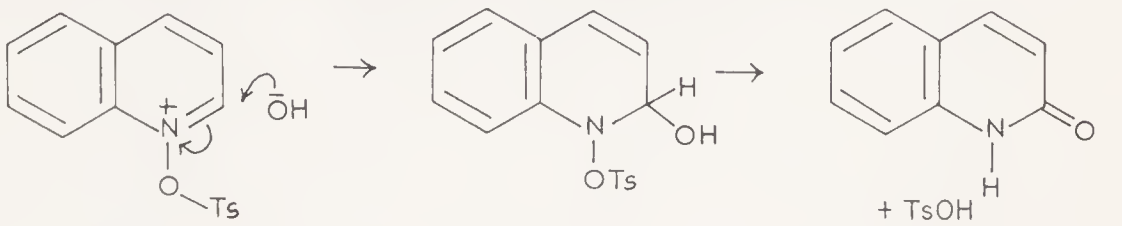
(269) (270)



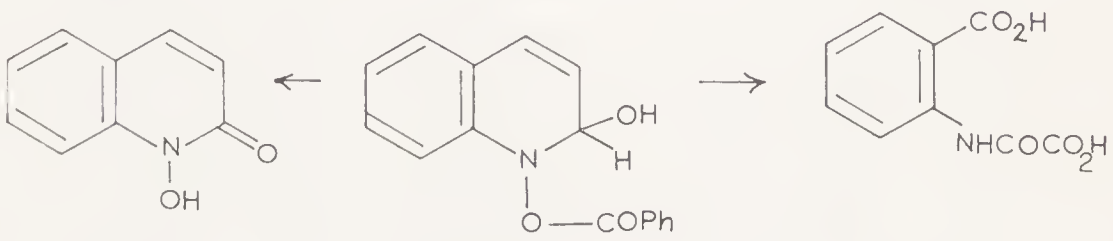
(271) (272)

c. In the Presence of an Acid Chloride. Nearly all of these reactions involve the use of either tosyl chloride or benzoyl chloride, and examples of each type are considered separately.

Perhaps the best known reaction involving nucleophilic attack by hydroxide ions on *N*-oxide rings is the treatment of an *N*-oxide with tosyl chloride in an aqueous alkaline medium. The hydroxide ion adds to the initial adduct to give an α-oxo compound (*273* → *275*). The intermediate from 5-methylquinoline 1-oxide corresponding to *274* has been isolated (61JJ1601). Reported examples of this reaction are given in Table 3.33. The main limitation of this reaction is its failure in the pyridine 1-oxide series. Examples are known in the quinazoline (64CT43) and quinoxaline series (62JJ1093) where some α-chloro compound is produced as a by-product. In non-aqueous media, complex reactions occur between tosyl chloride and *N*-oxides; see Sections III-4B and III-4Ciiib.*



(273) (274) (275)



(278) (276) (277)

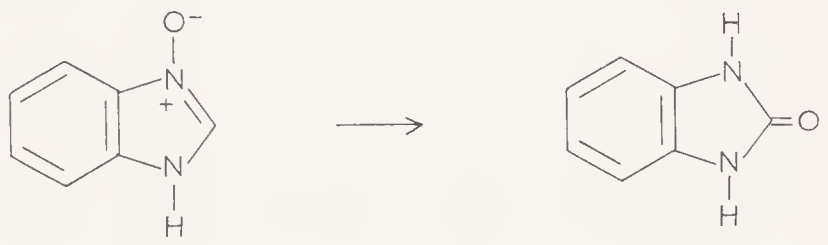
* See addendum in the Appendix.

Table 3.33. Conversion of *N*-Oxides into α-Oxo-heterocycles by Hydroxide Ions in the Presence of Tosyl Chloride (cf. 273 → 275)

Ring system	Substituents	Position of oxo group	Yield, %	References
Quinoline 1-oxide	—	2	ca. 80	55JJ213, 60JJ1027
	4-(4-dimethylaminostyryl)	3	—	63JJ342
	6-methoxy	2	—	66JJ1090
	4-methyl	2	90	58JJ611
	5-methyl	2	60	61JJ1601
Isoquinoline 2-oxide	1-oxo	3	see note [a]	58JA3443
Phenanthridine 5-oxide	—	6	88	60JJ834
Pyrimidine *N*-oxide	4-methoxy-6-methyl	2	—	55CT175
Quinazoline 1-oxide	4-isopropyl	2	23[b]	64CT43
	4-alkoxy	2	33	59JJ699
Quinoxaline 1-oxide	—	2	—	62JJ1093
Benzimidazole 1-oxide	—	2	—	10CB3012

[a] In addition to 1,3-dioxo-1,2,3,4-tetrahydroisoquinoline, 4-hydroxyisocarbostyril is formed.
[b] 2-Chloro-4-isopropylquinazoline (36% yield) was produced.

The conversion of quinoline 1-oxide into 2-quinolone on treatment with benzoyl chloride and alkali was demonstrated by Henze (36CB1566). Later, Japanese investigators (60JJ1031) isolated an intermediate, suggested to be *276*, which can be oxidized by potassium permanganate in good yield to the oxalanilide *277*. Additional support for the correctness of structure *276* was provided by the observation that oxidation with ferricyanide yields 1-hydroxy-2-quinolone (*278*) (62CT51). Further, 2-quinolones (53G273) and benzo-2-quinolones (53G622) have been obtained in good yield from the corresponding *N*-oxides using benzoyl chloride and aqueous alkali: benzimidazole 1-oxides are converted into benzimidazolones (*279* → *280*) (62AJ792). α-Oxo-heterocycles are frequently obtained as by-products in the preparation of α-cyano compounds by reaction of heterocyclic *N*-oxides with benzoyl chloride and aqueous potassium cyanide; cf. reference 60CT286 and Section III-4Fia.



(279) (280)

The quinoline 1-oxide–boron trifluoride complex (*281*) gives 2-quinolone (*282*) and other products on heating with phosphoric acid (58JJ1083).

(281) (282)

ii. Acetate Ions alpha *to an* N-*Oxide Group*: *Acetic Anhydride Reaction*

a. Preparative Aspects. Katada first reported that pyridine 1-oxide is rearranged by acetic anhydride to 2-acetoxypyridine (*288* → *291*), which is usually isolated as 2-pyridone (*292*) (47JJ51). The reaction has since been considerably developed and found to be general for most ring systems; examples are collected in Table 3.34. The product normally isolated is the α-oxo compound because of the easy hydrolysis of α-acetoxy derivatives. Although there is a very strong tendency for the reaction to occur at the α-position, if both the α-positions are occupied, reaction occurs at the γ-position, e.g. at the 9-position with acridine 10-oxides (66T3143), and if all the positions on the hetero ring are substituted, reaction can occur in a fused benzene ring, see below.

Table 3.34. The Conversion of *N*-Oxides into α-Oxo-heterocycles by Reaction with Acetic Anhydride (cf. 288 → 292)

Ring system	Substituents	Position of oxo group introduced	Yield, %	References
Pyridine 1-oxide	—	2	100	47JJ51, 56USP2752356, 63JA958
	3-carboxy	2 and 6	ca. 35 and 3	60CI402
	4-ethoxy, 4-methoxy	2	—	51SR1
	3-ethoxycarbonyl	2 and 6	28 and 16	61JO428
	3-halogeno	2	50–65	58JO1616
	2-methoxy	6	34	61JO428
	4-methoxy	2	56	61JO428
	3-methyl	2 and 6[a]	40 and 40	60CI402, 56USP2752356
	3-nitro	2	50	60JO1716
	2-(1-oxido-2-pyridyl)	6, 6′	—	56NK682
	2-styryl	6	(data)	59JJ487
Quinoline 1-oxide	—	2	20–35	48JJ88, 53G278
	4-amino	2	see note [b]	44JJ6, 48JJ88
	6-amino	2 and 6	50	66JJ1090
	3-aryl (various)	2	ca. 44	58JO271
	3-aryl-5-nitro	2	72	58JO271
	5,6- and 7,8-benzo	2	—	51JJ1288, 53G622
	3-, 4-, 5-, 6-, and 7-bromo	2	ca. 70	48JJ88
	4-(1-hydroxyalkyl)-6-methoxy[c,d]	2	—	48JJ109
	6,7-methylenedioxy	2	63	60JO1365
	6-nitro	2	45	66JJ1090
	*			
Isoquinoline 2-oxide	—	1	50–64	55CT454, 56JO1337

[a] 3-Methyl-*N*-(5-methyl-2-pyridyl)-2-pyridone formed as a by-product.
[b] 4-Amino → 4-acylamino.
[c] Quinine 1-oxide.
[d] Dihydroquinine 1-oxide reacts analogously (48JJ109, 50JJ391).

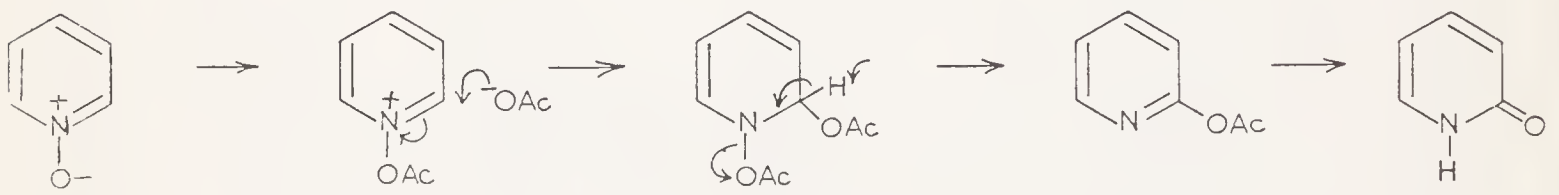
Table 3.34. The Conversion of *N*-Oxides into α-Oxo-heterocycles by Reaction with Acetic Anhydride (cf. 288 → 292)—*continued*

Ring system	Substituents	Position of oxo group introduced	Yield, %	References
Isoquinoline 2-oxide, *cont'd.*	3-chloro	1 and 4	ca. 1 and 61	58JA3443
	3-methyl	1	ca. 40	56JO1337
	4-phenyl	2	—	66JJ59
Acridine 10-oxide	—	9	—	50MI144
Phenanthridine 5-oxide	—	6	—	60JJ834
7-Azaindoline 7-oxide	—	5 and 6	(data)	59JA743
1,6-Naphthyridine 1-oxide	—	2	10	69CT1045
1,6-Naphthyridine 6-oxide	—	5	23	69CT1045
Pyrimidine 1-oxide	—	6	(data)	58CB2832
Quinazoline 1-oxide	4-alkoxy	2	60–64	59JJ699, 64CT43
	4-isopropyl	2	56[e]	64CT43
Purine 1-oxide	8-hydroxy	2	—	58AA(134)15-P
Quinoxaline 1-oxide	—	2	see note [f]	67JJ942
	3-phenyl	2	—	64JJ163, 68JO201
Quinoxaline 1,4-dioxide	—	2	30[g]	60ZO2967
Pyrazine 1-oxide	2*H*-3-oxo	6[h]	—	59CT938
Pteridine 5-oxide	2,4-dioxo	6	—	65AG(E)1075
Benzimidazole 1-oxide	—	2	(data)	53G278, 62AJ792, 63AJ729, 64CT282
	3-methyl	2[i]	—	64CT783

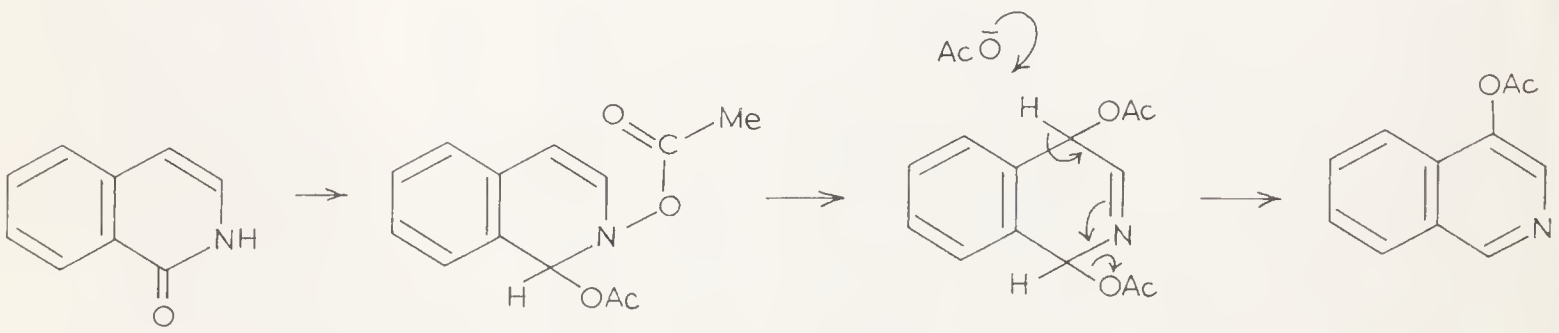
[e] 4-Substituted-quinoxaline also formed (27%).
[f] 1-(2-Quinoxalinyl)-2-quinoxalinone also formed on prolonged reaction.
[g] 4-Oxide group lost.
[h] Maleic acid hydrazide.
[i] 1-Acyl-3-methyl-2-benzimidazolinone formed.

In a typical reaction the *N*-oxide is heated under reflux with excess acetic anhydride as solvent for 0·5–5 h. Other anhydrides can be used: benzoic anhydride behaves similarly to acetic anhydride (47JJ51), whereas trifluoroacetic anhydride effects the rearrangement under very mild conditions (58H2148). Neither 2- nor 4-cyanoquinoline 1-oxide yield quinolones with acetic anhydride, but with trifluoroacetic anhydride 2-cyano-4- and 4-cyano-2-quinolone are formed.

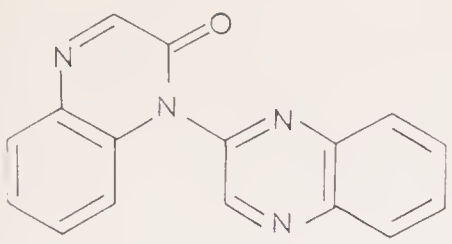
Side reactions are rare in the pyridine series, but the addition of mercaptans to the reaction mixture has a marked effect and causes some β- and/or γ-substitution for reasons not yet understood (69JO655). Isoquinoline 2-oxide gives 1-isoquinolone (*293*) (53% yield) together with 4-hydroxyisoquinoline (9%) (56JO1337), which probably arises by the sequence *294* → *296*. 3-Methylisoquinoline 2-oxide forms an analogous by-product (56JO1337). Quinoxaline 1-oxide gives 2-quinoxalinone together with the quinoxalinyl-quinoxalinone *297* as by-product (67JJ942), which probably arises via a mechanism of the type discussed in Section III-4Eii. 2,3-Disubstituted quinoxaline 1-oxides yield 6-acetoxy derivatives, probably by a mechanism similar to that involved in the chlorination reactions discussed in Section III-4Biii (68JO201; see also Section III-5Ciiia). Adenine 1-oxide (*298*) undergoes ring opening with acetic anhydride to give the imidazole *299* (60JA1148). Recently, it has been shown (69JO981) that several purine 3-oxides unsubstituted in the 2-position can be rearranged by acid anhydrides to give purin-2-ones whereas 2-subsituted derivatives yield purin-8-ones: the mechanism of the oxygen rearrangement to the 8-position is not yet clear.



(288) (289) (290) (291) (292)



(293) (294) (295) (296)



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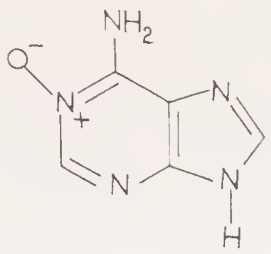

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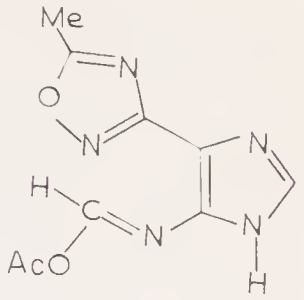
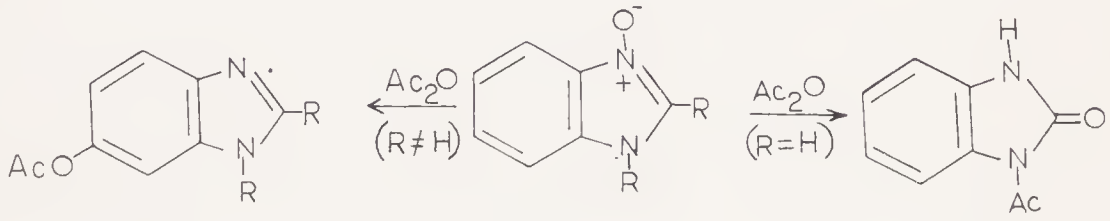


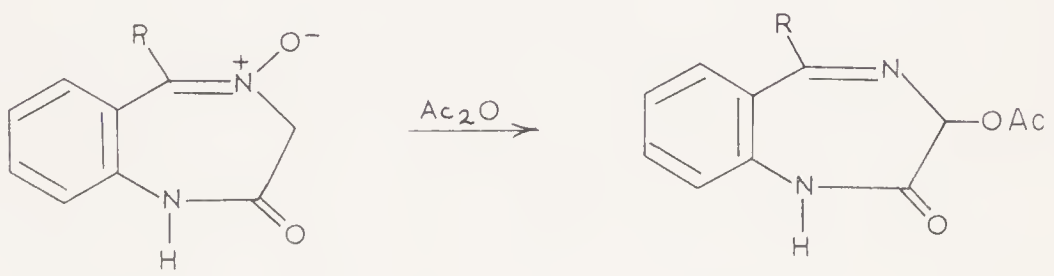
(299)

The pyrazine 1-oxide nucleus has been reported to be resistant to attack by acetate ions, although substituent methyl groups do react (61JO126; cf. Section IV-2Bia). Other investigators, however, claim to have obtained 2-acetoxypyrazine from pyrazine 1-oxide in low yield (59JJ1273).

This reaction has been applied to *N*-oxides with five- and seven-membered rings. Thus, on treatment with acetic anhydride, benzimidazole 3-oxide (*300b*, R = H) yields 1-acetyl-2-benzimidazolone (*301*) (62AJ792). 1,2-Disubstituted benzimidazole 3-oxides (*300b*, R ≠ H) yield 6-acetoxybenzimidazoles (*300a*) on reaction with acetic anhydride (68CT527). Benzodiazepine *N*-oxides (cf. *302*) are rearranged by acetic anhydride to products of type *303* [62JO1691; 63JO3010; 64AA(146)46-C; 64JO332; 64JO1621; 68JO2963; 68MC774].



(300a) (300b) (301)

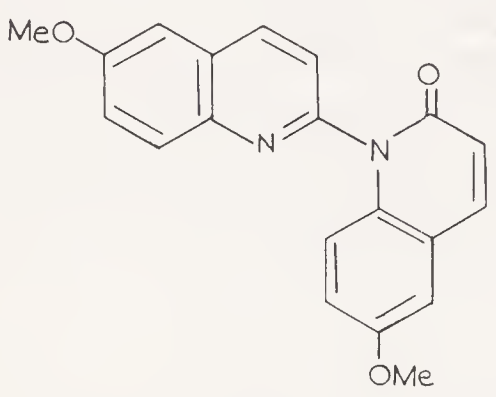


(302) (303)

b. Effect of Substituents and Orientation of Reaction. The data in Table 3.34 indicate that the following substituents are unaffected in the reaction: fused benzene rings; aryl, ester, and styryl groups; and β- or γ-halogeno, -nitro, and -methoxy groups. However, 2-chloro-, 2-ethoxy-, and 2-phenoxy-pyridine 1-oxide are each converted into 1-hydroxy-2-pyridone under the usual conditions (61JJ574). α-Carboxylic acids are decarboxylated, see Sections IV-2Cib and III-3Evi; 3-carboxypyridine 1-oxide with acetic and propionic anhydrides gives the corresponding

2-acyl-3-carboxy derivative (*173*) by a reaction of the Friedel-Crafts type, see Section III-3Evi. α-Alkyl groups are acetoxylated (see Section IV-2Bia), and α-vinyl groups also react (see Section IV-2Bia). α-Cyano groups inhibit reaction in the pyridine (61JO428) and quinoline 1-oxide series (see above). The effect of substituents in the quinoline 1-oxide series was investigated by Hamana (66JJ1090) who found that the 6-nitro, 6-amino, 6-acetamido, and 6-methoxy derivatives all react normally, although the quinolyl-quinolone *304* is formed as a by-product in the last case (cf. Section III-4Eii).

For 3-substituted pyridine 1-oxides, the 2- and 6-positions are both available for reaction. A methyl group (54JA1286), halogen atom (58JO1616), or nitro group (60JO1716) in the 3-position of pyridine 1-oxide appears to direct reaction to the adjacent 2-position, but this is not the case for 3-carboxylic acids and esters (see Table 3.34). With 7-azaindoline 7-oxide (*305*) 5- and 6-substitution occurs (59JA743).



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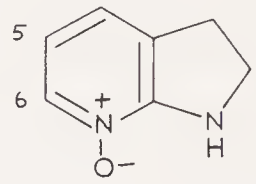
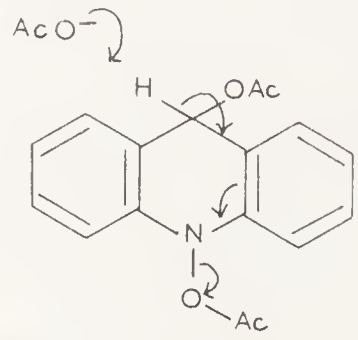


(305)

c. Mechanism. Markgraf *et al.* (63JA958) investigated the kinetics of the reaction of acetic anhydride with pyridine 1-oxide and obtained Arrhenius parameters: they concluded that the rate-determining step is the attack of acetate ion on the *N*-acetoxy cation, as in structure *289*. The rearrangement of 3-picoline 1-oxide to 2- and 6-acetoxy-3-methylpyridine was investigated by Oae and Kozuka (64T2691) using ^{18}O-labelled acetic anhydride; the results strongly support the intermolecular ionic reaction path (cf. *288* → *291*). The Japanese workers (65T1971) later reported that pyridine-2,6-d_2 1-oxide also shows only a very small isotope effect in its reaction with acetic anhydride, which is in agreement with preceding work in the acridine 10-oxide series (see below); the reaction rate is, however, ca. 10^6 times slower for pyridine 1-oxide.



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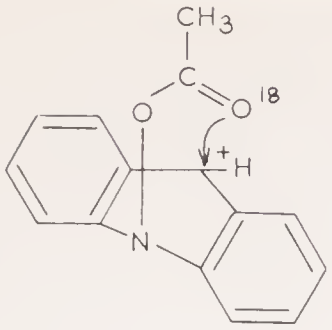

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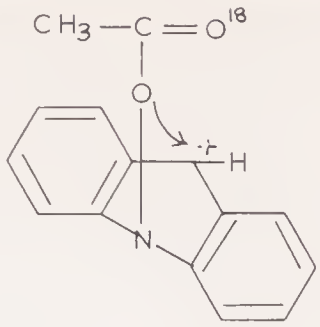


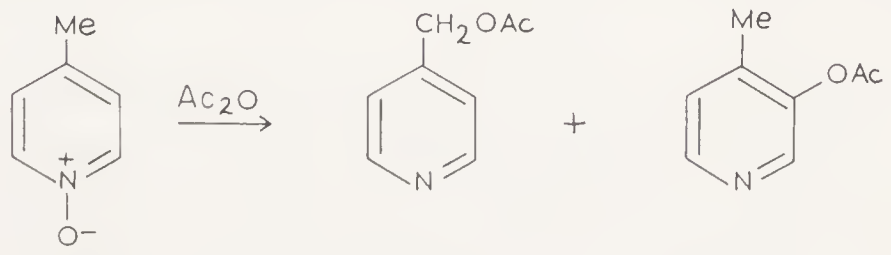
(308)

Kinetic studies on acridine 10-oxide (64JA2699) were later extended to 9-deuteroacridine 10-oxide (64JO2806). The absence of a primary deuterium isotope effect appears to indicate that the reaction step shown in structure *306* is fast, and that the step corresponding to that shown in structure *289* is rate-determining. However, on the basis of later ^{18}O-tracer experiments, the mechanism of the reaction between acridine 10-oxide and acetic anhydride appears to be complex, involving two distinct *intramolecular* paths which are shown in structures *307* (cyclic) and *308* (sliding) (66T3143).

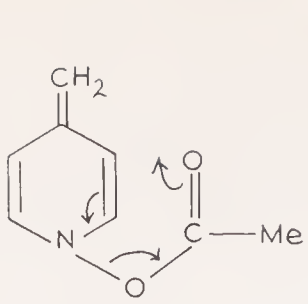
iii. Acetoxylation and Sulphonyloxylation beta *to an* N-*Oxide Group*

a. Acetoxylation. Treatment of α- and γ-alkyl *N*-oxides with acetic anhydride gives mainly the acetoxyalkyl derivative (cf. *309* → *310*) (Section IV-2Bi); however, acetoxylation of the ring in the β-position (cf. *311*) occurs as a side reaction (see Table 4.01). These products arise by rearrangements of type *312* as is discussed in detail in Sections IV-2Bib and 2Bic. Acetoxylation in the β-position may generally account for a larger proportion of the reaction than was first thought; for example, careful analysis shows that 2-picoline 1-oxide gives 17% each of 3- and 5-acetoxy-2-picoline (65AJ867).

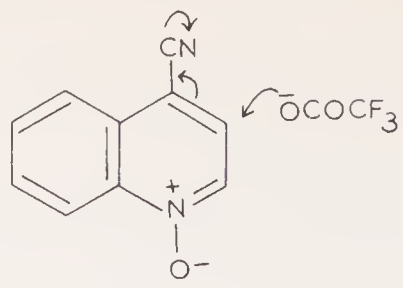
Substitution at the β-position is a side reaction in the reaction of 4-cyanoquinoline 1-oxide with trifluoroacetic anhydride; the β-position is activated by the cyano group (cf. *313*) (58H2148). β-Acetoxy by-products are also formed in the reaction of isoquinoline 2-oxide with acetic anhydride (see Section III-4Ciia). A striking example of attack *beta* to an *N*-oxide group is seen in the case of quinoxaline 1,4-dioxide, which reacts with acetic anhydride to give 1-hydroxy-2-quinoxalinone; on irradiation, however, the expected 3-acetoxyquinoxaline 1-oxide is formed (62ZO2967). The mechanism of the former reaction probably involves a process of the type shown in structure *314*. Quinoxaline 1,4-dioxide is reported to yield 2-benzoyloxyquinoxaline 1-oxide with benzoyl chloride (67KG724).



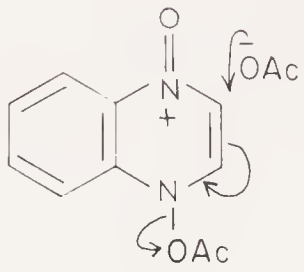
(309) (310) (311)



(312)



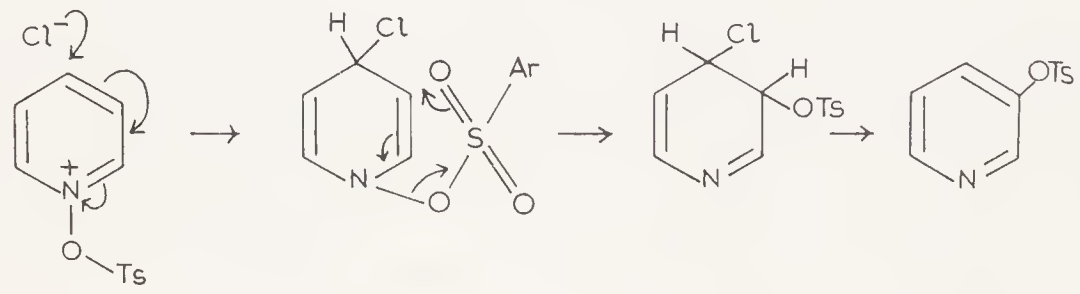
(313)



(314)

b. Arylsulphonyloxylation. The reaction of sulphonyl chlorides with *N*-oxides, which in the presence of aqueous alkali gives α-oxo products (Section III-4Cic), takes a different course in the absence of base, when α- or γ-chloro compounds (Section III-4B), pyridyl-pyridones (Section III-4Eii), and sulphonyloxy derivatives are formed. The formation of the last-named products will now be considered; for an overall survey of these reactions, see reference 58MIa. Sulphonyloxylation generally occurs *beta* to the *N*-oxide but several examples of substitution in a fused benzene ring are known.

On heating with tosyl chloride, pyridine 1-oxide yields 3-tosyloxypyridine by the reaction sequence *315* → *318* (49NK393; 50JP1535). 3-Picoline 1-oxide similarly gives 3-methyl-5-tosyloxypyridine (52MO1; 53NK446), but with 2-picoline 1-oxide and other α-alkyl *N*-oxides reaction occurs at the methyl group to yield 2-chloromethylpyridine, etc. (see Section IV-2Biia), and α-carboxy *N*-oxides are converted into α-oxo heterocycles (53NK547; 62MO191) (cf. Section III-4Cic).

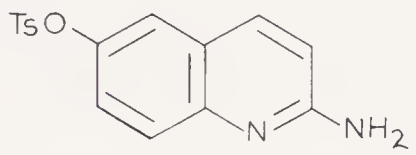


(315) (316) (317) (318)

Quinoline 1-oxide reacts with tosyl chloride at 200° to give 2-quinolone, 2,2′-diquinolyl ether, 4-chloroquinoline, and 1-(2-quinolyl)-2-quinolone (51MR168; 51NK509). However, the reaction can yield β-sulphonyl compounds in other cases, thus both 2,4-diphenylquinoline 1-oxide (66JJ59)

and 4-styrylquinoline 1-oxide (63JJ342) yield the corresponding 3-tosyloxyquinolines. The quinoline 1-oxide–boron trifluoride complex on heating with tosyl chloride gives 3-tosyloxyquinoline together with 4-chloroquinoline and 2-quinolone (58JJ1083). Alternatively, substitution is directed into the benzene ring: 2-aminoquinoline 1-oxide affords 2-amino-6-tosyloxyquinoline (*319*) (59CT887), and 2-hydroxyquinoline 1-oxide yields 8-tosyloxy-2-quinolone (*320*) (see Section III-4Eiia) (64JJ28). The mechanism of the latter reaction has been discussed by Hamana (64JJ28).

Similar reactions of *N*-oxides in the isoquinoline series with tosyl chloride afford good yields of 4-tosyloxyisoquinoline (55CT454; 65NK93), the corresponding 3-methyl (63ZK473) and 5-nitro (58CT495) derivatives, and 4-tosyloxy-1-isoquinolone (58JA3443). Phenazine 5-oxide yields 1-tosyloxyphenazine; the 5-oxide (*321*) of the latter compound gives on further treatment with tosyl chloride 1,6- and 1,4-ditosyloxyphenazine (60NK515). In an analogous reaction, 2-aminoquinoxaline 1-oxide yields the 3-benzenesulphonyloxy derivative on treatment with benzenesulphonyl chloride (66KG101).



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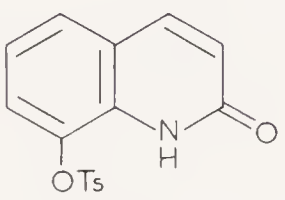
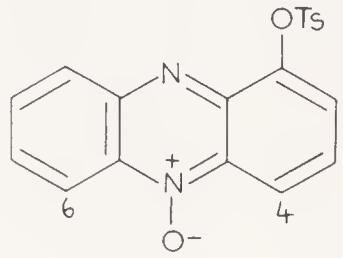


(320)



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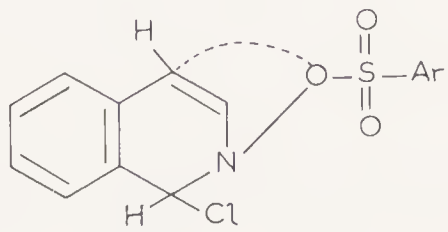

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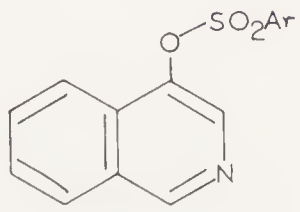
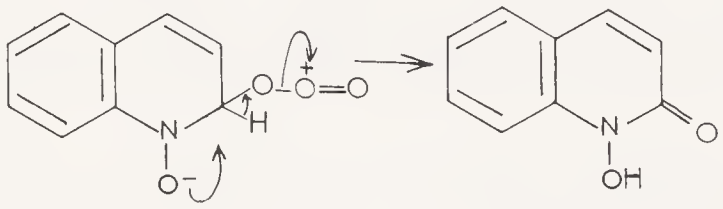


(323)

Isotopic labelling studies by Oae *et al.* (63T827) on isoquinoline 2-oxides apparently indicate that rearrangement of the type shown in structure *322* occurs. However, the question cannot be considered completely settled: possibly hydrolysis of 4-sulphonyloxyisoquinoline (*323*) does not proceed entirely by S-O bond cleavage; even though this is the case for phenyl sulphonates (63RU1), it may not be true in the activated system *323*.*

iv. Carbon–Oxygen Bond Formation with Retention of the N-*Oxide Function*

a. Ozone. Ozone forms complexes with *N*-oxides, probably at the *N*-oxide oxygen atom (see Section III-1Ci). In addition, electrophilic ring attack can occur as discussed in Section III-3Ev but other reactions, studied by Moriconi, Spano, *et al.* (63JO2215; 64JA38), can be rationalized in terms of an initial nucleophilic attack by ozone at an α-position. Quinoline 1-oxide yields 1-hydroxy-2-quinolone (*325*) by collapse of the initial adduct *324*: 2-quinolone, *o*-nitrocinnamaldehyde, and *o*-nitrobenzaldehyde are also obtained, the last two probably arising by oxidation of *325*. Isoquinoline 2-oxide similarly yields 2-hydroxy-1-isoquinolone, and acridine 10-oxide gives 10-hydroxyacridone plus acridone. Phenanthridine 5-oxide also forms 5-hydroxyphenanthridone (*326*) together with phenanthridone and the ring-opened compound 2′-nitro-2-biphenylcarboxaldehyde.



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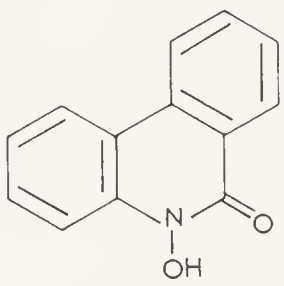
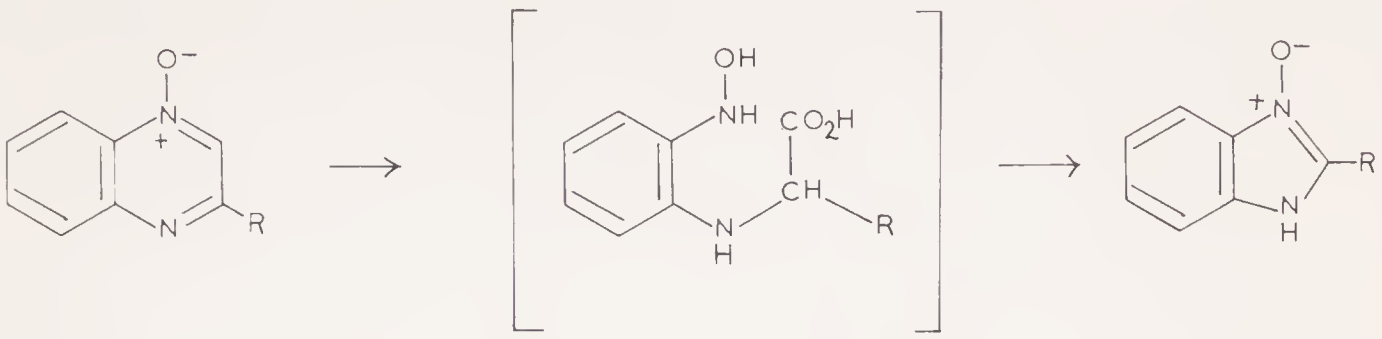


(326)

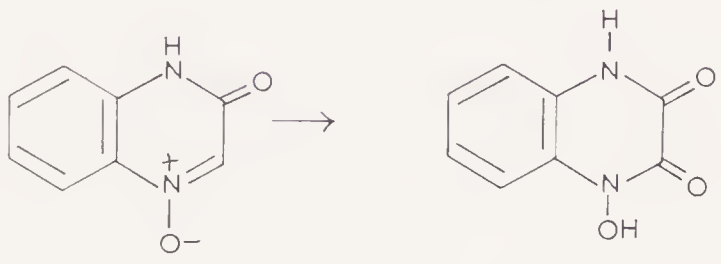
b. Hydroperoxide Ion. Phenanthridine 5-oxide has also been converted into compound *326* by alkaline hydrogen peroxide (60JJ834), and the formation of *N*-oxides from heterocyclic bases by peracid oxidation sometimes gives ring-oxidized compounds as by-products (see Section II-1Cii). These reactions probably involve nucleophilic attack by hydroperoxide ions in the α-position, followed by breakdown of the intermediate as illustrated (*206*, X = H). 3-Phenyl- (62JJ1093), 3-alkyl-, and 3-alkoxy-quinoxaline 1-oxides are converted by alkaline hydrogen peroxide into the corresponding

* See addendum in the Appendix.

benzimidazole *N*-oxides (*327* → *329*) (67JJ648; cf. 62JJ1093); nucleophilic attack at the α-position by hydroperoxide ion followed by ring opening to a derivative of type *328* is probably involved.



(327) (328) (329)



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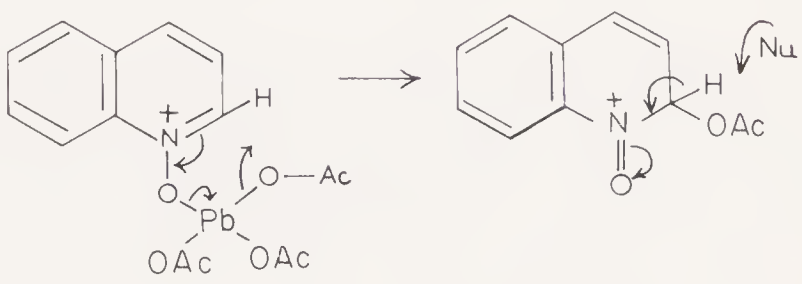
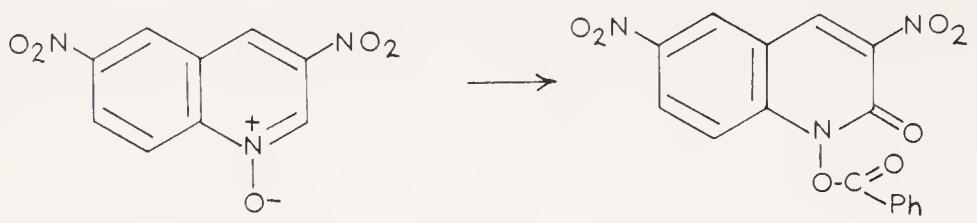


(332) (333)

c. Lead Tetraacetate and Tetrabenzoate. Lead tetraacetate and tetrabenzoate also oxidize quinoline 1-oxides to products of type *325* (62CT1260; 63CT1586). The conversion of quinoxalin-3-one 1-oxides (cf. *330*) into 1-hydroxy-2,3-quinoxalinediones (cf. *331*) is another reaction of this type (53J2830; 63J2428); similar oxidations have been reported in the quinazoline series (59CT152). These reactions may be rationalized by the formation and further transformation of intermediates of types *332* and *333* as indicated.

d. Miscellaneous. Quinoline 1-oxide is oxidized by potassium ferricyanide to 1-hydroxy-2-quinolone (*325*); the 4-methyl analogue behaves similarly, but the 2-methyl derivative gives only a small yield of quinaldic acid 1-oxide (62CT51). A combination of strongly basic and oxidizing reaction conditions (potassium *t*-butoxide, tetrahydrofuran, and oxygen) also leads to the conversion of quinoline 1-oxide in good yield into 1-hydroxy-2-quinolone via an initial adduct which is subsequently oxidized (66CT557).

1-Hydroxy-2-quinolone derivatives are obtained by the action of benzoyl nitrate on quinoline 1-oxide derivatives, e.g. *334* → *335* (cf. *128* and *129*). These reactions involve the addition of a nitrate ion at the α-position and breakdown of the adduct as shown in the structure *336*; see also the discussion in Section III-3C. Finally, it is possible to isolate, and then oxidize in a separate stage, initial adducts of type *276*; see Section III-4Cic.



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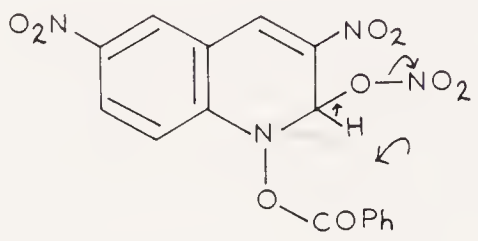
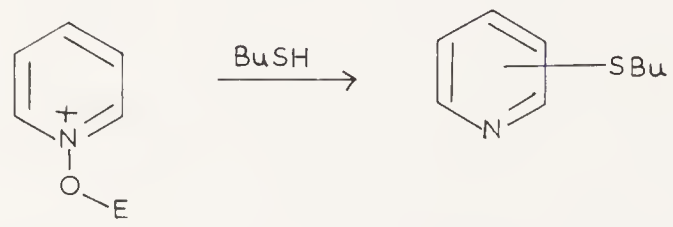


(336)

D. FORMATION OF A CARBON–SULPHUR BOND BY NUCLEOPHILIC ATTACK

i. Mercaptans

Bauer and Gardella (63JO1320) found that 1-alkoxypyridinium salts react with propyl and octyl mercaptide ions to give mixtures of 3- and 4-alkylthiopyridines together with an appreciable amount of pyridine (see Section IV-4Ai); the relative proportions of the products resulting from substitution and deoxygenation vary with the solvent. Nuclear substitution also occurs, together with methyl substitution, in the reaction of picolyl 1-oxide quaternary salts with mercaptide ions (63JO1323); see Section IV-2Biv. 1-Acyloxy- and 1-sulphonyloxy-pyridinium cations of type *337*, where E is benzoyl, alkylsulphonyl, benzenesulphonyl, or acetyl, also react with butanethiol to give 2-, 3-, and 4-substituted products of type *338*



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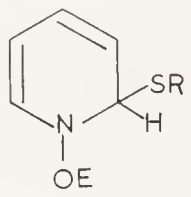

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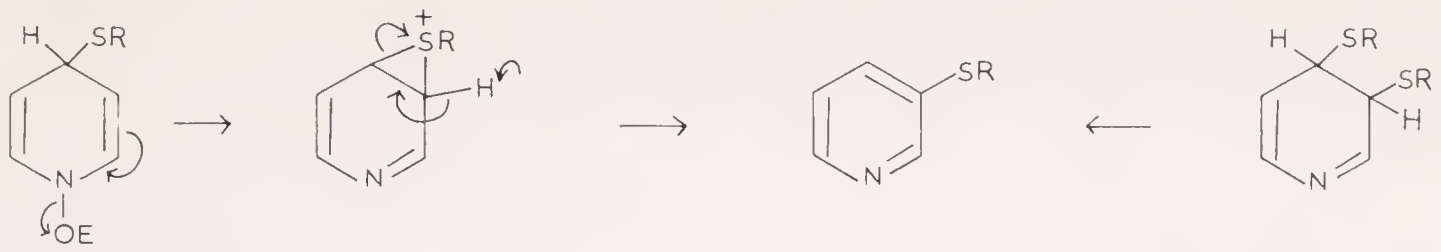
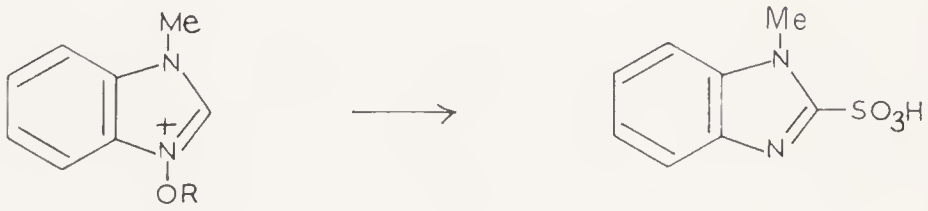


(340) (341) (342) (343)

(344) (345)

(64JO2183). When E is an alkyl or sulphonyl group, 3-substitution predominates, but if E is an acyl group the 2-isomer is the major product. It was suggested that 2- and 4-substitution involve intermediates of types *339* and *340*, and that *340* can rearrange to give 3-substituted products (*342*) via *341*. Alternatively, *340* (or *339*) can react with another mole of mercaptide to yield *343* which gives *342* by elimination. Similar results have been reported for the corresponding reactions of methyl-substituted pyridine 1-oxides (66JO1210) and quinoline 1-oxides (66JO939).

Recently many further examples have been reported of the reaction of mercaptans with pyridine 1-oxide and its substituted analogues in acetic anhydride to yield 2- and 3-alkylthiopyridines (69JO655). It was found that *para*-substitution occurs only if the adjacent α-position is free, and therefore the results were interpreted in terms of episulphonium intermediates of type *344*, and this was supported by the isolation of by-products of type *345* (69JO660).



(346) (347)

ii. Other Sulphur Nucleophiles

Relatively little is known about the reaction of sulphur nucleophiles other than mercaptans with heterocyclic *N*-oxides. No sulphur-containing product derived from pyridine 1-oxide could be isolated following its reaction with *p*-nitrobenzenesulphenyl chloride (65BJ58), and *p*-nitrobenzenesulphinyl chloride merely causes deoxygenation (66BJ1306); for

more recent work in this area, see reference 67BJ1420. 1-Alkoxybenzimidazolium salts (*346*) react with bisulphite ions to give sulphonic acids (*347*) (66CT375).

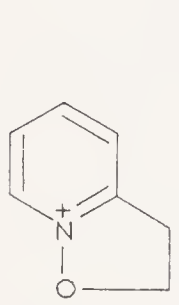
E. FORMATION OF A CARBON–NITROGEN BOND BY NUCLEOPHILIC ATTACK

Surprisingly little work has appeared on the nucleophilic attack of heterocyclic *N*-oxides by nitrogen-containing compounds: more activity may be expected in this area in the future.*

i. Amines and Amides

Amines are not sufficiently nucleophilic to react with simple *N*-oxides unless these are in the activated form of quaternary cations or adducts with Lewis acids. Fragmentary work indicates that α- and γ-amino derivatives are formed in the normal way from the adducts and that *N*-alkoxy cations can undergo ring opening. *N*-Oxides which are reactive towards nucleophiles, such as isatogens and furoxans, react directly with amines.

Boekelheide and his co-workers found that the bicyclic cation *348* gives an addition product with piperidine (58JA2217), to which they later ascribed structure *349* (61JO3802). However, it has recently been shown by the Norwich group that, although *349* is probably a transient intermediate, it undergoes spontaneous ring opening to the butadiene derivative *350* (67T2775).



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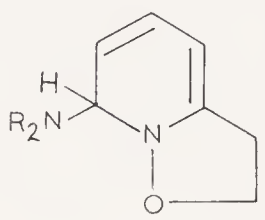

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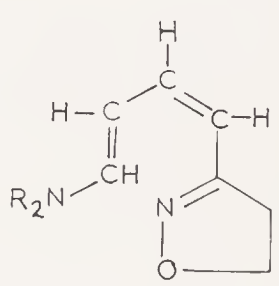
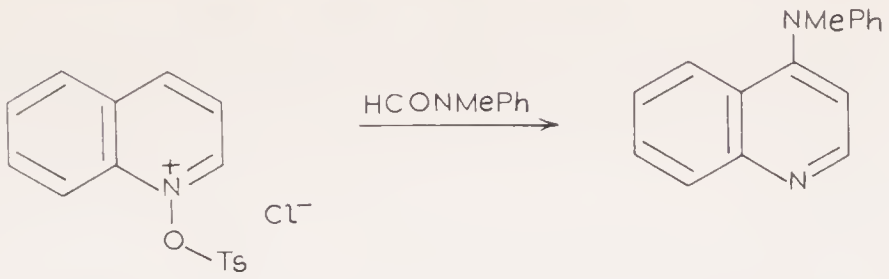


(350)

The reaction of quinoline 1-oxide with ammonia or primary or secondary amines in the presence of tosyl chloride yields 2-amino- or 2-substituted-amino-quinolines together with a smaller amount of the corresponding 4-substituted derivative (64JJ35). Quinoline 1-oxide on successive treatment with tosyl chloride (or boron trifluoride) and *N*-methylformanilide gives 2- and 4-(*N*-methylanilino)quinoline (cf. *351* → *352*) (59CT944). In a similar reaction, quinoline 1-oxide is converted into 2- and 4-dimethylamino-quinoline by heating with tosyl chloride and boron trifluoride in dimethylformamide; 1-dimethylaminoisoquinoline has been prepared analogously (58JJ608; 61JP17464). 2-Nitrophenazine 10-oxide yields 1-amino-2-nitrophenazines with primary and secondary amines (67G1817).

* See addendum in the Appendix.



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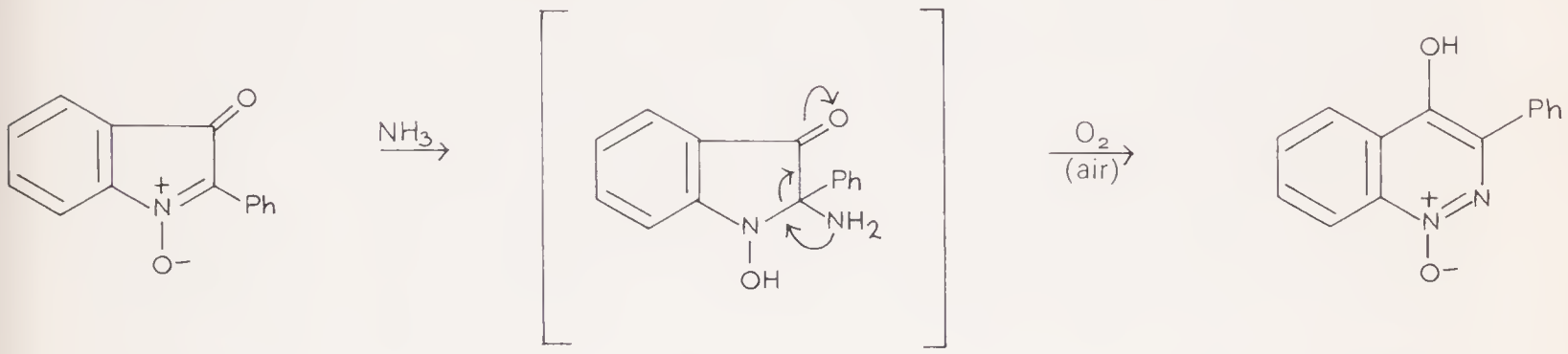

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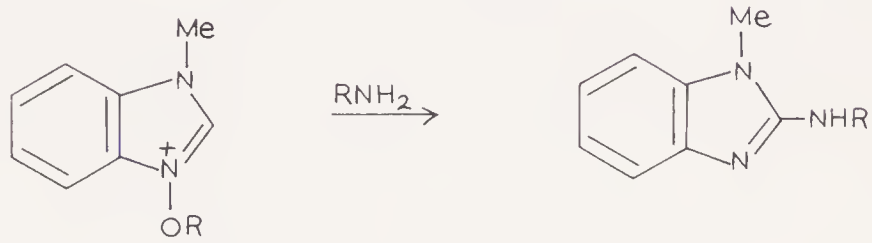
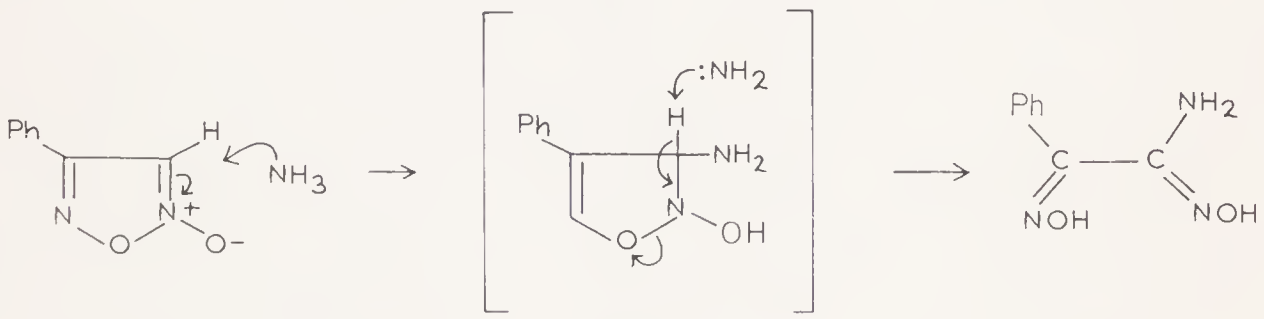
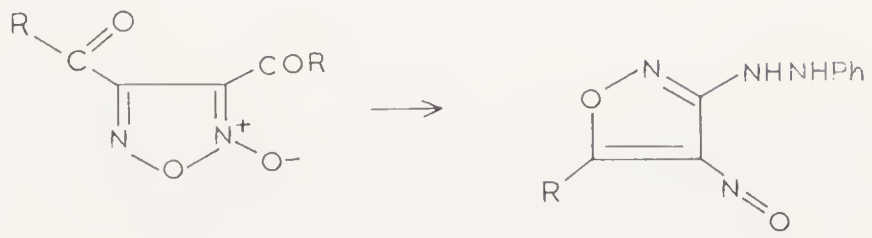


(356) (357)

The conversion of isatogens into 4-hydroxycinnoline 1-oxides by ammonia is thought to be initiated by nucleophilic attack at the α-carbon atom followed by aerial oxidation as indicated: *353* → *355* (62JO341). Amino compounds react with 1-alkoxybenzimidazolium salts (*356*) to yield products of type *357* (66CT375).



(358) (359) (360)

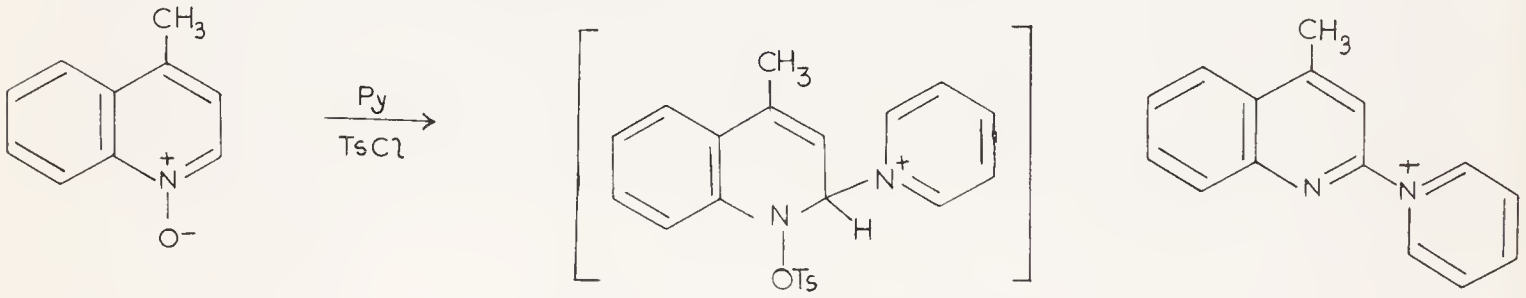


(361) (362)

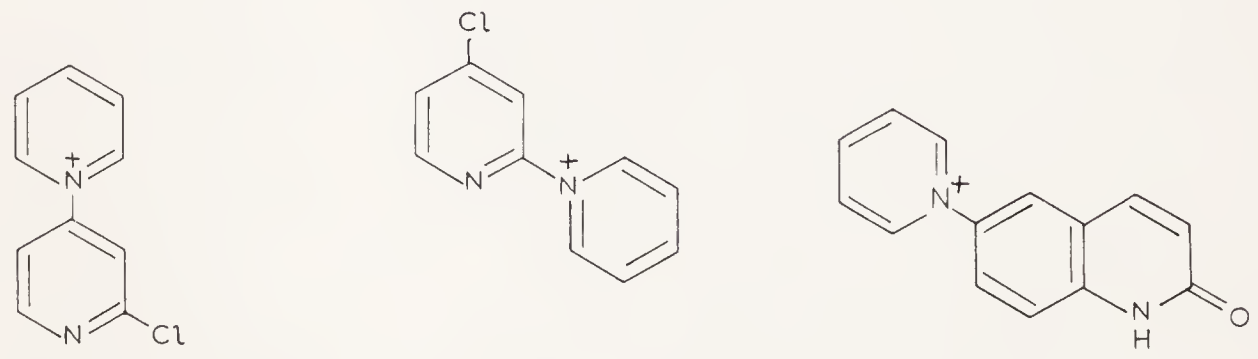
The reaction of furoxans with ammonia probably occurs by the route shown in the scheme *358* → *360* [08LA(358)36]: the transformation of *361* into *362* is rather more complex, but it can be rationalized in a similar manner (68JO866).

ii. Nitrogen-containing Heterocycles

a. Not Containing Halogen. Heteroaromatic compounds not containing halogen also react with *N*-oxides in the presence of tosyl chloride to give quaternary derivatives: substitution occurs at the α- or γ-positions, thus 4-methylquinoline 1-oxide (*363*) yields cation *365* via intermediate *364*; 2-methylquinoline 1-oxide reacts at the 4-position (62JJ512). With quinoline 1-oxide itself, a mixture of 2- and 4-substitution products is obtained (62JJ512). 4-Phenylquinoline 1-oxide with pyridine yields a 2-quinolylpyridinium cation (66JJ59). The reaction of pyridine with 2- or 4-chloropyridine 1-oxide in the presence of tosyl chloride yields *366* or *367*, respectively; the chlorine atoms do not take part in the reaction. 4-Hydroxypyridine 1-oxide also undergoes this reaction, however the 2-hydroxy analogue is merely tosylated (64JJ23). 4-Chloroquinoline 1-oxide reacts similarly, but 2-hydroxyquinoline 1-oxide surprisingly gives a good yield of the 8-tosyloxy derivative (*320*) (cf. Section III-4Ciiib) together with a small amount of *368*; 4-hydroxyquinoline 1-oxide reacts normally with aqueous alkali, but in the presence of pyridine yields the 6-substituted cation (cf. *368*) as a by-product (64JJ28). Quinoxaline 1,4-dioxide gives the 1-[1-oxido-3-quinoxalyl]pyridinium ion, as expected (67KG724).



(363) (364) (365)

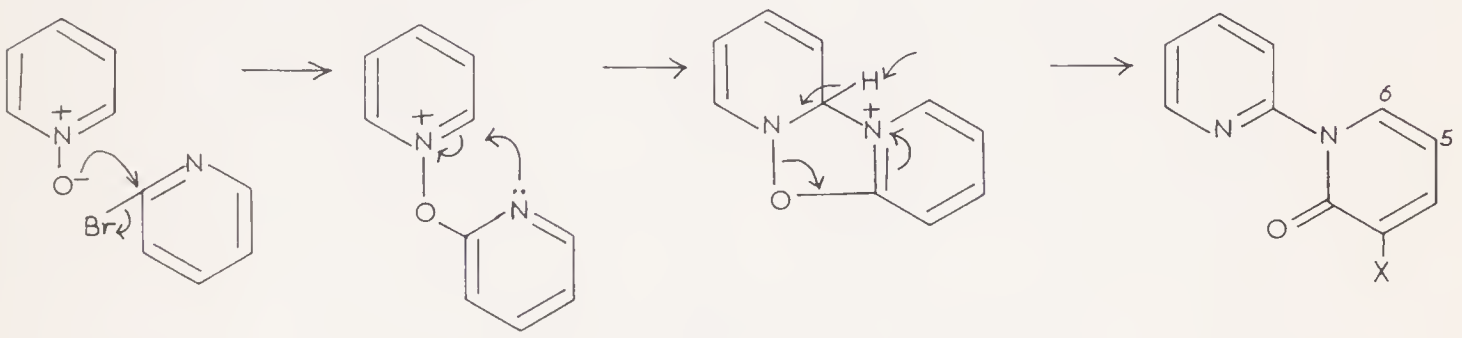


(366) (367) (368)

b. Halogeno Heterocycles. 2-Halogenopyridines react with pyridine 1-oxides to give 1-(2-pyridyl)-2-pyridones. The mechanism of the reaction is probably that shown in the scheme *369* → *372* (X = H), as suggested by

Ramirez and von Ostwalden (59JA156). This is a general reaction of α-halogeno heterocycles and *N*-oxides, and examples are collected in Table 3.35.

A monobromo derivative of *372* is a by-product of the reaction; although it was first considered to be the 6-bromo derivative and to arise by initial attack of the pyridine 1-oxide at the 6-position of the 2-bromo derivative [56AA(130)73-O], this by-product was later proved to be the 3-bromo compound (*372*, X = Br) and its appearance is probably a manifestation of the fact that hydrobromic acid can be oxidized by the *N*-oxide group, since the 3,5-dibromo analogue of *372* is also formed in trace amounts (57CI46; 59JA156). The reaction is facilitated by electron-donating groups and hindered by electron-accepting groups on the pyridine 1-oxide ring; this finding indicates that the conversion of *369* into *370* is probably the rate-determining step (65NK839).



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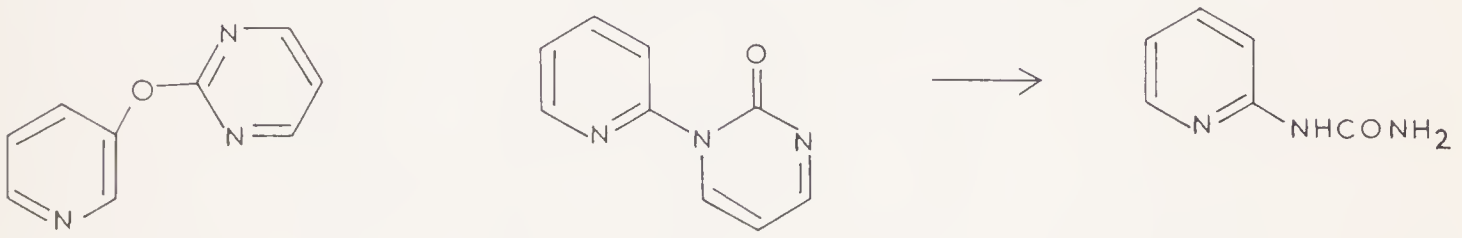

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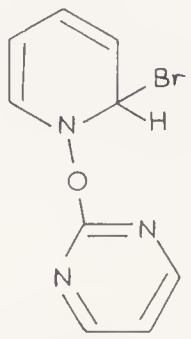


(376)

2-Bromopyrimidine reacts with pyridine 1-oxide to yield the β-pyridyl ether *373* and 2-ureidopyridine (*375*). The latter is considered to be formed by the hydrolysis of the expected product *374*; small amounts of ethers are often obtained as by-products, and they probably arise via intermediates

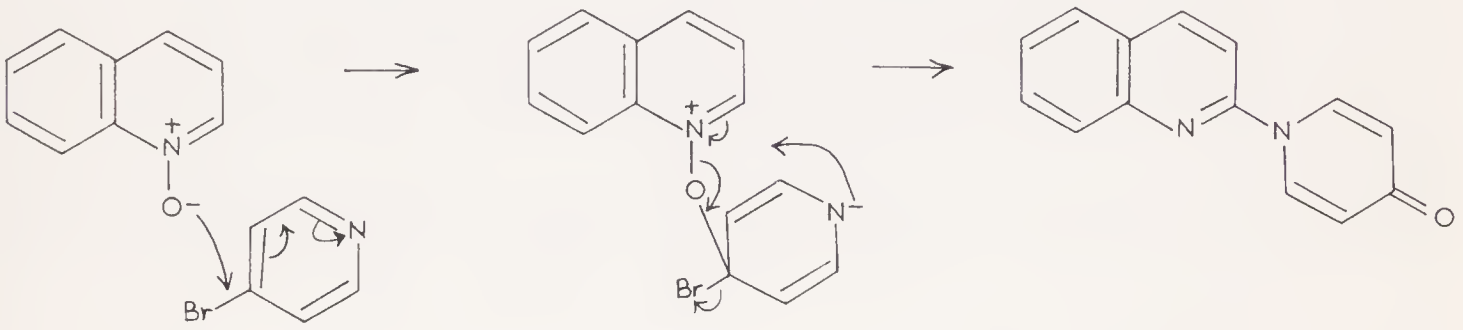
Table 3.35. The Reaction of *N*-Oxides with α- and γ-Halogeno-heterocycles (cf. 369 → 372; 377 → 379)

Heterocyclic *N*-oxide	Halogen compound	Product (Yield, %)	References
Pyridine 1-oxide	2-bromopyridine	1-(2-pyridyl)-2-pyridone (20–30)[a] and 3-bromo-1-(2-pyridyl)-2-pyridone (20–30)	52JJ1427, 57CI46, 59JA156, 65NK839, 65NK1060
	2- and 4-bromoquinoline	1-(2-pyridyl)-2- and -4-quinolone	52JJ1427, 64NK672
2-, 3-, and 4-Picoline 1-oxide	2-bromopyridine	1-(4-, 5-, and 6-methyl-2-pyridyl)-2-pyridone (10–30)[b]	57CI46, 59JA156
Quinoline 1-oxide	2- and 4-bromopyridine	1-(2-quinolyl)-2- and -4-pyridone (ca. 40)	53JJ1158, 64NK672
	2- and 4-bromoquinoline	1-(2-quinolyl)-2- and -4-quinolone (ca. 24)	53JJ1158, 64NK672
Isoquinoline 2-oxide	2- and 4-bromopyridine	1-(1-isoquinolyl)-2- and -4-pyridone (ca. 30)	64NK672, 65NK93, 65NK1060
	2- and 4-bromoquinoline	1-(1-isoquinolyl)-2- and -4-quinolone (ca. 22)	64NK672, 65NK93
	1-bromoisoquinoline	2-(1-isoquinolyl)-1-isoquinolone	65NK93

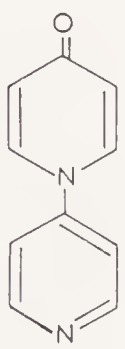
[a] In toluene, using hydrogen bromide–acetic acid as catalyst, only 1-(2-pyridyl)-2-pyridone (53 %) was formed.
[b] Reaction carried out in toluene using hydrogen bromide as catalyst.

of type *376* (cf. Section III-4Ciiib). Similar reactions occur between quinoline or isoquinoline *N*-oxides and 2-bromopyrimidine (66NK884).

Kajihara (64NK672) found that 4-bromopyridine surprisingly also reacts with quinoline 1-oxide to yield the 4-pyridone *379*; the reaction path shown in scheme *377* → *379* was suggested. The reaction of pyridine 1-oxide and 4-tosyloxypyridine to give the pyridyl-pyridone *380* (57R647) is related. In the corresponding reaction between 4-bromopyridine and isoquinoline 2-oxide, 4-bromoisoquinoline is obtained as a by-product. No reaction occurs between β-bromo heterocycles and *N*-oxides (65NK1060). 2-Tosyloxypyridine can be used in place of the 2-halogenopyridine in this reaction,



(377) (378) (379)



(380)

but a complex mixture of products, of which compound *372* (X = H) is the major component, is obtained (57R647). In the reactions of tosyl chloride with *N*-oxides to give β-tosyloxy compounds, discussed in Section III-4Ciiib, by-products of the heteroaryl-heteroarylone type (*372*, X = H) also result: e.g. pyridine 1-oxide gives some *N*-2-pyridyl-2-pyridone (*372*) (56JJ1421) together with the corresponding 5- (56R1303) and 3-chloro derivative (61R325).

F. FORMATION OF A CARBON–CARBON BOND BY NUCLEOPHILIC ATTACK

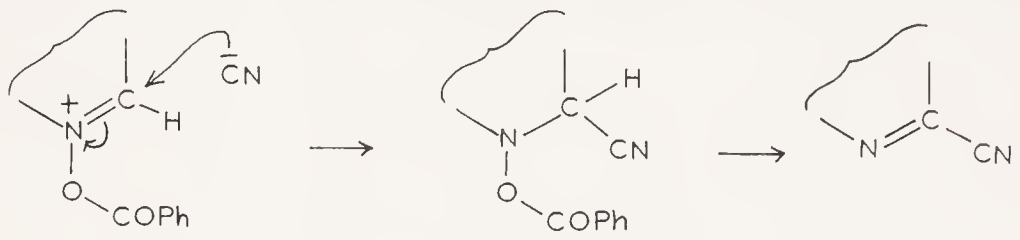
Two very useful procedures for introducing a cyano group into a heterocyclic ring involve the reaction of cyanide ions with an *N*-oxide in the presence of an acyl chloride (Reissert-type reaction), or with an *N*-oxide quaternary salt. Grignard reagents and other organometallic compounds react with *N*-oxides and *N*-oxide quaternary salts; yields are better in

reactions of the latter type, and substitution usually occurs in an α-position. Finally, *N*-oxides have been successfully condensed with the carbanions derived from a number of active hydrogen compounds, and with enamines.

Formation of a bond between a substituent carbon atom and an *N*-oxide ring by nucleophilic attack can also occur via rearrangement of a suitable substituent. These reactions are considered as substituent reactions and are discussed under the substituent involved: sulphonamido groups in Section IV-3Diii, and anilide groups in Section IV-2Cid.

*i. Cyanide Ions**

a. In the Presence of Benzoyl Chloride. One of the most general reactions of heteroaromatic *N*-oxides (with the exception of pyridine 1-oxides themselves!) is their conversion by Reissert-type reactions into α-cyano derivatives (*381* → *383*). Examples of this reaction are collected in Table 3.36, and an early review is available (55CR511). In typical reactions, the *N*-oxide, benzoyl chloride, and aqueous potassium cyanide are kept at 20° for



(381) (382) (383)

2–48 h. However, the reaction is sometimes fast; for example, in the case of benzimidazole 1-oxide a reaction time of 10 min has been used (64CT783). With the more reactive heterocyclic *N*-oxides, the presence of an acid chloride is not necessary. Silver cyanide (60CT286; 60CT487) and acetyl cyanide (63CT411) have been used occasionally in place of potassium cyanide, and can be advantageous in special cases. Yields are frequently high, but the corresponding α-oxo compound is sometimes obtained as a by-product (see footnotes to Table 3.36) via a reaction of the type discussed in Section III-4Cic.

The reaction generally fails completely in the pyridine 1-oxide series (59CT130); 4-chloropyridine 1-oxide (59JA4004) and trifluoromethylpyridine 1-oxides (69CT510) are exceptions to this generalization. In contrast, excellent results are usually obtained with quinoline and isoquinoline *N*-oxides. A γ-nitro group is sometimes replaced during the reaction; thus, 4-nitroquinoline 1-oxide yields 4-chloro-2-cyanoquinoline [45JJ(9/10A)7; 63JJ348]. If a free α- or γ-position is not available, as for example in 2,4-diphenylquinoline 1-oxide, other products can be formed, in this case 3-, 6-, and 8-benzoyloxy-2,4-diphenylquinoline. Similar by-products are produced in the reaction of 2-phenylquinoline 1-oxide, although here the 4-cyano derivative is the predominant product (66JJ59). Acridine 10-oxide is very

* See addendum in the Appendix.

Table 3.36. Reissert-type Reactions of *N*-Oxides to Form Cyano-heterocycles with Loss of the *N*-Oxide Group (381 → 383)

Ring system	Substituents	Position of cyano group introduced	Yield, %	References
Pyridine 1-oxide	—	2	—	40BS133
	4-chloro	2	—	45JJ7
Quinoline 1-oxide	—	2	60–90[a]	36CB1566, 40BS133, 58H2148, 60CT286
	4-alkoxy	2	80–92	45JJ7, 50JJ355, 50JJ423, 50JP3621, 59CT887
	6-alkoxy	2	ca. 70	53G273, 57JJ1243, 60CT487
	6-alkoxy-2-(1-hydroxyalkyl)[b]	2	(data)	60CT487
	4- and 6-alkyl	2	(data)	45JJ7, 53G273
	4-benzylamino	2	—	45JJ7
	4-halogeno	2	ca. 30[c]	45JJ7, 60CT286
	6- and 7-halogeno	2	75–77	57JJ1243
	3-, 4-, and 6-nitro	2	see note [d]	45JJ7, 60CT286, 66JJ1090
	2- and 4-phenyl	4 and 2	—	66JJ59
	4-styryl	2	—	63JJ342
Isoquinoline 2-oxide	*5-hydroxy	1	100	62JO4571
	5-phenylcarbonyloxy	1	53	62JO4571
Acridine 10-oxide	—	5	—	50MI144
Benzo[*f*]quinoline 1-oxide	—	4	—	53G622
Benzo[*h*]quinoline 1-oxide	—	2	—	51JJ1288, 53G622
Phenanthridine 5-oxide	—	6[e]	—	60JJ834
Pyridazine 1-oxide	3-alkoxy, -alkyl, and -aryl	6	10–42	63CT1522
Phthalazine 3-oxide	1-phenyl	4	—	66JJ576

[a] Carbostyril is also formed in 8 % yield (60CT286).
[b] Quinine and dihydroquinine *ar*-*N*-oxide.
[c] 4-Chlorocarbostyril (23–33 %) also formed.
[d] Yields of 81 and 89 % have been reported for 3- and 6-nitroquinoline 1-oxide, respectively (60CT286).
[e] 6-Phenanthridinone also formed.
* 3- and 4-Trifluoromethyl; see addendum in the Appendix.

Table 3.36. Reissert-type Reactions of *N*-Oxides to Form Cyano-heterocycles with Loss of the *N*-Oxide Group (381 → 383)—*continued*

Ring system	Substituents	Position of cyano group introduced	Yield, %	References
o-Phenanthroline 1-oxide	—	2	71	65JO288
Pyrimidine 1-oxide	4-alkoxy	2	(data)	59CT297
	4-alkoxy-6-alkyl	2	77–90	55CT175, 58CT633
	4-alkyl	2	—	55CT175
	2,3-dialkyl	4	—	55CT175
	6-alkyl-4-aryloxy	2	48	58CT633
Quinazoline 1-oxide	4-alkoxy	2	70–96	59JJ699
	4-alkyl	2[f]	33	64CT43
	4-aryloxy	2	17	59JJ699
Quinoxaline 1-oxide	3-phenyl	2[g]	—	62JJ1093
Benzimidazole 1-oxide	3-methyl	2	(data)	64CT783

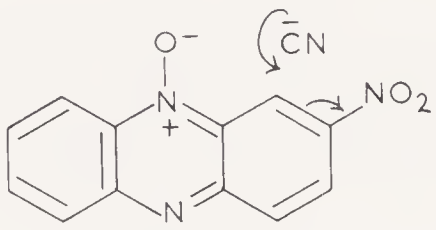
[f] α,α-Dimethyl-4-quinazolineacetamide (35%) also formed.

[g] 2-Chloro-3-phenylquinoxaline and 3-phenyl-2-quinoxalinone also formed.

readily converted into 9-cyanoacridine; simple treatment with hydrogen cyanide suffices (36CB1155).

Poor yields have been reported with pyridazine *N*-oxides (63CT1522). In reactions with pyrimidine *N*-oxides, a 2-cyanopyrimidine is always formed provided the 2-position is free. The same applies to quinazoline 1-oxides. With the usual reaction conditions, quinazoline 3-oxide undergoes ring opening, but 4-cyanoquinazoline can easily be obtained on simple treatment of the 3-oxide with hydrogen cyanide (61CT635). With 4-isopropylquinazoline 1-oxide, the cyano group can also enter the side-chain (see Section IV-2Biv). The reaction occurs particularly easily with quinoxaline 1-oxides; refluxing them with potassium cyanide in methanol brings about the reaction, no acid chloride being required (67JJ942).

If no free α-position is available, the reaction will sometimes take place in a fused benzene ring. Thus, 2-nitrophenazine 10-oxide (*384*) gives 1-cyano-2-nitrophenazine (67G1817; cf. 67G1826), and 1,2-dimethylbenzimidazole 3-oxide forms 6-cyano-1,2-dimethylbenzimidazole (66CT1219).



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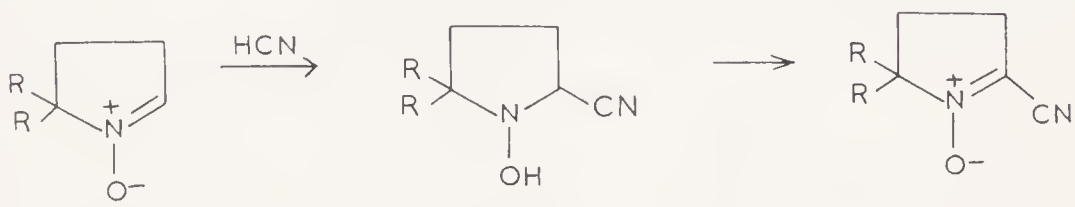
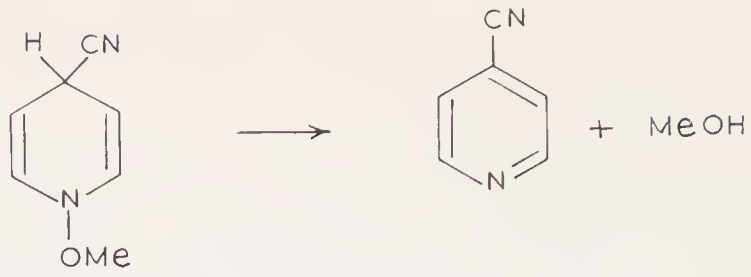


(385) (386) (387)

Pyrroline 1-oxides (*385*) yield addition products (*386*) with hydrogen cyanide which are readily reoxidized to the nitrone oxidation level (*387*) (59J2094).

b. On N-*Alkoxy Quaternary Salts.* 1-Alkoxypyridinium and other *N*-alkoxy heterocyclic quaternary salts react with cyanide ions to give α- and γ-cyano derivatives (cf. *389*) via intermediates of type *388*, as was discovered independently by Okamoto and Tani (59CT130; 59CT925) and by Feely and Beavers (59JA4004). Methanol has been proved to be a by-product of the reaction (59CT925). The reaction has been applied mainly in the pyridine 1-oxide series where the introduction of cyano groups cannot normally be effected under Reissert conditions. However, it does appear to be general.

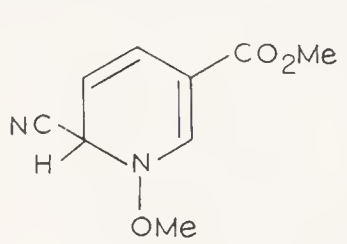


(388) (389)

Typical reaction conditions involve heating the *N*-alkoxy quaternary salt with cyanide ions for 15–45 min at 20–60° in water, ethanol, aqueous ethanol, or dioxane; reaction times of up to two days have been used when reaction is difficult. Yields are generally good. The optimum pH is ca. 11, and yields tend to decrease with reaction temperatures above 60° (59CT930). Examples of the reaction are recorded in Table 3.37.

The orientation of the reaction with 1-alkoxypyridinium ions is affected by the reaction temperature, the solvent, and the steric effect of the *O*-alkyl group. At temperatures of 0–20°, 2-cyanopyridine is the major product, but at 50–60° the 4-cyano derivative predominates. The amount of 4-substitution increases with increasing polarity of the solvent, and increasing the size of the alkyl group decreases the amount of substitution in the 2-position. By appropriate combinations of these factors, 4-cyanopyridine can be obtained in 70% yield *or* 2-cyanopyridine in 80% yield (59CT930; cf. 68CZ3848).

The reaction between cyanide ions and 1-methoxy-3-methoxycarbonylpyridinium ion has been investigated by ultraviolet spectroscopy: the intermediates *390* and *391* were identified spectrally, and it was shown that the slow step in the reaction is the loss of methoxide ion to give 4- or 6-cyano-3-methoxycarbonylpyridine (59CT930).



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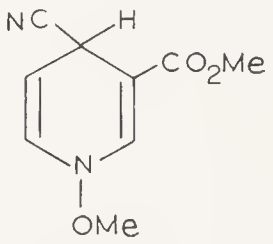

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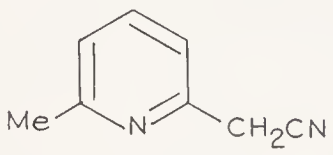

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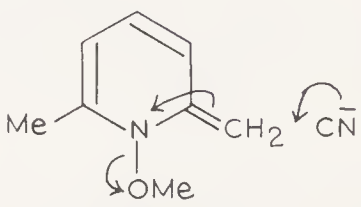

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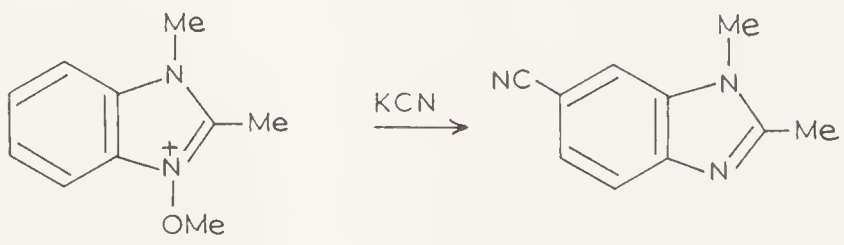

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Table 3.37. Reaction of *N*-Alkoxy Quaternary Salts with Cyanide Ions (cf. 388 → 389)

Ring system	Substituents	Position of cyanation	Yield, %	References
1-Alkoxypyridinium	—	2 and 4	45–50 and 24–32	59CT130, 59CT925, 59CT930, 59JA4004, 60JJ1418
	3,5-dibromo	2	70	61JJ141
	3-*n*-butyl	4	—	66CZ3008
	2-chloro	6	47	60JJ1418
	4-chloro	2	56	60JJ1418
	2-cyano	6	84	60JJ1418
	3-cyano	2 and 6	28 and 18	61JJ141
	4-cyano	2	54–70	59JA4004, 60JJ1418
	5-cyano-4-hydroxy-2-methyl	4	(data)	65CT878
	3-ethoxycarbonyl	4 and 6	32 and 19	61JJ141
	3-ethoxycarbonyl-6-methyl	4	66	61JJ182
	3-ethoxycarbonylmethyl	4	36	65TL2737
	2- and 4-ethyl	2	(data)	63AG169
	2-methoxy	2, 6	15	60JJ1418
	3-methoxy	2	68	61JJ141
	4-methoxy	2, 4	40	60JJ1418
	2-methoxycarbonyl	6	50	60JJ1418
	4-methoxycarbonyl	2	69	60JJ1418
	2-methyl	4 and 6	10–18 and 45–48	59CT130, 59CT925, 59JA4004
	3-methyl	2 + 4 + 6[a]	30–36 + 6–15 + 6[a]	59CT130, 59CT925, 59JA4004, 68CZ3848
	4-methyl	2	28–40	59CT130, 59CT925, 59JA4004, 60JJ1418
	2,6-dimethyl	4[b]	13–40	59CT130, 59CT925, 59JA4004,
	4,6-dimethyl	2	73	59JA4004
	4-nitro	2	54	60JJ1418
	3-trimethylsilyl	4	—	67JJ1374

[a] The 4 and 6 isomers were separated gas chromatographically (59JA4004).
[b] 6-Cyanomethyl-2-picoline (33 %) also formed (59CT130).

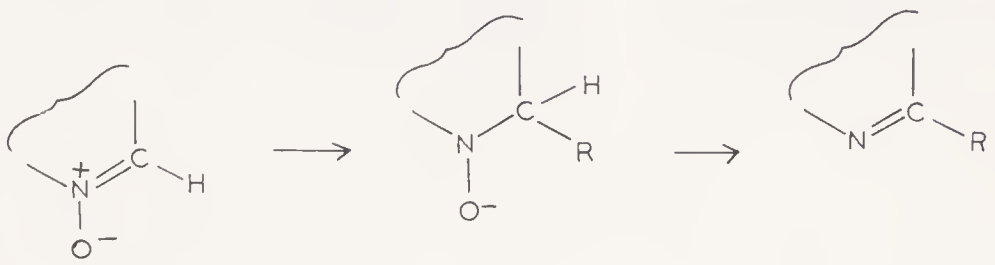
Table 3.37. Reaction of *N*-Alkoxy Quaternary Salts with Cyanide Ions (cf. 388 → 389)—*continued*

Ring system	Substituents	Position of cyanation	Yield, %	References
1-Alkoxyquinolinium	—	2 and 4	79–93 and "trace"	59CT130, 59CT925, 59JA4004
	6-methoxy	2	—	62JJ1076
	2-methyl	4	7	59JA4004
	4-methyl	2	65	59JA4004
2-Alkoxyisoquinolinium	—	1	49–95	59CT925, 59JA4004
10-Alkoxyacridinium	4-oxo	4	—	39CB1071
N-Alkoxypyridazinium	3-alkoxy and -aryloxy	6	57–72	63CT1472, 63CT1522
	3-chloro	6	35	63CT1522
	3-methyl	6	35	63CT1522
1-Alkoxybenzimidazolium	5-chloro-3-methyl	2	(data)	68CT527
	3-methyl	2	—	66CT375

The reaction reportedly fails with 4-dimethylamino- and 2-ethoxycarbonylamino-1-methoxypyridinium salts (60JJ1418). Side reactions include the partial replacement of ring methoxy groups (60JJ1418) and the formation of cyanomethyl derivatives; for example, 1-methoxy-2,6-dimethylpyridinium ion gives *392*, probably by a mechanism of the type shown in structure *393* (59CT925). The introduction of a cyano group into the benzene ring of the quaternary salt of benzimidazole 1-oxide is an exception to the normal α- or γ-substitution (*394* → *395*) (66CT375).

ii. Organometallic Compounds

a. On Free N*-Oxides.* Grignard reagents and organolithium compounds react with heterocyclic *N*-oxides to give α-alkyl and α-aryl heterocycles (*396* → *398*). Examples are collected in Table 3.38. The intermediates (*397*) are generally converted into the aromatic products (*398*) in the course of the reaction, or oxidized by the unreacted *N*-oxide in the reaction mixture to form α-substituted *N*-oxides as by-products (65JJ331; 65JO910; 67JJ942). In the reaction of 2-phenylquinoxaline 4-oxide with aryl Grignard reagents, addition of *p*-benzoquinone prior to hydrolysis gives the 3-arylquinoxaline 4-oxides (66JJ571), and similar results have been reported in the phthalazine series (68JJ1333).



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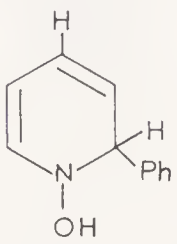


(399)

Yields are generally poor, but can be much improved by carrying out the reaction in tetrahydrofuran as solvent when the intermediates (*397*) are more stable and are protonated to give isolatable hydroxy compounds, e.g. *399* (65JO910), which on heating (with or without isolation) readily lose water to give the aromatic compounds.

The *N*-oxide also reacts with the Grignard reagent as an oxidizing agent and the deoxygenated heterocycle is often formed as a by-product; sometimes deoxygenation occurs exclusively (54RS2351). α-Methoxy groups are

Table 3.38. Reactions of *N*-Oxides with Organometallic Compounds (396 → 398)

Ring system	Substituents	Organometallic compound	Products (% yield)	References
Pyridine 1-oxide	—	PhMgBr	2-phenylpyridine	40BS133
	—	PhMgBr	2-phenylpyridine (13) and 2,2′-diphenyl-4,4′-bipyridine (4)	49JJ51
	—	PhMgBr[a]	1,2-dihydro-1-hydroxy-2-phenylpyridine (60–80)[b]	65JO910
	2-methyl	PhMgBr	1,2-dihydro-1-hydroxy-6-methyl-2-phenylpyridine (54)	65JO910
	4-methyl	PhMgBr	2-phenyl-4-picoline (23)	65JO910
	3-(2-methyl-1-oxido-6-piperidyl)[c]	MeMgI	6-methyl-3-(1-methyl-2-piperidyl)pyridine	63ZO1038
	2-phenyl	PhMgBr	2,6-diphenylpyridine (50)	58AN1395
	4-phenyl	PhMgBr	2,4-diphenylpyridine (20)	58AN1395
Quinoline 1-oxide	—	PhMgBr	2-phenylquinoline (90)	40BS133, 53G58, 65JO910
	—	PhMgBr[a]	2-phenylquinoline 1-oxide (60) and 2-phenylquinoline (30)	65JO910
	—	PhMgBr[d]	1,2-dihydro-1-hydroxy-2-phenylquinoline (25), 2-phenylquinoline (20), and 2-phenylquinoline 1-oxide (40)	65JO910
	—	Alkyl-MgBr (various)	quinoline (3–18), 2-alkylquinoline (8–85), and 2-alkylquinoline 1-oxide (5–32)	65JJ331
	2-alkoxy	PhMgBr	2-phenylquinoline 1-oxide[e]	54AN1029

[a] Reaction carried out in tetrahydrofuran.
[b] Easily dehydrated to give 2-phenylpyridine; 2-phenylpyridine and 2,2′-diphenyl-4,4′-bipyridine obtained as by-products.
[c] Together with 3-(1-methyl-2-piperidyl)pyridine 1-oxide.
[d] Reaction carried out at 15–20°.
[e] 2-methoxy → 2-phenyl; if excess PhMgBr is used, the product is 2-phenylquinoline.

Table 3.38. Reactions of *N*-Oxides with Organometallic Compounds (396 → 398)—*continued*

Ring system	Substituents	Organometallic compound	Products (% yield)	References
Quinoline 1-oxide, *cont'd.*	4-alkoxy	PhMgBr	4-alkoxy-2-phenylquinoline (13–16) and 4-alkoxy-2-phenylquinoline 1-oxide (64–65)	65JO910
	6-alkoxy	PhMgBr	6-alkoxy-2-phenylquinoline (data)	53G58
	6-alkoxy-4-(1-hydroxyalkyl)[f]	PhMgBr, PhLi	2-phenyl-4-substituted-quinoline (data)	50JJ381
	4-chloro	PhMgBr	4-chloro-2-phenylquinoline (data) and 4-chloro-2-phenylquinoline 1-oxide (63)	65JO910
	4-methyl	PhMgBr	4-methyl-2-phenylquinoline (30) and 4-methyl-2-phenylquinoline 1-oxide (45)	65JO910
	6-methyl	PhMgBr	6-methyl-2-phenylquinoline	53G58
Benzo[*f*]- or -[*h*]-quinoline 1-oxide	—	PhMgBr	2-phenylbenzo[*f*]- or -[*h*]quinoline	53G622
Phthalazine 3-oxide	1-phenyl	PhMgBr	1,4-diphenylphthalazine and 3-oxide	66JJ576
	1-phenyl	MeMgI	4-methyl-1-phenylphthalazine 3-oxide	67JJ940
Quinoxaline 1-oxide	—	PhMgBr, PhLi	2-phenylquinoxaline, 2-phenylquinoxaline 1-oxide, 2,3-diphenylquinoxaline, and 2,2′-biquinoxaline	67JJ942
	3-ethyl and 3-phenyl	PhMgBr, EtMgBr	2-ethyl-3-phenyl- and 3-ethyl-2-phenyl-quinoxaline	66JJ571, 67JJ643
	3-phenyl	PhMgBr, PhLi	2,3-diphenylquinoxaline and 1-oxide	62JJ1093

[f] Quinine *ar*-*N*-oxide; hydroquinine *ar*-*N*-oxide reacts analogously.

Table 3.38. Reactions of *N*-Oxides with Organometallic Compounds (396 → 398)—*continued*

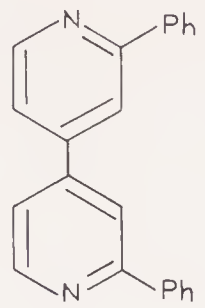
Ring system	Substituents	Organometallic compound	Products (% yield)	References
Δ^1-Pyrroline 1-oxide	2-ethyl-5,5-dimethyl	EtMgBr	5-ethyl-1-hydroxy-2,2-dimethylpyrrolidine (89)	59J2094
	5,5-dimethyl	MeMgBr	2,5,5-trimethyl-Δ^1-pyrroline 1-oxide (data)	59J2094, 64T291S
	3,3,5,5-tetramethyl	MeMgBr	1-hydroxy-2,2,4,4-tetramethylpyrrolidine (81)	59J2094
Indoline 1-oxide	2-phenyl-3-oxo[g]	PhMgBr	2,2-diphenyl-3-oxo-1-hydroxyindoline	39H411

[g] 2-Phenylisatogen.

Table 3.39. Reactions of Grignard Reagents with *N*-Alkoxy Quaternary Salts

Ring system	Substituents	Anion	Position of substitution	Yield, %	References
N-Alkoxypyridinium	1-ethoxy	Br^-	2	—	60CI1482, 62CZ567
	1-ethoxy-3- and -4-methyl	Br^-	2	—	60CI1482
N-Akoxyquinolinium	1-ethoxy	I^-	2	50–60	63CZ535
	1-ethoxy-4-methyl	I^-	2	ca. 70	63CZ535
N-Alkoxybenzimidazolium	1-methoxy-3-methyl	I^-	2	—	66CT375

often replaced in the reaction (54AN1029). The bipyridyl derivative *400* is formed as a by-product in the reaction of phenylmagnesium bromide with pyridine 1-oxide (49JJ51; 65JO910). Nitrones and simple cyclic nitrones



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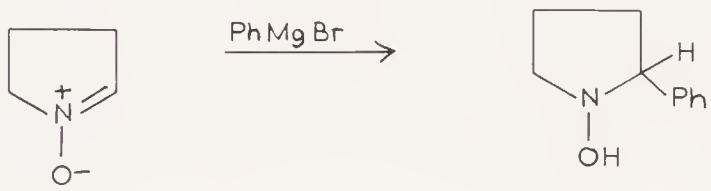

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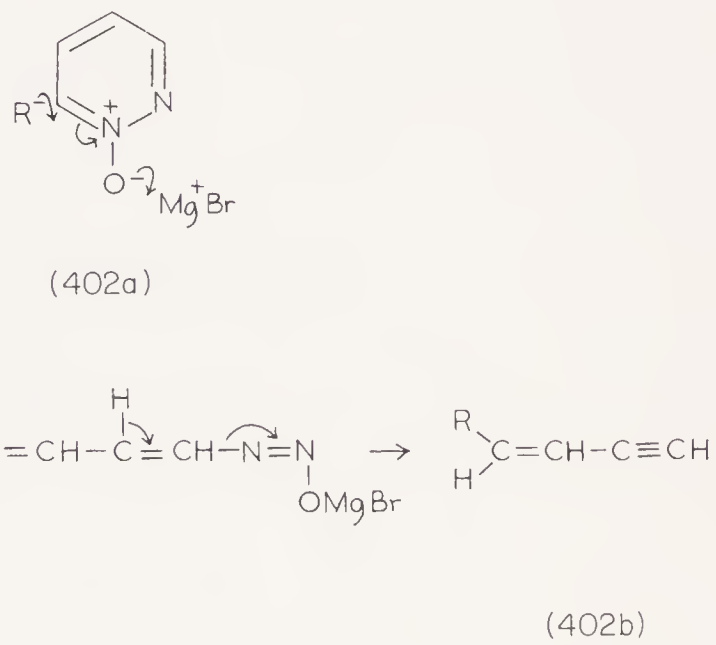


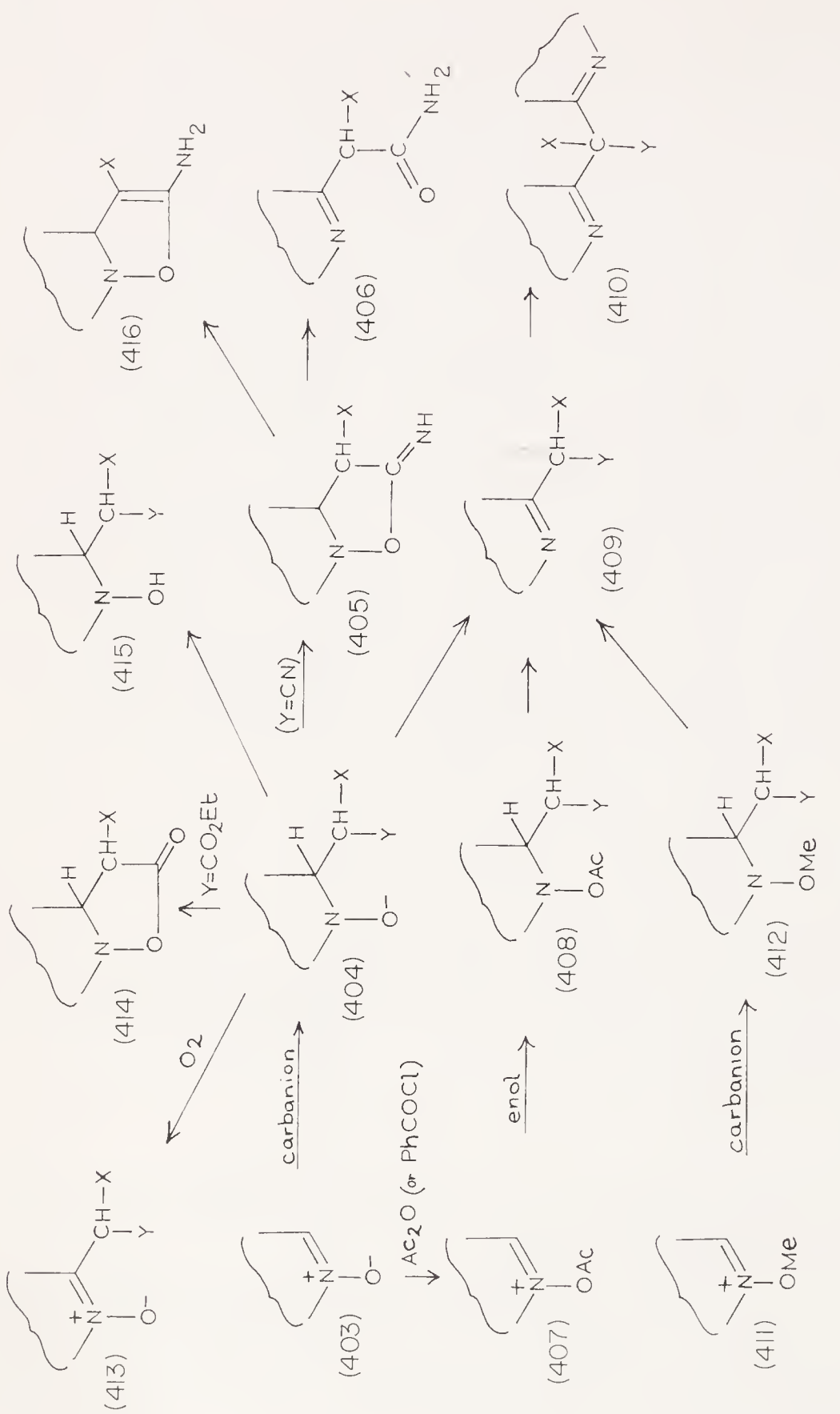
(402a)

(402b)

react with Grignard reagents to yield hydroxylamine derivatives: e.g. *401* → *402* [59CB1748; 64T291(S1)].

With pyridazine 1-oxides, the reaction takes an extraordinary course to yield vinyl acetylenes, apparently by the mechanism *402a* → *402b*, as reported simultaneously by two Japanese groups (69CH710; 69TL2667). Some butadienes are formed as by-products in reactions involving two moles of Grignard reagent.

b. On N-*Alkoxy Quaternary Salts*. Grignard reagents react with 1-alkoxypyridinium and other *N*-alkoxy cations to give the corresponding 2-substituted heterocycles. Examples are tabulated in Table 3.39. Although this reaction has not yet been extensively studied, the yields appear to be


(416)
(406)
(410)
(415)
(405)
(409)
(Y=CN)
(414)
(404)
(408)
(412)
Y=CO2Et
O2
carbanion
Ac2O (or PhCOCl)
enol
carbanion
(413)
(403)
(407)
(411)

much better than those reported for the reaction of Grignard reagents with simple *N*-oxides, thus the reaction is potentially interesting from a synthetic viewpoint.

iii. Active Hydrogen Compounds

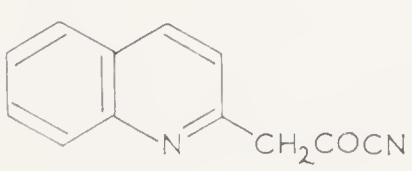
The reactions of *N*-oxides with active hydrogen compounds occur under a wide variety of conditions and depending on the nucleophile and the *N*-oxide give an array of different products, some of which are given in the scheme *403–416*. Reactions of this type are summarized in Table 3.40. Free *N*-oxides, *N*-oxides and acylation agent, and quaternized *N*-oxides can all be used in the reaction.

Reaction of the free *N*-oxide with the active hydrogen compound as its carbanion (base catalysis) (*403* → *404*) succeeds only (*a*) for reactive systems such as pyrroline 1-oxide, isatogen, and 3-quinoxalinone 1-oxide; (*b*) where there is extra activation by a nitro group; and (*c*) in the special case of acetylene where the reaction apparently succeeds even with pyridine 1-oxide (59USP2874162; 63ZK269).

In the presence of acetic anhydride, quinoline 1-oxide reacts with a variety of active hydrogen compounds (*407* → *408* → *409*); e.g., acetyl cyanide (63CT411) and ethyl cyanoacetate (63CT415) give the adducts *417* and *418*, respectively. However, the reaction fails with acetone, acetophenone, and phenylacetonitrile. Pyridine and 2-picoline 1-oxides condense similarly with ethyl cyanoacetate, but the yields are poor (63CT415). Quinoline 1-oxide also undergoes reactions of this type in the presence of benzoyl chloride, thus cyclohexanone yields the adduct *419* (67AN688).

Quaternized *N*-oxides react under mildly basic conditions in sequences of type *411* → *412* → *409*. For example, 1-methoxyquinolinium salts react with simple ketones to give quinolyl ketones (*420*) in reasonable yield, but this reaction fails in the pyridine series (63CT514). Quaternary salts of benzimidazole 1-oxides react similarly (66CT375).

If a free α-position is available, it is usually attacked. One exception is the reaction of 4-nitroquinoline 1-oxide with diethyl malonate, which gives the 3-substituted product *421*, the nitro group changing the orientation; in this case, addition is followed by oxidation, some of the nitro compound acting as the oxidizing agent (64JO3381). If an α-position is not available, reaction occasionally occurs in a fused benzene ring; e.g., 2-nitrophenazine 5,10-dioxide yields *422* (67G1826), and 1,2-dimethylbenzimidazole 3-oxide gives the 6-substituted derivative *423* (66CT1219).



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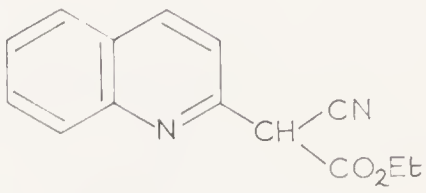

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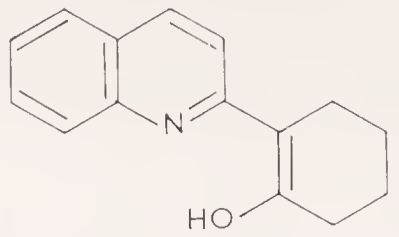

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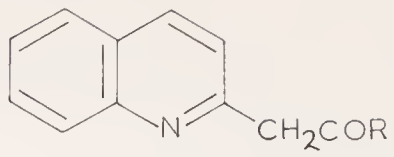

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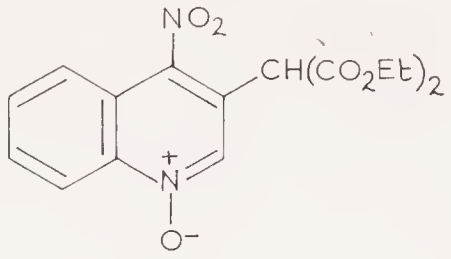

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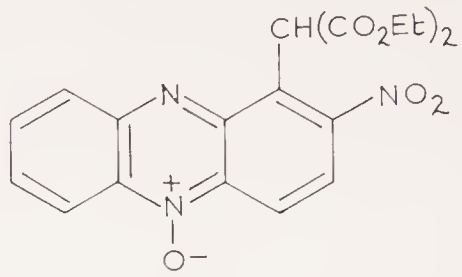

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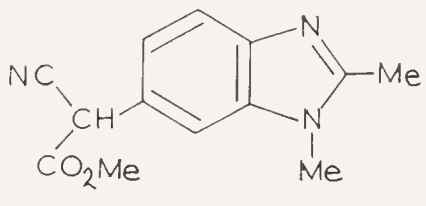

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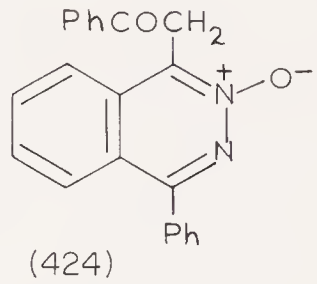

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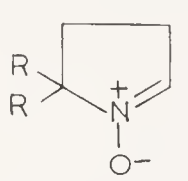
The usual products from reactions with "aromatic" *N*-oxides are of type *409*; however, three variations are known. (*a*) Further reaction can occur to give a bis-heteroaryl derivative (*410*), as is found in the reaction of quinoline 1-oxide with diethyl malonate, probably because the initial adduct in this case is easily soluble in the reaction mixture (63CT415). (*b*) Nitriles are sometimes hydrolyzed to amides via reaction sequences of the type *404* → *405* → *406*; the addition of either ethyl cyanoacetate or malonitrile to 3-quinoxalinone 1-oxide is of this type (64CI1622). (*c*) The intermediate *404* can be reoxidized to a substituted *N*-oxide (*413*), as in the reaction of 1-phenylphthalazine 3-oxide with acetophenone to give *424* (67JJ940).



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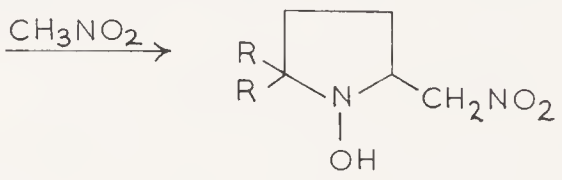

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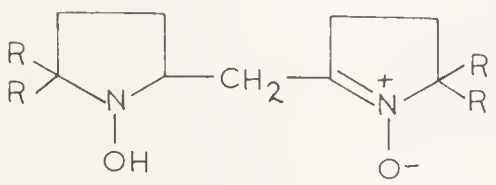

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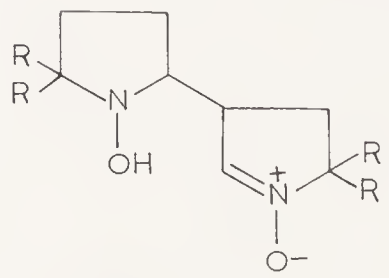

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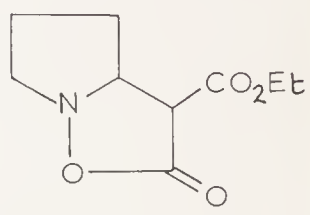

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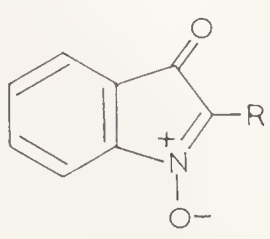

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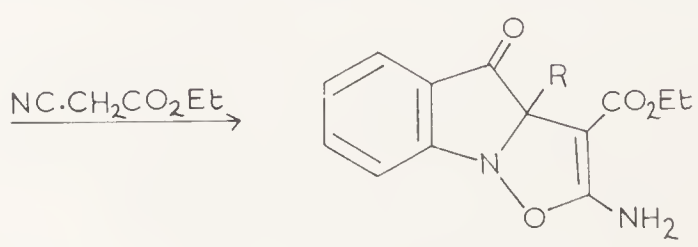

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Table 3.40. Reactions of *N*-Oxides with Active Hydrogen Compounds (cf. 403 → 416)

Ring system	Substituents	Active hydrogen compound	Catalyst	Group introduced (or structural formula)	Yield, %	References
Pyridine 1-oxide	—	$R\text{-}C{\equiv}C^-Na^+$	—	2-R-C≡C-	—	59USP2874162
	— and 2-methyl	$CN\text{-}CH_2CO_2Et$	Ac_2O	2-(or 6)-$CH(CO_2Et)$-CN	26 and 17	63CT415
Quinoline 1-oxide	—	CH_3COCN	Ac_2O	2-CH_2COCN	25	63CT411
	—	cyclohexanone, acenaphthenone, oxindole	PhCOCl	2-(-C=C-OH-$(CH_2)_3CH_2$)	—	67AN688
	—	$R\text{-}C{\equiv}C^-Na^+$	—	2-R-C≡C-	—	59USP2874162
	— or 4-methyl	$CN\text{-}CH_2CO_2Et$	Ac_2O	2-$CH(CN)CO_2Et$	88, data	63CT411, 63CT415
	—	$CH_2(CN)_2$	Ac_2O	2-$CH(CN)_2$	—	69T4291
	1-methoxy[a]	CH_3COR (various)	Na_2CO_3	2-CH_2-CO-R	4–38	63CT514
	4-nitro	$CH_2(CO_2Et)_2$	NaOEt	3-$CH(CO_2Et)_2$	36	64JO3381
Phthalazine 3-oxide	1-phenyl	$PhCOCH_3$	NaOH	4-CH_2COPh	69	67JJ940
Quinoxaline 1-oxide	3-oxo	$CH_3COCH_2CO_2$-Et, $CN\text{-}CH_2CO_2$-Et, $CH_2(CN)_2$	piperidine	2-$CH(COCH_3)CO_2$-Et, 2-$CH(CO_2Et)$-$CONH_2$, 2-$CH(CN)CO_2NH_2$	—, 60, 78	64CI1622
	4-H- or -methyl-3-oxo	$CH_3COCH_2CO_2$-Et, $PhCOCH_2$-CO_2Et, $CO(CH_2CO_2$-$Et)_2$, CH_3-$COCH_2$-$COCH_3$, $PhCOCH_2CN$	piperidine	2-CO_2Et, 2-$COCH_3$, 2-CN	60–90, 64, 50–86[b]	64J1986

[a] 1-Methoxyquinolinium salt.
[b] Lower yields were obtained with the 4-methyl derivative.

Table 3.40. Reactions of *N*-Oxides with Active Hydrogen Compounds (cf. 403 → 416)—*continued*

Ring system	Substituents	Active hydrogen compound	Catalyst	Group introduced (or structural formula)	Yield, %	References
Phenazine 5-oxide *	—	RCH_2COR'	NaOMe	1-CHR′COR	(data)	68AN1380
Phenazine 5,10-dioxide	2-nitro	$CH_2(CO_2Et)_2$	NaOEt	1-$CH(CO_2Et)_2$	(data)	67G1826
Pyrroline 1-oxide	5,5-disubstituted	CH_3NO_2	NaOEt	2-CH_2NO_2	74	59J2094
	5,5-dimethyl	$CH_2(CO_2Et)_2$	NaOEt	(see structure *429*)	96	67J(C)1683
	5,5-disubstituted	Δ^1-pyrroline 1-oxides	Ph_3CNa	(see structures *427* and *428*)	ca. 35	59J2109, 59J2116
Isatogen	2-substituted	CN-CH_2-CO_2Et	piperidine	(see structure *431*)	55–90	66TL3857
Benzimidazole 1-oxide	1-methoxy-3-methyl	CN-CH_2-CO_2Me, $CH_2(CN)_2$	None	2-$CH(CN)CO_2Me$, 2-$CH(CN)_2$	(data)	66CT375
	3-methyl	CN-CH_2CO_2Me	None	2-$CH(CN)CO_2Me$	(data)	64CT783
	2,3-dimethyl	CN-CH_2-CO_2Me	Ac_2O	5-$CH(CN)CO_2Me$	(data)	66CT1219
Benzofuroxan	—	$CH_2(Bz)_2$, $AcCH_2$-$COCH_3$	Et_3N	see note [c]	78	66JO4067

[c] Quinoxaline 1,4-dioxides are formed.

* Phenazine 10-oxide; see addendum in the Appendix.

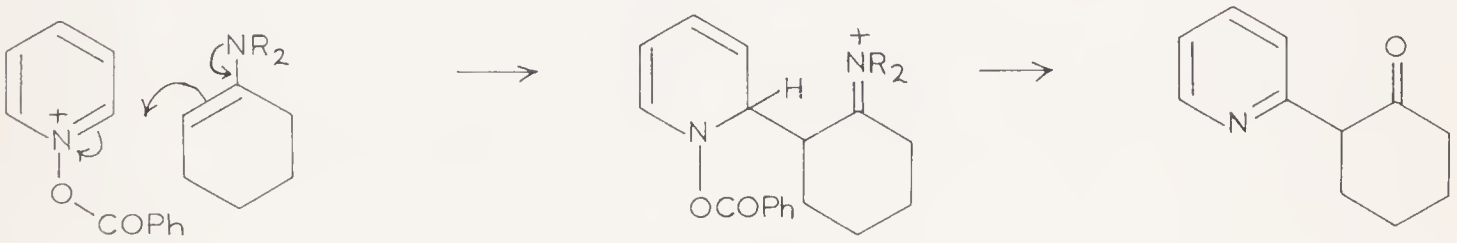
Non-aromatic *N*-oxides usually yield simple adducts (*415*). Thus, pyrroline 1-oxides add nitro compounds to give adducts (*425* → *426*) (59J2094), and react with anions derived from the same or other pyrroline 1-oxides to yield dimeric products of type *427* or *428* (59J2109; 59J2116). However, intramolecular cyclization can occur with an ester (*404* → *414*, Y = CO_2Et) or nitrile group (*404* → *405* → *416*, Y = CN), as in the reaction of pyrroline 1-oxide with malonic ester to form *429* [67J(C)1683] and of isatogens (*430*) with ethyl cyanoacetate to yield Δ^4-isoxazolines (*431*) (66TL3857).

Benzofuroxans also react with enolate anions; see Section III-5Ci.

iv. Enamines

N-Oxides react with enamines in the presence of benzoyl chloride or tosyl chloride to give ketones in good yield by sequences of the type *432* → *434*. These reactions are summarized in Table 3.41.

Dimethylaniline, indole, and antipyrine can enter into reactions of this type as enamines. Thus, quinoline 1-oxide reacts with dimethylaniline in the presence of benzoyl chloride to form 2-(*p*-dimethylaminophenyl)quinoline (64JJ35). Indoles react with quinoline 1-oxides in the presence of an acylating agent to yield *β*-indolyl derivatives, *435* → *436*; this reaction usually fails in the pyridine series, but the presence of an electron-accepting substituent in 3-ethoxycarbonylpyridine 1-oxide facilitates reaction and *437* is obtained (67CT363). Antipyrine yields products of type *438* (67CT1380).



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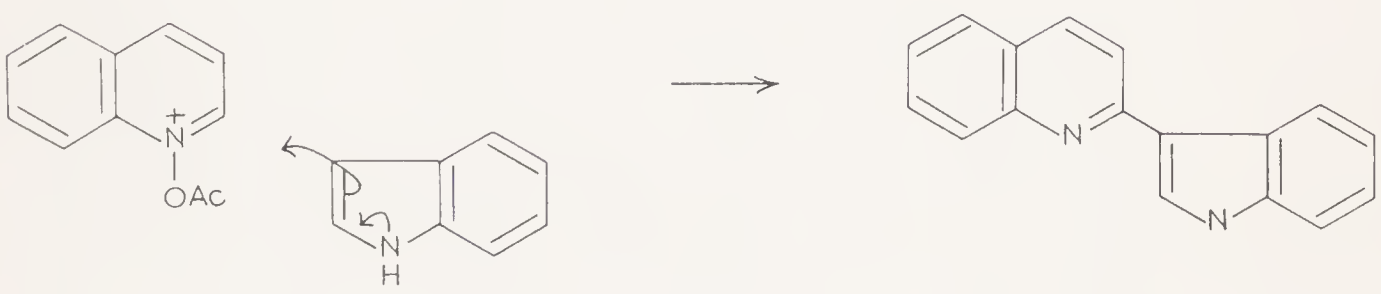

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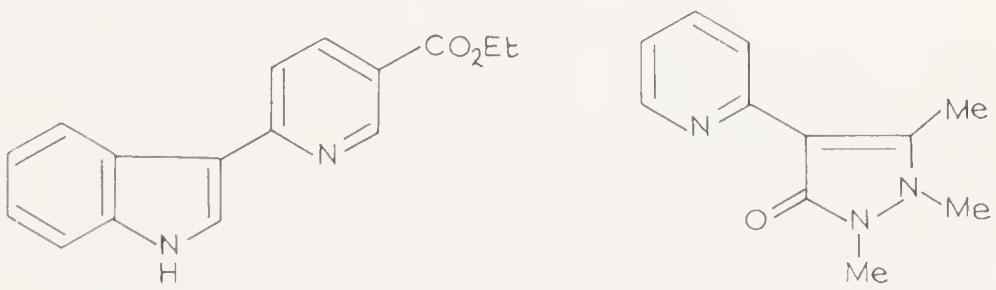


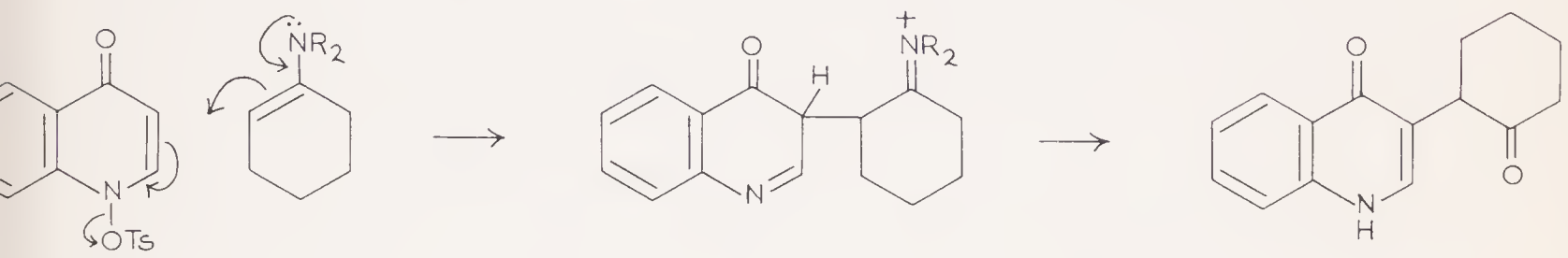
(437) (438)

Table 3.41. Reactions of *N*-Oxides with Enamines in the Presence of Acylating Agents (432 → 434)

Ring system	Substituents	Enamine	Catalyst	Group introduced	Yield, %	References
Pyridine 1-oxide	—	$C_4H_8CH{=}C\text{-}NR_2$	Ac_2O	2-C_4H_8-CO-CH	good	65CT912
	—	Antipyrine	BzCl	2-$C_{11}H_{11}N_2O$[a]	5	67CT1380
	—, 4-Cl	$Me_2C{=}CHNR_2$	BzCl, TsCl	2-CMe_2CHO	—	69JJ641
	2- or 4-chloro	*N*-(1-cyclohexenyl)-morpholine	BzCl	6- or 2-(2-ketocyclohexyl)	(data)	67CT474
	3-ethoxycarbonyl	Indole	BzCl, TsCl	6-(3-indolyl)	30, 5	67CT363
Quinoline 1-oxide	—	$PhNMe_2$	BzCl	2-(*p*-Me_2N-C_6H_4-)	—	64JJ35
	—	Various enamines of cyclohexanone[b]	BzCl, TsCl, Ac_2O, AcCl	2-(2-ketocyclohexyl)	5–74	63CT1331
	—	$C_4H_8CH{=}C\text{-}NR_2$	Ac_2O	2-C_4H_8-CO-CH	good	65CT912
	—; 2- or 4-chloro	Indole	BzCl, TsCl, Ac_2O	2-(3-indolyl)	10–67	67CT363
	—; 4-chloro	Antipyrine	BzCl	2- and 4-$C_{11}H_{11}N_2O$[a]	63 and 19[c]	67CT1380
	2- or 4-chloro	*N*-(1-cyclohexenyl)-morpholine	BzCl	4- or 2-(2-ketocyclohexyl)	(data)	67CT474
	4-hydroxy	*N*-(1-cyclohexenyl)-morpholine	TsCl	3-(2-ketocyclohexyl)	(data)	67CT474
	2-methyl	*N*-(1-cyclohexenyl)-morpholine	TsCl	3-(2-ketocyclohexyl)	(data)	66CT762
	—, 4-Me	$Me_2C{=}CHNR_2$	BzCl, TsCl	2-CMe_2CHO	—	69JJ641
Isoquinoline 2-oxide	—	Antipyrine	BzCl	1-$C_{11}H_{11}N_2O$[a]	79	67CT1380
	—	$Me_2C{=}CHNR_2$	BzCl, TsCl	1-CMe_2CHO	—	69JJ641

[a] $C_{11}H_{11}N_2O$ denotes -C=C(CH_3)-N(Me)-N(Ph)-CO.
[b] Morpholine, piperidine, and pyrrolidine enamines of cyclohexanone.
[c] With 4-chloroquinoline 1-oxide, the 2-substituted product is obtained in 88 % yield.

These reactions occur preferentially in the α-position. However, if this position is blocked, as in quinaldine 1-oxide, the enamine attacks the γ-position provided tosyl chloride is used as the catalyst; 3-tosyloxyquinaldine is produced as a by-product (cf. Section III-4Ciiib) (66CT762). One example of reaction at a β-position is known: enamines react with 4-hydroxyquinoline 1-oxides in the presence of tosyl chloride to give the 3-substituted derivative, presumably by the mechanism shown (*439* → *441*) (67CT474). This reaction fails with 2-hydroxyquinoline 1-oxide and with 2- and 4-hydroxypyridine 1-oxide.



(439) (440) (441)

5. Other Reactions at Ring Carbon Atoms or at an *N*-Oxide Oxygen Atom

The major categories of electrophilic and nucleophilic attack at an *N*-oxide oxygen atom and at the ring carbon atoms of heterocyclic *N*-oxides are considered in Sections 1–4 of this chapter. In the present section, thermally initiated free radical and photochemical reactions at ring carbon atoms or at *N*-oxide oxygen atoms, and reactions involving a cyclic transition state (Diels-Alder and 1,3-dipolar additions) are discussed.

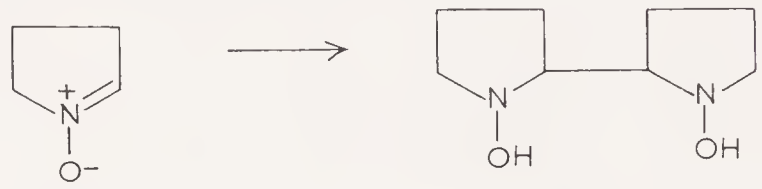
A. FREE-RADICAL REACTIONS

Kubota *et al.* (68JA5080) have prepared anion radicals derived from substituted pyridine and other *N*-oxides polarographically and analyzed the hyperfine coupling constants.

The preparative free-radical reactions of *N*-oxides have been little studied. Pyridine 1-oxide reacts with aryldiazonium salts to give 2-arylpyridine 1-oxides (59AL39). The relative reactivities of the nuclear positions in pyridine 1-oxide were shown by Dyall and Pausacker (61J18) to be in the order $2 > 4 > 3$ on the basis of the composition of the mixture of isomeric phenylpyridine 1-oxides formed in the reaction between pyridine 1-oxide and phenyl radicals derived from diazoaminobenzene. The relative reactivities of the nuclear positions agree quite well with those obtained from molecular orbital calculations (cf. Section I-2D).

Japanese investigators found that the reaction of phenyl radicals with 4-nitroquinoline 1-oxide gives 4-nitro-2-phenylquinoline 1-oxide together

with the deoxygenated product, 4-nitroquinoline (65JJ66). Quinoline 1-oxide is benzylated in the 2-position, and isoquinoline 2-oxide in the 1-position, by treatment with toluene and *t*-butyl peroxide (68AI9; 68AI21). Similar reactions occur in the carboline series (68AI21). Irradiation of quinoline 1-oxide in the presence of nitrosyl chloride or butyl nitrite yields 3-nitroquinoline 1-oxide, which is considered to be formed via a free-radical reaction (65CT1480). The conversion of 4-methylquinoline 1-oxide in methanolic hydroxylamine-*O*-sulphonic acid into 2-hydroxymethyl-4-methylquinoline 1-oxide is probably also a free-radical reaction involving attack by $\dot{C}H_2OH$ radicals (68TL2147).*



(442) (443)

(444) (445)

Reactions with alkali metals give various products (67CT435); pyridine 1-oxide yields the 4,4′-bipyridyl radical-anion, other pyridine 1-oxides give a substituted pyridine radical-anion with loss of the *N*-oxide oxygen atom. When an electron-withdrawing substituent such as a nitroso or nitro group is present, stable substituted pyridine 1-oxide anion-radicals are obtained. Pyrroline 1-oxides (*442*) also undergo reductive dimerization with sodium–potassium alloy to yield bimolecular products (*443*) (59J2123). Bis-azopyrroline 1-oxides (*444*) give stable radical-anions (*445*) on air oxidation (62P360; 65J1224); the formation and properties of more complex radicals of this type are discussed in reference 68J(C)1311 [cf. 65J1224]. Radical reactions are common in *N*-hydroxyindole chemistry (these compounds are tautomeric with benzo-3*H*-pyrrole 1-oxides) (67G1569; 67G1584).†

B. PHOTOCHEMICAL REACTIONS

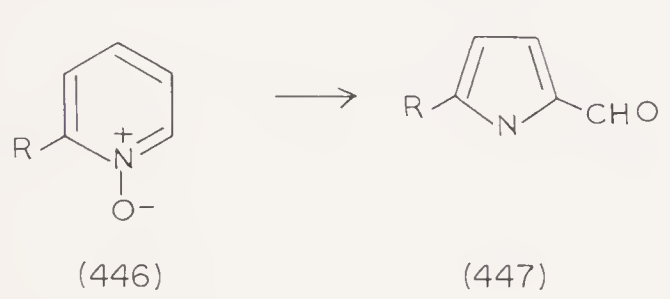
Photochemical deoxygenation of heterocyclic *N*-oxides is considered in Section III-2Giii; other photochemical reactions which do not involve substituents are collected here. Recently there has been intense activity in this area, particularly in Danish, Japanese, and French laboratories, and a fascinating variety of reactions has been reported.

*, † See addenda in the Appendix.

i. Pyridine 1-Oxides

Pyridine 1-oxide and its 2-methyl derivative are photolysed in an undefined solvent to 2-formylpyrroles (*446* → *447*); this reaction may occur by valence tautomerism of the oxazepine *448* (66TL1347), or by a reaction similar to that described below for the indoles with an additional N → C acyl migration. The French investigators found that in diethyl ether, 2-picoline 1-oxide gives some 3- and 5-hydroxy-2-methylpyridines together with the expected pyrroles (67CH979). More recent work (68CH292) shows that in ethanol or methanol solution the major reaction product is pyridine but that both 2-formyl- and 1-formyl-pyrrole are formed as by-products. The aldehyde corresponding to the alcohol used as solvent was also isolated by these investigators and considered to be evidence for the occurrence of the oxaziridine intermediate.

Kumler and Buchardt (68CH1321) have found that irradiation of 2,4,6-triphenylpyridine 1-oxide in acetone or methanol yields (in addition to the simple product of deoxygenation) a 1,3-oxazepine (*499*), 3-hydroxy-2,4,6-triphenylpyridine, and the pyrrole *450*. The primary photoproduct *451* is considered to isomerize either to *452* (the precursor of *449* and the 3-hydroxy derivative) or to *453* (the precursor of *449*). 2,6-Dicyanopyridine 1-oxide also yields such products (69T295).



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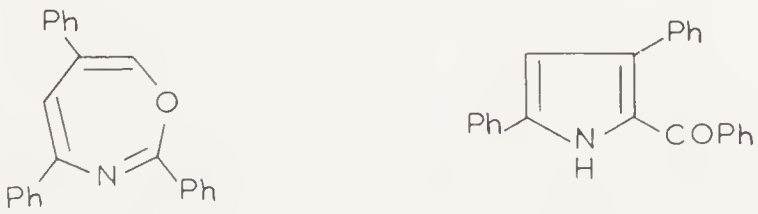

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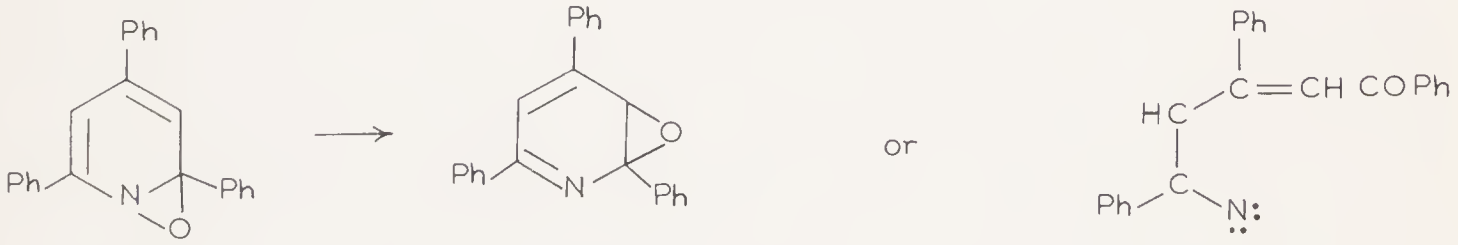
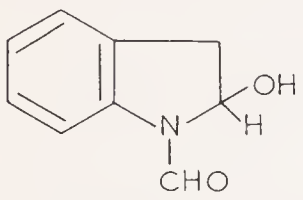


(451) (452) (453)

ii. Quinoline 1-Oxides and Isoquinoline 2-Oxides

Although the first reports indicated that quinoline 1-oxides are merely converted into 2-quinolones on irradiation (63AS1461; 65AS1120), it later

became clear that the reaction is considerably more complex. Streith *et al.* (66TL5555) found that irradiation of quinoline 1-oxide in aprotic solvents gives a mixture of 2-quinolone (15%), quinoline (7%), 1-formylindole (3%), and the dihydroindole derivative *454*. The Japanese group also found that 1-acylindoles are formed as by-products in these reactions; e.g., 1-formylindole was isolated from the reaction of quinoline 1-oxide, and 1-formyl-3-methylindole from that of lepidine 1-oxide (66CT1102). These reactions probably occur via oxaziridine intermediates (*455*); cf. the conversion of nitrones into compounds of this type on irradiation (59J2102). Attempts were made to isolate these oxaziridines and they first appeared to succeed, but it later became clear that the first isolable products are usually oxazepines.



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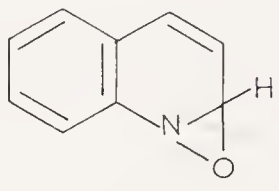

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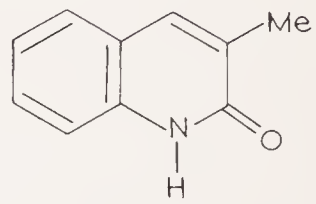

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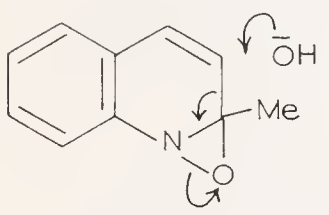

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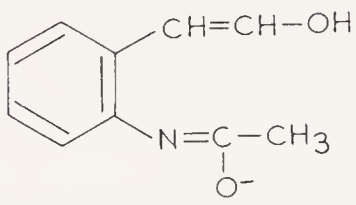

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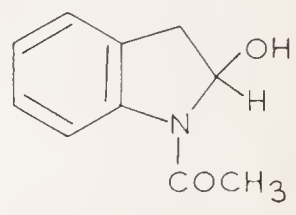

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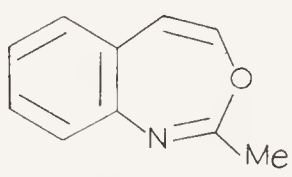
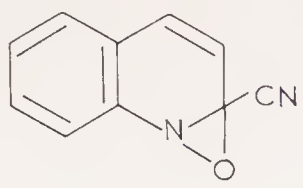


(460)

1-Acyl-2-hydroxydihydroindoles have been obtained from the reactions of various quinoline 1-oxides without a substituent in the 2-position (66TL4355); however, the results obtained with 2-substituted quinoline 1-oxides allow clearer insight into the reaction mechanism. 2-Methylquinoline 1-oxide on irradiation in methanol solution yields 3-methyl-2-quinolone (*456*) (65AS1120), together with 1-methyl-2-quinolone and *N*-acetylindole (65CT747). If the irradiation is carried out in benzene solution, 2-methylquinoline 1-oxide is converted mainly into the 1-acetyl-2-hydroxydihydroindole *459*, whereas in aqueous solution both *459* and 3-methyl-2-quinolone are formed (66AS262; cf. 65AS1120). The isolation of 1-acyl-2-hydroxydihydroindoles (*459*) following irradiation of various substituted 2-methylquinoline 1-oxides has been reported (66AS2467). Reaction paths of type *457* → *458* → *459* were first considered, but it is now more probable that *460* is an intermediate. Recently a detailed account of the photolysis

of 2-unsubstituted quinoline 1-oxides has appeared (69AS159); protic solvents favour the formation of 2-quinolones, aprotic solvents lead to the production of 1-formyl-2-indolinols.*



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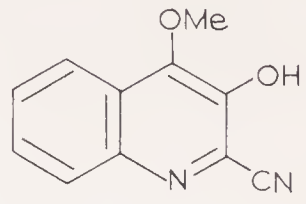

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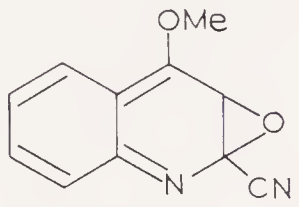

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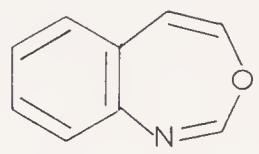
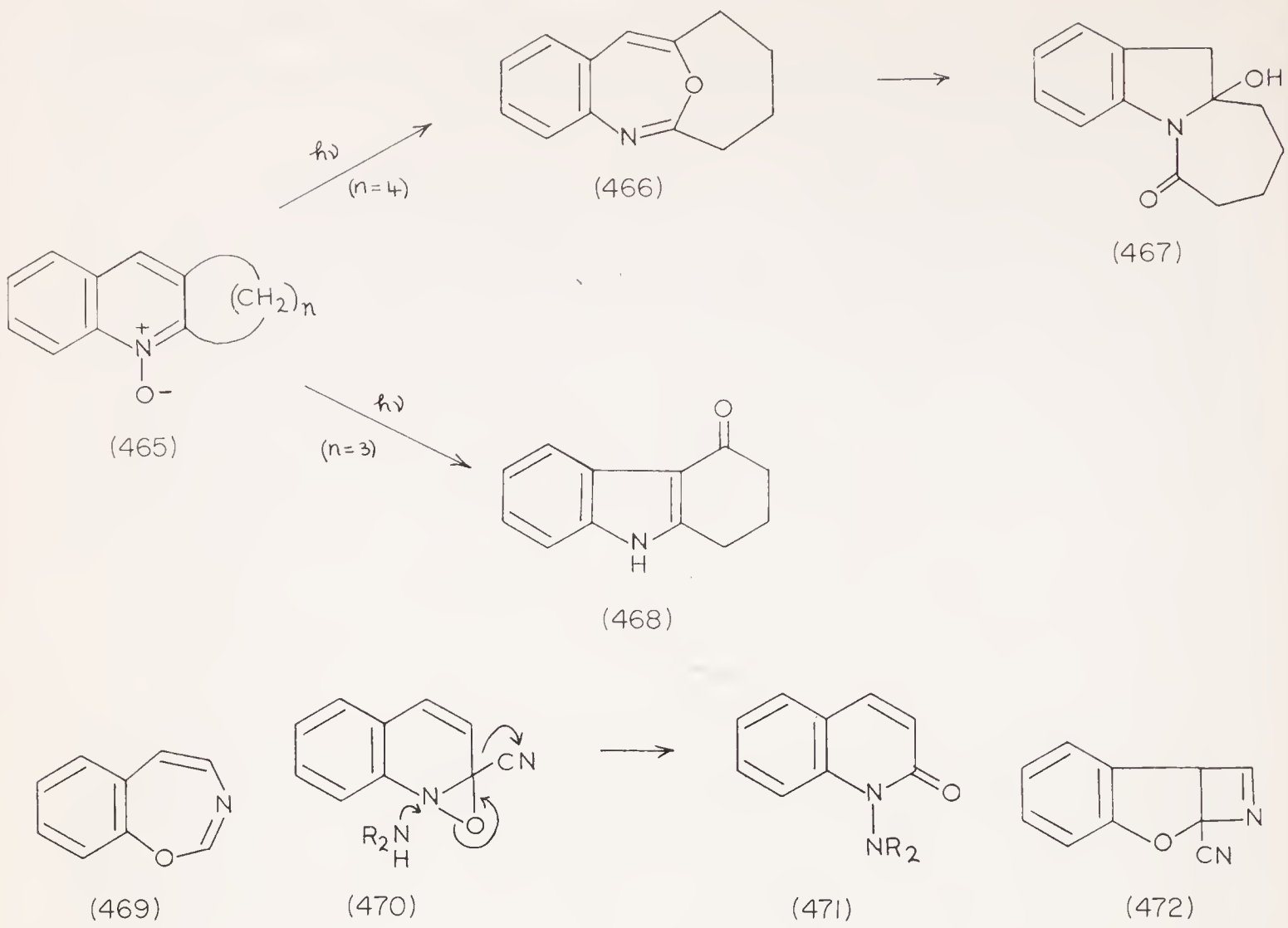


(464)

The irradiation of 2-cyano- and 2-phenyl-quinoline 1-oxide and isoquinoline 2-oxide was first studied by Kaneko and Yamada (66CT555; 66TL2145) who formulated the products of these reactions as oxaziridines (*461*). 2-Cyano-4-methoxyquinoline 1-oxide gives a 3-hydroxyquinoline product (*462*) which was considered to arise by isomerization of the oxirane *463* (66RD804; 66TL2145). Although the Japanese group recognized that oxazepines (*464*) were probably involved in some further reactions of the oxaziridines (66TL4701; cf. 67CT663), it was Buchardt who later showed by spectral, chemical, and X-ray evidence (66TL6221; 67AS1841) that the first products isolated after irradiation of 2-phenyl- and 2-cyano-quinoline 1-oxides are oxazepines (*464*) and not oxaziridines, which must be considered as unstable intermediates. Subsequently, Kaneko's group (67RD1; 67TL1873) adduced further evidence for the correctness of the oxazepine structure: photolysis of the 2,3-disubstituted quinoline 1-oxide *465* (n = 4) gives the expected oxazepine *466*, which is easily transformed into *467*. The homologue *465* (n = 3), however, photolyses to give the oxotetrahydrocarbazole *468* as the first isolable product; in this case Bredt's rule precludes the existence of the oxazepine as a stable compound. The photo-products from isoquinoline 2-oxides also have benzoxazepine structures (*469*) (67TL2741). The intermediate oxaziridines can be trapped in certain cases by carrying out the reaction in the presence of a secondary amine; for example, 2-cyanoquinoline 1-oxide affords 1-dialkylaminocarbostyrils (*471*) (67TL5237). 1-Cyano-3-methylisoquinoline 2-oxide, however, yields the azete *472*, presumably by valence tautomerism (probably photo-catalysed) of an intermediate oxazepine of type *469* (68TL5625).

* See addendum in the Appendix.

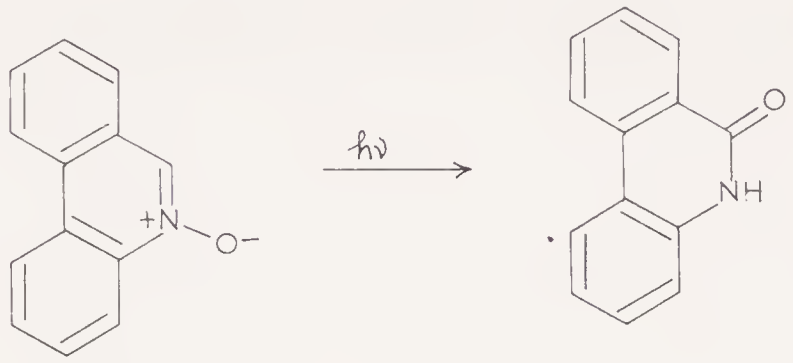


Irradiation of 4-nitroquinoline 1-oxide produces stable free radicals, the structures of which have been investigated by labelling methods (66CT897). This work has been extended (66CT1171) to many analogues, and it has been concluded that the 4-nitroquinoline 1-oxide is required for stable radical formation. Apparently two distinct radicals may be produced, depending on the solvent used. It is claimed that free radical production is greater in the presence of DNA and has been suggested that this may be connected with the carcinogenic activity of this compound (68CT1411).

iii. Phenanthridine and Acridine N-*Oxides*

Phenanthridine 5-oxide (*473*) is converted into phenanthridone (*474*) on irradiation (65JA1400). Photolysis of 6-substituted phenanthridine 5-oxides in ethanol gives 5-substituted phenanthridones by group migration from the 6-position to the 5-position, presumably via oxaziridine intermediates *475* (66CH767); small amounts of the deoxygenated phenanthridines are formed as by-products (66CT1102). However, irradiation of 6-phenylphenanthridine 5-oxide in benzene yielded only 17% of 5-phenyl-6-phenanthridone, together with 2-phenyldibenz[*d*,*f*-1,3]oxazepine (3%), 9-benzoylcarbazole (1%), 6-phenylphenanthridine (11%), and 2-benzamido-2′-hydroxybiphenyl (35%) (68CH1037). These and similar products arising from analogous reactions can be explained by the homolysis of the oxaziridine *475* to the diradical *476*.

The photolysis of acridine 10-oxide in ethanol solution yields 9-ethoxy-10-hydroxy-9,10-dihydroacridine by addition of a molecule of ethanol (66TL4211); however, in non-polar solvents the cycloheptindolone *477* is produced (68TL4519). Recently, it has been shown that the compound formed in ethanol is 11-ethoxy-5,11-dihydrobenz[*b*,*e*]-1,4-oxazepine [69LA(723)95].*



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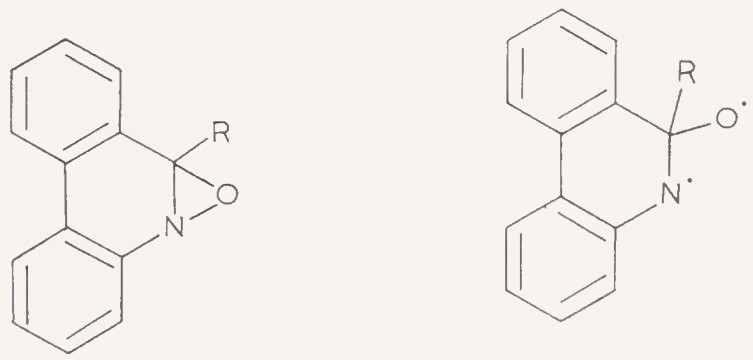

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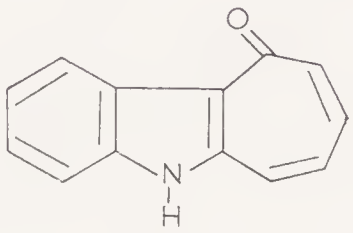


(477)

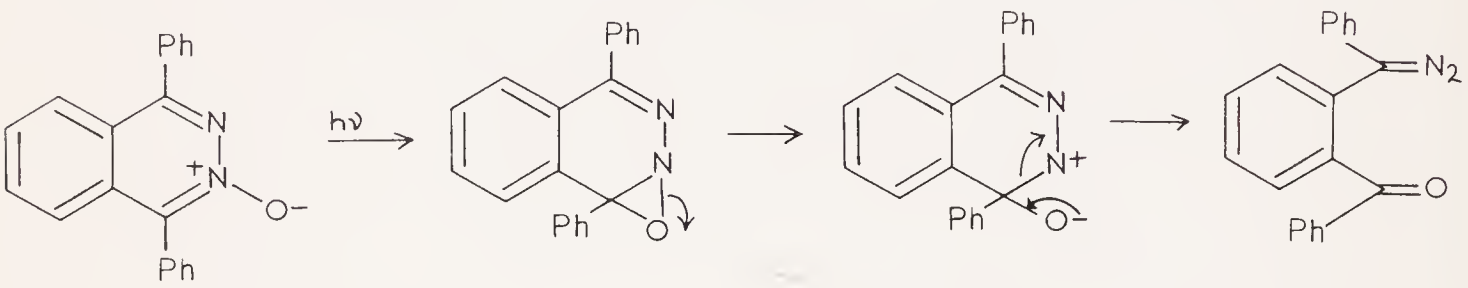
iv. Pyridazine, Phthalazine, and Quinazoline N-Oxides

Irradiation of pyridazine *N*-oxides in methanol solution yields pyrazoles and hydroxymethylpyridazines. The pyrazoles arise by a mechanism which is discussed below, while the hydroxymethyl derivatives are probably formed by a radical-chain mechanism involving CH_2OH species (67CH1176). Buchardt (68TL1911) has shown that the photolysis of 1,4-diphenylphthalazine 2-oxide (*478*) yields, in addition to the simple deoxygenation product, 1,3-diphenylisobenzofuran (*480*). The suggested mechanism is shown in the scheme *478* → *480*. Support for this scheme was obtained (68JA5640) by the conversion of the monocyclic analogue *481* into 3-benzoyl-1-phenylpyrazole (*482*) on irradiation: the formation of *482* may be rationalized by

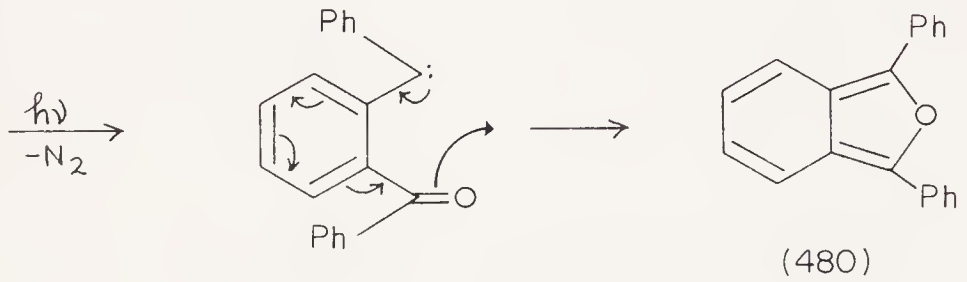
* See addendum in the Appendix.

the cyclization of a product of type *479*. Spectroscopic evidence for a diazo intermediate (cf. *479*) was obtained. Various pyridazine 1-oxides on irradiation in the presence of olefins transfer their oxygen yielding epoxides and the parent pyridazine (69TL2747).

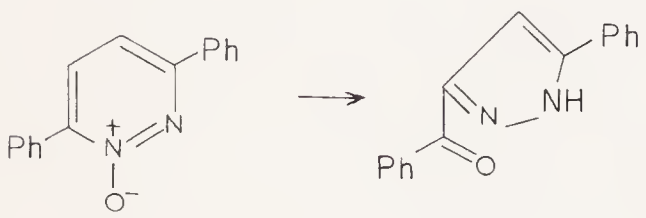
*4-Phenylquinazoline 3-oxide is photolyzed to 2-phenylbenz[*f*]-1,3,5-oxadiazepine (*483*) (67TL5233); this appears to be a general reaction (68JO4438). 6-Chloro-2-methyl-4-phenylquinazoline 1-oxide yields 1-acetyl-5-chloro-3-phenylindazole on irradiation (68JO4438).



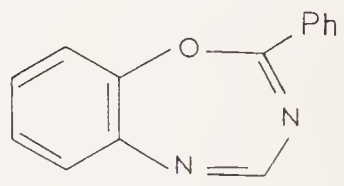
(478) (479)



(480)



(481) (482)

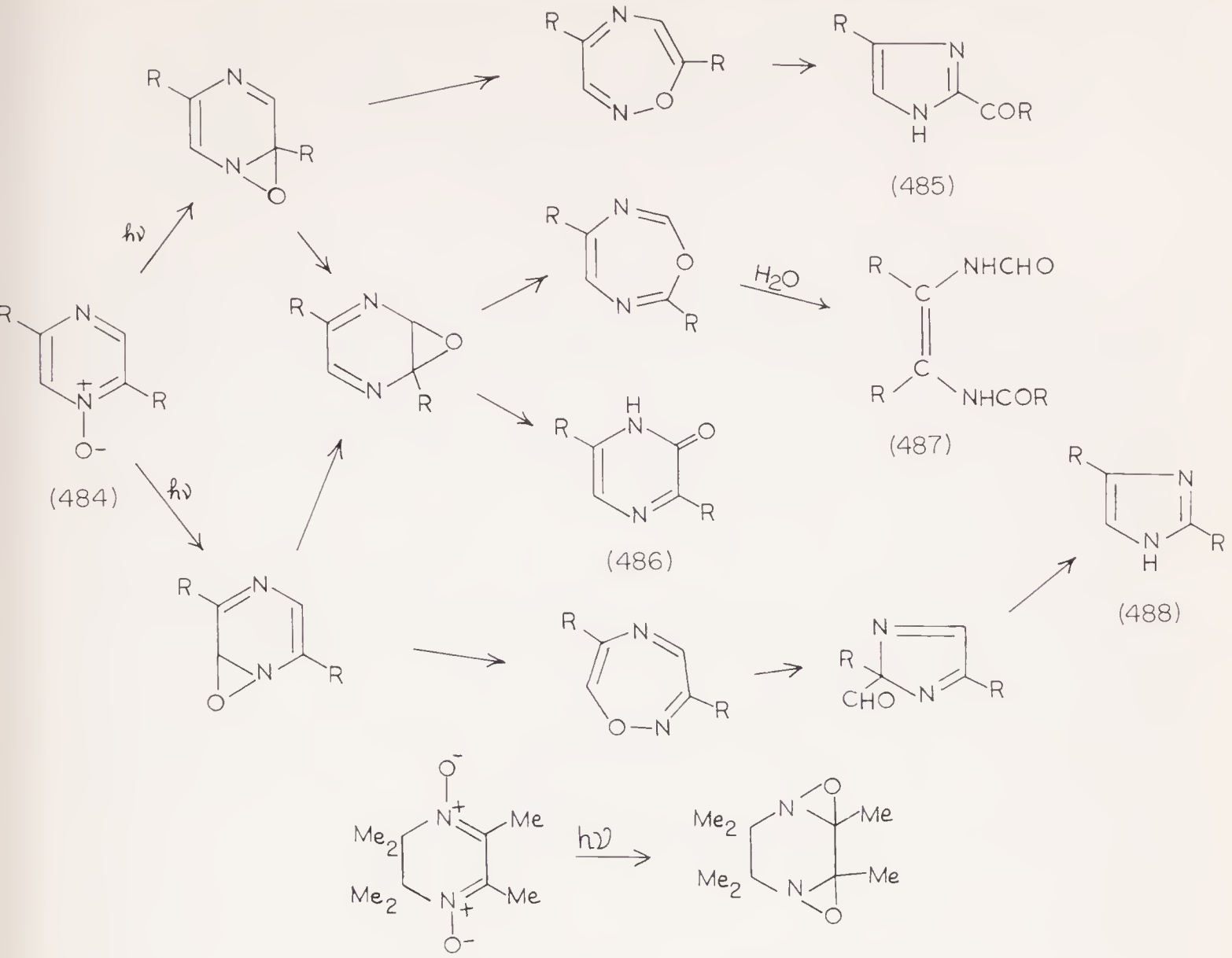


(483)

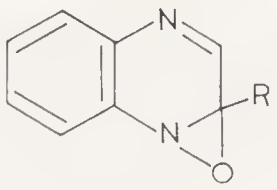
v. Pyrazine and Quinoxaline N-*Oxides*

On irradiation of 2,5-dialkyl- and 2,5-diphenyl-pyrazine 1-oxides (*484*), pyrazinones, imidazoles, and open-chain compounds can all be obtained. Ikekawa and Honma (67TL1197) have suggested a reaction scheme involving oxaziridines and oxadiazepines (*484–488*) to account for the various transformations. In benzene solution, 2-acylimidazoles (*485*) and 2-alkylimidazoles (*488*) are formed, whereas in aqueous solution, pyrazinones (*486*) and di(acylamino)ethylenes (*487*) predominate. The dihydropyrazine 1,4-dioxide *489* is photochemically isomerized to the bis-oxaziridine *490* [68J(C)1917].

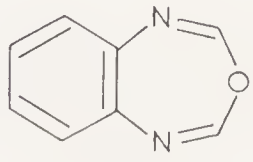
* See addendum in the Appendix.



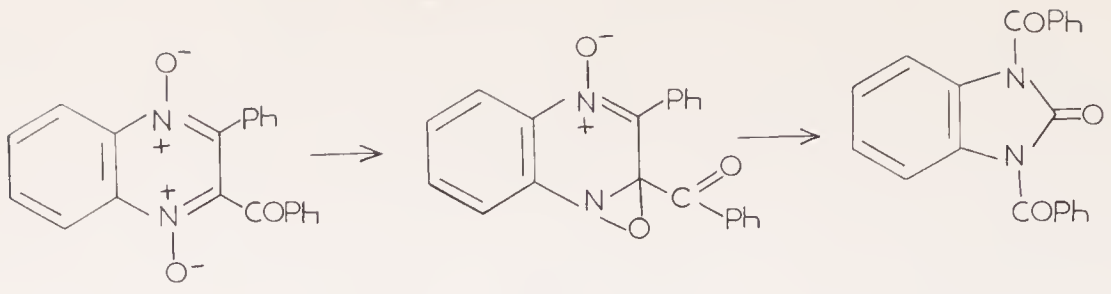
Early reports indicate that on irradiation in aqueous solution, quinoxaline 1-oxides yield 2-quinoxalinones, and the 1,4-dioxides give 3-quinoxalinone 1-oxides (53J2830). Photolysis of quinoxaline 1,4-dioxide in dilute hydrochloric acid leads to the formation of 2-chloroquinoxaline 1-oxide [66J(C)157; cf. 53J2830]. Various substituted quinoxaline mono-*N*-oxides have been irradiated in benzene solution: the intermediates were isolated and initially formulated as oxaziridines (*491*); further reaction of the intermediates gives diacyl-*o*-phenylenediamines (66CT1316). The unstable primary photo-products were later shown to be symmetrical oxadiazepines of type *492* by demonstrating that 3-phenyl- and 2-phenyl-quinoxaline 1-oxide yield the same derivative (67TL1873); NMR studies on the photolysis product from 2,3-diphenylquinoxaline 1-oxide also provided supporting evidence (67AS1399). The oxadiazepine structure is confirmed by X-ray crystallographic work (68AS877).



(491)



(492)



(493) (494) (495)

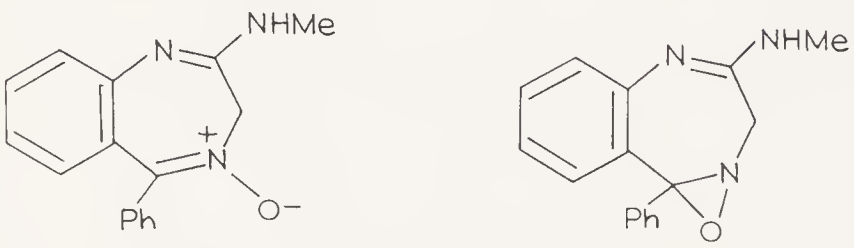
The photolysis of 2-benzoyl-3-phenylquinoxaline 1,4-dioxide (*493*) takes a different course, affording 1,3-dibenzoylbenzimidazolone (*495*); the authors have suggested that the benzoyl group in the intermediate *494* migrates and further oxaziridine formation then occurs (67TL753).

vi. Other N-*Oxides*

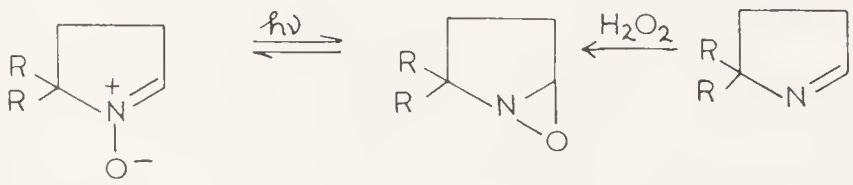
On photolysis, adenine 1-oxide yields 2-oxoadenine (64B880) together with adenine itself and the ring-opened product *496* (64TL3201). Triazolo-pyridazine *N*-oxides (*497*) are converted photochemically into the α-oxo-heterocycles (68JH513).

Little work has been reported on the photochemistry of *N*-oxides with five-membered rings; however, 2-phenylisatogen is converted smoothly into 2-phenyl-4*H*-3,1-benzoxazin-4-one (69CH312).*

(496) (497)



(498) (499)



(500) (501) (502)

The benzodiazepine 2-oxide *498* and the oxaziridine *499* are interconvertible photochemically [62JO4671; 63AB(5)195; cf. 68JO4438; 69AP152]; the same is true of pyrroline 1-oxides (*500*) and the isomeric oxaziridines

* See addendum in the Appendix.

(*501*), and in the benzothiadiazocine series (68M1117). Oxaziridines of type *501* can also be prepared from pyrrolines (*502*) as shown [59J2102; 68AJ2507; cf. 66J(C)2295]. Saturated seven-membered-ring azine *N*-oxides undergo ring opening to yield δ-diazoketones (69JA2818).

C. REACTIONS INVOLVING CYCLIC TRANSITION STATES

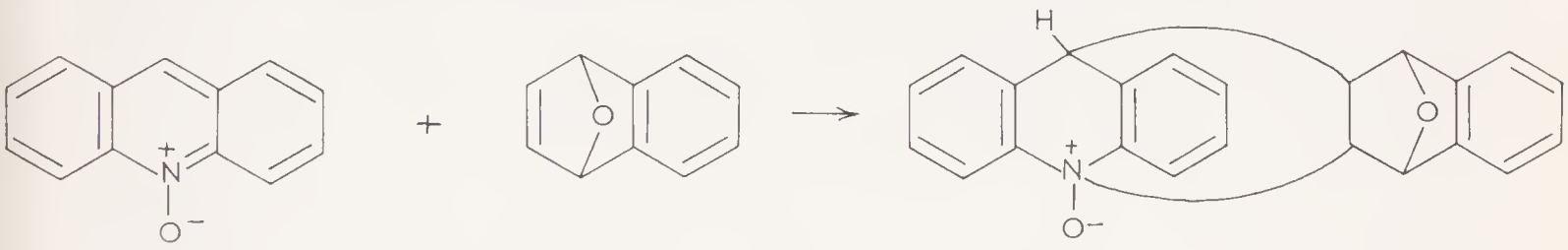
Three classes of reactions may be distinguished under this heading: the well-known Diels-Alder type, 1,3-dipolar additions, and spontaneous ring-opening reactions.

i. Diels-Alder Reactions

Examples of reactions of this type are sparse. Acridine 10-oxide (*503*) combines with 1,4-dihydro-1,4-epoxynaphthalene (*504*) to give *505* (62CB203).

Benzofuroxans (*506*) and enamines (*507*) react to form quinoxaline 1,4-dioxide derivatives (*508*) in good yield (65TL3253; 67AN1414). Benzofuroxans also react smoothly with various enolate anions (dibenzoylmethane acetylacetone, etc.) to yield quinoxaline 1,4-dioxides; *509* → *510* (66JO4067).*

Oxazole 3-oxides (*511*) react with phenyl isocyanate to give products which were originally formulated as bicyclic compounds (*514*) (15CB897), but which are now considered to be imidazole 3-oxides (*513*) (47J96). The mechanism of this transformation is unknown, but *512* may be formed from *511* and converted into an intermediate oxadiazepinone (*512a*).



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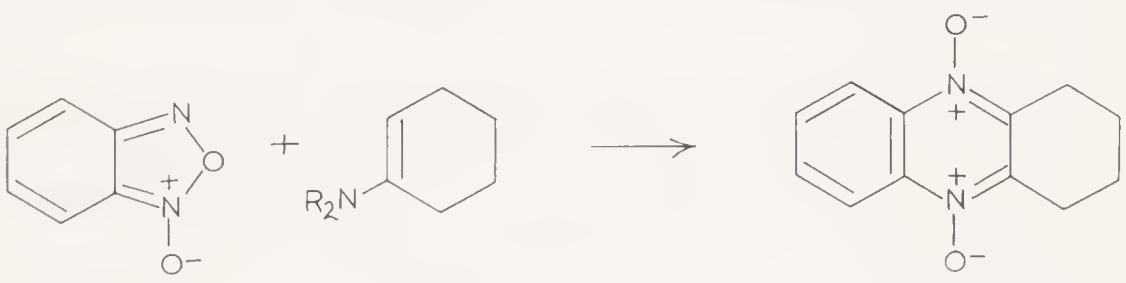
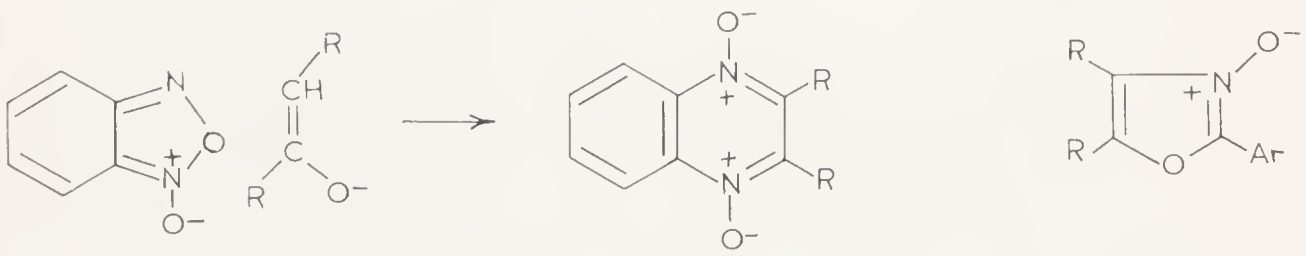
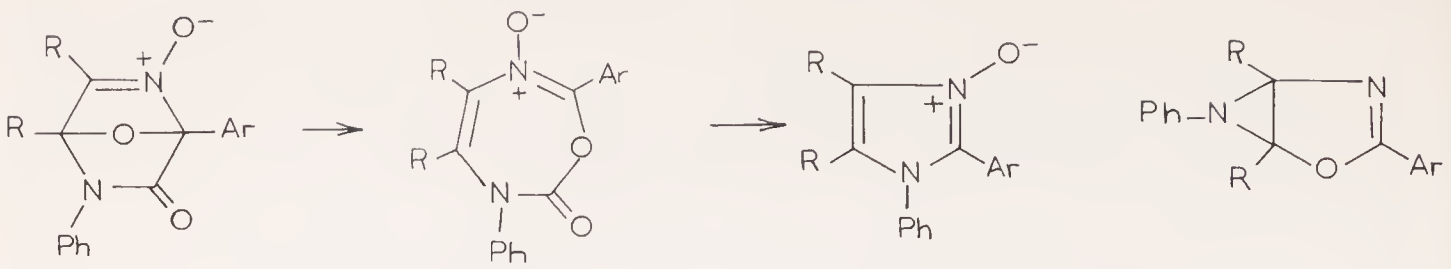


(506) (507) (508)



(509) (510) (511)

* See addendum in the Appendix.



(512) (512a) (513) (514)

ii. 1,3-Dipolar and Related Additions

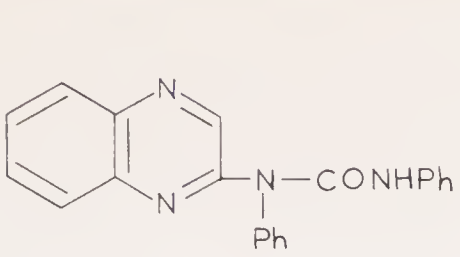
Huisgen and his co-workers, as well as Japanese chemists, have applied 1,3-dipolar addition reactions to heterocyclic *N*-oxides; for an early review of this field, see references 63AG(E)565 and 63AG742. Included in this section are a few reactions that are not strictly 1,3-dipolar additions, in which seven-membered rings are formed.

a. Heteroaromatic Six-membered Ring N-*Oxides.* In these reactions the aromaticity of the *N*-oxide ring is lost during formation of the adduct, and there is a strong driving force to regain this aromaticity by further transformation of the adduct. The reaction with phenyl isocyanate is typical. Adducts of type *515* breakdown spontaneously into carbon dioxide and α-anilino derivatives (*516*): this reaction has been observed with pyridine and quinoline 1-oxides and isoquinoline 2-oxide [63AG(E)565; 69CB926], phenanthridine 5-oxide (61JJ1030), 4-phenylphthalazine 2-oxide (66JJ576), and 3-phenylquinoxaline 1-oxide (62JJ1093). Quinoxaline 1-oxide reacts with phenyl isocyanate to give 2-anilinoquinoxaline, together with 2-[1-(1,3-diphenylureido)]quinoxaline (*517*) and an oxidized cyclization product of the latter (*518*) (67JJ164); 3-phenylquinoxaline 1-oxide similarly yields 2-anilino-3-phenylquinoxaline (62JJ1093).

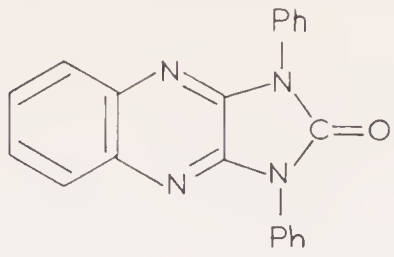
Recently, *N*-sulphinyltoluenesulphonamide (TsNSO) has been shown to react with quinoline 1-oxide and isoquinoline 2-oxide to yield 2-tosylaminoquinoline and 1-tosylaminoisoquinoline, respectively. These compounds are formed by the decomposition of intermediate adducts with the loss of sulphur dioxide (68AI29).

Pyridine 1-oxide reacts with perfluoropropene to give, presumably via adduct *519*, the α-alkylated product *520* and carbonyl fluoride, COF_2 (68JO3343). This is apparently the only 1,3-dipolar addition known of an olefinic compound with a pyridine 1-oxide.

(515) (516)



(517)



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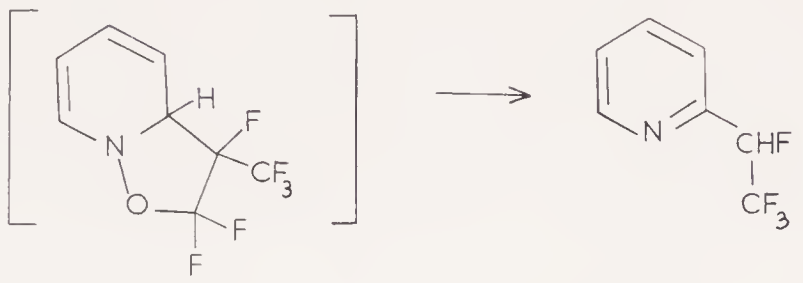
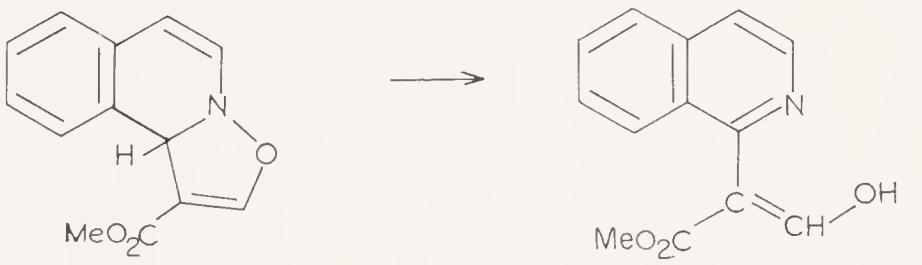
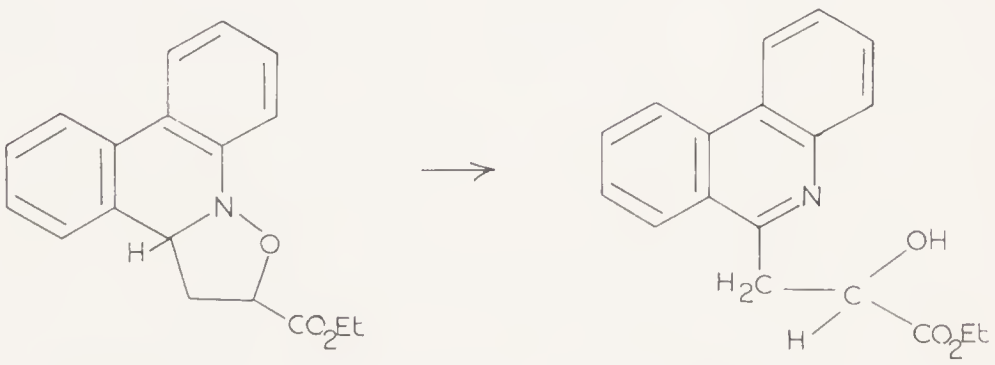


(519) (520)

Isoquinoline 2-oxides and phenanthridine 5-oxides react with acrylic and propiolic esters to form intermediate cyclic adducts which spontaneously ring open. However, the addition occurs in the opposite sense for these two types of esters; thus, isoquinoline 2-oxide yields the α-(1-isoquinolyl)-β-hydroxyacrylate *522* via *521* with propiolic esters, and phenanthridine 5-oxide the β-(6-phenanthridyl)-α-hydroxypropionate *524* via *523* with acrylic ester (63TL2023). Dimethyl acetylenedicarboxylate and phenanthridine 5-oxide give, by oxygen migration, the zwitterionic adduct *525* [66CH835; 67J(C)2066]. Diketene reacts with quinoline 1-oxide to yield the pyrone derivative *526* (64CT18): the mechanism of this reaction may involve a 1,3-dipolar addition to give *527* leading to *528*, which then reacts with a further molecule of diketene. Recently, Huisgen has shown (69CB915) that structure *522* is incorrect and that this product is also a zwitterion of type *525*.



(521) (522)



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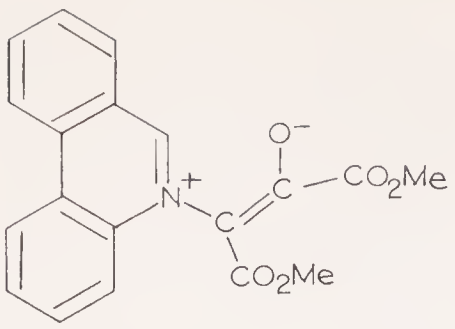

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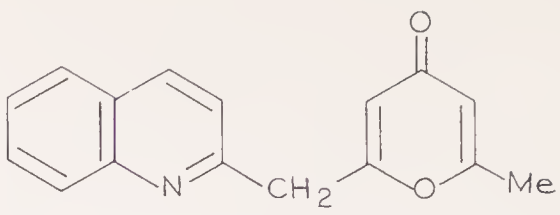

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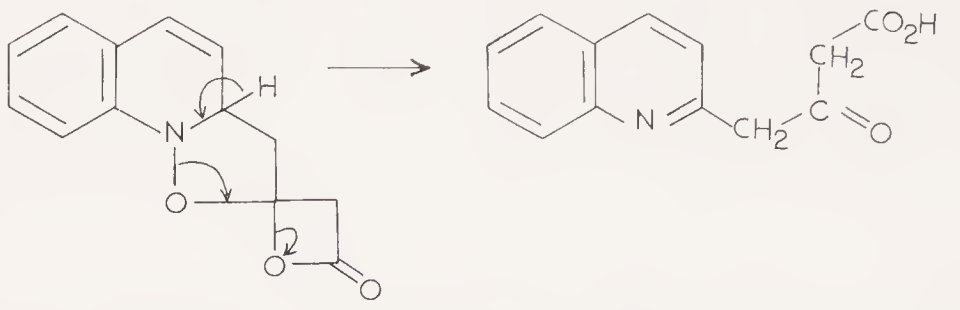
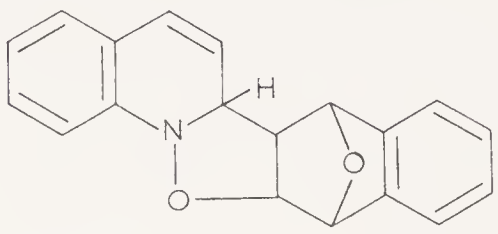


(527) (528)

A rare example of the formation by an aromatic *N*-oxide of a stable 1,3-dipolar adduct (*529*) is apparently furnished by the addition of 1,4-dihydro-1,4-epoxynaphthalene to quinoline 1-oxide [64LA(676)21]. Dimethylketene was shown by Pratt and Taylor [68J(C)1653] to yield the adduct *530* with phenanthridine 5-oxide together with phenanthridine and phenanthridone, presumably formed by decomposition of the adduct. The corresponding adduct for isoquinoline 2-oxide is very unstable and in the quinoline series it could not be isolated. The initial adduct (*531*) from acridine 10-oxide and benzyne rearranges spontaneously to *532* [64LA(676)21].



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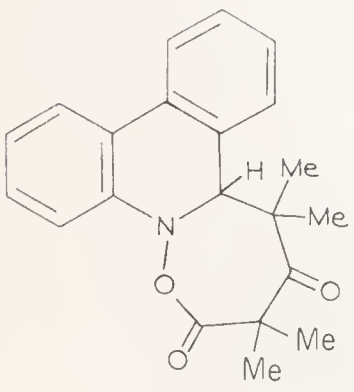

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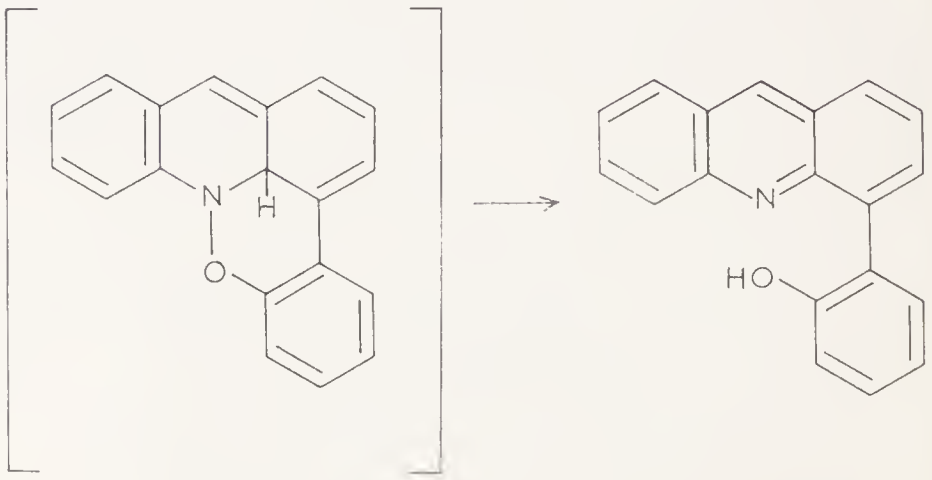
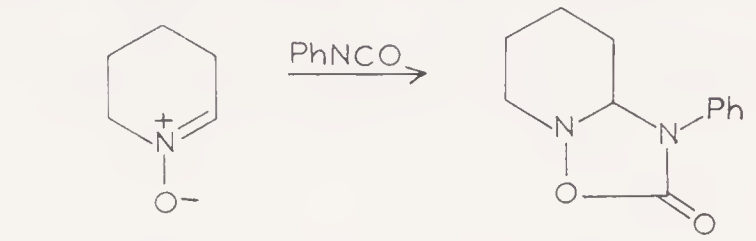
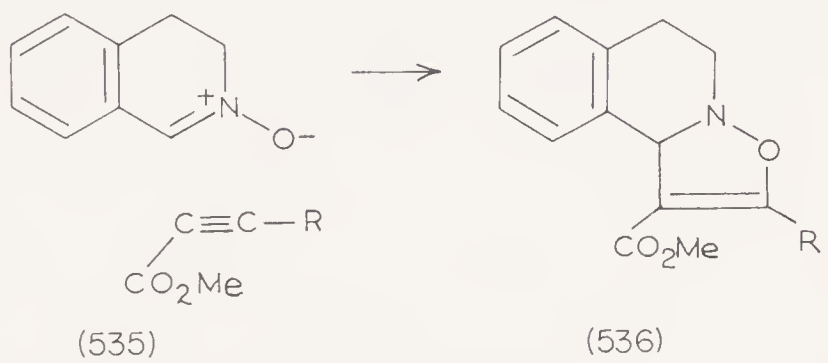


(531) (532)

b. Partially Saturated Six-membered Ring N-*Oxides.* These compounds behave rather like acyclic nitrones and form adducts with 1,3-dipolarophiles which are normally stable. Thus, tetrahydropyridine 1-oxide reacts with isocyanates (*533* → *534*) (59CB1748), and with various olefins and bis-olefins [60P254; 60BP850418; 63AG(E)565]. 3,4-Dihydroisoquinoline 2-oxide undergoes 1,3-dipolar addition with olefins (60P254) and propiolic esters (*535* → *536*) (63TL2019; 68CB2043; 69CB904) and benzyne (69CB904). The reaction between dihydroisoquinoline 2-oxide and maleic or fumaric esters is stereospecifically *cis* (69CB736). 5,6-Dihydropyrazine 1,4-dioxides react similarly with acrylonitrile [68J(C)1917], as does 2,3-dihydro-1,4-oxazine 4-oxide with various 1,3-polarophiles [68J(C)2423].

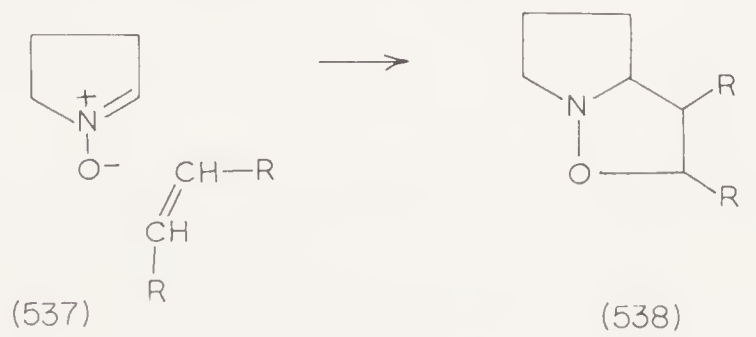


(533) (534)



(535) (536)

c. Pyrroline N-*Oxides and Isatogens.* Pyrroline *N*-oxides behave as cyclic nitrones and react with a variety of olefins (*537* → *538*); e.g., allyl alcohols and ethyl acrylate (60PC386; 63J4693), cyclopentadiene, crotonyl nitrile, and allylacetone (60P254; 60BP850418), acrylic esters and amides [66J(C)1338], and acetylenedicarboxylic and propiolic esters (66CH607). It has been suggested, however, that the products from the acetylenic esters may have structures of type *539*, in analogy with the corresponding phenanthridine 5-oxide adducts (see above) (66CH835). 4,5,5-Trimethylpyrroline 1-oxide reacts with *N*-sulphinylaniline (PhN:S:O) to yield 2-anilino-4,5,5-trimethylpyrroline (*541*) by the elimination of sulphur dioxide from the adduct *540*; the corresponding reaction with the 2,5,5-trimethyl 1-oxide is more complex (68TL3877).



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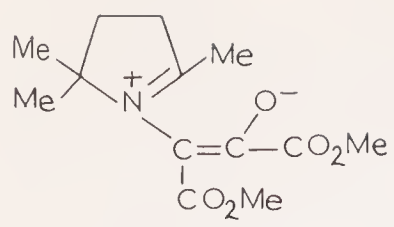

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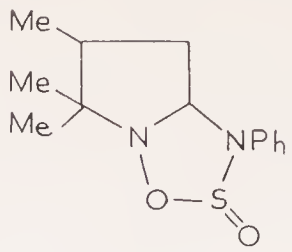
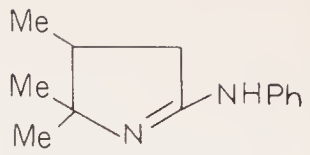
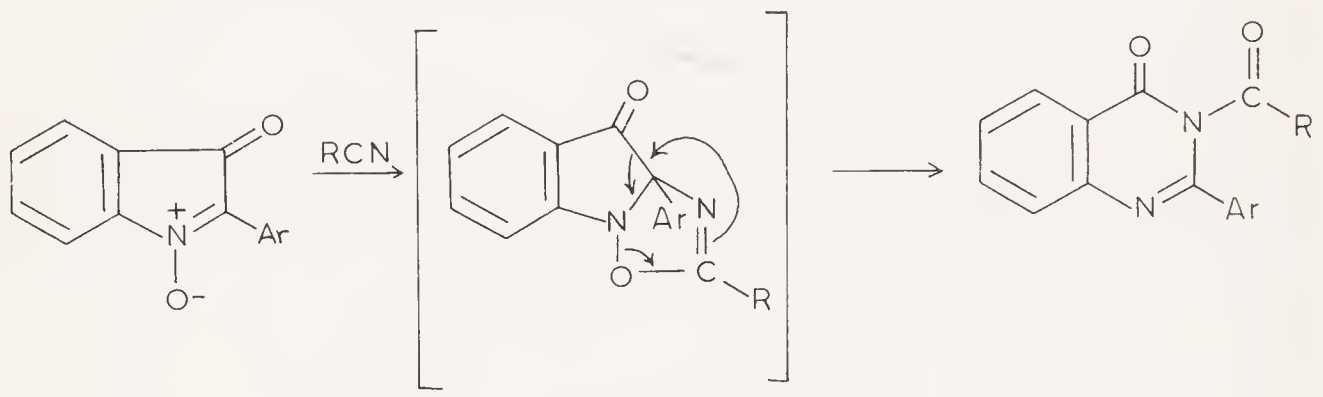


(540)



(541)

Several examples of 1,3-dipolar additions are available in isatogen chemistry. The cyano groups in both tetracyanoethylene (62JO341) and trichloroacetonitrile (64JA2086) react to yield finally the same quinazolinone, probably by the route shown (*542* → *545*). Olefins yield stable adducts of type *546* (62CI363), but the initial adduct formed by acetylenes (*547*) decomposes into 4-quinolones (*547* → *549*) or 2-acyl-4-quinolones (*547* → *551*), depending on the substituents present (64JA2086).



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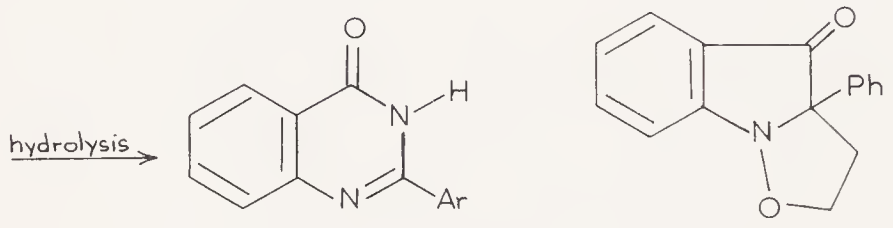
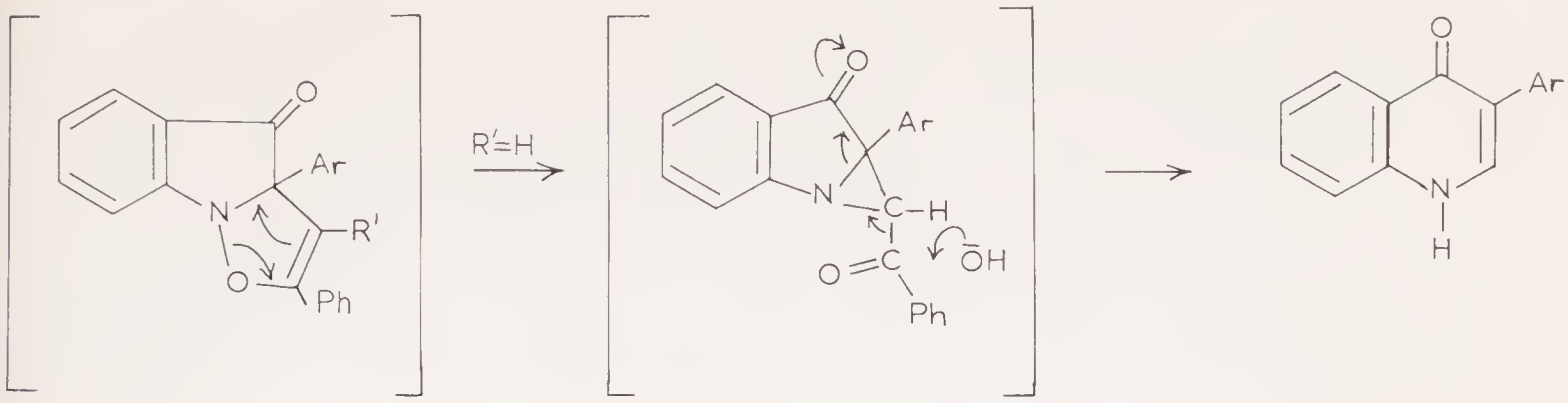


(545) (546)

d. Imidazole N-*Oxides*. 1,3-Dipolar additions with imidazole *N*-oxides have been studied by Takahashi and Kano. A marked similarity in the behaviour of these compounds and that of six-membered ring heteroaromatic *N*-oxides is found. Phenyl isocyanate and phenyl isothiocyanate react with 1-methylbenzimidazole 3-oxide to yield 2-anilinobenzimidazoles (*552* → *554*, X = O or S) with loss of carbon dioxide or carbon oxysulphide; acetylenes and nitriles give products which undergo ring fission, but not fragmentation, to form acetamido compounds or ketones (*555*→*557*, Y = N or CR′); benzyne similarly gives the *ortho*-phenolic product *558* (63TL1687; 64CT1290).

With 1,2-dimethylbenzimidazole 3-oxide, the reaction takes a different course and the initial adducts (cf. *556*) rearrange into zwitterionic derivatives (*559*) (65JO1118; 68CT527) or substitution occurs in the benzenoid ring; e.g., phenyl isocyanate yields *560* (66CT1219).



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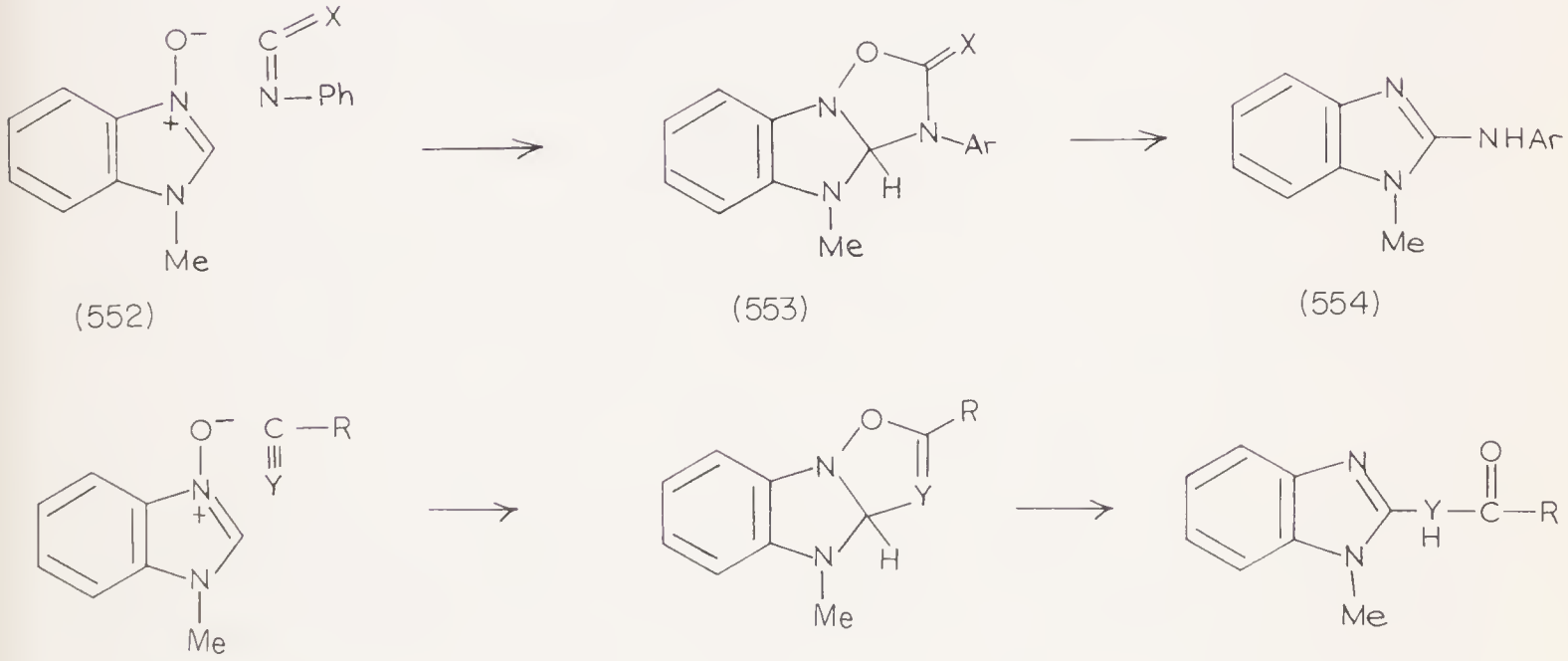
(550) (551)



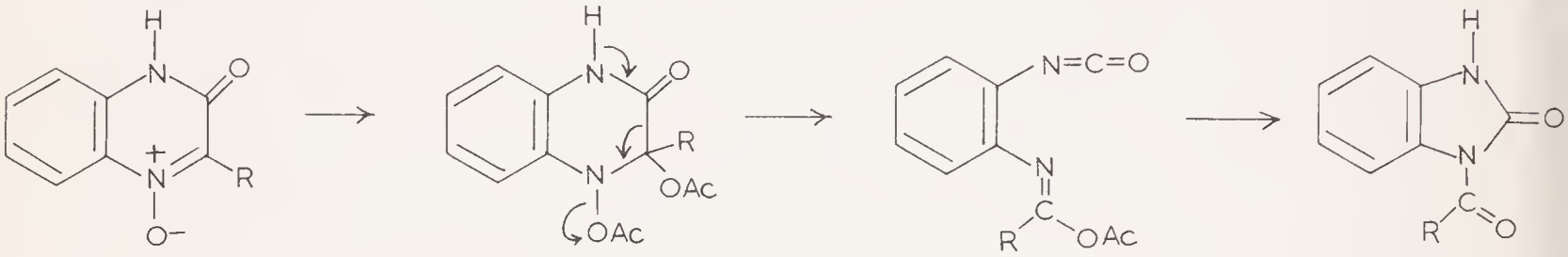
(552) (553) (554)

(555) (556) (557)

(558) (559) (560)

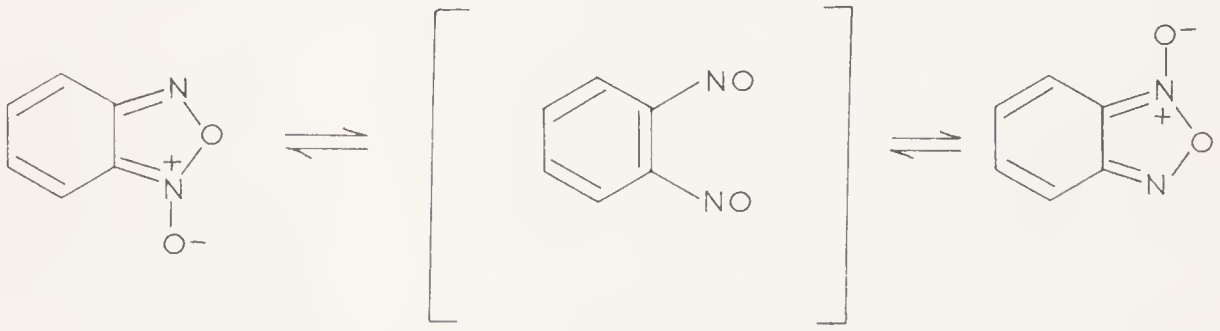
iii. Spontaneous Ring-opening Reactions

a. Quinoxaline N-*Oxides.* Ahmad and co-workers (68JO201) have shown that 2-substituted 3-quinoxalinone 1-oxides unsubstituted at the 4-position are rearranged by acetic anhydride to yield, ultimately, benzimidazolones. The mechanism of this reaction is possibly that shown in the scheme *561* → *564*, in which the key step, *562* → *563*, is a type of Grob fragmentation. If the 4-position is substituted, the 3-quinoxalinone ring is preserved and attack occurs at the 6-position (see Section III-4Ciia).*



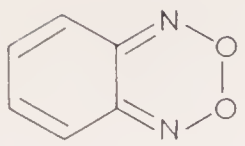
(561) (562) (563) (564)

b. Furoxans and Benzofuroxans. Benzofuroxan undergoes rapid isomerization, *565* → *567*, via a transient dinitroso intermediate (*566*). Previously, benzofuroxan had been formulated successively as the dinitroso compound *566* [94Z1095; 99LA(307)28], the cyclic peroxide *568* (07J1942), and *569*, which is the early equivalent of *565* (12J2452). However, unsymmetrical formulae (*565* or *569*) were erroneously ruled out by Green and Rowe (13J897; cf. 13J1918), because they could not obtain isomeric pairs such as *570* and *571*. Hammick suggested (31J3308) that this might be a consequence of rapid isomerization of type *565* ⇌ *567*. Still another formulation (*572*) was put forward in 1955 (55JA5688), but rapid isomerization was finally proved independently by British, German, and American groups (61CI990; 61PN697; 61ZN413). The unsymmetrical structure was established by the proton magnetic resonance low temperature spectrum, and the rapid equilibration was confirmed by the NMR temperature dependence. These conclusions have been fully supported by ^{17}O-magnetic resonance spectral data (62H504) and by the PMR spectra of various substituted benzofuroxans: methyl-, bromo- (61ZE854), and nitro-benzofuroxans (63J197)

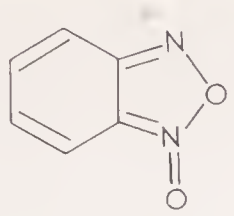


(565) (566) (567)

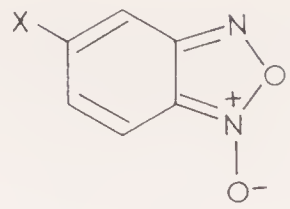
* See addendum in the Appendix.



(568)



(569)



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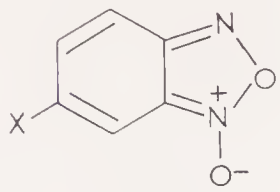

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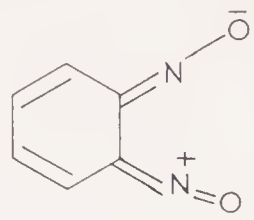
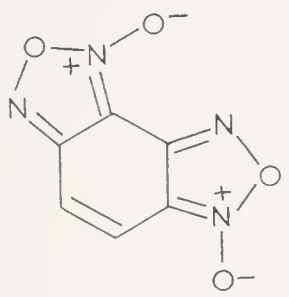
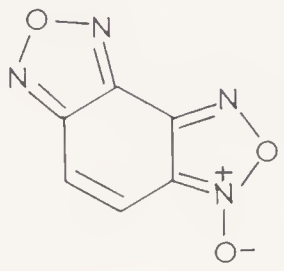


(572)

were studied first, and more recently, data on a further series of derivatives have been reported [67J(B)914; 68J(B)334].* Rearrangements of the more complex benzodifuroxan *573* and furazanobenzofuroxan *574* have also been elucidated by NMR spectral studies (65J5958) as have those involving naphtho- and quinolino-furoxans [68J(B)1516]. Support for occurrence of the rearrangement via the dinitroso compound *566* is found in a study of the rates and activation parameters for these reactions (65JA5433), and in the fact that 5- and 6-substituted derivatives of benzotriazole 1-oxide (cf. *575*) do not interconvert (62JO4109).



(573)



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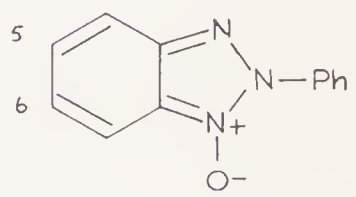
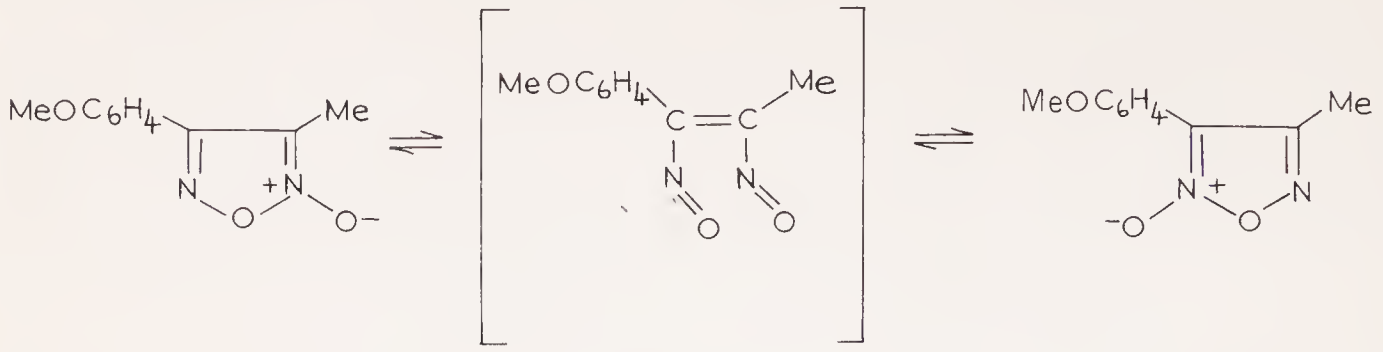


(575)

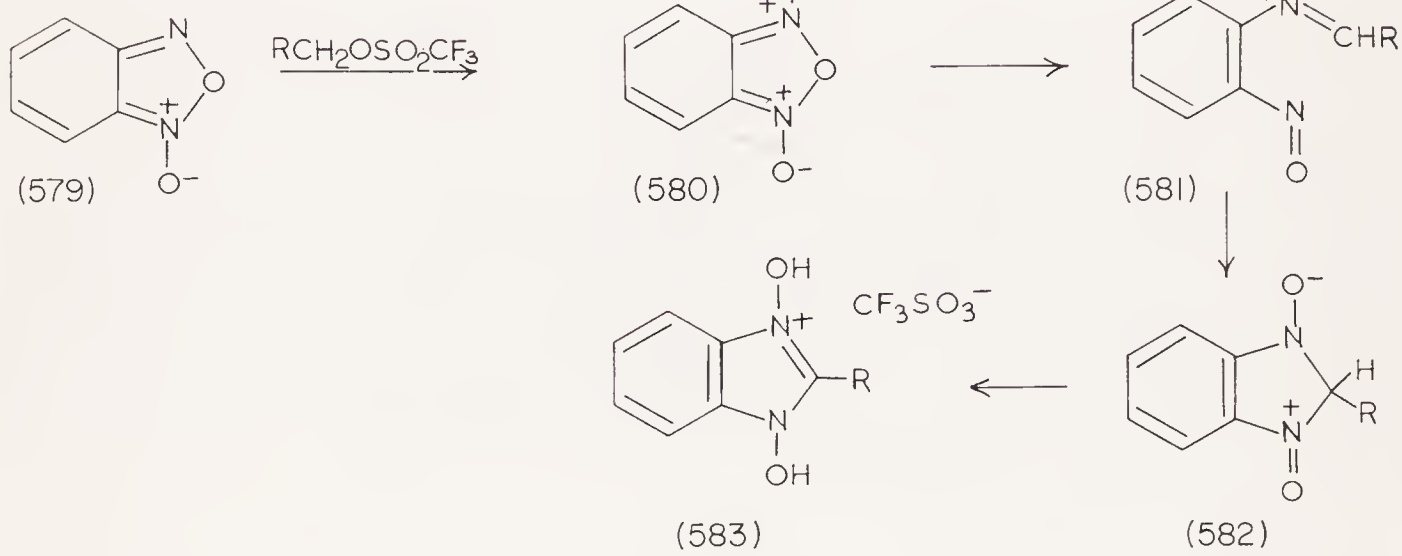
The unsymmetrical structure for monocyclic furoxans has been demonstrated by the preparation of individual pairs of isomers. The dinitroso intermediate (*577*) derived from furoxan is much less stable than the corresponding intermediate in the benzofuroxan series, because there is no extra benzene resonance to be gained on ring opening of the monocyclic compounds. However, at high temperatures spontaneous ring opening can occur, resulting in the interconversion of isomer pairs (*576*⇌*578*) (29G713). The kinetics of this conversion have been carefully studied by Mallory and Cammarata (66JA61). Early investigators have discussed in detail the merits of the various possible structures for the furoxans; see, e.g., references 08LA(358)36, 16AL7, and 21LA(424)107. 3,4-Diacylfuroxans react with

* See addendum in the Appendix.

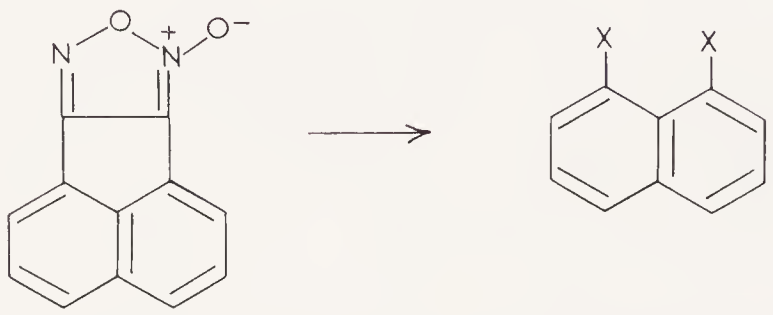
phenylhydrazine to yield 1-phenyl-4,5-dioximino-2-pyrazolines by ring opening and further transformations of the hydrazones (69JH317).*



(576) (577) (578)



(579) (580) (581) (582) (583)

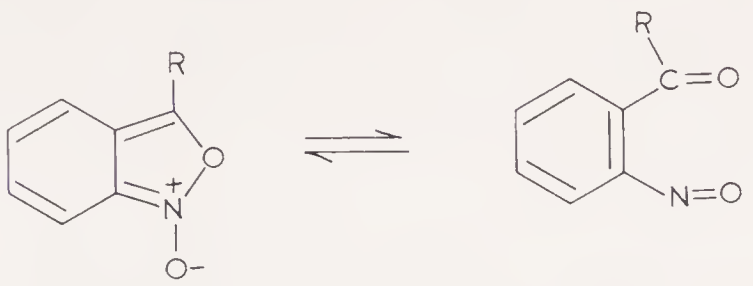


(584) (585)

3-Alkylbenzofuroxanonium salts (*580*, R = H or Ph) undergo spontaneous ring opening, and subsequent reclosure gives 1-hydroxybenzimidazole 3-oxide salts of type *583*. The mechanism is believed to be as shown: *579* → *583* (66CH741). To account for the formation of a bisnitrile (*585*, X = CN) on treatment of the strained furoxan *584* with trialkyl phosphites, Altaf Ur Rahman and Boulton (68CH73) have postulated that the reaction proceeds through an intermediate nitrile oxide (*585*, X = CNO), and this represents yet another example of spontaneous ring opening in the furoxan series.

* See addendum in the Appendix.

c. Other N-*Oxides*. The reactions of anthranil 1-oxides (*586*) suggest that these compounds may react in the ring-opened form (*587*) (cf. Section II-2Bia) [59JA962; cf. 66J(C)2020]. Another type of spontaneous ring opening is the ring-chain tautomerism exhibited by 5*H*-pyrrole 1-oxides: *588*⇌*589* (36JA590).



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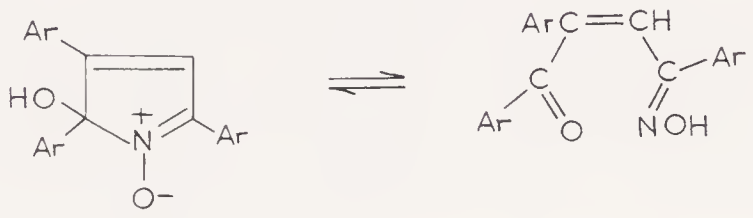


(588) (589)

(590) (591)

(592) (593)

D. TAUTOMERISM

In certain cases tautomerism involving the transfer of a hydrogen atom between ring carbon and the *N*-oxide oxygen can occur.

In the indole-indolenine series, the tautomeric equilibrium *590*⇌*591* has been studied carefully; the equilibrium is very dependent on the nature of the solvent; the *N*-oxide (*591*) is favoured in solvents which can form hydrogen bonds, and 1-hydroxyindole (*590*) is the predominant species in other solvents (67BF1296; 67SA717).

Similar tautomerism (*592*⇌*593*, Z = CH_2 or O) has been postulated for tetrahydropyridine 1-oxide and 2,3-dihydro-1,4-oxazine 4-oxide on spectroscopic evidence [68J(C)2423].

6. Reactions at Ring Nitrogen or Hydrogen Atoms

Reactions at a free ring nitrogen atom in mono-*N*-oxides of diazines and triazines, the deprotonation of *N*-oxide rings by nucleophilic attack at a ring hydrogen atom, as well as π and charge-transfer complexes are considered in this section.

A. REACTIONS AT RING NITROGEN ATOMS

Ring nitrogen atoms can react with electrophiles, for example, in alkylation and protonation reactions: here it is convenient to distinguish between six-membered rings, where tautomerism cannot occur, and five-membered rings where this is possible. Reductive (nucleophilic) attack also occasionally occurs at ring nitrogen atoms, and some examples are known of cyclic transition state rearrangements. Diels-Alder reactions of benzofuroxans, which involve reaction at ring nitrogen, are included for consistency in Section III-5Ci.

i. Tautomerism

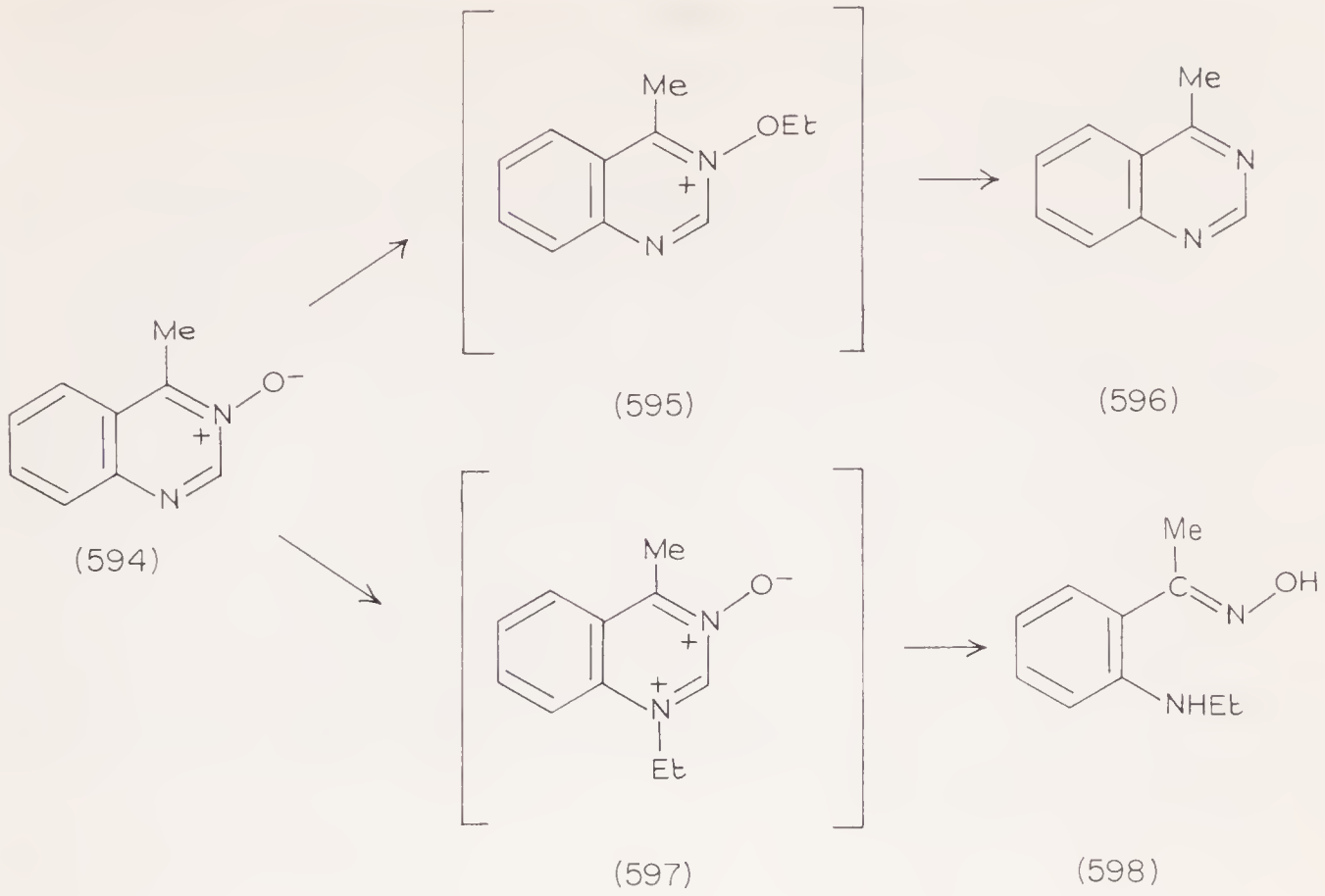
Where the *N*-oxide contains an NH-group in the ring, tautomerism with a *N*-hydroxy compound is possible.*

Benzimidazole *N*-oxides (63CT1375) and their 6-nitro derivatives [67J(C)1764] are considered to exist mainly in the *N*-hydroxy form in organic solvents but in the amino form in aqueous media on the basis of ultraviolet spectral comparisons. However, other workers claim that various physical measurements indicate that under most conditions the hydroxy form predominates (66JH51).

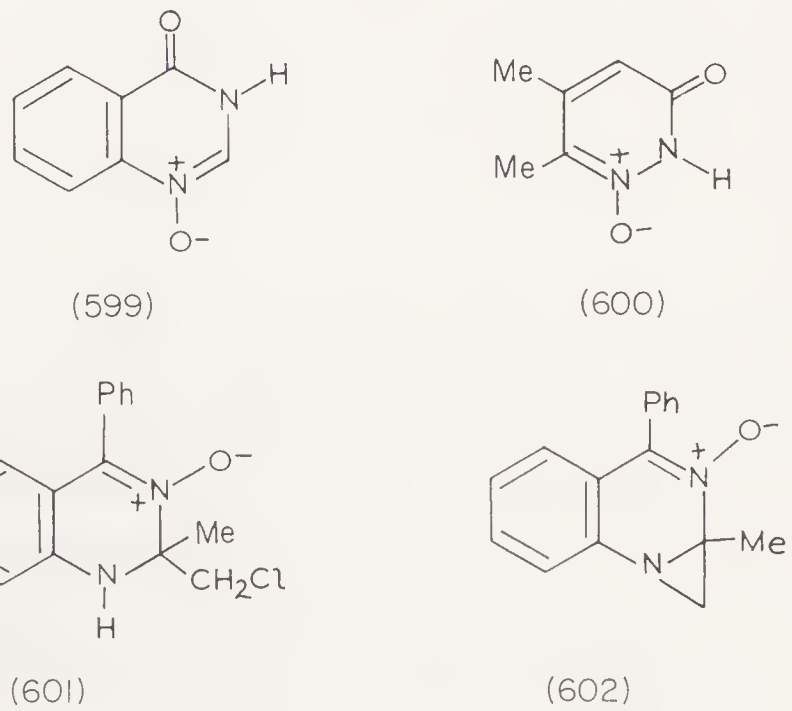
ii. Alkylation and Salt Formation

a. Non-tautomeric N-*Oxides.* In diazine mono-*N*-oxides, alkylation can conceivably occur at either a ring nitrogen atom or the oxide oxygen atom. With 4-methylquinazoline 3-oxide (*594*), evidently reaction occurs at both sites; on reaction of *594* with ethyl iodide and subsequent treatment with sodium hydroxide, a mixture of the deoxygenated product *596* and the ring-opened compound *598* is obtained (57JJ514). However, quinazoline 3-oxide itself apparently yields only the ring-opened product, and thus *N*-alkylation is evidently the favoured reaction in this case (57JJ507). Other reactions of this type include the *N*-methylation of 4-quinazolinone 1-oxides (*599*) with methyl iodide–silver hydroxide (59CT152), 3-pyridazinone 1-oxides (*600*) with dimethyl sulphate (63CT721), and 1,2,4-triazin-3-one 2-oxides with methyl iodide–sodium methoxide (66JO3914).

* See addendum in the Appendix.



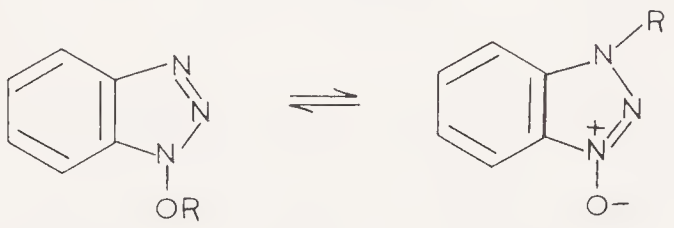
The dihydroquinazoline 3-oxide *601* undergoes internal alkylation with formation of the aziridino derivative *602* (67JA332). Alkylation of 1-alkoxyadenine salts yields 1-alkoxy-9-alkyladenine salts; however, when the alkyl group of the alkylating agent (RX) is less stabilized for carbonium ion formation than that in the 1-alkoxy group, alkyl-exchange reactions occur (66CT1452). 3-Hydroxyxanthine is alkylated by dimethyl sulphate at the 7- and 9-positions (69JO978).



Quinoxaline 1-oxide forms a 4-methiodide (53J2816); for the *N*-methylation of 3-quinoxalinone 1-oxides, see reference 63J2428. Russian investigators have studied the quaternization of nitrogen in a series of quinoxaline

and phenazine mono-*N*-oxides (59ZO228; cf. 60ZO1661). The effect of steric hindrance on this reaction in the phenazine *N*-oxide series has been considered (61ZO283).*

b. Tautomeric N-*Oxides*. The tautomerism of five-membered ring *N*-oxides is considered in Section III-6Ai. Benzimidazole *N*-oxides are tautomeric with 1-hydroxybenzimidazoles. Alkylation of these compounds in strongly basic media generally gives 1-alkoxybenzimidazole derivatives (64CT282; 67MC211). Benzotriazole 1-oxides (*603*⇌*604*, R = H) are tautomeric and form a mixture of alkyl derivatives corresponding to alkylation of both tautomers (23J2258; 63JO2326). The structure of the *N*-methyl derivatives (*604*, R = methyl) has been proved by reduction (31J1273; cf. 28J193). The relative proportions of *N*- and *O*-alkylation depend on the type of alkali used in the reaction (50J767). Benzotriazole 1-oxide forms salts (*605*) (64JI793) which have been used analytically for the determination of silver (65BJ1086). For alkylation and acylation of the pyrazole *N*-oxide *606*, see reference 62JO2881.



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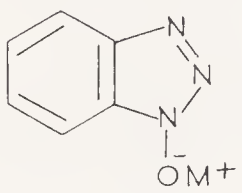

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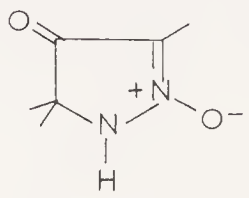
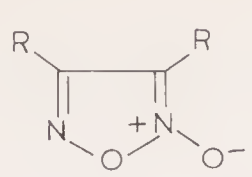


(606)

iii. Nucleophilic Attack at Ring Nitrogen Atoms

Nearly all reductions of *N*-oxides result in loss of the *N*-oxide oxygen atom. However, furoxans, which are catalytically reduced to α-dioximes (*607*→*608*), are an exception; examples of this reaction are included with other catalytic reductions in Table 3.07. Benzofuroxan rings can also be opened by reduction: cf. *609*→*610* (55JA5688; cf. 63JO1656), and reductive ring-cleavage is involved in the conversion of the benzotriazole 3-oxide *611* into the indazole *612* (27CB1736). One of the compounds formed by the reaction of triphenylphosphine with benzotrifuroxan is the ring-opened trinitro compound *613* (67CH455).

* See addendum in the Appendix.



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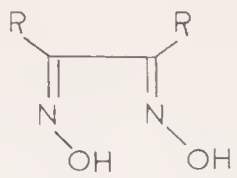

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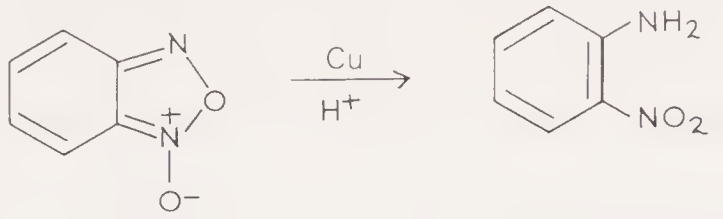

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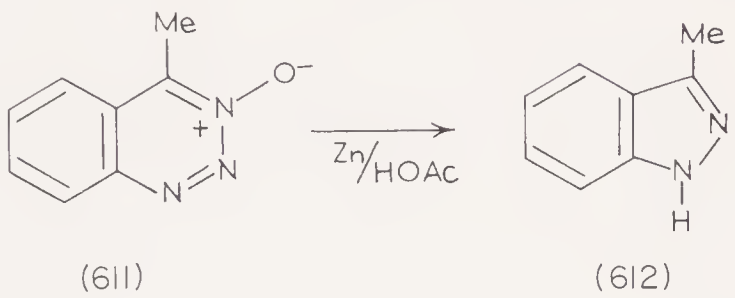
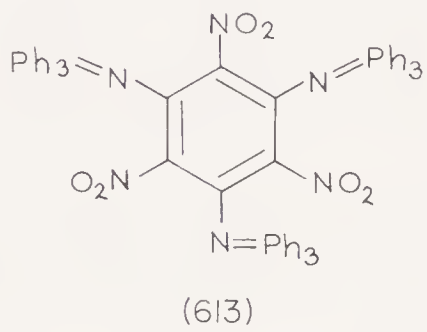


(611) (612)



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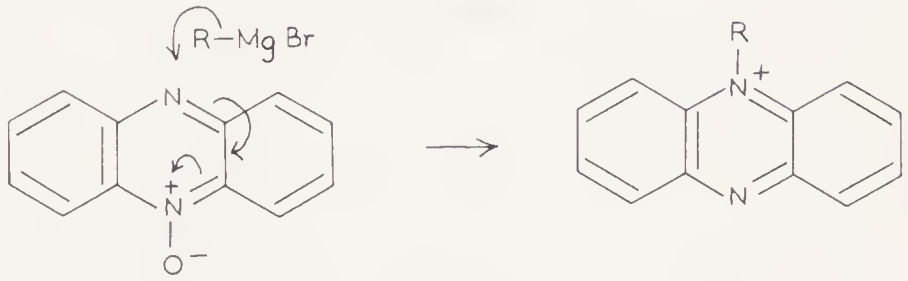


(614) (615)

An interesting variation of the usual reaction with organometallic reagents is observed with phenazine 5-oxide (*614*); in this case nucleophilic attack occurs at N-10 to give the 10-phenazinium cation *615* (59ZO1020).

iv. Other Reactions at Ring Nitrogen Atoms

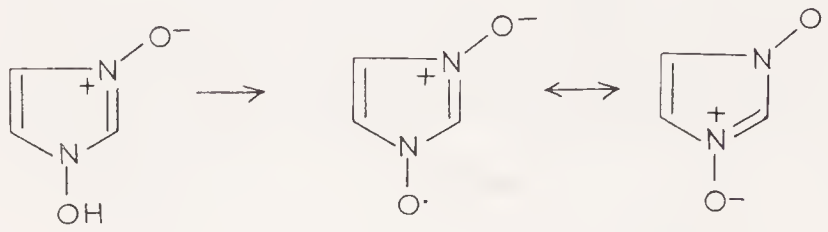
1-Hydroxy-imidazole [67AG(E)947] and -benzimidazole 3-oxides (68CI651) yield stable free radicals on oxidation: *616* → *617*, *618*.*

4-Substituted benzofuroxans of type *619* have been reported by Boulton, Katritzky, *et al.* to undergo rearrangement to nitro compounds of type *620* when A=B is $N^+(O^-)$=O (62P257; 62RR691), N=O or N=N [64AG816;

* See addendum in the Appendix.

66J(B)1004], and C=O or C=N [66J(B)1011]. Ghosh [68J(B)334] has shown that the course of this rearrangement is influenced by the substituents present: in particular, 7-anilino-4-nitrobenzofuroxan (*621*, X = NHPh) rearranges on heating to the sterically more hindered 5-anilino-4-nitro derivative (*622*), probably because the hydrogen-bonding possibilities are better in the latter. For further examples, see reference 68MC305.

Ring closure of the triazine hydrazone *623* to give the triazolo-triazine *N*-oxide *624* probably involves formation of an intermediate diazo derivative and its spontaneous cyclization [67J(C)2658]. Pyridazine *N*-oxide hydrazones (*625*) are cyclized to the triazolo-pyridazine *N*-oxides (*626*) by lead tetraacetate (68JH513).



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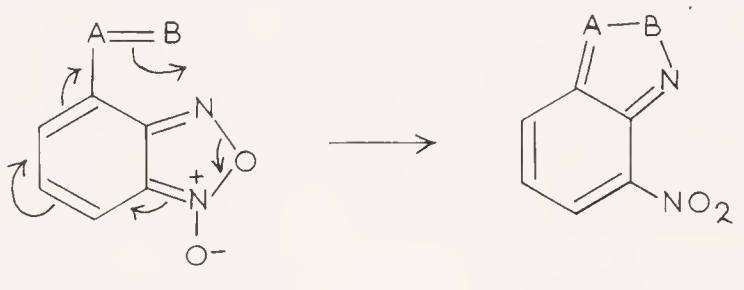

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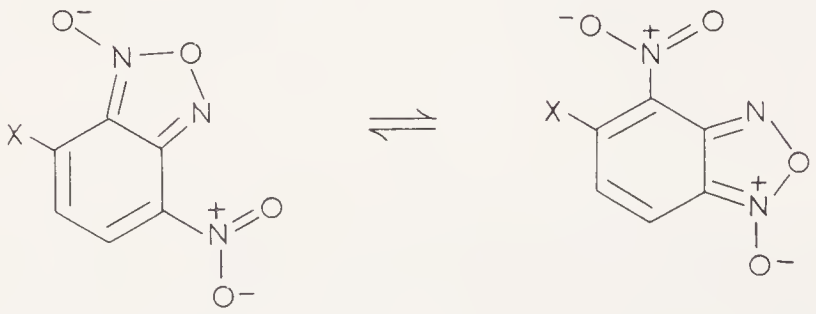
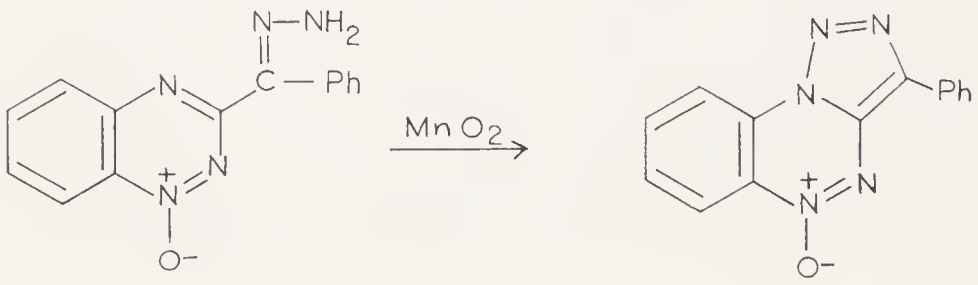


(621) (622)



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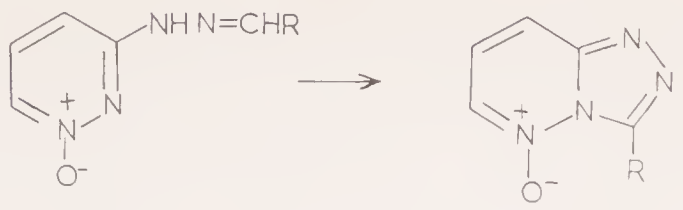


(625) (626)

B. NUCLEOPHILIC ATTACK AT RING HYDROGEN ATOMS

i. Hydrogen Atoms Attached to sp^2*-Hybridized Ring Carbon Atoms*

a. Base-catalysed Hydrogen Exchange. Pyridine 1-oxide is deuterated at the 2- and 6-positions by sodium deuteroxide–deuterium oxide at 100°, or by deuterium oxide at 180°; further deuteration at the 3-, 4-, and 5-positions can be accomplished by heating the *N*-oxide with alkali at 180° (64CT1384; cf. 69JO660). 3,5-Dichloropyridine 1-oxide undergoes ready hydrogen exchange, first at the 2- and 6-positions, then at the 4-position, with aqueous sodium deuteroxide. The hydrogen atoms in 3-chloropyridine 1-oxide are successively exchanged at the 2-, 6-, and 4-positions (67TL337); similar results have been reported for 3-bromopyridine 1-oxide (67CH55). The relative rates of exchange in pyridine 1-oxide correlate well with those for the decarboxylation of the analogous *N*-methylpyridinium carboxylic acid betaines (68JA5939).

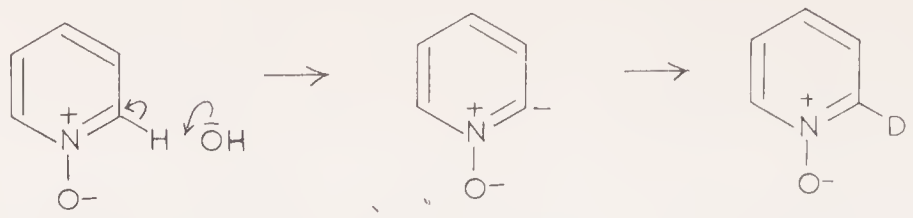
Zoltewicz and Kauffman (69JO1405) have recently published an extensive study of the base-catalysed hydrogen exchange reactions of pyridine *N*-oxides. The *N*-oxide group strongly activates the exchange (relative to the parent pyridines): the rates are in the order 2,6 $\gg$ 3,5 $>$ 4. Several alternative mechanisms were considered but it was concluded that the exchange involves simple deprotonation.

Quinoline 1-oxide undergoes ready base-catalysed hydrogen exchange at the 2-, 3-, and 4-positions (67CT826), the 2-position reacting most readily (68CT1696). The hydrogen atom in the 1-position of isoquinoline 2-oxide exchanges; for other examples and typical reaction conditions that have been used in the pyridine and quinoline 1-oxide series, see reference 67CT1225. Under these conditions methyl groups on the ring are also deuterated (see Section IV-2Biiia).

Pyridazine 1-oxide is deuterated successively at the 6-, 5-, 3-, and 4-positions on being heated with alkali at 20–120° (64CT1384). 3-Hydroxypyridazine 1-oxide also undergoes base-catalysed deuteration at the 4- and 6-positions (67CT1411).

b. Other Reactions of the N*-Oxide Carbanions.* All the reactions in the preceding section probably involve nucleophilic attack on ring hydrogen atoms as shown: *627* → *629*. This mechanism has been elegantly confirmed by Abramovitch *et al.* (67JA1537), who found that treatment of pyridine 1-oxides with an ethereal solution of butyl-lithium at −65° gives organo-

metallic derivatives of type *630*, which react with carbon dioxide to give α-carboxylic acids or with ketones to yield α-pyridyl carbinols.*



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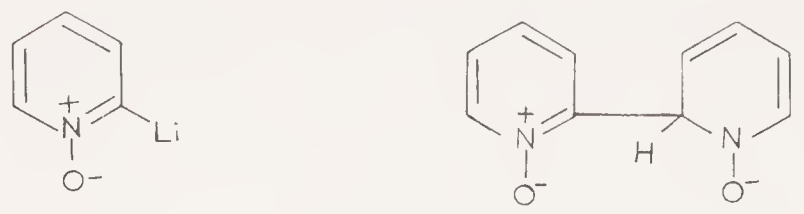
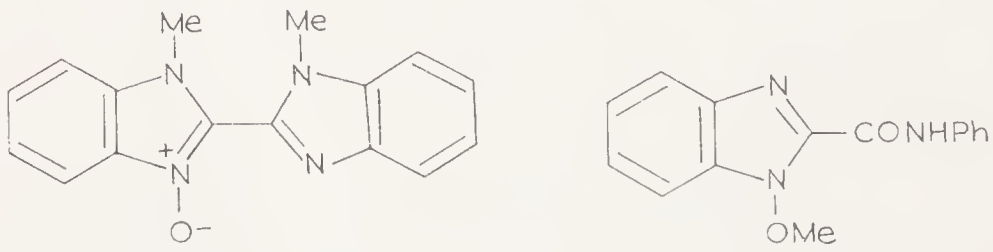


(630) (631)

Possibly the reported formation of 4,4′-bipyridyl at −40° and of 2,2′-bipyridyl at 20° on treatment of ammonia solutions of pyridine 1-oxide with sodium and ammonium chloride are related reactions (54JJ1404): addition of a sodio derivative analogous to *630* to another molecule of *N*-oxide would yield *631* from which bipyridyl results by loss of hydroxide ion and reduction. Quinoline 1-oxide on heating with potassium *t*-butoxide yields 2,2′-biquinolyl 1-oxide (66CT557), probably by a similar mechanism (by-products are formed; see Section III-4Cia). Quinoxaline 1-oxide and phenyl-lithium yield 2,2′-biquinoxalyl; this product is formed even with the use of the milder base sodium methoxide (67JJ942).

The conversion of 3-methylbenzimidazole 1-oxide into *632* on heating (64CT783) is probably another reaction of this type in which the deprotonated intermediate adds to a second molecule of the *N*-oxide. A similar reaction occurs with 1-methoxybenzimidazole on treatment with dimethylaniline–sodamide; this benzimidazole also reacts with phenyl isocyanate to yield *633* (64CT282). 1-Methoxy-3-methylimidazoline salts (*634*) react with a wide variety of hydrogen compounds to yield products of type *635* (65TL3789; 66CT375); some of these reactions may involve XH reacting as a weak *electrophile* on the heterocyclic carbene, rather than as a nucleophile on the cation.



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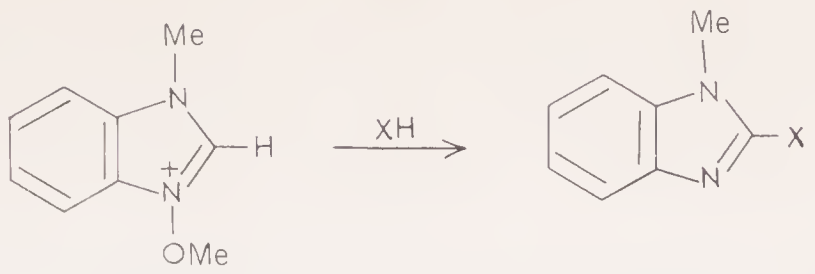
* See addendum in the Appendix.



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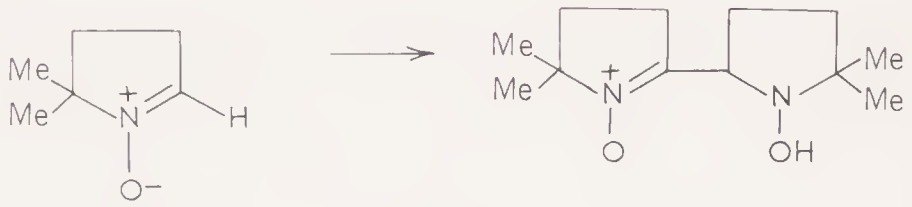

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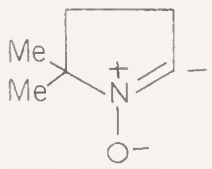

(638)

The benzoin-type dimerization of the pyrroline 1-oxide *636* to yield *637*, which is catalysed by sodamide, involves deprotonation of *636* to give the anion *638* (59J2116): this mechanism is supported by the fact that *636* undergoes hydrogen–deuterium exchange (65J2337).

Although it was originally suggested that 4,6-dinitrobenzofuroxan formed salts by loss of a proton from the 7-position [99LA(307)28], these compounds are now known to be Meisenheimer complexes (see Section III-4Cia).

ii. Hydrogen Atoms Attached to sp^3*-Hybridized Ring Carbon Atoms*

A somewhat different type of reaction is involved in nucleophilic attack at hydrogen atoms attached to sp^3-hybridized carbon atoms in a partially saturated heterocyclic *N*-oxide. The overall result of such reactions is usually the loss of the *N*-oxide oxygen atom and complete aromatization of the ring.

Isoindoline *N*-oxides (*639*) react with acetic anhydride to give isoindoles (*640*); this reaction provides an advantageous synthetic route to the latter class of compounds [64AG682; 64LA(671)119]. Δ^3-Pyrroline 1-oxides are similarly converted into pyrroles (66TL2591) and the conversion of Δ^1-pyrroline *N*-oxides into 5*H*-pyrroles (*641* → *642*) is somewhat analogous (61JA1128). Isoxazoline 2-oxides are converted by hydroxide ions into isoxazoles (cf. *643* → *644*) (24JA2105; 35JA2299); treatment with acetic anhydride effects a similar reaction (24JA1733).

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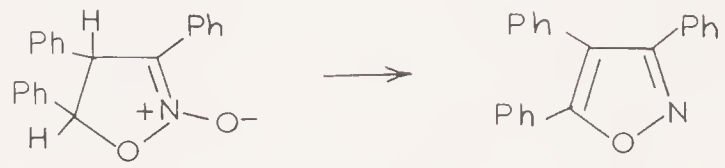
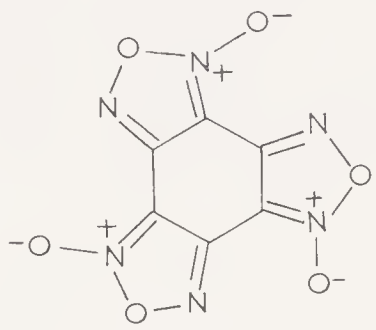
(641) (642)



(643) (644)

C. *Pi* AND CHARGE-TRANSFER COMPLEXES*

Complex formation between pyridine 1-oxide and 1,3,5-trinitrobenzene can be detected in solution, but solid complexes have not been isolated (56JA3625). However, 3,5-dinitropyridine 1-oxide forms a solid complex with the hydrocarbon retene (60CT28), and benzotrifuroxan (*645*) readily



(645)

yields characteristic complexes with many naphthalenes and other aromatic hydrocarbons [58T(3)113; 64J5110; cf. 63T161; 65J2579]. 4-Nitroquinoline 1-oxide complexes with deoxyribonucleotides (67CT1812), with nicotinamide (69JJ297), with thiamine (68JJ1103), and with amino acids and proteins (68CT556); this property may be related to its carcinogenic activity.†

* Meissenheimer and σ-complexes are mentioned in Section III-4A.

† See addendum in the Appendix.

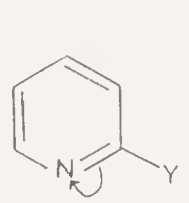
CHAPTER IV

Reactions of Substituents on Heterocyclic *N*-Oxides

Substituents on heterocyclic *N*-oxides are classified here according to the atom which is attached directly to the ring. Following a general consideration of the effect of the *N*-oxide function on the reactivity of substituents, the reactions of the substituents are discussed in detail. Most of the substituents are linked to ring carbon atoms, and these are treated first. A much smaller number of substituents are linked to the *N*-oxide oxygen atom; these are considered in the final section of the chapter.

1. Influence of the *N*-Oxide Function on Substituent Reactivity

Substituents on heterocyclic *N*-oxides which are *alpha* or *gamma* to an *N*-oxide function display chemical properties distinctly different from those of the same substituents on either benzene rings or the parent heterocycles. In our textbook "The Principles of Heterocyclic Chemistry" (67MIb), we have shown that the reactivity of a substituent, Y, in the α-position of pyridine (cf. *1*) is, in some respects, midway between the reactivity of the same group



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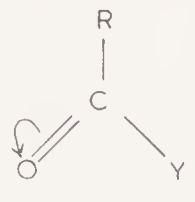

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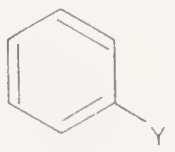

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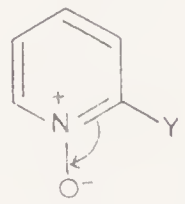


(4)

in the carbonyl derivative *2* and that of the same substituent on benzene (cf. *3*). In the case of α-substituted pyridine 1-oxides (*4*), the stronger electron-attracting ability of the charged nitrogen atom displaces the reactivity of group Y towards that of Y in compounds of type *2*. The pull of electrons towards the heterocyclic group is intensified in quaternary derivatives of

N-oxides: because of the inductive effect of the oxygen atom, the electron-withdrawing power of $:N(OR)^+$ is greater than that of $:NR^+$. The following consequences of the "carbonyl analogy" concerning the reactivity of substituents in the α- and γ-positions of pyridine are noted.

(*a*) Substituents which can form stable anions can undergo nucleophilic displacement. The following order has been observed: nitro (most readily) > halogeno > alkoxy > amino.

(*b*) Substituents in which the atom adjacent to the ring carries a hydrogen atom can easily lose an α′-hydrogen atom as a proton; that is, the acidity of α′-hydrogen atoms is enhanced.

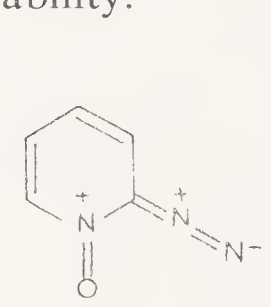
(*c*) Compounds carrying substituents with an α′-hydrogen atom can tautomerize as a consequence of *b*.

(*d*) α-Carboxymethyl ($-CH_2CO_2H$) and α-carboxyl groups decarboxylate readily.

(*e*) Effects *a–d* can be transmitted through a vinyl group. Furthermore, nucleophiles can add to C=C and C≡C groups in Michael-type addition reactions.

Substituents in the α- and γ-positions of *N*-oxides also show these properties and indeed, because the electron-withdrawing ability of the *N*-oxide group is greater than that of the ring nitrogen atom, substituents *beta* to the *N*-oxide group show some reactivity of this type. Quantitative measurements are not common, but the activating ability of an *N*-oxide group towards nucleophilic displacement is somewhat greater than that of a nitro group [66J(B)1058].

In addition to its electron-withdrawing ability, the *N*-oxide group can act as an electron donor, and this property is important in some substituent reactions. Thus, mesomeric forms of types *5* and *6* probably stabilize α- and γ- diazonium salts and -nitro derivatives. Both of these classes of compounds are important synthetic reagents in *N*-oxide chemistry despite the fact that the corresponding derivatives of the parent heterocycles are not often used because of their poor stability.



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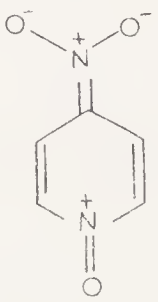

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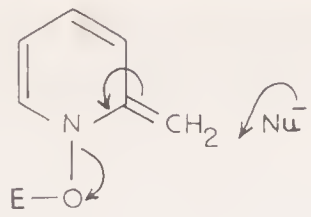

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In an important group of substituent reactions, the *N*-oxide oxygen atom is lost during the substituent transformation. Thus, a series of reactions of α-picoline 1-oxide (*7*) to give substituted compounds of type *8* is known. Some of these reactions proceed by a mechanism involving the intermediate step shown in structure *9*.

For convenience in discussion, substituents attached to ring carbon atoms are generally classified according to the atom which is directly linked to the ring carrying an *N*-oxide group. The reactions of carbon-, halogen-, oxygen-, nitrogen-, sulphur-, and mercury-linked substituents are considered successively. A discussion of the reactions of substituents attached to the *N*-oxide oxygen atom rather than to a ring carbon atom concludes the chapter.

2. Functional Groups Linked to Ring Carbon by a Carbon Atom

A. BENZENOID RINGS

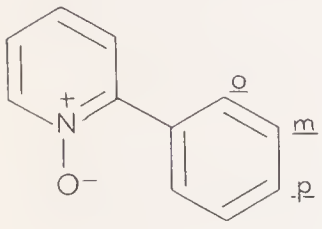
i. Fused Benzenoid Rings

In many ways it is convenient to consider a fused benzenoid ring as a substituent, i.e. to consider quinoline as a substituted pyridine; this procedure was adopted in our text book (67MIb). However, in the present monograph fused benzenoid rings are considered as part of the parent heterocyclic system rather than as a substituent. For example, electrophilic substitution reactions occurring on fused benzenoid rings and reactions involving the heterocyclic ring are treated together (Section III-3A to E), because the two types of reactions frequently occur simultaneously, and sometimes there is a transition, depending on the reaction conditions, from predominant electrophilic substitution at a carbon atom in a fused benzenoid ring to predominant attack at a carbon atom in the *N*-oxide ring. The reactions of halogen atoms and of hydroxyl groups attached to benzenoid rings are discussed immediately following consideration of those attached to heterocyclic rings (Sections IV-3Av and IV-3Bii, respectively). An example of the nucleophilic replacement of a nitro group on a benzenoid ring is also included in this chapter (Section IV-3Ciib). The furoxan ring in benzofuroxan acts as a strong electron-withdrawing group, and 4,6-dinitrobenzofuroxan undergoes covalent hydration (65JO2407); the hydrate is acidic and consequently can form salts. Other substituents on benzenoid rings usually exhibit normal

reactivity similar to that found for the correspondingly substituted naphthalene and for the most part are not discussed.

ii. Aryl Substituents

The nitration of phenylpyridine 1-oxides (e.g. *10*) was originally studied by Katritzky and Hands (58J1754) who found that nitration always occurs in the phenyl group. The 2- and 4-phenyl derivatives yield predominantly *meta*-substituted products, but with 3-phenylpyridine 1-oxide only the *para*-nitro compound is obtained. Although it was first suggested that the nitration of 2-phenylpyridine 1-oxide occurs on the free base, later detailed kinetic work has shown that the conjugate acid is the species undergoing nitration [68J(B)862]. The diphenylpyrazine 1,4-dioxide *11* also undergoes nitration in the *meta* positions of the phenyl groups (55J3094). For the nitration of the phenyltriazole 1-oxide *12*, see reference 99G277.



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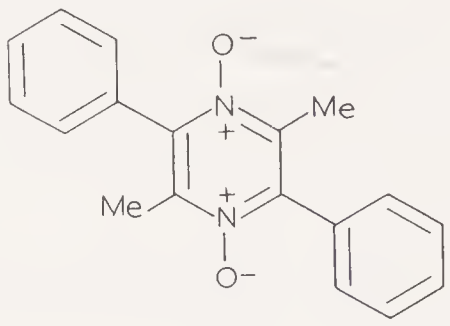

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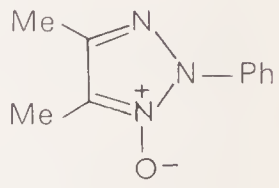

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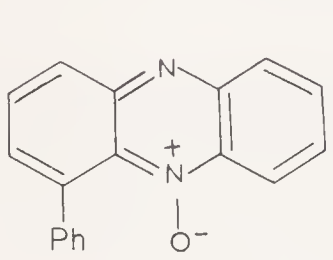

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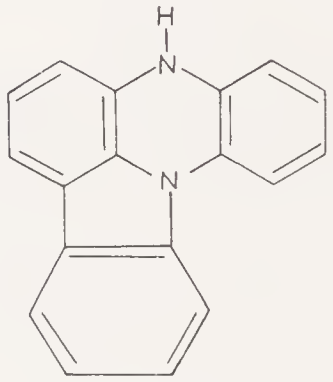


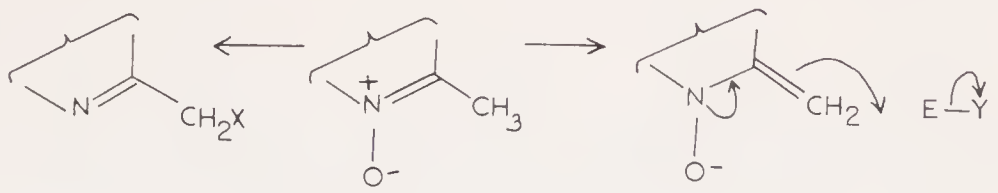
(14)

The curious ring closure of 4-phenylphenazine 5-oxide, *13* → *14*, which involves an *N*-oxide group and a phenyl substituent, has been reported (58J4492).

B. ALKYL GROUPS

The reactions of alkyl groups in heterocyclic *N*-oxides fall into two classes. The first class is comprised of rearrangement reactions in which a functional group such as an acetoxy or halogeno group is introduced into the alkyl substituent and the *N*-oxide function is lost (*15* → *16*). Reactions in the second class involve initial proton loss to form a mesomeric anion of type *17*, which

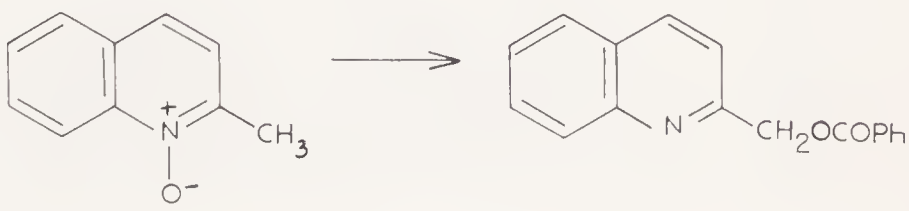
then reacts with an electrophile as shown. The latter group of reactions includes halogenation, hydrogen exchange, some oxidation reactions, and reactions with aldehydes and alkyl nitrites.



(16) (15) (17)

i. Side-chain Acyloxylation

a. Scope and Preparative Aspects. In 1936, Henze (36CB534) reported that quinaldine 1-oxide (*18*) reacts with benzoyl chloride and sodium hydroxide to give a product which was shown considerably later to be 2-benzoyloxymethylquinoline (*19*); the correct formulation of the product was made by Pachter (53JA3026). At about the time of Pachter's work, the reaction of 2-picoline 1-oxide (*20*) with acetic anhydride to form 2-pyridylmethyl acetate (*21*) was independently discovered by four groups (53CT347; 54JA1286; 54JA1370; 55JA1281). This side-chain acyloxylation by acid anhydrides has since been shown to be a general reaction for the *N*-oxides of quinoline, isoquinoline, pyridazine, pyrimidine, pyrazine, quinoxaline, thiazole, and other heterocyclic systems provided they are substituted at an α- or γ-position by practically any alkyl group; a saturated carbocyclic ring fused to a heterocyclic *N*-oxide behaves as an alkyl group. Examples of the side-chain acyloxylation of *N*-oxides are recorded in Table 4.01. In typical reactions, the *N*-oxide is heated with an excess of the acid anhydride for 1–6 h at 100°; yields are often in the range of 50–70 %.



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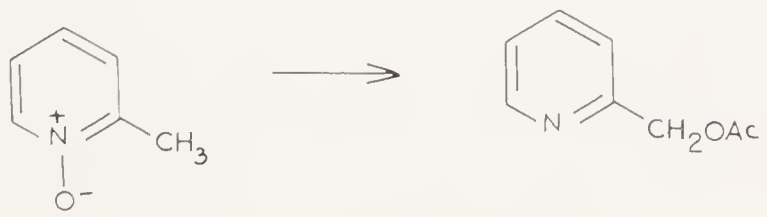


(20) (21)

Table 4.01. Conversion of α- and γ-Alkyl *N*-Oxides by Acetic Anhydride into Acetoxyalkyl Heterocycles with Loss of the *N*-Oxide Function (cf. *20* → *21*)

Ring system	Substituents unaffected	Site of acetylation	Yield, %	References
Pyridine 1-oxide	—	2-Me	—	54JA1286
	—	2-CH_2-CHOAc-CH_2OAc	—	54JA1286
	2-CH_2OAc	6-Me	—	54JA1286
	3-OAc or -Me	2-CH_2OAc	—	57JA481
	—	2-CH_2OAc-4-NHAc	(data)	59JJ492
	6-Me	2-CH_2OAc-4-NHAc	(data)	59JJ492
	—	2- and 4-CH(OAc)Ph	—	56USP2748141
	4-OCH_2Ph	2-Me	47	58CB2194
	—	2-CH(OAc)C_3H_7	—	54JA1286
	5-*n*-Bu	2-CH(OAc)C_2H_5	(data)	57H1016
	3-CO_2H	4-Et	see note [a]	57JA481
	4-Cl-5-Et	2-Me	48	60JJ875
	2-Cl	4-Me	see note [b]	61JJ574
	4-Cl	2-Me	(data)	57JJ11
	6-Cl	2-Me	see note [c]	61JJ574
	4-Cl-6-Me	2-Me and 3-H	—	57JJ11
	4-CN-6-Me	2-Me	(data)	59JJ492
	2,6-$(CH_2)_{10}$	α-H	80	57JA5558
	3-CO_2Et	2-Me and 5-H	—	60CT427, 63LA(670)69
	5-CO_2Et	2-Me	(data)	63J1841
	—	2-Et	—	53USP2662711, 54JA1286
	—	4-Et and 3-H	—	60CT1106

[a] The product isolated is the 3,4-[-CO-O-CH(Me)-] derivative.

[b] A mixture of products is obtained: 4-acetoxymethyl-2-methylpyridine (33%), 3-(or 5)-acetoxy-2-chloro-4-methylpyridine (3%), and 1-hydroxy-4-methyl-2-pyridone (13%).

[c] A mixture of products is obtained: 2-acetoxymethyl-6-chloropyridine, 3-(or 5)-acetoxy-6-chloro-2-methylpyridine (trace), and 1-hydroxy-6-methyl-2-pyridone (9%).

Table 4.01. Conversion of α- and γ-Alkyl *N*-Oxides by Acetic Anhydride into Acetoxyalkyl Heterocycles with Loss of the *N*-Oxide Function (cf. *20* → *21*)—*continued*

Ring system	Substituents unaffected	Site of acetylation	Yield, %	References
Pyridine 1-oxide, *cont'd.*	5-Et-4-MeO	2-Me	54–63	60JJ875
	5-Me	2-Et	(data)	60JJ875
	3-Et	4-Me	64	58JA1181
	5-Et	2-Me	—	53USP2662711, 54JA1370
	2-(2-furyl)vinyl-6-Me	6-Me and 3-H	—	66JJ1014
	—	3-OH-2-CH_2OH[d]	50	57AS1496
	4-Me	2-CH_2OH	—	61JJ88
	—	3-H-2-CH_2OH-6-Me	—	62JJ1647
	—	2-$(CH_2)_3OH$	71	57JO589
	4-C(Ph)HOH-6-Me	2-Me	see note[e]	55JJ1233
	3-CO_2Me	2-Me and 5-H	—	63LA(670)69
	4-MeO	2-Me and 6-Me	—	63LA(670)69
	4-MeO-6-Me	2-Me and 5-H	major and —	57JJ11
	3-CH_2OMe	2-Me and 3-H	major and —	57JJ11
	—	2-Me	ca. 95	58CT222, 59CT241
	—	2-Me	—	53USP2662711, 54JA1286, 55CI1423, 55CT232
	—	2-Me and 3,5-diH	66 and 30	65AJ867
	—	2-Me and 6-H[f]	45–50 and ca. 20	53CT347, 55CT316
	—	4-Me and 3-H[g]	20–58 and 7–14	53USP2662711, 54JA1286, 55JA1281, 60JA2744, 63ZK475, 65JA5710

[d] 3-Acetoxy-2-diacetoxymethylpyridine.
[e] A mixture of products obtained: 4-benzoyl-2,6-dimethyl- (65%) and 2-acetoxymethyl-4-(1-hydroxy-1-phenyl)methyl-6-methyl-pyridine (20%).
[f] See text.
[g] Only the 4-CH_2OAc compound reported to be formed (53USP2662711; 54JA1286).

Table 4.01. Conversion of α- and γ-Alkyl *N*-Oxides by Acetic Anhydride into Acetoxyalkyl Heterocycles with Loss of the *N*-Oxide Function (cf. *20* → *21*)—*continued*

Ring system	Substituents unaffected	Site of acetylation	Yield, %	References
Pyridine 1-oxide, *cont'd.*	3-Me	2-Me	70	57JA481
	—	2- and 4-Me[h] and 5-H[i]	30 and 6 and 2	55CT413, 56JJ900, 61JJ88
	4-Me-3- and 5-nitro	2-Me and 3-H	(data)	68RC1499
	5-Me	2-Me	(data)	59JJ108
	6-Me	2-Me[j]	73	54JA1286, 54JJ790, 57H2428
	6-Me	2-Me and 3- and 5-H	—	62JJ1647
	6-Me	2- or 4-Me, or 3-H	(data)	67RC1027
	6-Me-3-NO_2	2-Me	—	66RC1215
	6-Me	2-Me, 4-NO_2[k]	—	57JJ11
	3-CH_2OPh	2-Me	65	59CT241
	(6-methyl-1-oxido-2-pyridyl)	2-Me	35	58J3594
	5-Me-4-NO_2	2-Me	(data)	68RC1873
	6-CH_2-CH_2R	2-Me	see note[l]	58J3594
	—	2-(1-oxido-2-pyridyl)-propyl	see note[m]	60BA285
	—	2-*n*-Pr and 5-H	49 and —	58J1306
	2,3-$(CH_2)_x$ (x = 3–4)[n]	α-H	71–80	58JA6254, 61AP759, 63RC403
	2,3-$(CH_2)_3$	6-Me and α-H	—	66RC149

[h] Only product reported (61JJ88).
[i] Originally incorrectly formulated as the 3-acetoxy isomer.
[j] Acetoxy-2,6-dimethyl compound also reported to be formed (54JJ790).
[k] 2-Acetoxymethyl-6-methyl-4-nitro- and 4-acetoxy-2-acetoxymethyl-6-methyl-pyridine formed.
[l] Both the 6-CH=CHR (ca. 20%) and 6-CH_2CH_2R (5%) derivatives formed.
[m] R = 2-Pyridyl 1-oxide; 3-(2′-pyridyl)pyrrocoline (28%) and 1,3-di(2-pyridyl)-1-propanone (18%) also formed.
[n] When x = 4, compound is 5,6,7,8-tetrahydroquinoline 1-oxide; when x = 3, compound is 6,7-dihydropyridine *N*-oxide.

Table 4.01. Conversion of α- and γ-Alkyl *N*-Oxides by Acetic Anhydride into Acetoxyalkyl Heterocycles with Loss of the *N*-Oxide Function (cf. *20* → *21*)—*continued*

Ring system	Substituents unaffected	Site of acetylation	Yield, %	References
Pyridine 1-oxide, *cont'd.*	2,3-$(CH_2)_x$-6-Ph (x = 3–5)	α-H	73–96	63RC403
	3,4-[CH(Me)$(CH_2)_2$-]	α-H	—	67AJ349
Quinoline 1-oxide	—	2-Me	30	54JJ791
	—	2-H and 4-Me	see note [o]	54JJ791
	4-Me	2-Me and 3-H	70 and 5	55CT413
	5,6,7,8-tetrahydro	2-Me and 2-, 3-, and 8-H	see note [p]	67CT1385
Pyridazine 1-oxide	6-Cl-3-MeO	4-Me	see note [q]	63JJ934
	3-MeO	6-Me	(data)	63CT29
	3,6-diMeO	4-Me	32[r]	63JJ934
	3-Ph	6-Me	"good"	60NK350, 60NK1148
	3-EtO-6-Me	6-Me	—	60NK1148
Pyrimidine 1-oxide	6-Me	4-Me	(data)	59J525
Quinazoline 3-oxide	6-Cl-4-Ph	2-Me	50	60JA475
Purine 1-oxide	—	6-Me	(data)	62JO567
Pyrazine 1-oxide	3-Cl	2-Me	ca. 37	63JO1682
	—	2-Me	ca. 26	58DI64, 58JO1603, 59JJ1273, 64JO2477
	5-Me	2-Me	ca. 33	58JO1603, 61JO126
	6-Me	2-Me	ca. 60	61JO126
	3,5,6-triMe	2-Me	57	61JO126

[o] 2-Acetoxy-4-methylquinoline is the major product.

[p] The 8-acetoxy compound is the major product.

[q] 4-Chloromethyl (11 %) and 4-hydroxymethyl derivatives (8 %) as well as 1-hydroxy-2-methoxy-4-methyl-6-pyridazinone (9·4 %) and the corresponding 1-H compound (8 %) are formed.

[r] In addition, 4-hydroxymethyl-3,6-dimethoxypyridazine (23 %) is formed.

Table 4.01. Conversion of α- and γ-Alkyl *N*-Oxides by Acetic Anhydride into Acetoxyalkyl Heterocycles with Loss of the *N*-Oxide Function (cf. *20* → *21*)—*continued*

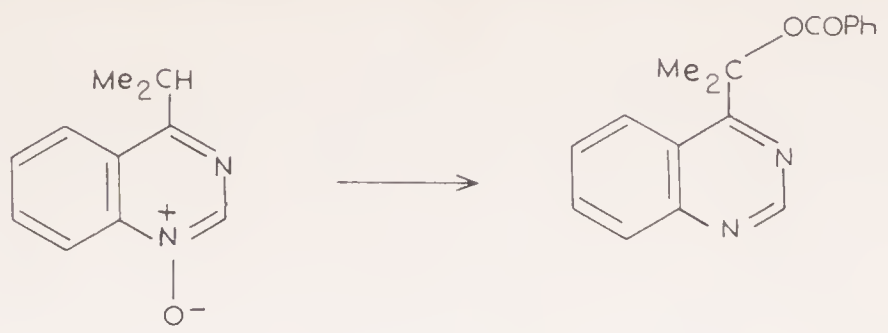
Ring system	Substituents unaffected	Site of acetylation	Yield, %	References
Pyrazine 1,4-dioxide	4-oxide	2-Me	ca. 36	59JJ1273, 61JO126
	see note [s]	2- and 5-Me	—	58JO1603
	see note [t]	2- and 5-Me	see note [t]	61JO126
	2-CH_2OAc	5-Me	see note [u]	58JO1603
Quinoxaline 1-oxide	3-Me	2-Me	56	61ZO1018
	—	2,3-diMe	54	61ZO1018, 68KG545
	4-oxide, 3-COPh	2-Me	"good"	68TL4609
Phenazine 5,10-dioxide	1,2,3,4-tetrahydro	1- and 4-H	—	68JO2127
Pteridine 5-oxide	1,3-diMe-2,4-dioxo	6-Me	—	67JH124
Benzimidazole 3-oxide	1-Me	2-Me	—	66CT1219
Thiazole 3-oxide	—	4-Me	(data)	64CC2375
	—	2- and 4-Me	see note [v]	64CC2375

[s] 2-Acetoxymethyl-5-methyl- and 2,5-diacetoxy-pyrazine formed.

[t] 2-Acetoxymethyl-5-methylpyrazine 1-oxide (30%) and 2,5-dimethylpyrazine 1-oxide reported to be formed. On prolonged heating, the 2,5-di(acetoxymethyl) derivative is formed in 6% yield.

[u] A mixture of products is obtained: 2,5-di(acetoxymethyl)pyrazine, and the corresponding *N*-oxide, as well as 2-acetoxymethyl-5-methylpyrazine *N*-oxide.

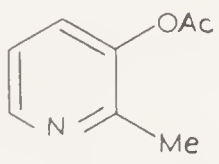
[v] 2-Acetoxymethyl-4-**meth**yl- (80–84%) and 4-acetoxymethyl-2-methyl-thiazole (16–20%) formed.



(22) (23)

Although acetic anhydride has been used in the great majority of the work that has been reported, other acid anhydrides, acid chlorides, and other reagents have also been employed. Acetyl chloride has been used in the thiazole 3-oxide series (64CB2165), and acyl nitrates in the quinoline 1-oxide series (59CT540). Benzoyl chloride has effected the conversion of *22* into *23* in the quinazoline series (64CT43). In the reaction of quinoline 1-oxides with benzoyl nitrate (see Section III-3C), introduction of a benzoyloxy group in an alkyl side-chain can occur as a side reaction (57CT313). Ketene has been used in place of acetic anhydride (58JJ422; 62JJ1649).

Kobayashi and Furukawa (53CT347) isolated a by-product from the reaction of 2-picoline 1-oxide with acetic anhydride. It was originally thought to be 6-methyl-2-pyridone, but was later shown to be a mixture of 3- (*24*) and 5-acetoxy-2-picoline (*25*) (ca. 3% yield of each isomer) (55CT316; 63ZK475; 65AJ867). 4-Picoline 1-oxide similarly yields 3-acetoxy-4-picoline as a by-product (55JA1281). Compounds arising from substitution at a β-position in the ring are now often observed as by-products in these reactions (see Table 4.01), and the extent of the side reaction, which is discussed in Section III-4Ciiia, is greater than was at first supposed (65AJ867). Other side reactions occasionally occur: 1,2-di(2-pyridyl)ethane 1,1′-dioxide yields the olefinic mono-*N*-oxide *26* (66BA505); 1,3-di(2-pyridyl)propane 1,1′-dioxide (*27*; $X = CH_2$) gives the ketone *28* ($X = CH_2$) (60BA285); and the dipyridyl carbinyl ether *27* ($X = O$) analogously forms the ester *28* ($X = O$) (65CT233). 2,6-Lutidine 1-oxide reportedly forms some of the dipyridylethane *29* as by-product (62JJ164). Not unexpectedly, the nitro group in 2-methyl-4-nitropyridine 1-oxide is lost during the reaction to yield 2-hydroxymethyl-4-pyridone (57JJ11). Recently it has been shown that alkyl groups can rearrange during the reaction: this rearrangement is discussed in Section IV-2Bib.



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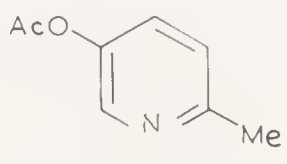

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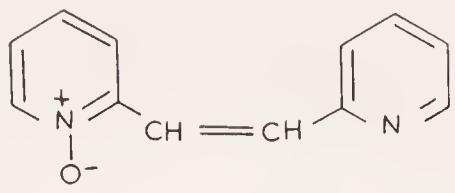

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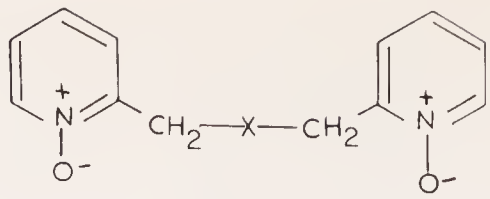

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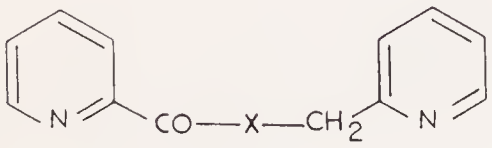

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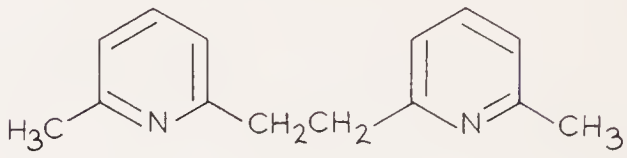

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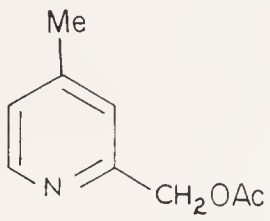

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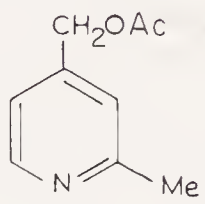

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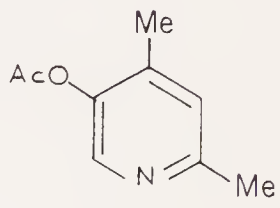
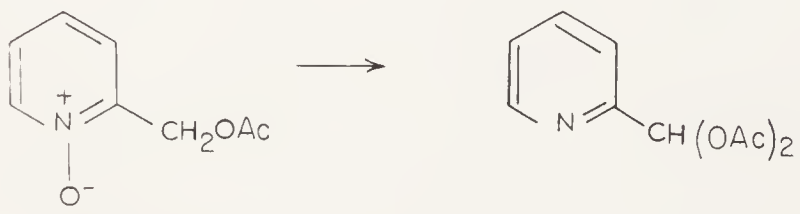


(32)

2,4-Lutidine 1-oxide reacts with acetic anhydride to give mainly the α-acetoxymethyl derivative *30*, together with the γ-analogue *31* and the 5-acetoxy compound *32*, not the 3-acetoxy isomer as originally reported (56JJ900). Reaction at the α-methyl group also greatly predominates in the quinoline 1-oxide series (55CT413), but it has recently been found that with collidine *N*-oxide the proportion of γ-attack increases with temperature (67RC1027). In the thiazole 3-oxide series, a 2-methyl group is attacked more readily than a 4-methyl group (64CC2375).

As was demonstrated by Boekelheide and Linn (54JA1286), this reaction not only provides a convenient synthesis for pyridyl carbinols, i.e. by hydrolysis of the pyridylmethyl acetates (cf. *21*), it is also a useful route to aldehydes. For example, conversion of the pyridylmethyl acetate *N*-oxide *33* into the acetal derivative *34* and subsequent hydrolysis gives 2-pyridinecarboxaldehyde.



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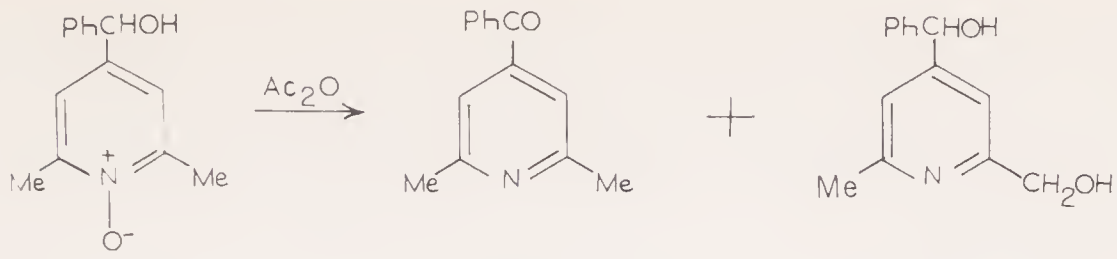
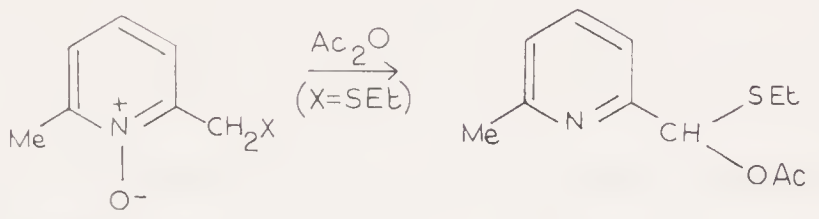
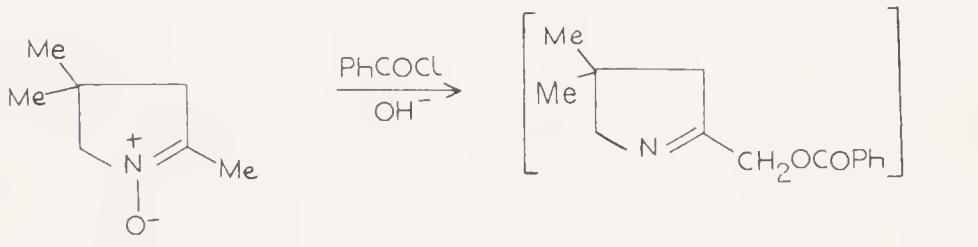


(35) (36) (37)



(38) (39)

(40) (41)



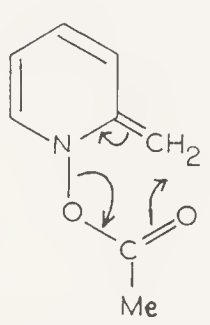
(42) (43)

(44a) (44)

The reaction occurs readily at hydroxyalkyl groups; thus, the phenyl pyridyl carbinol *35* yields *more* of the ketone *36* (65%) than of the diol *37* (20%) (55JJ1233). Acetic anhydride reacts with the thioether *38* (X = SEt) to give the hemithioacetal *39*; however, with 2-bromomethyl-6-methylpyridine 1-oxide (*38*; X = Br) reaction also occurs in the methyl group, and the corresponding mercaptan (*38*; X = SH) is only deoxygenated (65CT233). 2-Styrylpyridine 1-oxide (*40*, R = Ph) reacts with acetic anhydride to give the diacetoxy derivative *41* (59JJ487), and 4-styrylquinoline 1-oxide similarly

yields the 4-quinoyl analogue of *41*, together with 3-acetoxy-4-styrylquinoline (63JJ342). In the reaction of pyrroline 1-oxides with benzoyl chloride, the pyrroline ring is considered to open after the rearrangement has occurred: *42* → *44* (59J2094). However, with acetic anhydride the reaction *42* → *44a* occurs (69JO1473).

b. Mechanism of the Reaction of 2-Picoline 1-Oxide with Acid Anhydrides. Japanese investigators (cf. 53CT347; 55CT316) originally suggested that the reaction mechanism involves ionization and anionotropic rearrangement, but Bullitt and Maynard (54JA1370) proposed that the reaction proceeds through a rearrangement of the anhydro-base *45*. Not only does rearrangement of the anhydro-base account for the production of the major α-acetoxymethyl product (*21*), but analogous rearrangements to intermediates of type *46* are logical routes to the β-acetoxy by-products (*24*, *25*). However, Boekelheide and Harrington (55CI1423) proved that the reaction mixture contains free radicals and proposed a radical-chain mechanism: *47* → *50*. It is certainly true that the somewhat analogous rearrangement of dimethylaniline *N*-oxide to *N*-methylacetanilide and *o*-acetyldimethylaniline occurs by a free-radical mechanism (59CB3223). Although Traynelis and Martello (58JA6590; cf. 61JO428 and 61JO4365) found additional evidence for the presence of free radicals in the α-picoline–acetic anhydride reaction mixture, they felt that free radicals could not be directly involved in the for-



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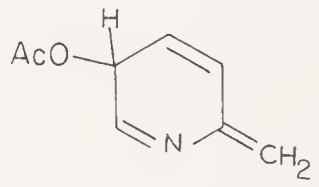

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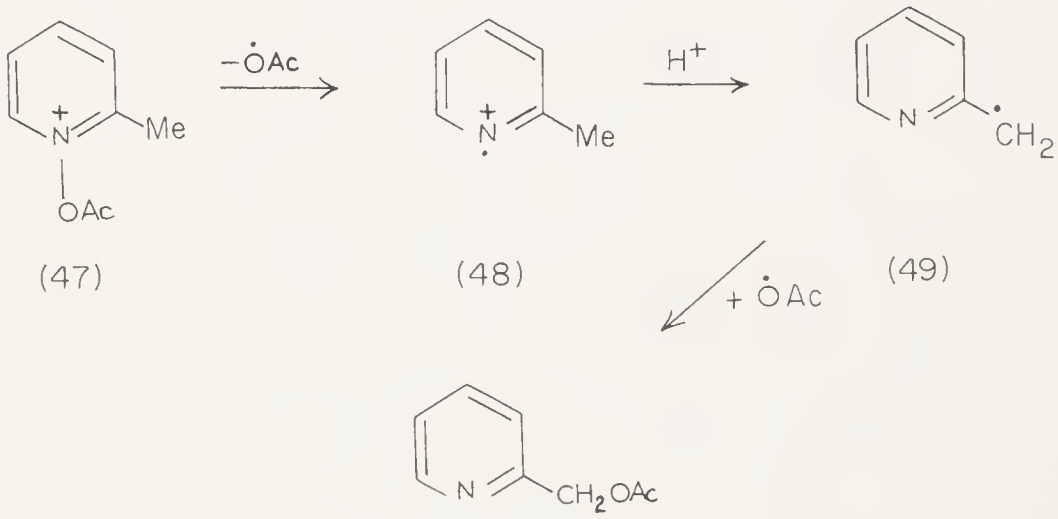
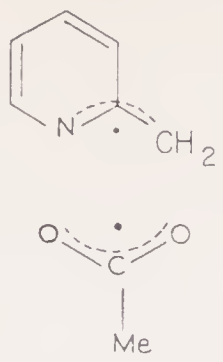


(47) (48) (49)

(50)

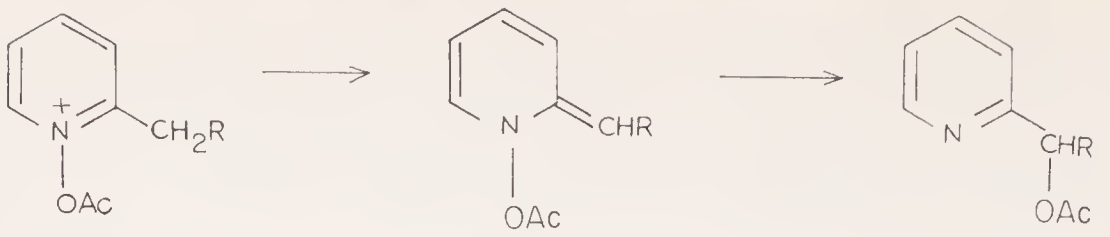


(51)

mation of the major products since radical-trapping agents did not lower the yield appreciably. By means of cross-over experiments, Traynelis and Martello proved that the reaction is intramolecular, but they pointed out that these results could be rationalized by either an ion-pair or a radical-pair mechanism as well as by the rearrangement path *45* → *21*.

Decisive evidence against the cyclic rearrangement mechanism (*45* → *21*) was provided by the ^{18}O-labelling work of Oae and his co-workers (61CI515; 62JA3359). They demonstrated that the rearrangement of 1-acetoxy-2-picolinium anhydro-base (*45* → *21*) is indeed intramolecular, but that the two oxygen atoms of the acetoxy group become equivalent in the product. Oae interpreted these results in terms of a radical-pair mechanism (*45* → *51* → *21*) in which the radicals are enclosed in a solvent cage and cannot react intermolecularly.

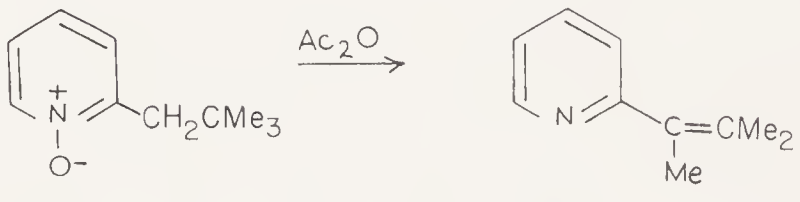
Traynelis and Pacini (64JA4917) studied the conversion of 2-benzyl- and 2-methyl-1-acetoxypyridinium cations (*52*; R = H, Ph) into α-acetoxy products (*54*). It was demonstrated spectroscopically that the anhydro-base (*53*) does not accumulate, and deuterium labelling of either the substrate or the solvent indicated that the conversion of *52* into *53* is the essentially irreversible rate-determining step, whereas conversion of the anhydro-base *53* into *54* is fast. It seemed anomalous that the anhydro-base (*53*) could break down into a radical pair more rapidly than it could abstract a proton from an acetic acid-containing solvent, and evidence against the radical-pair mechanism soon began to accumulate. Cohen and Fager (65JA5701) showed that the reaction of 2-picoline 1-oxide with phenylacetic anhydride gives some radical-decomposition products, but substantial amounts of the pyridylmethyl esters are also formed. The authors considered phenylacetoxy radicals to be so unstable that any radical-pair pathway for the production of the ester products is excluded. Koenig (66JA4045) has reported similar work for the reaction of 2-picoline 1-oxide with phenylacetic, trichloroacetic, and trifluoroacetic anhydride. Good yields of the esters are obtained, making a radical intermediate very unlikely. With trichloroacetyl chloride, 2-pyridylmethyl chloride is produced by further reaction of 2-pyridylmethyl trichloroacetate with chloride ion (68JO1530).



(52) (53) (54)

Bodalski and Katritzky [68J(B)831 ; 68TL257] have confirmed Oae's labelling results. They have shown that the scrambling of the oxygen atoms in the acetoxy radical occurs during, rather than before or after, the rearrangement, and that with certain 2-alkylpyridine 1-oxides rearrangements of the alkyl group typical for carbonium ion intermediates occur. In particular, 2-neopentylpyridine 1-oxide (*55*) yields the olefin *56*, and the 2-*n*-propyl analogue gives an appreciable amount of 2-(prop-1-enyl)pyridine. Recently Oae *et al.* (68TL4765) have carefully reinvestigated the deuterium isotope effect on the reaction and the nature of the rate-determining step. It transpires that the isotope effect is sensitive to substitution, and that the balance between proton removal and N-O bond fission as the rate-determining step is finely balanced : the intermediacy of the anhydro-base is further supported. Similar kinetic work by Muth *et al.* (68JO2762) on the reaction of 2-methylquinoline 1-oxide demonstrates the fleeting existence of the anhydro-base in this system.

Taking the evidence as a whole, it now seems conclusively proved that 2-picoline 1-oxide reacts with acetic anhydride via ion-pair intermediates of type *57*. This conclusion explains *inter alia* why electron-donating substituents favour the reaction (59JJ492). This conclusion probably also applies to the reaction of 2-methylquinoline 1-oxide with benzoyl chloride for which Oae and Kozuka (64T2671) have reported similar labelling results. For additional, but probably ill-founded, speculations on the reaction mechanism, see reference 66JI613.



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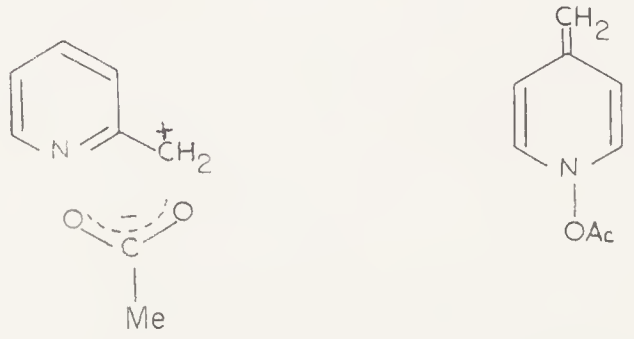
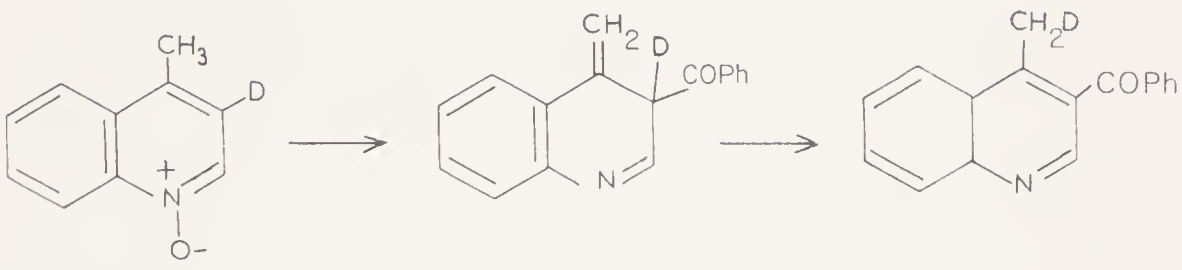


(57) (58)

c. Mechanism of the Reaction of 4-Picoline 1-Oxide with Acid Anhydrides. The earlier mechanistic proposals for the reaction of 4-picoline 1-oxide with acetic anhydride closely parallelled those for the 2-isomer; see, e.g., reference 55JA1281. Traynelis and Martello (60JA2744) found that free radicals are present in the reaction mixture, but that the reaction is relatively insensitive to the presence of radical acceptors, thus ruling out the radical-chain mechanism. Experiments with sodium acetate in butyric anhydride demonstrated the intramolecular character of the reaction, and these investigators favoured the radical-pair formulation on the basis of some sensitivity towards radical acceptors.

In contrast, the first ^{18}O-labelling experiments with 4-picoline 1-oxides appeared to favour an intermolecular reaction and were interpreted as attack of acetate anions on the anhydro-base *58* (62JA3362). Later work by Oae and his group (64T2677; 64T2685) indicated that the reaction has both inter- and intra-molecular components, and that their relative importance varies with the solvent composition. Traynelis and Gallagher have since claimed, however, that these results, as well as some new evidence, can be accommodated by the radical-cage hypothesis (65JA5710).

Oae *et al.* (66TL1513) have shown that the reaction of 3-deuterio-4-methylquinoline 1-oxide (*59*) with benzoyl chloride produces a selectively labelled derivative (*61*) which is good evidence for the anhydro-base intermediate *60*. The most recent evidence favours the involvement of 4-picolyl cations rather than 4-picolyl radicals in the 4-picoline 1-oxide rearrangement. Cohen and Deets (67JA3939) found that if the reaction is carried out in the presence of anisole, *o*- and *p*-picolylanisoles are formed, and that in the presence of benzonitrile *62* is formed, probably via *63*.



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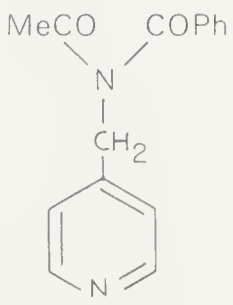

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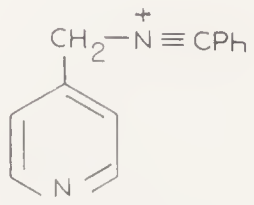
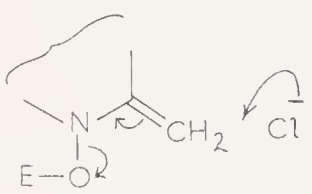


(63)

ii. Halogenation

Halogenation can occur with loss of the *N*-oxide function by nucleophilic attack by halide ions (*64*) or with retention of the *N*-oxide function by electrophilic attack of halogen molecules (*65*).

a. With Loss of the N-*Oxide Function.* The reaction of arylsulphonyl chlorides or phosphorus oxychloride with α- or γ-methyl *N*-oxides can introduce a chlorine atom into the methyl group with simultaneous loss of the *N*-oxide oxygen atom; the mechanism is of the type shown in the scheme *66* → *68*. Minor by-products resulting from side-chain halogenation are often formed in the nuclear halogenation of *N*-oxides by reaction with phosphorus oxychloride; for references, see Section III-4B. Side-chain halogenation is occasionally the major reaction with phosphorus oxychloride, for example 4-picoline 1-oxide reacts to give the 4-chloromethyl derivative (63JO1323), and it is generally the predominant reaction with a sulphonyl chloride. The reaction of α- or γ-alkyl *N*-oxides with sulphonyl halides to yield α- or γ-chloroalkyl heterocycles (Table 4.02) takes precedence over the sulphonyloxylation in a β-position of the ring which occurs in the absence of α- or γ-alkyl groups (Section III-4Ciiib).



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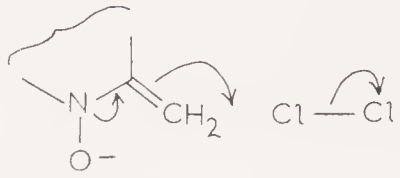

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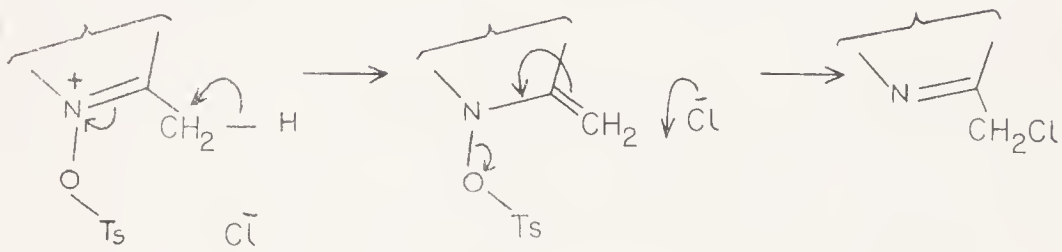


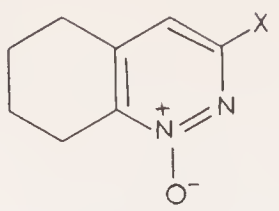
(66) (67) (68)

b. With Retention of the N-*Oxide Group.* Apparently alkylpyridine *N*-oxides have not been brominated, but 2-methylquinoline 1-oxide is converted by *N*-bromosuccinimide in carbon tetrachloride solution into the corresponding 2-bromomethyl and 2-(dibromomethyl) *N*-oxides (53JJ1326). 5,6,7,8-Tetrahydrocinnoline 1-oxides (*69*) undergo bromination in the alicyclic ring (63CT1527). 2-Methyl- and 2,3-dimethyl-quinoxaline 1,4-dioxides react with bromine to give the corresponding bromomethyl derivatives, apparently by way of unstable intermediate addition products (56J2052).

Table 4.02. Conversion of α- and γ-Alkyl *N*-Oxides by Acid Chlorides into Chloroalkyl Derivatives with Loss of the *N*-Oxide Function (cf. *66* → *68*)

Ring system	Reagents	Substituents: Unaffected	Substituents: Affected[a]	Yield, %	References
Pyridine 1-oxide	TsCl, AcCl, PhCOCl, $PhSO_2Cl$	—	2-Me → 2-CH_2Cl	(data)	52MO1, 53NK363, 62JO3856
	TsCl	5-Et	2-Me → 2-CH_2Cl	71	61NK616
	TsCl	5-Me	2-Me → 2-CH_2Cl	—	61NK104
	TsCl	6-Me	2-Me → 2-CH_2Cl	43	61NK104, 61NK616
Quinoline 1-oxide	TsCl	—	4-Me → 4-CH_2Cl	—	58JJ611
	TsCl	4-Me	2-Me → 2-CH_2Cl	—	58JJ611, 63CT415
Phenanthridine 10-oxide	$POCl_3$	—	9-Me → 9-CH_2Cl[b]	—	50J703
Pyrimidine 1-oxide	TsCl	4-Me	6-Me → 6-CH_2Cl	—	59J525
Quinoxaline 1-oxide	CH_3SO_2Cl	3-Ph	2-Me → 2-CH_2Cl	51	64JA1830
Benzimidazole 1-oxide	TsCl	3-Me	2-Me → 2-CH_2Cl[c]	—	66CT1219
Purine 1-oxide	CH_3SO_2Cl	—	6-Me → 6-CH_2Cl	30	62JO3545
Thiazole 3-oxide	TsCl	4-Me	2-Me → 2-CH_2Cl	—	61NK616

[a] Substituents affected *in addition to* the *N*-oxide function.
[b] 3-Chloro-9-methylphenanthridine is also formed.
[c] 6-Chloro-2,3-dimethylbenzimidazole also obtained.



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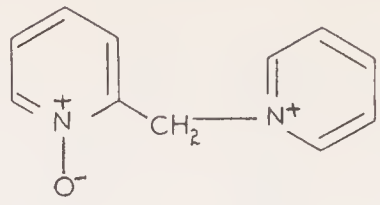

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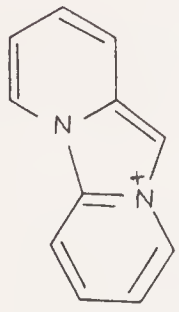

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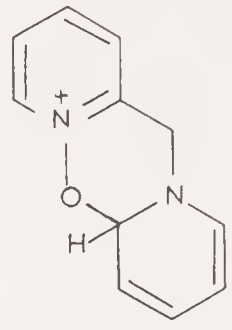


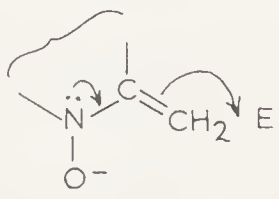
(72)

2-Picoline 1-oxide undergoes the King reaction with iodine and pyridine to yield the quaternary derivative *70*, probably via 2-iodomethylpyridine 1-oxide (60CT692). If the reaction mixture is heated, the bis-pyridino-imidazolium salt *71* is formed as a by-product (63CT694), possibly by the cyclization of *70* to *72* and subsequent elimination of water to give *71*. The King reaction has also been successfully applied to 2- and 4-methylquinoline 1-oxide (61G34).

iii. Other Reactions with Retention of the N-*Oxide Group*

Most of the reactions considered here proceed by proton abstraction from the *N*-oxide and reaction of the resultant anion with an electrophile (*73*). The electrophile can be a proton (hydrogen exchange occurs), an acylating agent (Claisen condensation), or an alkylating agent. Somewhat more complex are reactions where E of *73* is a carbonyl or nitroso compound; here the initial product (*74*, Z = CH or N) usually loses water to give a double-bonded compound (*75*). If E is a nitroso or diazonium compound, then the first products of type *76* (Z = O or NR) undergo tautomerization into oximes or hydrazones.

Oxidations are also included in this section; they may, however, proceed by initial free-radical abstraction of a hydrogen atom rather than a proton.



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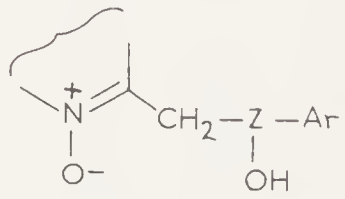

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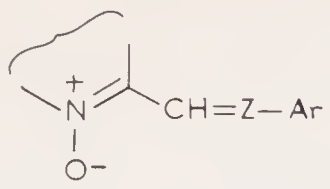

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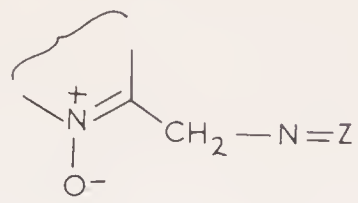


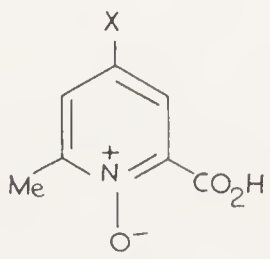
(76)

a. Base-catalysed Hydrogen Exchange. α-Methyl and -methylene groups can be deuterated readily under base catalysis. Preparative details for 2-methylquinoline 1-oxide (68JO2762) indicate easy reaction at 100° in deuterium oxide solution.

Russian workers have studied kinetically the hydrogen–deuterium exchange by α-methyl groups on heterocyclic *N*-oxides (64ZO4130). The mobility of the methyl hydrogen atoms increases in the order: α-picoline 1-oxide < quinaldine 1-oxide < 6-methylphenanthridine 5-oxide. The rates are correlated with delocalization energies and the N=C-Me bond order, and they also show a relation with the chemical shifts of the NMR absorption bands associated with the methyl group. Further work (67CT1225) has shown that the hydrogen atoms in methyl groups *gamma*, as well as *beta*, to the *N*-oxide function also exchange. As expected, the methylene protons of an ethyl group react less readily than those of a methyl group directly attached to the ring.

The hydrogen atoms in the methyl groups of all the isomeric methylpyridazine 1-oxides undergo easy base-catalysed hydrogen–deuterium exchange at rates which are comparable to each other (6-Me > 5-Me > 4-Me ≃ 3-Me) and significantly faster than those of the corresponding methylpyridazines (67CT2000).

b. Oxidation. Carboxy *N*-oxides have been prepared from alkyl *N*-oxides by permanganate or chromic acid oxidation. 4-Substituted 2,6-dimethylpyridine 1-oxides give monocarboxylic acids of type *77* (64RC1793) on treatment with permanganate, and 4-methylquinoline 1-oxide yields 4-carboxyquinoline 1-oxide (48JJ123), but the reaction fails with 4-chloro-3-methylpyridine 1-oxide (56JA214). Chromic acid oxidation of 3-methyl-4-nitropyridine 1-oxide gives the 3-carboxylic acid (61JO122), and ethylpyridine 1-oxides are converted into the corresponding acetylpyridine 1-oxides (56JJ1308).



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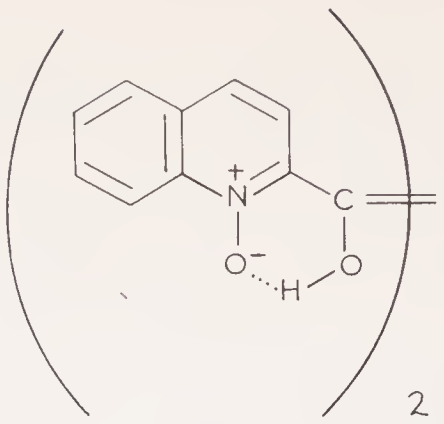

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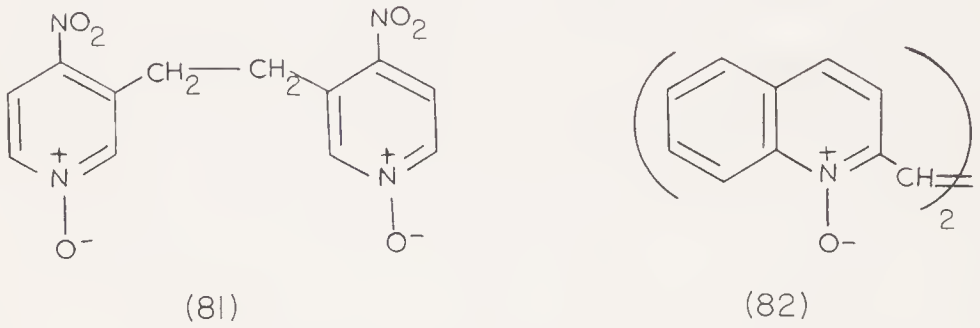

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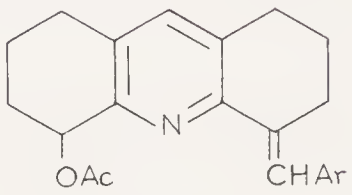


(82a)

Attempted conversion of 2-methylpyridine 1-oxide into the 2-formyl compound by oxidation with chromyl chloride (Etard reaction) failed (58CC949). However, formyl *N*-oxides are conveniently available by the oxidation of α- and γ-methylpyridine 1-oxides with selenium dioxide in pyridine; by contrast, if dioxane is used as solvent, the corresponding pyridinecarboxylic acids are formed with simultaneous loss of the *N*-oxide oxygen atom [58LA(613)153; see also 55JP974; 63CT348]. Oxidation of alkylquinoline 1-oxides with selenium dioxide gives the corresponding formylquinoline 1-oxides (62CT961; cf. 63JJ348) or in the 2-methyl case, the benzoin condensation product quinaldoin 1,1′-dioxide (*78*) (61JO1410). Selenium dioxide

oxidations have also been used in the 6-methylphenanthridine 5-oxide (62ZO2217) and in the quinoxaline *N*-oxide series (55ZO161). Treatment of pyrroline 1-oxides (*79*) with selenium dioxide yields ring-expanded products (*80*) by rearrangement of an intermediate aldehyde (59J2105), but the reaction conditions can be adjusted to give the 2-formylpyrroline 1-oxide (69JO1473).

3-Methyl-4-nitropyridine 1-oxide undergoes a facile coupling reaction on oxidation with aerial oxygen, sodium nitrite, or nitrite esters to give the dimeric product *81* (57JA3549); activation by the 4-nitro group is essential for the reaction, which probably is of the free radical dimerization type: the corresponding ethene is often formed as a by-product (61JO3796). Somewhat similar is the oxidation of 2-methylquinoline 1-oxide by nitrobenzene or nitrosobenzene to give the diquinolylethene *82* (62G301) (see also Section IV-2Biiie).

c. Reactions with Aldehydes. α- or γ-Methyl groups on heterocyclic *N*-oxides condense with aldehydes to yield styryl *N*-oxides in the presence of piperidine acetate (58JO201; these authors report that neither acidic nor mildly basic catalysts alone were effective), potassium methoxide [58LA-(613)171], potassium hydroxide [58J150; 61T(14)151], or other catalysts. Deoxygenation often occurs simultaneously. A 3-methyl group on pyridine 1-oxide does not react unless it is further activated by a nitro group, and a 4-methyl group reacts faster than a methyl group in the 2-position. In the pyridazine 1-oxide series the reactivities of the mono-methyl compounds are in the order $5 > 4 \simeq 6 > 3$ (63CT1146). Examples of the reaction are collected in Table 4.03. Some failures have been reported: 2,3-dimethylquinoxaline 1,4-dioxide failed to react with *p*-dimethylaminobenzaldehyde (53J2822), and 1,2-dimethylbenzimidazole 3-oxide did not condense with benzaldehyde (66CT1219). The relative reactivity of methyl groups in the parent heterocycles, *N*-oxides, and quaternary salts has been compared [58LA(613)171]; in the base-catalysed reactions, the *N*-oxides react faster than the parent heterocycles but slower than the quaternary salts. In the quinoxaline 1- or 1,4-di-oxide series, reaction with formaldehyde (66KG432) or aromatic aldehydes (66KG272) occurs under base-catalysed conditions, but stops at the intermediate carbinol stage.

If 2- or 4-methylpyridine 1-oxide is allowed to react with an aryl carbinol ($ArCH_2OH$) in the presence of a base, the styrylpyridine ($PyCH{=}CHAr$) is formed by initial oxidation of the aryl carbinol to the corresponding aldehyde with simultaneous reduction of the *N*-oxide to the parent heterocycle (67CT511). Reaction of octahydroacridine 10-oxide with aryl aldehydes in the presence of acetic anhydride yields products of type *82a* (69KG175/2).

d. Reactions with Alkyl and Acyl Nitrites. 2-Picoline 1-oxide reacts with amyl nitrite in the presence of sodamide in liquid ammonia to form the hydroxyimino *N*-oxide *83* by a Claisen-type reaction (cf. *84*); a small amount

Table 4.03. Reactions of Alkyl *N*-Oxides with Aldehydes

Ring system	Position of alkyl group attacked	Aldehyde, R of R-CHO	Catalyst	Yield, %	References
Pyridine 1-oxide	2	*p*-dimethylaminophenyl	$C_5H_{12}N^+OAc^-$, C_5H_5N–KOH	12–56[a]	58JO201, 61T(14)151
	4	*p*-dimethylaminophenyl	C_5H_5N–KOH	40–78	61G991, 61T(14)151
	2,6	*p*-dimethylaminophenyl	37% HCl	—	52JJ1188
	2	2-furyl-5-nitro	Ac_2O	(data)	65JJ565, 66JJ1014
	4	*o*-nitrophenyl	—	(data)	61JO418
	2	phenyl	KOMe; $C_5H_{11}N$–EtOH	22–56	58J150, 58LA(613)171, 60JO850
	3	phenyl	$C_5H_{11}N$–MeOH	46	58LA(613)171
	4	phenyl	KOMe	11–76	58J150, 58LA(613)171
	2	substituted phenyl, various	$C_5H_{11}N$–EtOH	11–73	60JO850
	4	4-substituted phenyl, various	KOMe	12–93	60J1516
Quinoline 1-oxide	2	aryl, various	KOMe	40–95	65PC(28)82
	2	*p*-dimethylaminophenyl	$C_5H_{12}N^+OAc^-$, 37% HCl, KOMe	17–70	52JJ1188, 58JO201, 63G1093
	4	*p*-dimethylaminophenyl	KOMe	70	49JJ240, 63G1093,
	4	(1-oxido-4-quinolyl)	NaOMe	50	60G1197
	2	phenyl	NaOMe, KOMe	—	62PC(18)175, 63AG172, 64PC(25)7
	4	phenyl	KOMe	—	63JJ342
Isoquinoline 2-oxide	1	2-furyl-5-nitro	Ac_2O	—	65JJ565

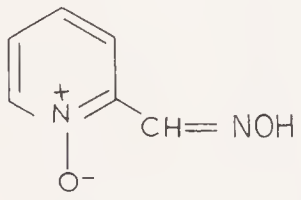
[a] Yields are dependent on reaction time.

Table 4.03. Reactions of Alkyl *N*-Oxides with Aldehydes—*continued*

Ring system	Position of alkyl group attacked	Aldehyde, R of R-CHO	Catalyst	Yield, %	References
Pyridazine 1-oxide	4,6	phenyl	NaOMe	51–75[b]	63CT1146
	2,4	4-substituted phenyl, various	NaOMe	18–80	63CT1146
	3,4,5,6	aryl	NaOMe	(data)	69JJ132
Pyrazine 1,4-dioxide	2,3,5,6	phenyl	37% HCl	—	52JJ1188
	2,5	*p*-dimethylaminophenyl	NaOH–alc.	(data)	58JO1603
	2,5	phenyl	—	—	58DI64
Quinoxaline 1-oxide	2	aryl	NaOMe	—	68KG729
Quinoxaline 1- and 1,4-di-oxide	2 and 2,3	aryl	C_5H_5N	—	66KG272

[b] Yields are best when reaction is carried out at 100°.

of 2-picolinamide 1-oxide is obtained as a by-product (63CT461; 65JJ451; 69AP494). 4-Methyl-, 2- and 4-ethyl-, and 2- and 4-benzyl-pyridine 1-oxides undergo similar transformations, but the corresponding 3-substituted derivatives do not react. Much better yields are obtained in these reactions with the alkylpyridine *N*-oxides than with the parent alkylpyridines, which is a reflection of the greater reactivity of the alkyl groups in the *N*-oxides. This reaction has been extended to quinoline (63JJ348; 64JJ290), benzimidazole (66CT1219; 68CT527), and pyridazine *N*-oxides (63CT1517). There is little difference between the reactivities of the two methyl groups in 3,6-dimethylpyridazine 1-oxide. The conversion of 6-methyl-4-nitropyridazine 1-oxides into 4-chloro compounds can also give hydroxyimino compounds as by-products, e.g., *85* → *86*; here it is nitrous acid liberated from the nitro group which reacts with the methyl group (63CT1511).



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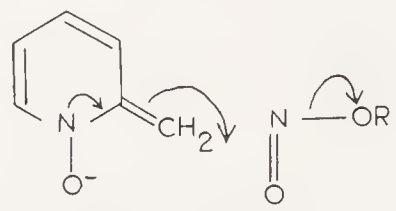

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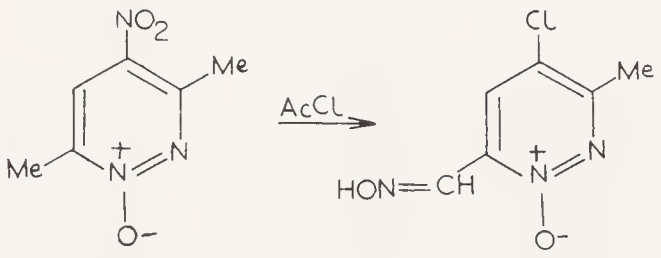
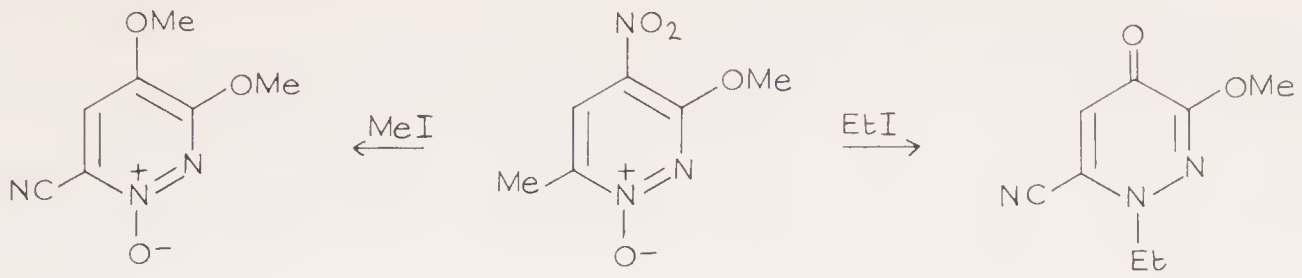


(85) (86)

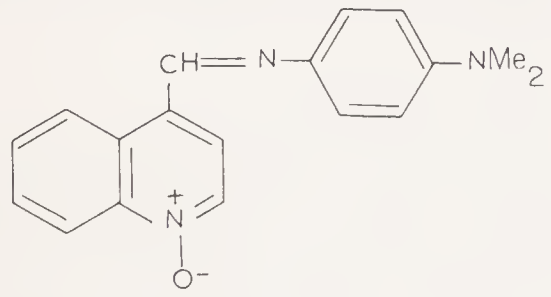
2-Picoline 1-oxide is converted by acetyl nitrite into 2-cyanopyridine; the reaction appears to be general (61USP2989543), and the mechanism probably involves formation of *83* via *84* and subsequent dehydration of the oxime by way of an acetylated intermediate. Nitration of methyl-substituted *N*-oxides with acetyl nitrate (see Section III-3C) yields, in addition to the expected *β*-nitro compounds, by-products resulting from conversion of the methyl groups into cyano groups (64CT228). Treatment of *α*-methyl-*γ*-nitro *N*-oxides with acetyl chloride to form *γ*-chloro compounds (see Section IV-3Ciib) also gives *α*-cyano derivatives as by-products; the acetyl nitrite formed in the reaction can effect conversion of an *α*-methyl group into a cyano group (63JJ352; 65J2096). In the pyridazine series the transformations of the nitromethyl *N*-oxide *88* into the cyanopyridazine *87* and the cyanopyridazinone *89* have a similar mechanism (68CT1221).



(87) (88) (89)

e. Reactions with Nitroso Compounds and Diazonium Salts. 2-Methylpyridine 1-oxides react with nitroso compounds to form azomethines (cf. 63J4600). 4-Methylquinoline 1-oxide condenses with *p*-dimethylaminonitrosobenzene to yield the Schiff's base *90* (60G1197). However with the 2-methyl analogue, compound *91* is formed (60G1179); evidently the first product (cf. *90*) reacts with a second mole of the *N*-oxide and eliminates *p*-dimethylaminoaniline, and 4-methylquinoline 1-oxide also reacts in this manner with nitrosobenzene (63JJ342).

The reaction with nitroso compounds succeeds with 9-methylacridine 10-oxide (62ZO2217) but fails with 2,3-dimethylbenzimidazole 1-oxide (66CT1219). Such reactions with nitroso compounds are known for the quaternary derivatives of α- and γ-methyl heterocycles, but do not usually succeed for the parent methyl heterocycles.



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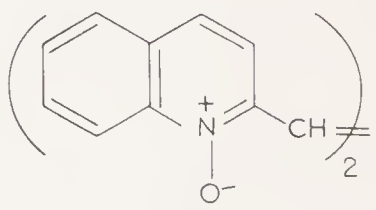

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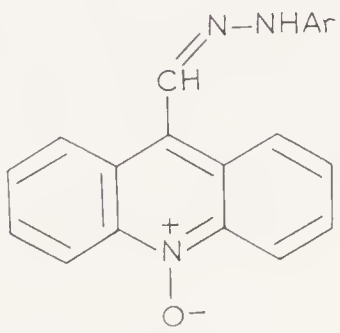

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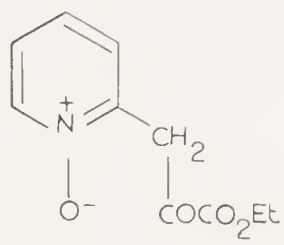

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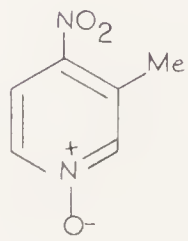


(94)

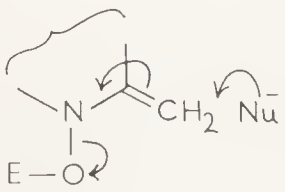
9-Methylacridine 10-oxide and 6-methylphenanthridine 5-oxide couple slowly with diazonium salts; the initial products spontaneously tautomerize to yield hydrazones, cf. *92*. Similar reactions take place in the 2- and 4-methylquinoline series only if the *N*-oxide is quaternized. The reaction does not occur in the pyridine series (62ZO2217), but succeeds with 2-methylquinoxaline 1-oxide (68KG729).

f. Claisen Condensation and Alkylation. 2- and 4-Picoline 1-oxides undergo Claisen condensation with ethyl oxalate to give products of type *93* (54JA3168; cf. 59JA1456; 59JA2537); the reaction has also been applied to methyl-substituted quinoline [59PC(9)54] and benzimidazole *N*-oxides (66CT1219). 3-Methyl-4-nitropyridine 1-oxide (*94*) does not undergo a Claisen condensation with ethyl oxalate, but the dimeric derivative *81* is formed instead (64AJ1399). Other Claisen-type condensation reactions between esters and alkyl *N*-oxides have been reported; for example, 2-picoline 1-oxide is benzoylated by methyl benzoate in the presence of sodamide (64JH138). Orthoformamide derivatives condense with α- and γ-methyl groups of heterocycles, e.g. $RMe + HC(OR)_2NMe_2 \rightarrow RCH{=}CHNMe_2$. This reaction also takes place with *N*-oxides, and the reactivity of a methyl group is enhanced in the *N*-oxide (68CB4048).

2- and 4-Picoline 1-oxides have been alkylated in the presence of sodamide in liquid ammonia, but the yields are low (62J1475; 64J5518; cf. 65DI96). 2,3-Dimethylquinoxaline 1,4-dioxide undergoes a Mannich reaction with formaldehyde and piperidine (56J2052).

iv. Other Reactions with Loss of the N-*Oxide Group*

Other examples of reactions of the general type *95* (cf. halogenation with loss of the *N*-oxide group, Section IV-2Biia) are not common, but examples are known where the nucleophile is a cyanide or phenylmercaptide ion. The reaction of 4-isopropylquinazoline 1-oxide with benzoyl chloride and cyanide ions, in addition to the normal Reissert product (cf. Section III-4Fia), gives some of the amide *96* by the hydrolysis of an intermediate nitrile, formed as shown in *97* (64CT43).



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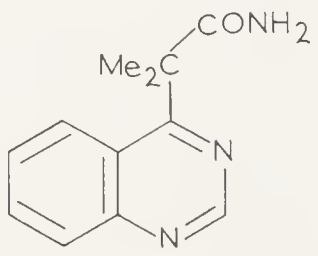

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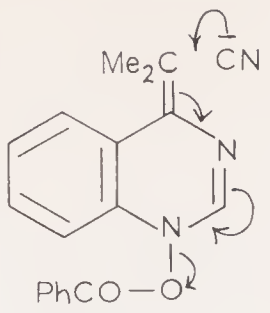

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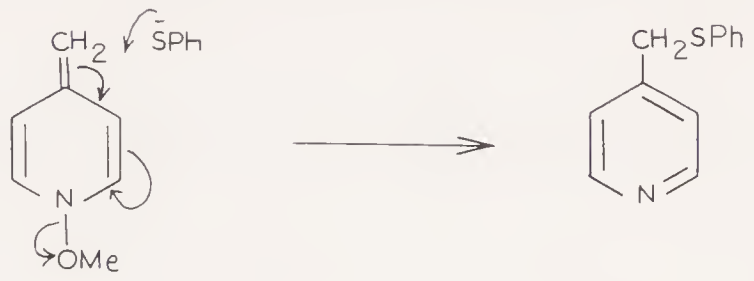


(98) (99)

The reaction of 1-methoxy-4-methylpyridinium cation with phenylmercaptide ions yields the 4-phenylthiomethyl derivative; the mechanism again probably involves deprotonation followed by nucleophilic attack (*98* → *99*) (63JO1323). Ring-substituted by-products are also formed (cf. Section III-4Di). Photochemical rearrangement of 2-picoline 1-oxide gives 2-hydroxymethylpyridine and 2-picoline [61BJ1440; 62JT(36)2072].*

C. OTHER CARBON-LINKED FUNCTIONAL GROUPS

The reactions of other carbon-linked substituents are considered under the heading of carboxylic acids, aldehydes/ketones, and alcohols and their derivatives. Most of the reactions undergone by compounds of this type are standard and are little affected by the presence of the *N*-oxide function; these reactions are simply collected in Table 4.04. Reactions with special features are treated explicitly in the text. *N*-Oxides with carbon-linked functional groups can be prepared by *N*-oxidation of the appropriate heterocycle (Chapter II), by ring synthesis (Chapter II), or from alkyl-substituted compounds (see Section IV-2Bi-iv).

i. Carboxylic Acids and Derivatives

a. Acid Strength and Metal Complexes of Carboxylic Acids. Carboxy *N*-oxides are usually stronger acids than the corresponding deoxygenated analogues: pK_a values are quoted in reference 61JO5230. The structures of α-carboxy *N*-oxides in the solid state and the question of intramolecular hydrogen bonding (cf. *100*) have been investigated using infrared spectroscopy by Szafran (65BA245; 65BA333; 69RC473; 69RC653); infrared work on β- and γ-carboxylic acids has also been reported (64BA387).

* See addendum in the Appendix.

Table 4.04. Reactions of Miscellaneous Carbon-linked Substituents

Reactions[a]	Ring system	Position of substituents	References
-CN → -CO_2H	pyridine 1-oxide	2	60JJ1519
→ -CS-NH_2[b]	pyridine 1-oxide	2 or 4	56AA(129)4-M, 61JJ1204
→ -CS-NH_2[b]	benzimidazole 1-oxide	2	68CT527
→ -C(=NH)OR[c]	benzimidazole 1-oxide	2	68CT527
→ -CO_2H	pyridine 1-oxide	4	69RC309
-CH_2OH → -CHO[d]	pyridine 1-oxide	2	58JJ957
→ -CH_2Cl[g]	pyridine 1-oxide	3	62H1860
-CH_2OH → -CH_2Cl	pyridine 1-oxide	4	68MC1172
-CH_2OH → -CO_2H	pyridine 1-oxide	2 or 2,6	69RC653
-CH_2OAc → -CH_2OH[h]	pyridine 1-oxide	2	65NK409
→ -CH_2OH[i]	quinoxaline 1,4-dioxide	2	56BC455
→ -CH_2Br → -$CH_2\overset{+}{N}C_5H_5$ → -$C{=}\overset{+}{N}(O^-)C_6H_4$-$NMe_2$	pyridine 1-oxide	4	62CT961
-CH_2NHNH_2 → -CH_2NH-N=CMeR[k]	pyridine 1-oxide	4	60F221

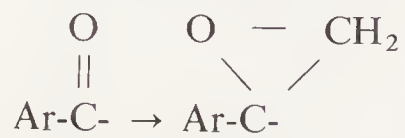
[a] Reagents are given in the footnotes.
[b] Et_3N–H_2S; NH_3–H_2S.
[c] ROH–NaOH.
[d] SeO_2; *N*-oxide group often lost simultaneously.
[e] SeO_2.
[f] *N*-Bromosuccinimide.
[g] $SOCl_2$.
[h] H_2/catalyst.
[i] 2N HCl.
[j] (1) 48% HBr, (2) K_2CO_3; C_5H_5N, (3) ON-C_6H_4-NMe_2–OH^-.
[k] 2-Acetylfuran (MeCO-R).

Table 4.04. Reactions of Miscellaneous Carbon-linked Substituents—*continued*

Reactions[a]	Ring system	Position of substituents	References
$-CH_2Br \rightarrow -CH_2OCH_2- \rightarrow -CH_2Br$[l]	pyridine 1-oxide	2	65CT233
$\rightarrow -CH_2-NC_5H_{10}$[m]	pyridine 1-oxide	2	63CT694
$-CH_2Cl \rightarrow -CH_2SMe$[n]	1,3,5-triazine 1-oxide	4	67JH268
$-CH_2Ph \rightarrow -CH_2-C_6H_4-NO_2(p)$[o]	pyridine 1-oxide	2 and 4	58J1754
$-CH_2CH(OH)Me \rightarrow -CH{=}CHMe$[p]	pyridine 1-oxide	2	59JJ487
$-CH_2-CHOH-Ph \rightarrow -CH{=}CHPh$[q]	pyridazine 1-oxide	4 and 5	63CT1146
$-CH{=}NOH \rightarrow -CN$[r]	pyridine 1-oxide	2	60JJ1519
$-CH{=}NOH \rightarrow$ various	furoxan	3	04LA(330)237
$-CH{=}N^+(O^-)Ar \rightarrow -CH{=}NAr + \dot{C}O\text{-}NHAr$[s]	pyridine and quinoline 1-oxides	2 or 4	62CT969
$-CH{=}N^+(O^-)C_6H_4-NMe_2 \rightarrow -CONHC_6H_4-NMe_2$[t]	pyridine 1-oxide	2	60CT698
$-CH{=}CH_2 \rightarrow -CH_2CH_2Z$[u]	pyridine 1-oxide	2	61JO3802
$-CHOH-CHOH- \rightarrow -CHO$[v]	pyridine 1-oxide	2,3, and 4	58LA(618)152
$-CHO \rightarrow -CH{=}CHCO_2H \rightarrow -CHO$[w]	quinoxaline 1,4-dioxide	2	58ZO1378
$\rightarrow -CO_2H$[x]	quinoxaline 1,4-dioxide	2	55ZO161

[l] (1) NaOH (cold) gives the bis-compound, (2) HBr reverses the reaction.
[m] Piperidine.
[n] NaOH (−70°), then methanethiol (20°).
[o] HNO_3–H_2SO_4.
[p] H_2SO_4–hydroquinone.
[q] NaOMe + heat.
[r] $POCl_3$–AcCl; Ac_2O–heat.
[s] CS_2.
[t] SO_2, PCl_3; deoxygenation can also occur.
[u] EtOH, pyrrole, ethyl acetoacetate, diethyl malonate.
[v] Bis derivative; $Pb(OAc)_4$.
[w] (1) $CH_2(CO_2H)_2 + C_5H_5N$, (2) $KMnO_4$ + acetone.
[x] H_2O_2–AcOH–Ac_2O.

Table 4.04. Reactions of Miscellaneous Carbon-linked Substituents—*continued*

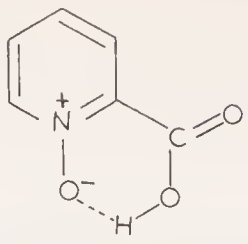
Reactions[a]	Ring system	Position of substituents	References
$-CONH_2 \rightarrow -CN$	pyridine 1-oxide	2	60JJ1519
$\rightarrow -CSNH_2$[y]	pyridine 1-oxide	3	57JO984
$\rightarrow -CO_2H$[z]	pyridine 1-oxide	4	59JJ492
$-CONHNH_2 \rightarrow -CONHN{=}CRR'$[aa]	pyridine 1-oxide	4	57F705, 60G1795
*			
$-COCH_3 \rightarrow -C(Me){=}NNHR$	pyridine 1-oxide	4	57F705
$\rightarrow -C(Me)\text{-}O\text{-}CH_2CH_2\text{-}O$[bb]	pyridazine 1-oxide	3	68JH379
$-COPh \rightarrow$ oxime $\rightarrow -NHCOPh \rightarrow -CONHPh$[cc]	pyridine 1-oxide	2, 3, and 4	66JJ1022
$\rightarrow -CHBrPh$[dd]	1,2,4-benzotriazine 1-oxide	3	67J(C)2658
	furoxan	4 and 5	67JO4050
$-CO_2H \rightarrow COCl$[ff]	benzofuroxan	5	66J(C)971
$\rightarrow -CONH_2$, $-CONHR$, $-CONHNH_2$, $-CONHOH$[gg]	pyridine 1-oxide	2	61PC(13)58

[y] (1) $POCl_3$, (2) MeOH–NH_3–H_2S.
[z] 30% H_2SO_4.
[aa] Various ketones.
[bb] Ethylene glycol and *p*-toluenesulphonic acid.
[cc] NH_2OH.
[dd] AcBr–AcOH.
[ee] X = Me or Cl; CH_2N_2.
[ff] Toluene and thionyl chloride.
[gg] (1) Thionyl chloride, (2) NH_3, NH_2R, NH_2NH_2, NH_2OH.
* $-COCH_3 \rightarrow -COCH_2CH_2CO_2Et$; see addendum in the Appendix.

Table 4.04. Reactions of Miscellaneous Carbon-linked Substituents—*continued*

Reactions[a]	Ring system	Position of substituents	References
→ H; *N*-oxide lost[ee]	pyridine 1-oxide	2	61PC(13)58
-CO_2Me → -$CONH_2$[hh]	benzofuroxan	4	66J(B)1004
→ -$CONHNH_2$ → -CONHN=CHR[ii]	quinoline 1-oxide	2 and 4	59JJ908
-CO_2Et → -CO_2H[jj]	pyridine 1-oxide	3	65CT113
→ -$CONH_2$, -$CONHNH_2$[kk]	pyridine 1-oxide	2 and 4	52JJ1474
→ -$CONHNH_2$ → -CONH-N=CHR[ii]	pyridine 1-oxide	4	53AN87
→ -$CONH_2$, -$CONHNH_2$, -CO-NHOH[ll]	quinoxaline 1-oxide	3	55ZO161
→ -$CONHNH_2$[mm]	benzimidazole 1-oxide	2	68CT527

[hh] EtOH and NH_4OH.
[ii] (1) $N_2H_4 \cdot H_2O$, (2) Ar-CHO.
[jj] 50% H_2SO_4.
[kk] $N_2H_4 \cdot H_2O$; NH_4OH.
[ll] NH_3, N_2H_4, NH_2OH.
[mm] N_2H_4.



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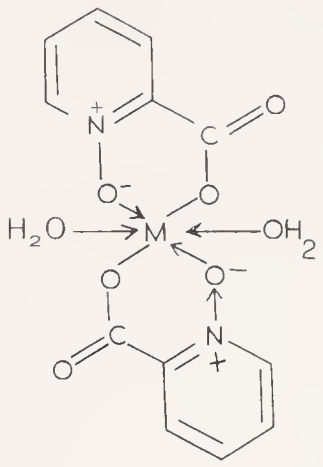

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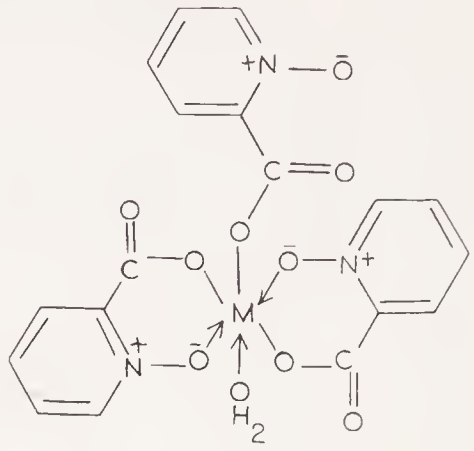
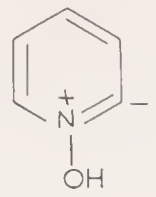


(102)

Metal complexes of 2-carboxypyridine 1-oxide have been extensively investigated by Lever, Lewis, and Nyholm (62J5262); see also references 58LA(613)144, 60MI245, and 62J4738. Structures of type *101* have been suggested for complexes with divalent manganese, iron, cobalt and nickel, and of type *102* for complexes with trivalent chromium and cobalt; the latter complexes cannot be dehydrated without decomposition. The rare earths also form complexes with 2-carboxypyridine 1-oxide (66CC1471).*

b. Decarboxylation of Carboxylic Acids. Carboxyl groups *alpha* to an *N*-oxide function decarboxylate readily on heating, as has been shown in the following series: pyridine 1-oxides (51CB452), pyridazine *N*-oxides (63CT-1511), phenanthridine 5-oxides (57JA6500), and pyrroline 1-oxides (59J2094). Dicarboxypyridine 1-oxides are decarboxylated in stages (60USP2953572). A kinetic study carried out on diethylene glycol solutions showed that the relative rates of decarboxylation of 2-carboxy-pyridine, -pyridine 1-oxide, and -1-methylpyridinium ion are 1 : 160 : 720 (64JA5230). The easy decarboxylation of α- carboxy *N*-oxides probably proceeds via zwitterions of type *103*; this mechanism is supported by the isolation of 2-(1-hydroxy-1-phenethyl)pyridine 1-oxide (*104*) following decarboxylation of 2-carboxypyridine 1-oxide in acetophenone (Hammick reaction) (61JO428). Divalent metal ions inhibit the decarboxylation of 2-carboxypyridine 1-oxide (64JA-5230). Decarboxylation of 2-carboxy-1-methylbenzimidazole 3-oxides are particularly facile (and occur spontaneously on hydrolysis of the corresponding esters) as would be expected in view of the appreciable stability of zwitterions of type *105* (68CT527).

* See addendum in the Appendix.



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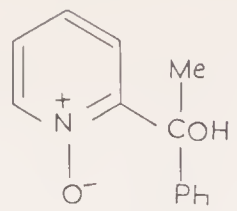

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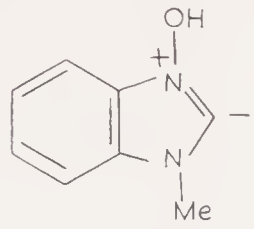

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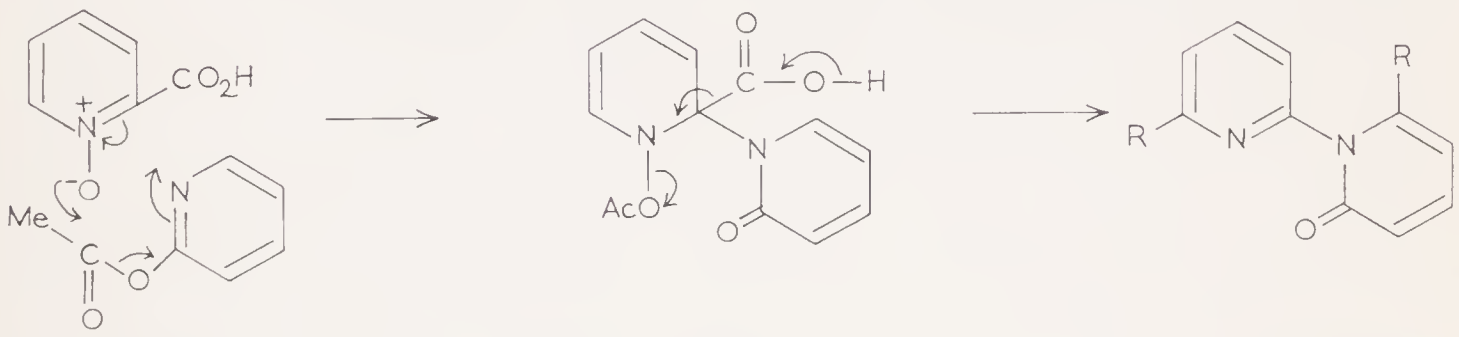


(106) (107) (108)

Decarboxylation of 2-carboxypyridine 1-oxide and its 6-methyl derivative in the presence of acetic anhydride is said to yield the pyridyl-2-pyridones *108* (R = H) and *108* (R = Me), respectively (60AP452). This reaction, which is reminiscent of that between α-halogenopyridines and pyridine 1-oxides (Section III-4Eiib), may involve initial formation of pyridine 1-oxide which is converted into 2-acetoxypyridine in the normal way (Section III-4Ciia). The 2-acetoxypyridine could then add another mole of the acid via intermediates *106* and *107*. However, Boekelheide and Lehn (61JO428) and Hamana and Yamazaki (61JJ574) reported that 2-carboxypyridine 1-oxide reacts with acetic anhydride to yield pyridine 1-oxide by simple decarboxylation, together with some 2-pyridone.*

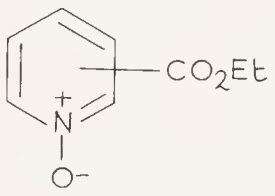
The reaction between 2-carboxy-5-methoxycarbonylpyridine 1-oxide and acetic anhydride was erroneously reported to yield dihydro-4-oxonicotinic acid (60JO565), and the product was later shown to be the expected product of simple decarboxylation, 3-methoxycarbonylpyridine 1-oxide (62JO551). Japanese investigators (53NK547) found that 2-carboxypyridine 1-oxide and tosyl chloride react to give 2-tosyloxypyridine as the major product.

2-Carboxymethylpyridine 1-oxide is somewhat more stable than 2-pyridylacetic acid, but it also undergoes facile decarboxylation to give 2-picoline 1-oxide (57JA2236). 2-Carboxymethylbenzimidazole 1-oxide also undergoes ready decarboxylation [67J(C)1764].

* See addendum in the Appendix.

c. Formation and Properties of Esters. Carboxyl groups attached to heterocyclic *N*-oxides may readily be converted into esters (see, e.g., 49J231S; 52JJ1474; 59JJ908; 61PC58; 62CB277). For example, 2-carboxy-4-nitro- and -4-chloro-pyridine 1-oxides can be esterified with diazomethane, and the esters readily form amides or hydrazides on treatment with amines or hydrazine (59CB155). Hydrazides show normal properties (57RC847). Kinetics of esterification are discussed in reference 62BD407.

Falkner and Harrison found that ethoxycarbonylpyridine 1-oxides (*109*) are hydrolysed ca. 1000 times as rapidly as ethyl benzoate and 10–50 times faster than the pyridine analogues without the *N*-oxide group; these rates reflect the strong electron-withdrawing effect of the *N*-oxide group (60J1171). Somewhat surprisingly, β-ethoxycarbonylvinylpyridine 1-oxides (*110*) hydrolyse more slowly than the pyridine analogues (62J2148).



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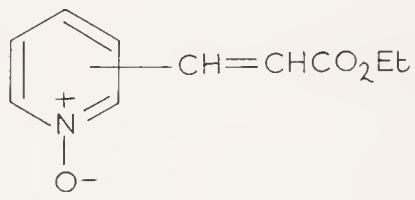

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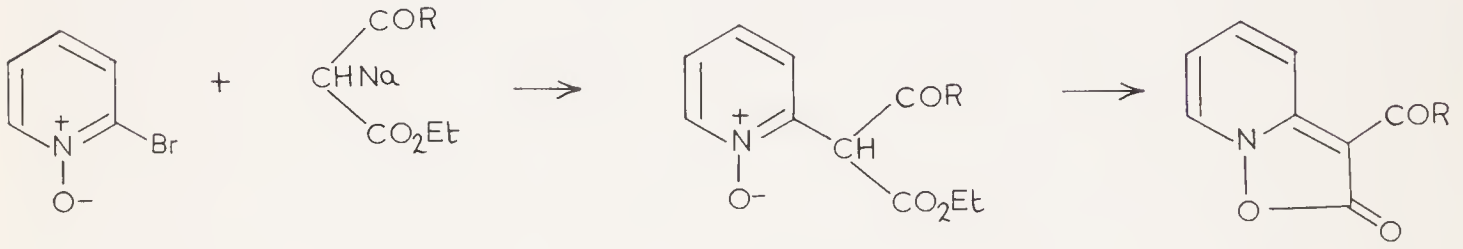


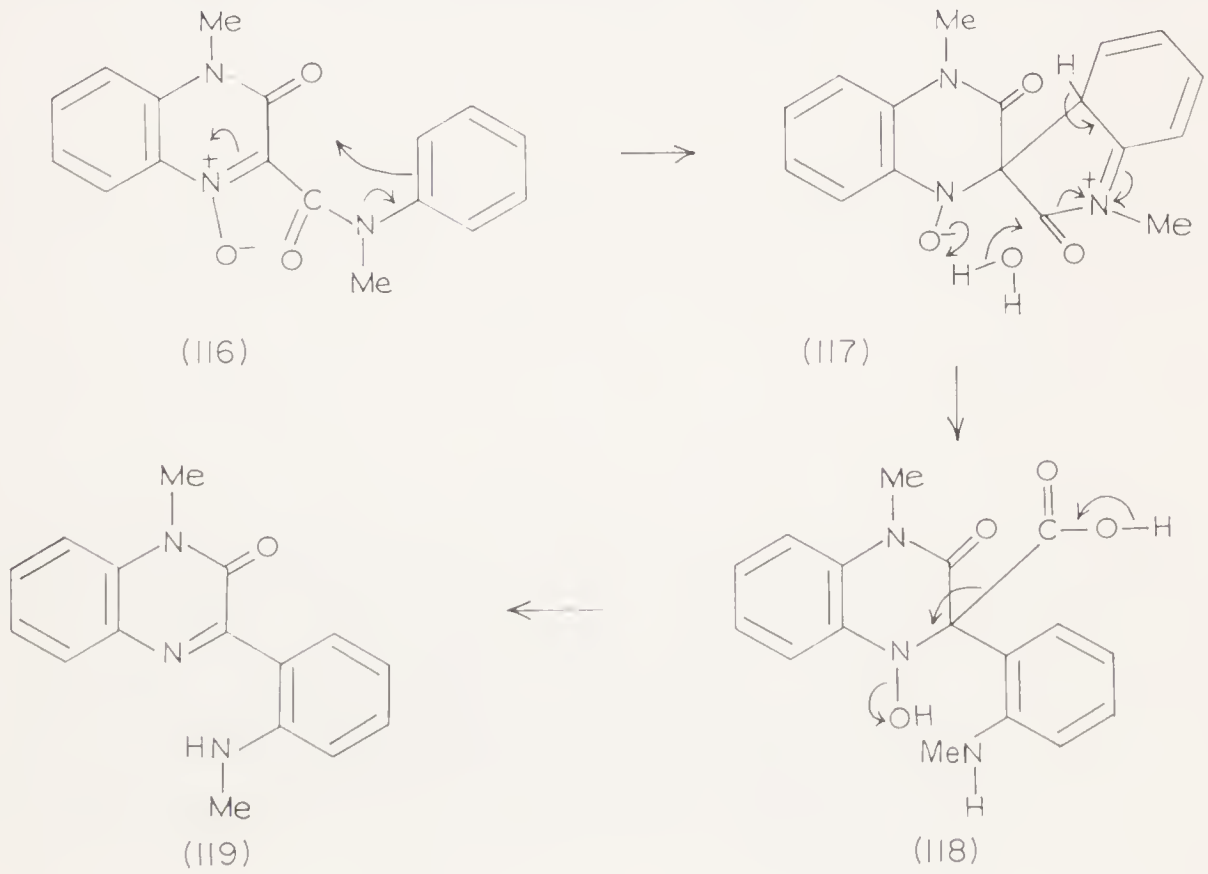
(111) (112) (113)

α-Ethoxycarbonylmethylpyridine *N*-oxides (cf. *112*) can undergo intramolecular cyclization to yield pyridino-isoxazoles of type *113*. These fused-ring compounds were first prepared by Adams and Reifschneider (57JA2236) by the reaction scheme *111* → *113*, without isolation of the intermediate (*112*). Another synthetic route which also involves an acetic ester intermediate is mentioned in Section IV-3Diii.

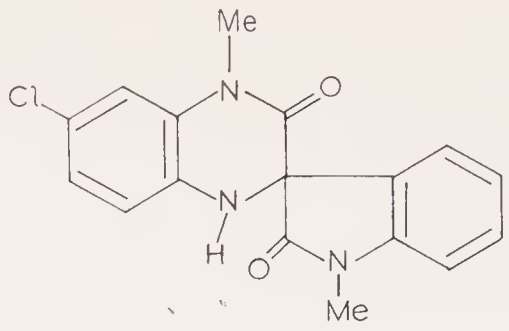
d. Formation and Properties of Amides. Amides (see, e.g., 60USP2945040; 63CB266) and hydrazides (58JA2716) can be prepared by conventional methods. 2-Picolinamide 1-oxide has been converted by the Hofmann hypobromite reaction into 2-aminopyridine 1-oxide (49J133S). Pyridine 1-oxides with amino acid side chains show usual properties (58JA2716). Intramolecular ring closures involving carboxyl groups are known; e.g., *114* → *115* (65AJ379).

(114) (115)

Certain *N*-methylanilides in the pyrazinone and quinoxalinone *N*-oxide series show special properties. The rearrangement of *116* in the presence of sulphuric acid was discovered by Usherwood and Whiteley (23J1069), and later clarified by Clark-Lewis (57J439; 59J2825) who suggested the mechanism shown in scheme *116* → *119*. If hydrogen chloride is used in place of sulphuric acid, the chloro-spiro compound *120* is obtained, possibly via *117* (59J2825), but alternatively by nucleophilic chlorination at an earlier stage (cf. Section III-4Biii and reference 65BJ1659). The mechanism of the reaction with sulphuric acid (*116* → *119*) was finally confirmed by Habib and Rees (59CI367; 60J3371; 60J3387), who found that one *ortho*-position in the benzene ring must be free, that electron-withdrawing substituents in the benzene ring hinder the reaction, and that the reaction is intramolecular ("crossed" products are absent). The effect of electron-donating substituents on the reaction has also been investigated (65CC3424). The reaction is limited to quinoxalinone and pyrazinone 1-oxides; evidently the α-carbon atom of the *N*-oxide must be highly electron-deficient (60J3371; 60J3387). In the pyrazine series, the spiro intermediate *121* is produced (61P167; 62J123). Hydrolysis of the anilide to the hydroxamic acid (*116* → *122*) by nucleophilic attack on the ring and elimination of formic acid has also been reported (23J1069).



(116) (117) (118) (119)



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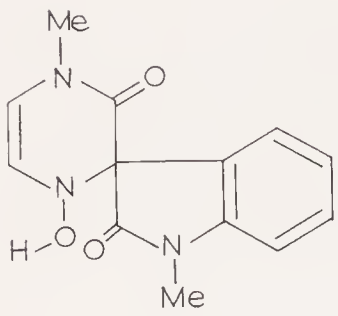

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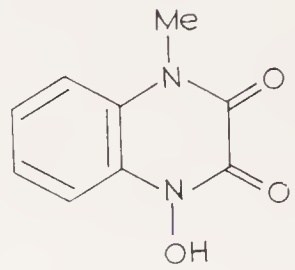
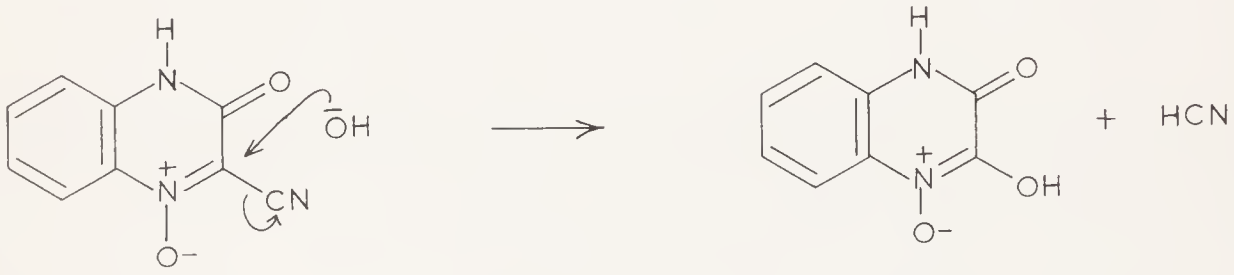


(122)

e. Cyano Compounds. In the preparation of *N*-oxides by direct oxidation of heterocycles with peracids, cyano groups are often converted into amido groups ($CONH_2$), as is mentioned in Section II-1Cia (61JO668). However, since the Radziszewski reaction ($RCN + H_2O_2 \rightarrow RCONH_2 + {}^1_2O_2$) is favoured by an alkaline reaction medium, whereas *N*-oxidation requires acidic conditions, selectivity can be achieved. Examples of the Radziszewski conversion of cyano *N*-oxides into amido *N*-oxides are known in the following series: phenanthridine (61JJ1033), quinoline (57JJ1244), benzimidazole (68CT527), and pyridine (46JJ21). However, α-cyano groups can be resistant to hydrolysis (61JO428).



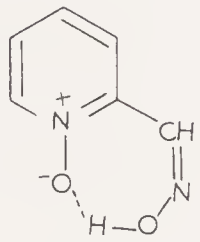
(123) (124)

Cyano groups are sometimes susceptible to nucleophilic replacement. 2-Cyanoquinoxaline 1-oxides (*123*) have been converted into 1-hydroxy-2-quinoxalinones (tautomeric with *124*) by treatment with aqueous potassium hydroxide (64T1107), ethanolic sodium ethoxide (64J2666), and fuming hydrobromic acid (65BJ562). 2-Cyanobenzimidazole 3-oxides also react with aqueous potassium hydroxide to give the corresponding 2-hydroxy derivatives (68CT527).

In general, cyano *N*-oxides react as normal aromatic nitriles and such conventional reactions have been reported for the following series: pyridine (55JO1461; 56JO1077; 58BF694; 61RC463), isoquinoline (69RC473), pyridazine (63CT1511), and phenanthridine *N*-oxides (57JA6500).

ii. Aldehydes and Ketones and their Derivatives

a. Aldehydes. Formyl-pyridine and -quinoline *N*-oxides react normally with amines to form anils (62CT961). With cyanide ions, formylpyridine 1-oxides yield cyanohydrins, and in the α-series, the cyanohydrins are readily converted into pyridoin 1,1′-dioxides [58LA(618)152] which show normal reactivities (61NK480). Oximes of formylpyridine 1-oxides are readily prepared (60AS1253). The *anti*-oximes are the most stable, except in the α-series where the *syn*-oxime is stabilized by intramolecular hydrogen bonding (*125*) (63CT461); however, it has recently been claimed that the *syn* isomer is the more stable also in the 4-series (69AP494). Both the *syn*- and *anti*-aldoximes of 3-, 4-, 5-, and 6-formylpyridazine 1-oxide have been isolated and their interconversion observed (63CT1517). Nitrones of type *126* behave as "masked" aldehydes, and react with suitable nucleophiles to give other derivatives typical of aldehydes (60JJ1519) (cf. Section IV-2Ciiic). The hydration of formylpyridine 1-oxides has been investigated polarographically (69TT293).



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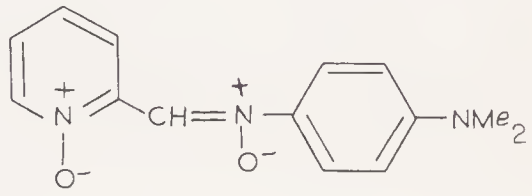

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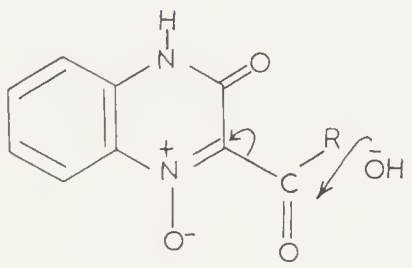

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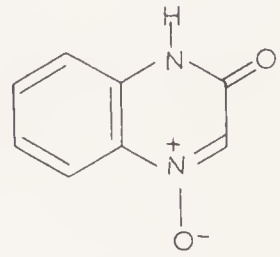

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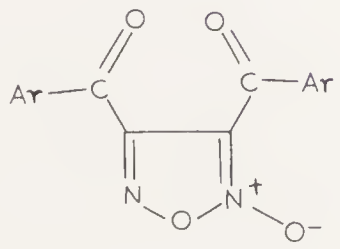

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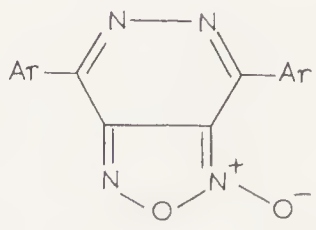


(130)

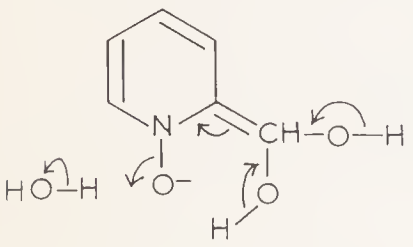
b. Ketones. Acetylpyridine 1-oxides on the whole exhibit normal properties (53JJ120). They form oximes but these oximes do not undergo the Beckmann rearrangement (67JJ689). Moreover, acyl groups attached to certain strongly electron-withdrawing *N*-oxide rings can be cleaved by nucleophilic attack, e.g. 2-acyl-3-quinoxalinone 1-oxides (*127*) (cf. 63J2428; 64T1107; 66JO4067). Diacylfuroxans (*129*) undergo similar cleavage reactions (58JO1024), and they can be reduced to alcohols (60JA2525) or converted by treatment with hydrazine into pyridazino-furoxans (*130*) (55JA4233; cf. 59CI730). Selective oxidation of acetyl groups to carboxyl groups can be achieved by sodium hypobromite in the pyridine 1-oxide (60CI402) and oxazole *N*-oxide series (65CI1340).

Nucleophilic cleavage of acylmethyl groups attached to heterocyclic *N*-oxides to give the corresponding methyl *N*-oxides has also been reported (67JJ940).

iii. Alcohols, Halogeno Compounds, and Amines

Compounds of these types are for the most part unexceptional. Emphasis is placed in the text on points in which the reactions of the *N*-oxides differ from those of other heterocyclic compounds (cf. Table 4.04).

a. Hydroxymethyl Groups. 2-Hydroxymethylpyridine 1-oxide reacts with hydroxydiphenylborane to yield a chelated betaine (69TL233).* An interesting internal oxidation–reduction is involved in the conversion of 2-hydroxymethylpyridine 1-oxide by an alkaline solution of phenylhydrazine into pyridine-2-carboxaldehyde phenylhydrazone. The reaction, which also succeeds in the γ-hydroxymethyl series and with quinoline and pyrazine *N*-oxides, probably involves formation of the aldehyde by a process of type *131* (67JO1270). The conversion of 2-hydroxymethylquinoxaline 1,4-dioxides into derivatives of 2-formyl- or 2-carboxy-quinoxaline 4-oxide on heating with dimethyl sulphoxide (69KG149) is a related reaction.



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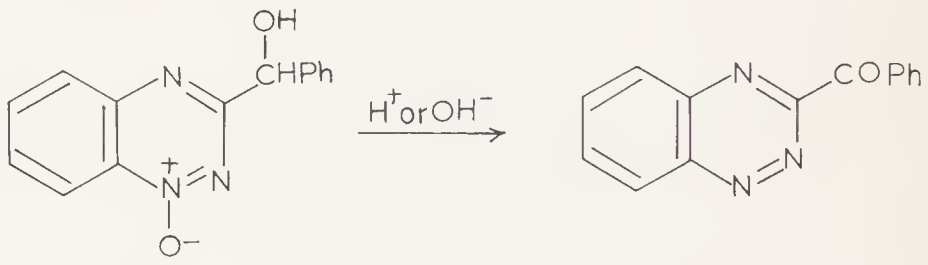
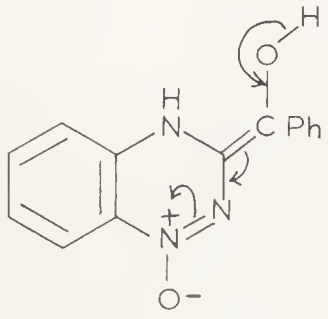


(132) (133)



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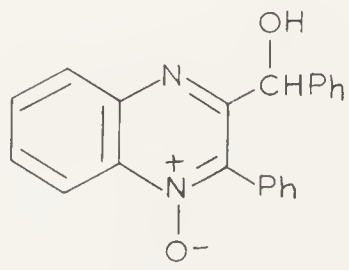
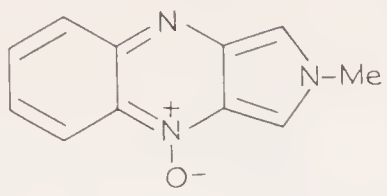


(135)

* See also reference 69CB4025.



(135a)

Although β-hydroxymethyl *N*-oxides do not undergo the reaction mentioned above, they will take part in an analogous oxidation–reduction if there is a nitrogen atom in the position *alpha* to the hydroxymethyl group. Thus, 3-(1′-hydroxybenzyl)benzotriazine 1-oxide (*132*) is converted into *133*, probably by a mechanism of type *134* [67J(C)2658], and similar conversions are known in the quinoxaline series, such as that of 3-(1′-hydroxybenzyl)-2-phenylquinoxaline 1-oxide (*135*) into 3-benzoyl-2-phenylquinoxaline (68TL4609).

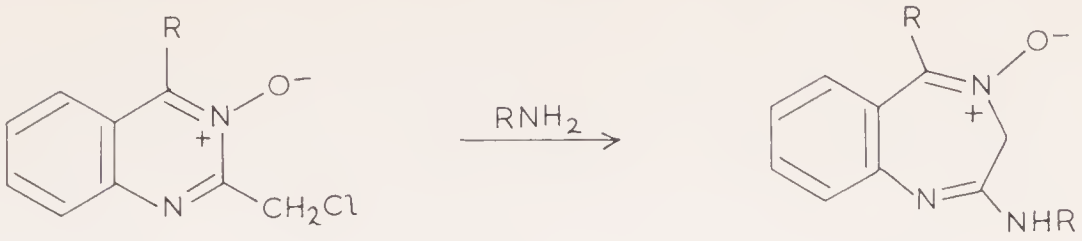
b. Halogeno-alkyl Groups. With the exception of the chloromethylquinazolines discussed below, comparatively little is known of the reactions of halogens attached to alkyl groups on heterocyclic *N*-oxides. The nucleophilic displacement reactions of 4-chloromethylpyridine 1-oxide with acetamidomalonic ester (68MC1172), of 2-bromomethylpyridine 1-oxide with pyridine (60CT692), of 2-chloromethyl-4-nitroquinoline 1-oxide and related quinoxalines (56J2052) with ethylene imine (64CT1495), and of 2-bromomethylquinoxaline 1-oxide with thiourea (69KG940) have been studied. 2,3-Bis(bromomethyl)quinoxaline 1,4-dioxide reacts with methylamine to yield the tricyclic *N*-oxide *135a* (69TL1581).

An important reaction of 2-chloromethylquinazoline 3-oxides (*136*) is their conversion by certain amines into benzodiazepine *N*-oxides (*137*); in some cases the "normal" displacement product (cf. *138*) is also formed (61JO1111). Compounds of type *136* also undergo ring enlargement to yield diazepinone *N*-oxides (*139*) on treatment with hydroxide ions. These reactions have been extensively studied (see Table 4.05) since benzodiazepine *N*-oxides are of pharmacological interest (for a review, see 68CR747). The 2,2′-dichloromethyl compounds analogously yield chlorobenzodiazepine *N*-oxides (*140*) (65JO4267). These reactions probably proceed by nucleophilic attack at the ring 2-position to give open-chain intermediates (e.g., *141* with hydroxide ion) which cyclize to form the seven-membered ring (65JO4267). With certain hydrazines, 2-chloromethylquinazoline 3-oxides (*136*) form the hydrazines of 2-formylquinazoline 3-oxides; in this reaction, an extra mole of hydrazine acts as the oxidizing agent [68J(C)1103]. The reaction of 2-halogenomethyl-1,2-dihydroquinazoline 3-oxides (*142*) with bases takes yet a different course yielding fused ethylene imines of type *143*; however, diazepines of type *144* are sometimes obtained as by-products (66TL2609).

Table 4.05. Conversion of 2-Chloromethylquinazoline 3-Oxides into Benzodiazepine 4-Oxides (*136* → *137*)

2-Chloromethylquinazoline 3-oxide	Reagent	3*H*-1,4-Benzodiazepine 4-oxide (% yield)	References
—	OH^-	2-oxo (data)	68JO2963
6-Chloro-2-dichloromethyl-4-phenyl	NaOH–dimethoxyethane	3,7-diCl-5-Ph-2-oxo	65JO4267
6-Chloro-4-phenyl	OH^-; alc. NaOH	7-Cl-5-Ph	61JO4936, 62JO562
6-Chloro-4-phenyl	$MeNH_2$; Me_2NH; N_2H_4	7-Cl-2-NHMe (-NMe_2, -$NHNH_2$)-5-Ph (57; 8[a]; 36)	64MC235, 68J(C)1103
6-Chloro-4-substituted	amines (various)	7-Cl-2-NHR-5-substituted	62MC63
6-Methoxycarbonyl-4-phenyl	$MeNH_2$–MeOH	7-CO_2Me-2-NHMe-5-Ph	63H1720
6-Nitro-4-phenyl	NH_3–EtOH; $MeNH_2$–MeOH	2-NH_2 (or NHMe) -7-NO_2-5-Ph (97 or 59)	63MC261
4-Phenyl-6-substituted	$MeNH_2$	2-NH_2-5-Ph-7-substituted	61JO4488
4-Phenyl-6-trifluoromethyl	NH_3–MeOH; $MeNH_2$–MeOH	2-NH_2 (or NHMe) -5-Ph-7-CF_3 (81–85)	62H2226

[a] With dimethylamine, 6-chloro-2-dimethylamino-4-phenylquinazoline 3-oxide (19%) is also formed.



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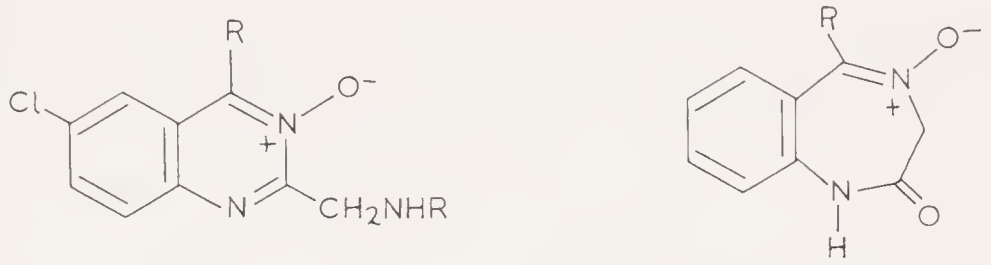

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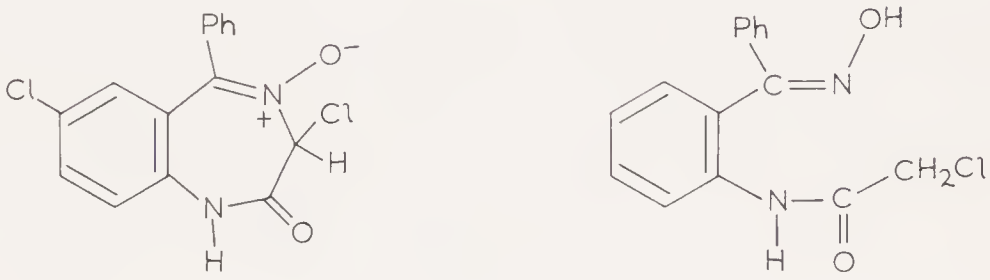

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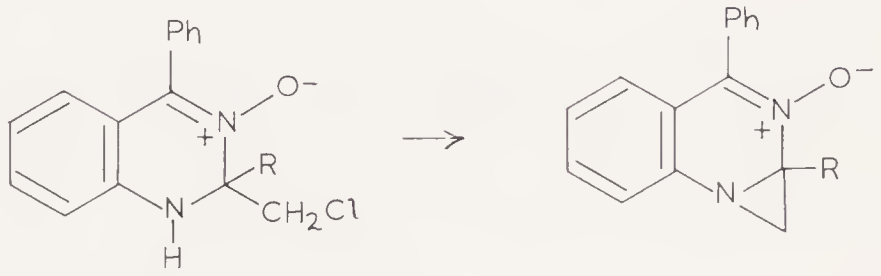

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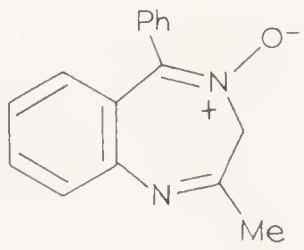

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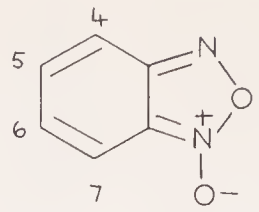
(145) (146)

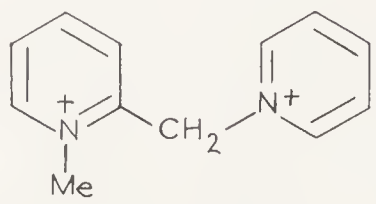


(147)

Tetrahydrocinnoline 1-oxides can be converted into dibromo derivatives (*145*) which can then undergo dehydrobromination to give cinnoline 1-oxides (62CT1123; 63CT1527). Dehydrobromination of the tetrabromobenzofuroxan *146* gives 4,7-dibromobenzofuroxan (31J3308; cf. 57JA1748) or a mixture of 4,5- and 4,6-dibromobenzofuroxan (cf. *147*) (64JO3722), depending on the reaction conditions.

c. 1-(1-Oxido-2-pyridyl)methylpyridinium Cation. The methylene group in the 1-(1-oxido-2-pyridyl)methylpyridinium cation (*148*), the readily available King-reaction product (Section IV-2Biib), is more reactive than that in the corresponding pyridine without the *N*-oxide group, but less than that in the bis-cation *150* (60CT918). Compound *148* does not undergo cleavage to give a pyridone as does the corresponding *N*-methyl bis-quaternary salt (*150*), but it does form the nitrone *149* with *p*-nitrosodimethylaniline (60CT692). The complete set of compounds in the 2- and 4-substituted pyridine and quinoline 1-oxide series, together with the corresponding *N*-oxides, have been studied (61G34; 62CT961). The nitrones (*149*) undergo either rearrangement, to give anilides (*151*), or deoxygenation, to form Schiff's bases (*152*), on treatment with reagents such as sulphur dioxide or triphenyl phosphite. Deoxygenation is favoured when the nitrone function is *alpha*, rather than *gamma*, to the hetero atom; it proceeds more readily in the quinoline series than in the pyridine series, and more readily with the parent heterocycles than with the *N*-oxides.

(148) (149)



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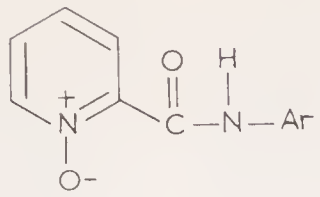

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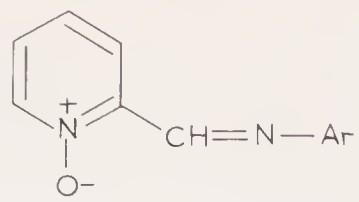


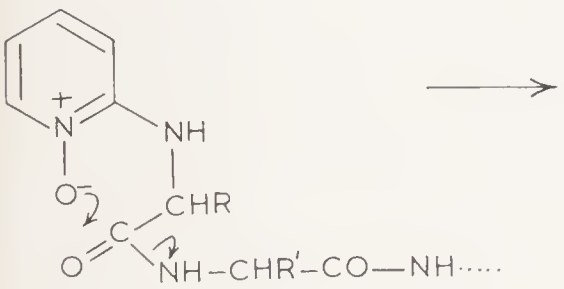
(152)

3. Functional Groups Linked to Ring Carbon by Other Atoms

A. HALOGEN ATOMS

Halogenated *N*-oxides may be prepared by direct *N*-oxidation (Chapter II), by ring synthesis (Chapter II), by nucleophilic displacement of a nitro group (Section IV-3Ciib), or by diazotization reactions (Section IV-3Cic). Halogen atoms attached to heterocyclic *N*-oxides can undergo nucleophilic displacement: the scope of this reaction as well as kinetic data are considered in this section. In some cases, the usual addition–elimination mechanism of aromatic nucleophilic substitution does not occur, but rather the elimination–addition or aryne mechanism operates. The reductions of halogen-containing *N*-oxides and the reaction of halogen atoms attached to benzenoid rings are also discussed.

Tortorella *et al.* (66CH105; 67G85) have shown that 2-fluoropyridine 1-oxide condenses readily with the *N*-terminal residue of peptides, and that subsequent treatment with formic acid leads to smooth cleavage of the terminal residue by the mechanism *153* → *154*. This potentially important new method for selective degradation of peptides is being intensely investigated [67G1479; 67G1487; 68J(C)72].



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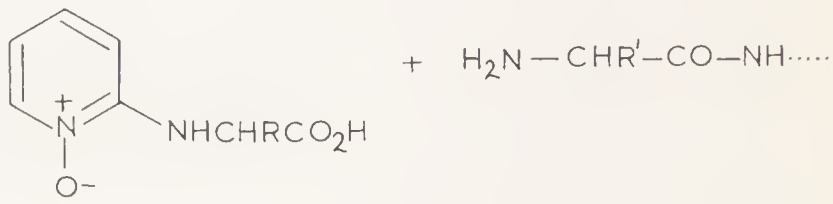


(154)

i. Nucleophilic Replacement of Halogen Atoms: Scope of the Reaction

Halogen atoms *alpha* or *gamma* to an *N*-oxide function are often easily displaced by nucleophiles; halogen atoms in a *β*-position also react reasonably readily. Table 4.06 summarizes the reaction, including *inter alia* examples from the following ring systems: pyridine, quinoline, isoquinoline, pyridazine, cinnoline, pyrazine, and phenazine *N*-oxides, and introduction of the

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Pyridine 1-oxide	2-Br	$NHEt_2$, KSCN, RCH_2CO_2Et,[a] NaN_3,[b] NaSH, NaS-aryl, NaS-alkyl, NaSCN, NaOMe, $PhCH_2SH$, thiourea[c] *	—	16–72	50JA4362,[c] 56AA(129)4-M, 56JO1077, 57JA678,[b] 57JA2236,[a] 61BA571, 62ZC86
	2-Br (Cl)	2-imidazolinethione	—	—	62USP3056798
	2-Br	NaS-aryl	5-Cl	66–71	61R1066
	2-Br	Et_2NH, NaOMe, NaSH, NaSCN	4-MeO, -alkyl, $-NO_2$	(data)	56AA(129)4-M, 56J3684, 61BA561
	2-Br	RCH_2CO_2Et,[a] NaOEt, NaOMe	6-Me	66–73	57JA2236,[a] 59JA2537
	2-Br	H_2Se	—	59	62JO3671
	2-Cl	$NHMe_2$, $NHEt_2$, HCl,[d] morpholine, $C_5H_{11}N$, $PhCH_2SH$, NaOH,[d] NaOMe, NaOEt, NaOPh, $NaOCH_2Ph$, NaSEt, $NaOCH_2CH{=}CH_2$, NaSPh, $NaSCH_2Ph$, Na_2SO_3, thiourea, C_4H_9N	—	23–99	57J191, 57J4375, 60J2937, 61BB480, 61BA571, 61JJ612,[d] 62JO1329, 62RC1183, 64JO1650, 68J(C)1537, 68JA4361
	2-Cl	2-imidazolinethione	—	—	62USP3056798

[a] Condensation with a series of active methylene compounds.
[b] Attempts to purify product by distillation led to an explosion.
[c] 2-Pyridyl 1-oxide isothiourea formed.
[d] 1-Hydroxy-2-pyridone formed.
* See addendum in the Appendix.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Pyridine 1-oxide, *cont'd.*	2-Cl	$NHEt_2$, NaOMe	4-MeO, $-NO_2$	(data)	61BA561, 61RC475
	2,6-diCl	NaOMe, R_2NH	—	80–90	67J(B)1213, 68J(C)1537
	2-F	glycine-*N*-cyclohexylamine, NH_2CH_2COOEt, $NaHCO_3$, amino acids	4-H and $-NO_2$	—	66CH105, 67G85, 68BA13
	2-I	$NHEt_2$, NaOMe	—	(data)	61BA561, 62RC1183
	2-I	$NHEt_2$, CuCN, NaOMe	4-MeO, $-NO_2$	(data)	61BA561, 61RC463
	3-Br	NH_4OH, KSCN, thiourea	—	(data)	54JO2008, 56AA(129)4-M, 57JO984, 61JJ1151
	3-Br	NH_2-alkyl, NH_2-aryl, NHR_2, N_2H_4, NaOR	$4-NO_2$	10–90	62J2379, 62RC539, 62RC1465, 62RC1563, 63RC495, 65MC296
	3-Cl	$C_5H_{11}N$, NaOEt, NaOMe, Na_2SO_3	—	(data)	59J3680, 61BB480, 62JO1329
	3-Cl	Et_2NH, NaOMe, NaOEt, $PhNH_2$, $C_5H_{11}N$	$4-NO_2$	(data)	62RC539, 62RC1465, 62RC1563, 65J2096
	3-F	NH_3, NH_2-alkyl, NH_2Ph, NaCNS, KOH, NaOEt,[e] $C_5H_{11}N$, NaOMe,[e] *p*-NO_2-C_6H_4-OH, Na_2SO_3, C_6H_5-SH	$4-NO_2$, 4-OR, and other substituents	47–99	64RC777,[e] 64RC785, 65J2096, 65RC601, 66RC1457, 66RC1675, 67RC279, 68BA1
	3-I	Et_2NH, $PhNH_2$, NaOMe	$4-NO_2$	(data)	62RC539, 62RC1465, 62RC1563
	4-Br	NaOMe*	2-H and -Me	—	48JJ126, 53JJ823
	4-Cl	N_2H_4, Me_2NH, $C_5H_{11}N$, morpholine, $PhNH_2$, NaN_3, thiourea	—	6–85	44PJ141, 56J2404, 57J4375, 60J2937, 61BB480, 61CT87

[e] Can also form $4-NO_2 \rightarrow 4$-OR depending on reaction conditions.
* See addendum in the Appendix.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Pyridine 1-oxide, *cont'd.*	4-Cl	KOH, NaOEt	—	70–80	52R745, 56J2404, 59R981
	4-Cl	Alkyl-SNa, aryl-SH,[f] aryl-SNa,[f] Na_2S,[g] Na_2SO_3, $Na_2S_2O_3$[h]	—	35–90	44PJ141, 49JJ545, 60JJ1145, 61JJ917, 61JJ1151,[g,h] 62JO1329, 62ZC86
	4-Cl	$HSCH_2CH_2NR_2$	—	—	69KG285
	4-Cl	EtSH, PrSH-KOH, PrSNa, NaOMe, Na_2SO_3	2-Me	58–81	48JJ126, 59WZ187, 60PC(11)22, 61JJ917
	4-Cl	$MeNH_2$, NaOR, Na_2SO_3	3-alkyl[i]	50–90	60J4953, 61AP292, 61JJ917, 61JO3796
	4-Cl	Na_2SO_3[j]	2,6-diMe	66–90	61JJ917, 62JO1665[j]
	4-Cl	NH_4OH, $MeNH_2$	3,5-diMe	(data)	60J4953
	4-Cl	*p*-R-C_6H_4-OH	2,6-diMe-3,5-diI	64–89	56CT1
	4-Cl	C_3H_7SNa	2-Me	78	60PC(11)22
	4-Cl	KSH	2-CO_2H	69	61PC(13)58
	4-Cl	NH_4OH, $MeNH_2$, N_2H_4, $RNHNH_2$,[k] KHS, NaOH	3-CO_2H	47–89	60JA3141, 64AJ1399, 65AJ379[k]
2,2′-Bipyridyl 1-oxide	4-Cl	NaOEt, NaOMe, $C_6H_5CH_2SNa$	—	40–80	67J(B)106

[f] Ph-SH, *p*-Me-C_6H_4-SH, *p*-NO_2-C_6H_4-SNa, and various heterocyclic-SH compounds such as 2-mercapto-4,6-dimethylpyrimidine.
[g] With 1:1 molar ratio of *N*-oxide to Na_2S, 4-mercaptopyridine 1-oxide is obtained; if ratio is 2:1, 4,4′-thiobipyridine 1,1′-dioxide is formed.
[h] 4,4′-Thiobipyridine 1,1′-dioxide is formed.
[i] Methyl, ethyl, isopropyl.
[j] Concomitant reduction of the *N*-oxide to the free base.
[k] When R = Ph, in addition to the expected product, 3-hydroxy-1-phenyl-1*H*-pyrazolo[4,3-*c*]pyridine 5-oxide is obtained; when R = Me, the product was not isolated.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Quinoline 1-oxide	2-Cl	N_2H_4[l]	—	—	61JJ1743
	2-Cl	NaOH, NaSH	4-Me-5,6-benzo	(data)	56J3684
	2-Cl	NaOEt, NaOMe, NaOPh, KCN, morpholine, $C_5H_{11}N$	4-H and -Me	(data)	66JJ749
	2-Cl	$CH_2{=}CHCH_2ONa$	—	63	68JJ661
	3-Br	NH_4OH, thiourea	—	—	54JO2008, 56AA(129)4-M
	3-F	N_2H_4, $C_5H_{11}N$, NaOH	—	—	63J4007
	3-F	$PhNH_2$, NaOMe, piperidine, $PhNHNH_2$	4-NO_2	43–79	68CT1742
	4-Br	KSeCN, KSCN, NaOEt, Na_2S_2,[m] $Na_2S_2O_3$,[n] NaSR	—	70–90	45JJ(5/6A)3(B), 61JJ1151, 68CT1390
	4-Cl	NaOEt, NaOMe	2-styryl	—	62PC(18)175
	4-Cl	NaOEt, NaSPh, NaS-alkyl, *p*-CH_3-C_6H_4-SH, PhOH	—	ca. 55–65	45JJ(5/6A)3(B), 45JJ(9/10A)8, 57CM388, 59EGP17051, 62ZC86
	4-Cl	NaSH, NaSR	—	—	68CT1390
	4-Cl	$H_2NCH_2CH_2OH$,[o] $N_2H_4{\cdot}H_2O$,[p] NH_2OH,[q] 8-HO-quinoline, morpholine, $C_5H_{11}N$, NaN_3[p]	—	ca. 45–67	45JJ(9/10A)8, 57CT310, 59EGP17051, 61CT87

[l] The corresponding hydrazo compound also formed.

[m] 4,4′-Thiobiquinoline 1,1′-dioxide formed if 2 moles of oxide and 1 mole of Na_2S_2 react; if molar ratio is 1:1, 4-mercaptoquinoline 1-oxide obtained in 90% yield.

[n] 4,4′-Thiobiquinoline 1,1′-dioxide formed.

[o] 4-(2-Aminoethyl)quinoline 1-oxide formed.

[p] Product is explosive.

[q] 4-Hydroxyaminoquinoline 1-oxide is formed.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Quinoline 1-oxide, *cont'd.*	4-Cl	$(H_2NCH_2CH_2S\text{-})_2$, $EtNH_2$	—	48	68JJ665
	4-Cl	H_2N-aryl, $H_2N\text{-}(CH_2)_x\text{-}NR_2$, PhOH	7-Cl	20–70	46JJ60, 64JH6
	4-Cl	*m*- and *p*-$NH_2\text{-}C_6H_4\text{-}NH_2$	2-Me	—[r]	62PC(16)225
	4-Cl	*p*-$CH_3\text{-}C_6H_4\text{-}NH_2$	2-Me	—	59EGP16921
	4-Cl	$BuNH_2$, N_2H_4, *p*-$NO_2\text{-}C_6H_4\text{-}NHNH_2$, NaOMe	6-Me	42–83	59WZ93, 60AF1029
	4-Cl	pyridine-2-CH_2CN	—	—	63AI25
	4-Cl	quinoline-2-CH_2CN	—	(data)	68AI1
	4-Cl-3-$(CH_2)_2Cl$	NaSH, $CS(NH_2)_2$	2-Me[s]	—	63JJ234
	4-Cl	$NaBH_4$	—	19	65CT1103
	4-I	NaOEt	—	—	45JJ(5/6A)3(B)
	5- and 7-F	N_2H_4, $C_5H_{11}N$, NaOH, NaOMe	—	—	63J4007
Isoquinoline 2-oxide	3- and 4-Cl or -F	N_2H_4, $C_5H_{11}N$, NaOH	—	—	64J4561
	6-F	$C_5H_{11}N$	—	—	64J4561
	8-F	NaOMe	5-H or -Cl	—	64J4561
Acridine 10-oxide	5-Cl	H_2NR, PhOH	H; 8-Cl-2- and/or 3-substituted	(data)	59TU36, 60BP829728

[r] *N,N*-Di-(4-quinaldine *N*-oxide)-*m*-aminoaniline, or the *p*-isomer, is formed.
[s] The 2,3-dihydrothienoquinaldine *N*-oxide is formed.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Acridine 10-oxide, *cont'd.*	9-Cl	NH_2R	1-NO_2	(data)	68RC1973
	9-Cl	H_2NR, NaOPh	various[t]	11–84	55DA257, 62MC1149, 62MC1153, 62MC1159
	9-Cl	$CH_2(CO_2Et)_2$	—	52	62ZO2217
Pyridazine 1-oxide	4-, 6-, and 4,6-di-Br	KSH	3-OH-4-, -5-, and -6-H or -Me	—	67CT1411, 69CT756
	3-Cl	NH_3, $EtNH_2$, N_2H_4,[u] NH_2OH, NaN_3, NaOH, NaOMe	—	44–80	60CT559, 63CT261, 63CT342, 63CT348
	3-Cl	$EtNH_2$, ROH, NaOMe	6-Cl[v]	(data)	62CT956,[t] 62JJ244, 63CT269
	3-Cl	NaOH, NaOMe	6-Me	(data)	61JJ1048, 62JJ249
	4-Cl	NaN_3, NaOMe	—	51–96	63CT1059
	4-Cl	NaOMe	3,6-disubstituted[w]	(data)	62CT933, 63CT337, 63CT1157, 66JJ314
	5-Cl	NaOMe, $EtNH_2$	3,6-diMe; 3-Me-6-CN[x]	75–87	63CT337, 64CT228[v]
	6-Cl	$EtNH_2$, NaOMe	—	79–84	63CT261
	6-Cl	NaOAc	3-MeO	—	61JJ1048

[t] 6-Chloro-2-methoxy; 7-chloro-3-methoxy; 2,3-dimethoxy-6-nitro.

[u] Converted into the corresponding azide without isolation.

[v] Some 3,6-di-displacement products formed, but mono-replacement is favoured.

[w] 6-Amino-3-methoxy; 6-chloro-3-methoxy; 3,6-dimethyl.

[x] Depending on reaction conditions, 6-cyano-5-methoxy-3-methylpyridazine 1-oxide (reflux 1 h) or 6-carboxamido-5-hydroxy-2-methylpyridazine 1-oxide (sealed tube, 100°, 6 h) is obtained.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
Pyridazine 1-oxide, *cont'd.*	6-Cl	NaOEt	4-alkyl[y]	—	67JJ114
	3,6-diCl	NaOEt, NaOMe	4-H and -MeO	(data)	62CT989, 63CT83
	various Cl and Br	NaOEt, $C_5H_{11}N$	—	—	66CT269
Cinnoline 1-oxide	4-Cl	NaOMe, NaOH	5-H- and -NO_2	67–85	64CT619, 64CT1090
Cinnoline 2-oxide	4-Cl	NaOEt, NaOMe	—	85–92	64CT619
Pyrimidine 1-oxide	4-Cl	NaOMe	2-oxo-1-$PhCH_2O$	—	65M169
Purine 1-oxide	2-Cl	Morpholine	6-NH_2	67	63JO2560
Purine 3-oxide	6-Cl	HI	—	81	69JO2157
	6-Cl	NaOMe, NaOH	—	—	69BJ750
Pyrazine 1-oxide	2- and 3-Cl	NaOEt, NaOH	—	70–83	63G339, 64JO2623
	3-Cl	NaOH, KOH-EtOH	2-Me; 2,5-diMe	60–77	64JO2623
	3-Cl	NH_4OH, Me_2NH	2,5-diMe[z]	(data)	67JO2412
Pyrazine 4-oxide	2-Cl	Me_2NH, $C_5H_{11}N$	3-Me	81–86	64JO1645
	2-Cl	H_2N-CS-NH_2	H; 3,6-diMe	74–88	66J(C)495
Pyrazine 1,4-dioxide	2-Cl	NaOH	3,6-diBu	(data)	69CT851
Quinoxaline 1-oxide	2-Cl	NH_3, NaOH, $ArSO_2NH_2$	—	(data)	66J(C)157, 69KG940
Phenazine 5-oxide	2-Cl	$ArSO_2H$	see note[aa]	(data)	62J4438

[y] 3-Methoxy group converted into 3-ethoxy; 6-chloro-3-ethoxypyridazine 1-oxide also formed.
[z] On more drastic treatment, the *N*-oxide is lost and diamino compounds are formed.
[aa] The phenyl group in position 7 is also replaced, giving 2,7-diphenylsulphonylphenazine as product.

Table 4.06. Nucleophilic Displacement Reactions of Ring Halogen Atoms in *N*-Oxides—*continued*

Ring system	Halogen(s) replaced	Nucleophilic reagents	Substituents unaffected	Yield, %	References
1,2,4-Benzotriazine 1 oxide	3-Cl	RNH_2, RCH_2NH_2, $RNHNH_2$, N_2H_4, BuOH–KF, NaCN–EtOH, H_2N-CS-NH_2, thiosemicarbazide	—	(data)	57J3186, 59JO813 59USP2911406, 60USP2966487
	3-Cl	RNH_2, R_2NH, Ar-NH_2, NaOMe	7-Cl	40–70	49USP2489355, 54JA4611
	3-Cl	NaOEt	7-CO_2H, 7-CO_2Et	(data)	66H651
Pyrido [2,3-*e*]-*as*-triazine 1-oxide	3-Cl	RNH_2, R_2NH, NaOR, H_2N-CS-NH_2[bb]	7-H and -Me	49–99	62JO2504
Benzofuroxan	7-Cl	RNH_2, R_2NH	4-NO_2	80–98	68J(B)334

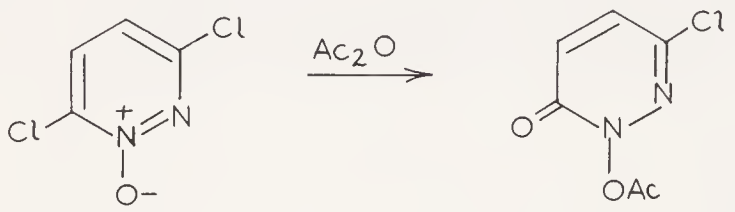
[bb] The 3-mercapto compound is formed.

following groups: alkoxy, aryloxy, amino, mono- and di-substituted amino, azido, sulphonic acid, arylsulphonyl, mercapto, and selenyl groups. Nucleophilic replacement of the halogen atoms in halogenopyridine 1-oxides by acyloxy groups is apparently followed by spontaneous rearrangement to 1-acyloxypyridones (66CH308). In some cases, halogeno *N*-oxides react with acetic anhydride to yield *N*-acetoxy-oxo compounds, as in the transformation of *155* into *156* (63CT269).

Mercapto *N*-oxides, which are tautomeric with *N*-hydroxy thiones, are readily obtainable by hydrolysis of the isothiouronium salts (e.g. *157*) formed by halogeno *N*-oxides and thiourea (49JJ542; 56USP2745826); cf. Section IV-3Ai.

An attempt to purify 2-azidopyridine 1-oxide, prepared from the corresponding bromo compound and sodium azide, resulted in an explosion (57JA678). 2-Bromopyridine 1-oxide does not react with potassium fluoride to give the 2-fluoro analogue (59JA2674), and various carbanions of the acetoacetic ester type failed to react with 4-bromoquinoline 1-oxide (51JJ-1391). Attempts to effect an Ullmann reaction between 4-chloropyridine 1-oxide and *o*-bromonitrobenzene probably succeeded, but the product could not be purified (64J2175). Pentachloropyridine 1-oxide undergoes ready nucleophilic displacement to yield 2-mono- or 2,6-di-substituted derivatives (67CH893).

The reaction of 2-bromopyridine 1-oxide with active methylene compounds gives products which cyclize onto the *N*-oxide oxygen atom; cf. Section IV-2Cic.



(155) (156)

(157) (158)

ii. Nucleophilic Replacement of Halogen Atoms: Kinetics and Relative Reactivities

Kinetic investigation of the reaction of 2-, 3-, and 4-chloropyridine 1-oxides with piperidine in methanol by a Belgian group (61BB480; 63BB572) demonstrated a rate sequence of $2 > 4 \gg 3$, the reactivity of each *N*-oxide

being greater than that of the analogous chloropyridine. The slightly increased reactivity of the 2-isomer over that of the 4-isomer was ascribed to hydrogen bonding in the transition state (cf. *158*). Kinetic data are also available for the reaction of 2- and 4-bromo- and 2-chloro-pyridine 1-oxide with piperidine in ethanol [66J(B)1062].

The kinetics of the reactions of halogenopyridine 1-oxides with methoxide (63J3486) and ethoxide ions [66J(B)1058] have also been reported; there is disagreement as to the relative reactivities of the 2- and 4-positions, the later paper claiming that the order of displacement is $2 > 4 \gg 3$. These papers report a detailed comparison of the effect replacement of a CH group of benzene with an N, NMe^+, N^+-O^-, or C-NO_2 group has on the reactivity of the halogeno groups. Methyl substituents exert the expected rate-lowering effect on the displacement reactions of 4-chloropyridine 1-oxides (67CT-1343), and the effects of 3- and 5-methyl groups on the displacement ratios for 2-bromopyridine 1-oxide have also been investigated [68J(B)492].

Japanese investigators (60CT892) have studied kinetically the reactions of 4-halogenoquinoline 1-oxides with piperidines in various solvents. For the 1-oxides, as for the quinolines themselves, the reactivity sequence is in the order Br > Cl > I. 4-Halogenoquinoline 1-oxides react faster than either the corresponding quinoline derivative or 1-halogeno-4-nitronaphthalene; this is a result of ΔH^* differences only, since the effect of the entropies of activation (ΔS^*), which are greater for the *N*-oxides (indicating greater solvation in the transition state), acts in the opposite direction.

Talik and Talik have made semi-quantitative studies of the relative reactivities of a large number of halogenopyridine 1-oxides.

(*a*) For 2-halogenopyridine 1-oxides (61BA571; 62RC1183) the reactivity sequence is Cl > Br > I for the reaction with methoxide ions, and Br > Cl > I for reaction with diethylamine. In every case the *N*-oxide reacts more quickly than the corresponding pyridine. 2-Fluoropyridine 1-oxide reacts much more rapidly than the chloro analogue, and has been proposed as a reagent for determination of *N*-terminal amino acid residues in peptides (66CH105); cf. the discussion in Section IV-3A.

(*b*) In the reaction of 2-halogeno-4-nitropyridine 1-oxides (61BA561; 61RC475) with methanolic sodium methoxide, the nitro group is lost first (cf. Section IV-3Ciib), but subsequent conversion into 2,4-dimethoxypyridine 1-oxide also occurs. However, with dimethylamine or diethylamine, the halogen atom in 2-halogeno-4-nitropyridine 1-oxide is replaced preferentially. The *N*-oxides are more reactive than the analogous pyridines (62RC-1313).

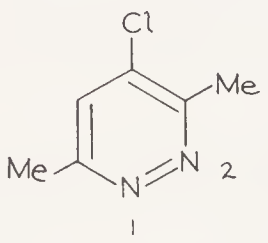
(*c*) If the halogeno group in 3-halogeno-4-nitropyridine 1-oxide is chloro, bromo, or iodo, the nitro group is preferentially replaced by methanolic sodium methoxide, but the halogen atom is substituted first by amines (62RC1465). However, with the 3-fluoro derivative the fluorine is preferen-

tially displaced by all the nucleophiles studied (68BA1), except that 4-chloro-3-fluoropyridine was produced with hydrogen chloride (68CT1742). These compounds are about as reactive towards amines as are the 2-halogeno analogues (62RC1563).

(*d*) The fluorine atom in 3-fluoro-4-nitropyridine 1-oxide is extremely reactive (64RC777; cf. 68CT1742), and this compound has been proposed as a reagent for the characterization of amino acids (64RC785; 68BA13). A similar proposal was made previously for the somewhat less reactive 3-bromo-4-nitropyridine 1-oxide (63RC495). Direct comparison shows that the corresponding pyridines are much less reactive (66RC1187). The methyl group in 3-fluoro-5-methyl-4-nitropyridine 1-oxide reduces the reactivity of the fluoro group (66RC1457; cf. 67RC1721; 68BA1).

The relative reactivities of chloropyridazine *N*-oxides have been investigataed by Sako. The reactivity of the chlorine atom in *159* is *increased* by *N*-oxidation at the 2-position, but *decreased* by *N*-oxidation at the 1-position (63CT337; cf. 62CT956). Nucleophilic attack on 3,6-dichloropyridazine 1-oxide (*160*) leads to preferential displacement of the 3-chlorine atom (63CT269), although 3- and 6-chloropyridazine 1-oxide appear to have approximately equal reactivities (63CT261). Other work indicates that a chlorine atom in the 6-position of pyridazine 1-oxides is less reactive than a 4-nitro group or even a 3-methoxy group (62CT933; see also Table 4.06). Sako and Itai (66CT269) later determined the rate constants for the reactions of all the isomeric monochloropyridazine 1-oxides with piperidine in ethanol and found the following order of reactivity: 5 > 3 > 6 > 4. Bromo compounds are somewhat more reactive than their chloro analogues, but the presence of methyl groups on the pyrazine ring decreases the reaction rate.

Chlorofuroxans are unreactive towards nucleophilic reagents and undergo ring-opening under forcing conditions [63T143(S1)].



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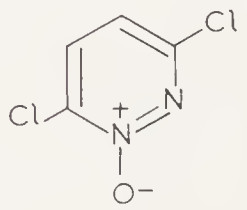

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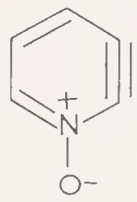
iii. Nucleophilic Replacement of Halogen Atoms: Pyridyne Mechanism

Although the great majority of nucleophilic displacement reactions involving halogen atoms on *N*-oxide rings undoubtedly occur by the usual bimolecular aromatic addition–elimination mechanism, evidence is available for an elimination–addition mechanism involving pyridyne *N*-oxide formation

in a few cases (63NK432; 64AG993; 64JJ432; 64R621). Thus, 2-chloropyridine 1-oxide with potassamide in liquid ammonia yields 3-aminopyridine 1-oxide (cf. *161*), although both 3- and 4-chloropyridine 1-oxide yield only the corresponding amino derivative. However, 2,6-dimethyl-3,4-pyridyne 1-oxide (*162*) is evidently formed from both 3- and 4-chloro-2,6-lutidine 1-oxide since the isomeric 3- and 4-amines are obtained from both starting materials in comparable amounts (65CT963). 2- and 3-Bromo-4-ethoxypyridine 1-oxides are also considered to react with sodamide largely via 4-ethoxy-2,3-pyridyne 1-oxide (*163*); in each case 3-amino-4-ethoxypyridine 1-oxide is the exclusive product, reflecting the strong directive effect of the *N*-oxide group on the pyridyne addition (64R621).



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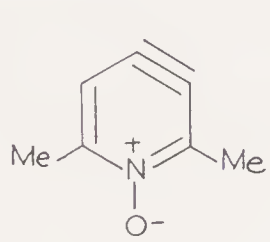

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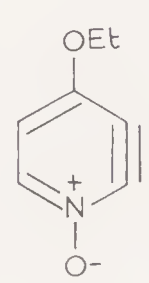

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Additional cogent evidence for the 2,3-pyridyne 1-oxide intermediate was more recently adduced by den Hertog (67R655). On treatment with sodamide in liquid ammonia, 3-fluoropyridine 1-oxide is unaffected, but the 3-chloro and 3-bromo analogues are converted into 3-aminopyridine 1-oxide. If the reaction proceeded by normal nucleophilic substitution, the fluoro derivative should react the fastest. 3-Bromo-5-ethoxy-, 2,6-dimethyl-, and 2,5-dimethylpyridine 1-oxide each react via the corresponding 3,4-pyridyne 1-oxide because each yields a mixture of the 3- and 4-amino products.

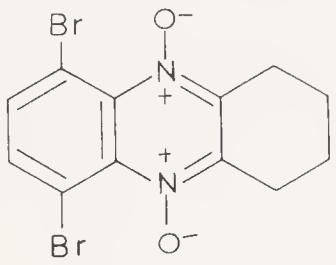
iv. Reduction of Halogen Derivatives

Halogen atoms are frequently eliminated in the reduction of halogeno *N*-oxides to the parent heterocycles; see Sections III-2A to 2G. In some cases it is possible to remove selectively the halogen atoms by catalytic reduction without affecting the *N*-oxide linkage: examples of selective catalytic reductions of this type are contained in Table 3.07 and are discussed in Section III-2B. Deuterium can be introduced in the 4-position of 4-chloro-2,6-

lutidine 1-oxide by reduction with zinc and dilute deuterosulphuric acid, but the *N*-oxide function is lost simultaneously [66J(B)870].

v. Reactions of Halogen Atoms Attached to Fused Benzenoid Rings

Halogen atoms attached to benzenoid rings which are fused onto *N*-oxide rings often exhibit an enhanced reactivity. Thus, Bellas and Suschitzky (63J4007) found that 6- and 8-fluoroquinoline 1-oxides are unreactive, the 5-isomer is slightly reactive, and 7-fluoroisoquinoline 2-oxide readily undergoes nucleophilic replacement reactions. Similar reactivities have been reported in the acridine 10-oxide series (59USP2880210; 60BF696).



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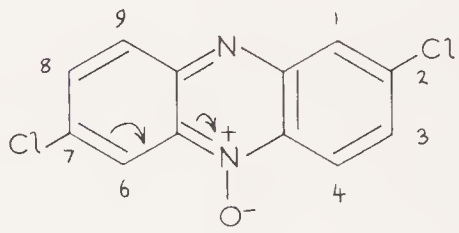

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The bromine atoms in both the 6- and 9-positions of the tetrahydrophenazine 5,10-dioxide *164* are labile towards nucleophiles [60AA(138)14-P], and other halogenophenazine 5,10-dioxides are also reactive (49JA1139). The 7-chloro group in 2,7-dichlorophenazine 5-oxide (*165*) is replaced preferentially, although both 2- and 3-chlorophenazine 5-oxide undergo nucleophilic displacement reactions (52JA971; cf. 51JA4958). For further references on the nucleophilic displacement of chlorine atoms on phenazine *N*-oxides, see references 51JA457, 55ZO2161, and 56J2550. Recently, direct comparison of the reactivities of the halogen atoms in 1- and 2-halogenophenazines and their *N*-oxides has confirmed the activating effect of the *N*-oxide group (69BJ502).

The chloro groups in chlorobenzofuroxans are susceptible to nucleophilic displacement provided the systems are additionally activated by the presence of nitro groups [66J(B)1004].

B. OXYGEN-LINKED FUNCTIONAL GROUPS

The properties of functional groups linked to the *alpha* and *gamma* positions of heterocyclic *N*-oxides by an oxygen atom are distinct from those of the corresponding groups in a β-position. In particular, α- and γ-hydroxy *N*-oxides possess uncharged tautomeric forms; for example, 4-hydroxypyridine 1-oxide (*166*) can also exist as 1-hydroxy-4-pyridone (*167*). Extensive investigations using physical methods have indicated that both forms of α- and γ-hydroxy *N*-oxides are of comparable importance. Chemically, reaction

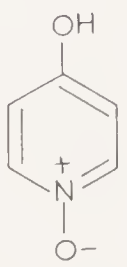
products derived from both forms are obtained, and these can in some cases be interconverted.

The only other oxygen-linked substituents of any importance in *N*-oxide chemistry are alkoxy and aryloxy groups. The alkoxy and aryloxy *N*-oxides are usually prepared by direct *N*-oxidation (Chapter II); hydroxy *N*-oxides can be obtained from these by dealkylation. α-Acyloxypyridine *N*-oxides appear to rearrange spontaneously into *N*-acyloxypyridones (66CH308).

i. Hydroxy N-*Oxides* (N-*Hydroxy-oxo Compounds*)

a. Structure. The tautomerism of 4-hydroxypyridine 1-oxide has been clarified by pK_a (57J4375) and NMR measurements (60CI870): in aqueous solution approximately equal amounts of the two forms, *166* and *167*, are present. Ultraviolet spectral data (49JA67; 57J4375), infrared spectral data [56ZP(7)123], Hammett treatments (55JA4445; 58JO1790), chemical methods (47JJ151; 51JJ213), and molecular orbital treatments (55JA4448) yield unambiguous results in this particular case.

2-Hydroxypyridine 1-oxide has also been extensively investigated. Both tautomeric forms, *168* and *169*, are expected to be highly intramolecularly hydrogen bonded, which hinders interpretation of the physical data, but the compound probably exists preferentially in the oxo form (*169*) (57J4375) on the basis of ultraviolet (49J2091; 49JA67) and infrared spectral evidence (60J2947). The structures of substituted 2-hydroxypyridine 1-oxides have also been investigated (54JA3168; 55JA3651; 56JA2393); the structure of 1,6-dihydroxy-2-pyridone (*170*) is discussed in reference 59J2310.



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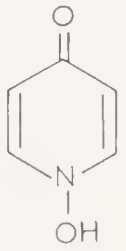

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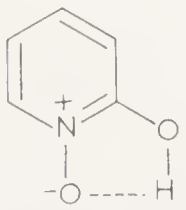

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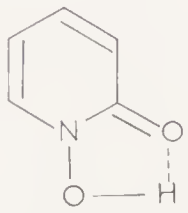

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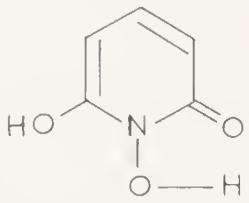

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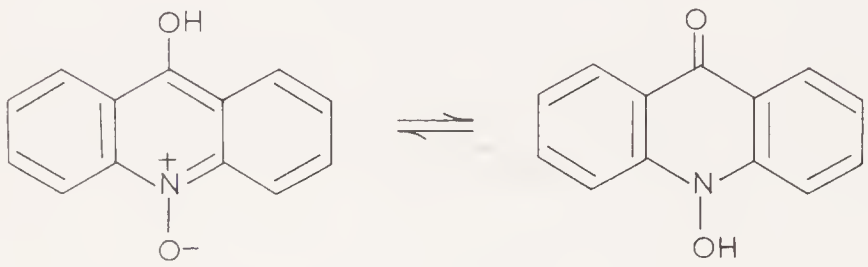
The infrared spectra of 2- and 4-hydroxyquinoline 1-oxide have been interpreted in favour of the oxo forms (59JJ428; cf. 47JJ154; 49J2091), and a similar view has been expressed for 6-hydroxyphenanthridine 5-oxide

(67JO1106). The tautomerism of 9-hydroxyacridine 10-oxide (*171* ⇌ *172*) has been the subject of much discussion [14CB1629; 35CB1455; 63CB1726; 68J(C)1045]; recently application of modern physical methods has shown that the two forms are of comparable stability in aqueous solution (66T3227). The following references give information on the structures of α-hydroxy *N*-oxides (which probably exist in the *N*-hydroxy-α-oxo form) in the series indicated: isoquinoline (55J3518), pyrimidine (64M1729), benzoxazine (55JA3651; 60AS499; 60AS502), pteridine (55JA3927; 66JH224), purine (65H1513; 67JO1151), and indazole (36BF1161).



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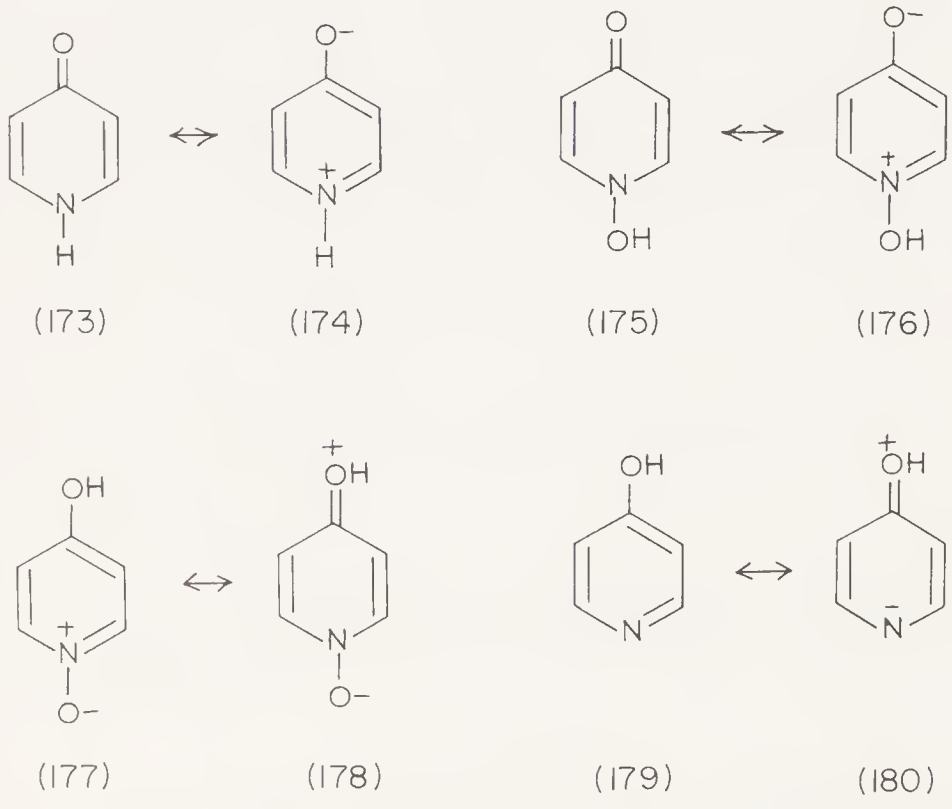


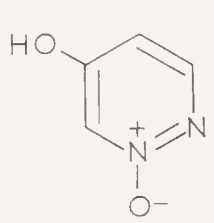
(173) (174) (175) (176)

(177) (178) (179) (180)

The tautomeric balance in γ-hydroxy *N*-oxides differs considerably from that which is prevalent in the analogous γ-hydroxy desoxy heterocycles; for the latter compounds, the oxo form is usually favoured by a factor of at least 10^3. This difference between the tautomeric equilibrium constants may be readily understood, because stabilization of the oxo form of 4-pyridone (*173*) by the charge-separated structure *174* will be greater than the stabilization

afforded to the *N*-hydroxy-oxo form (*175*) by mesomerism with *176*, where the hydroxyl group exerts an unfavourable inductive effect. Conversely, stabilization of the hydroxy *N*-oxide tautomer *177* by canonical form *178*, in which the negative charge resides on oxygen, will be greater than the stabilization of *179* by *180*, which carries the negative charge on nitrogen.

β-Hydroxy *N*-oxides generally exist in the hydroxy form. This apparently even applies to 5-hydroxypyridazine 1-oxides (*181*), where tautomerism to the 2*H*-5-oxo form (*182*) is not favoured by the weakly basic properties of the ring nitrogen atom in the 2-position (68CT142); this view is supported by infrared spectral data (68CT939). Recently, a similar view has been postulated for 3-hydroxypyridazine 1-oxides and supported by NMR data (69CT763).



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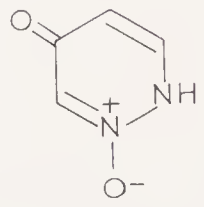

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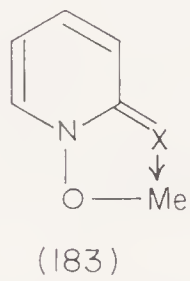

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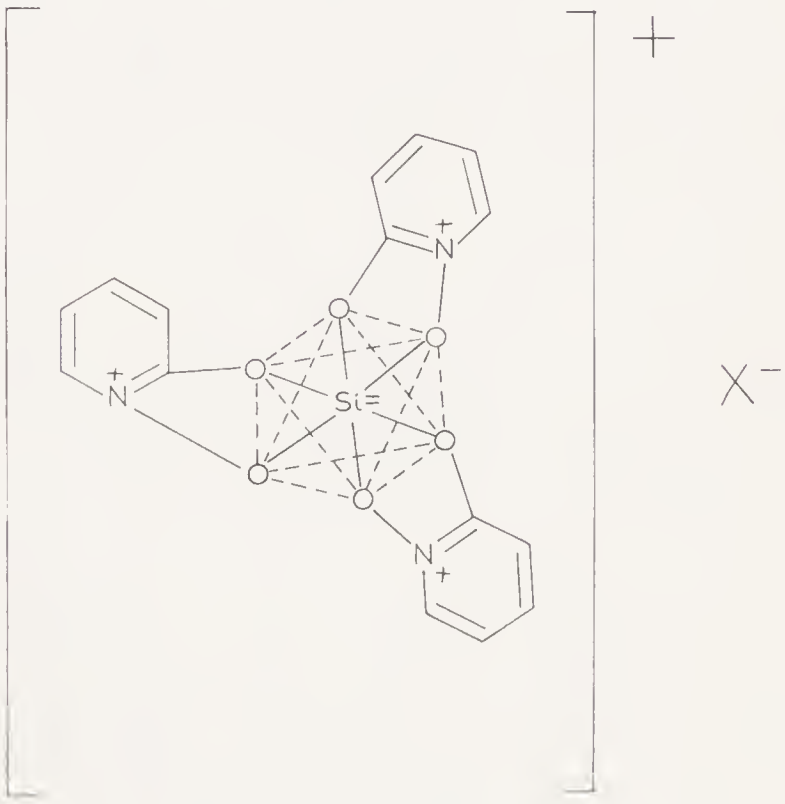

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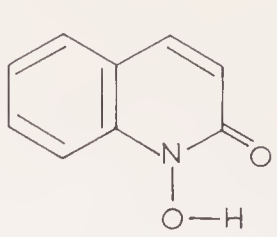

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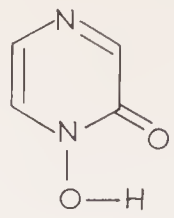

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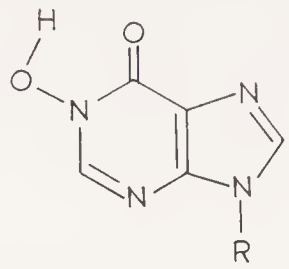


(187)

b. Complex Formation. α-Hydroxy *N*-oxides are bidentate anionic ligands of type *183* (X = O), forming stable complexes with several bivalent ions (Zn, Cu, Ni, Co, Mn), and have been suggested for use as analytical reagents (64AC2485). 1-Hydroxy-2-pyridone forms a cationic complex (*184*) with silicic acid [64AG(E)698], the resolution of which provides evidence for octahedrally coordinated silicon [65AG(E)357]. Cyclic hydroxamic acids in the quinoline and pyrazine series (*185*, *186*) give red complexes with Fe(III) (48J1864). A series of complexes formed by inosine 1-oxide (*187*) has been described (65H1519).

c. Other Reactions. 4-Hydroxypyridine 1-oxide reacts with diazomethane to give a mixture of 1-methoxy-4-pyridone and 4-methoxypyridine 1-oxide (47JJ151); however, with methyl *p*-toluenesulphonate and a base a good yield of 1-methoxy-4-pyridone is obtained (57J4375). Substituted 4-hydroxypyridines and other hydroxy *N*-oxides react analogously with diazomethane, and substituted alkyl groups may be introduced using other diazoalkanes; see Table 4.07 for examples. The reaction is subject to steric hindrance (59R981). The acidity of the hydroxyl group in these compounds can be considerably increased by suitable substitution: 4-hydroxy-3,5-dinitropyridine 1-oxide forms stable salts with bases (50JJ142).

1-Methoxy-2-pyridone (*188*, R = Me) is obtained from the reaction of 1-hydroxy-2-pyridone (*188*, R = H) with methyl *p*-toluenesulphonate and base (57J4375); for additional examples, see Table 4.07. 1-Hydroxy-2-pyridone reacts with tosyl chloride to give 1-tosyloxy-2-pyridone (64JJ23) and with benzoyl chloride to yield *188* (R = PhCO), which is also a good benzoylating agent (64J4651). 1-Acetoxy-, 1-benzoyloxy-, and 1-tosyloxy-2-quinolones have been prepared similarly (59CT273; cf. 21CB1067); see Table 4.07 for details. *N*-Acyloxy groups are easily removed by hydrolysis (cf.

Table 4.07. Alkylation and Acylation of Hydroxy *N*-Oxides

Ring system	Substituents	Reagent	*N*-Alkoxy-oxo derivative: Position of oxo group	*N*-Alkoxy-oxo derivative: *N*-OR (yield, %)	C-Alkoxy *N*-oxide	References
Pyridine 1-oxide	2-OH	NaOEt	2	1-OEt (77)	—	57J4375
	4-OH	$ClCH_2CO_2H$	4	1-OCH_2CO_2H	—	58R331
	4-OH	CH_2N_2	4	1-OMe	4-MeO	45JJ(5/6A)1, 47JJ151
	4-OH	NaOEt	4	1-OEt (68)	—	57J4375
	4-OH-3,5-diI	$ClCH_2CO_2H$	—	—	4-HO_2C-CH_2O (85)	59R981
	4-OH-3,5-diI-2-Me	$ClCH_2CO_2H$	—	—	4-HO_2C-CH_2O (35–48)	59R981
	2-OH-6-Me	NaOMe + MeI	2	1-OMe (90)	—	59JA2537
	4-OH-2-Me	$ClCH_2CO_2H$	—	—	4-HO_2C-CH_2O (25)	59R981
	3,6-$(OH)_2$-2-Me	Ac_2O	—	—	3,6-$(AcO)_2$ (71)	55AS9
Quinoline 1-oxide	2-OH	EtI	2	1-OEt	—	48J1864
	2-OH	acetobromoglucose	2	1-glucosyloxy	—	65AP481
	2-OH	$CH_2{=}CHCH_2Br$	2	1-$OCH_2CH{=}CH_2$	80	68JJ661
	4-OH	CH_2N	4	1-OMe	—	45JJ(5/6A)3(B)
	4-OH	CH_2N_2	4[a]	1-OMe	4-MeO[a]	47JJ154
	4-OH	MeI	4[b]	1-OMe	4-MeO[b]	47JJ154
Acridine 10-oxide	9-OH	NaOH + Me_2SO_4	9	10-OMe	—	14CB1629

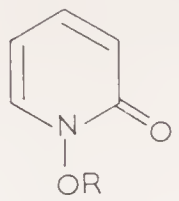
[a] 1-Methoxy-4-quinolone (9 parts); 4-methoxyquinoline 1-oxide (2 parts).
[b] 1-Methoxy-4-quinolone (major); 4-methoxyquinoline 1-oxide (minor).

Table 4.07. Alkylation and Acylation of Hydroxy *N*-Oxides—*continued*

Ring system	Substituents	Reagent	*N*-Alkoxy-oxo-derivative: Position of oxo group	*N*-Alkoxy-oxo-derivative: *N*-OR (yield, %)	C-Alkoxy *N*-oxide	References
Pyridazine 1-oxide	4-Cl-6-OH-3-OMe[c]	Me_2SO_4	6	1-OMe	—	63CT1073
	3-OH	MeI	—	—	3-MeO	59CT938
	4-OH	TsOMe-NaOMe	4	1-OMe	—	63CT83
	4-OH-3-OMe	$PhCH_2Cl$, NaOMe	6	1-OCH_2Ph (68)	—	62JJ244
	4-OH-3-OMe	MeI	6	1-OMe	—	62JJ244
Pyridazine 2-oxide	3-OH-6-OMe[d]	MeI	3	2-OMe	—	61JJ1048
	3-OH-6-Me[d]	MeI	3	2-OMe	—	62JJ249
	6-OH-3-Me	MeI	—	—	6-MeO	61JJ1048
Cinnoline 1-oxide	4-OH	MeI	4	1-OMe (28)	4-MeO(4)	64CT619
Cinnoline 2-oxide	4-OH	MeI	—	—	4-MeO (50)	64CT619
Pyrazine 1,4-dioxide	3,6-diBu-2-OH	CH_2N_2	2	1-OMe	—	69CT851
Indazole 1-oxide	3-OH-2-Ph	EtI + Ag_2O	—	—	3-EtO	33BF1436

[c] 4-Chloro-1-hydroxy-3-methoxy-6-pyridazinone.
[d] 2-Hydroxy-3-pyridazinone.

54JO1140), and the 1-acyloxy-2-pyridones have been described as a new class of activated esters (65JA1407).



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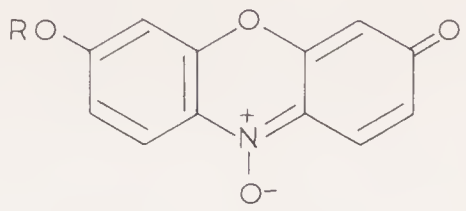

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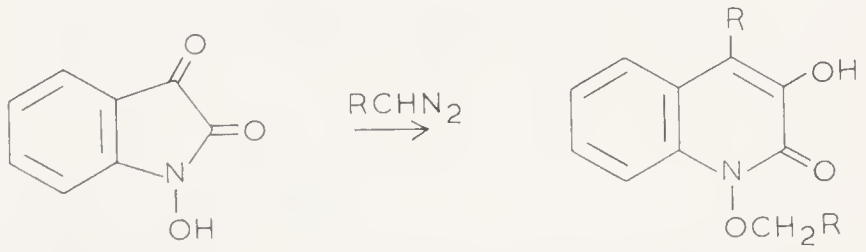
1-Benzoyloxy-2-quinolone has also been prepared by benzoylation of 2-ethoxyquinoline 1-oxide (60CT286) and by permaleic acid oxidation of 2-benzoyloxyquinoline (63CT1586); evidently the last reaction involves the rearrangement of 2-benzoyloxyquinoline 1-oxide. Resazurin ethers (*189*, R = alkyl) are made by treatment of resazurin (*189*, R = H) with diazoalkanes (66M129).

α- and γ-Hydroxyl groups on *N*-oxides are converted into chloro groups by the action of phosphorus oxychloride or phosphorus pentachloride; details are given in Table 4.08. Under the vigorous reaction conditions, the *N*-oxide function is frequently lost giving the chloro-heterocycle (see Tables 3.29 to 3.31); alternatively, an additional chlorine atom is introduced into the ring, cf. Section III-4B.

Comparatively little is known of the corresponding reactions for β-hydroxy *N*-oxides (cf. 49JA67), although alkylation and acylation appear to occur at the hydroxyl group. β-Hydroxypyridine 1-oxides have been acylated (55AS9) and methylated (by diazomethane) (57R58). Methylation with diazomethane has also succeeded for β-hydroxy-quinoline (60CT126) and -pyridazine *N*-oxides (59CT938). 3-Hydroxypyridazine 1-oxides have also been methylated using methyl iodide and silver oxide (62JJ249).

A rather different type of reaction is the conversion of 1-hydroxyisatin into a 1,3-dihydroxyquinoline derivative by the reaction sequence *189a* → *189b* [69LA(725)37].



(189a) (189b)

ii. Hydroxyl Groups Attached to Fused Benzene Rings

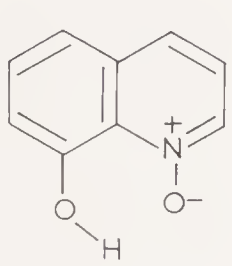
Hydroxyl groups attached to fused benzene rings generally exist as such; for example, it was shown by ultraviolet spectroscopy that 5-hydroxybenzofuroxan exists in the *C*-hydroxy form [66J(C)971].

Table 4.08. Replacement of Hydroxyl or Potential Hydroxyl Groups in *N*-Oxides with Chloro or Bromo Groups

Ring system	Reagent	Substituents		Yield, %	References
		unaffected	affected[a]		
Pyridine 1-oxide	$POCl_3$, 60° [b]	3-chloro *N*-oxide	4-OH → 4-Cl	80	55R59
	$POCl_3 + PCl_5$	—	4-OH → 4-Cl, *N*-oxide	"good"	55R59
	$POBr_3$	3,5-dibromo	2-OH → 2-Br, *N*-oxide	(data)	56R1259
Quinoline 1-oxide	PCl_5	—	2-OH → 2-Cl, *N*-oxide	—	82CB332
	$POCl_3$	3-chloro	2-OH → 2-Cl, *N*-oxide	(data)	59CT273
	$POCl_3$	3,6-dinitro	2-OH → 2-Cl, *N*-oxide	(data)	59CT191
Pyridazine 1-oxide	$POCl_3$	3-methyl, *N*-oxide	5-OH → 5-Cl, 6-$CONH_2$ → 6-CN	(data)	64CT228
2-Pyrimidinone	$POCl_3$	1-benzyloxy, 2-oxo	4-OH → 4-Cl	94	64CT228
1,2,4-Benzotriazine 1-oxide	$POCl_3$, $POBr_3$, or $POCl_3 + PCl_5$	7-substituted, *N*-oxide	3-OH → 3-Cl (Br)	(data)	49USP2489354, 54JA4611, 59JO813
	$POCl_3$	*N*-oxide	3-OH → 3-Cl	ca. 64	49USP2489354, 57J3186
Pyrido[2,3-*e*]-*as*-triazine 1-oxide	$POCl_3$	7-hydrogen or -methyl, *N*-oxide	3-OH → 3-Cl	79–90	62JO2504

[a] *N*-Oxide in this column indicates that the *N*-oxide group is lost during the reaction.
[b] If the reaction is carried out at 90–100° (sealed tube; 1·5 h), the *N*-oxide group is lost.

An important exception to the "normal" reactivity of substituents on fused benzenoid rings (cf. Section IV-2Ai) is the formation of complexes by various *peri*-substituted *N*-oxides. 8-Hydroxyquinoline 1-oxide (*190*) is a more selective metal-complexing agent than is 8-hydroxyquinoline; of seventeen ions precipitated by oxine, the corresponding *N*-oxide (*190*) forms insoluble complexes with fourteen and soluble complexes with three (62PI-360). The stoichiometry of the complexes formed by Cu(II) and Mn(IV) is reported to be 2 : 1 (complexing agent: metal), and for Fe(III) it is 3 : 1 (54NK1180). The complexes of 8-hydroxyquinoline 1-oxide with copper (59CT84), cerium (61JI327), and ferric ions have been studied spectrophotometrically. The complex formed with uranium has been investigated for analytical use (60JY16), and the boron–catechol complex *191* has been described (64J2382). Complexes derived from 5,7-dibromo-8-hydroxyquinoline 1-oxide are also known (67IJ110). 1-Hydroxyphenazine 5,10-dioxide acts as a bidentate ligand in the copper complex *192* (58CT556). The dihydroxy di-*N*-oxide iodinin (*193*) is a bis-bidentate ligand and forms polynuclear coordination compounds (58CT563).*



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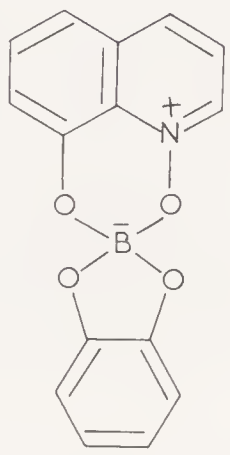

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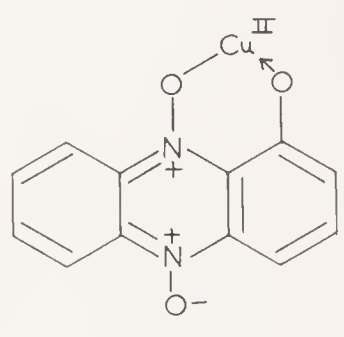

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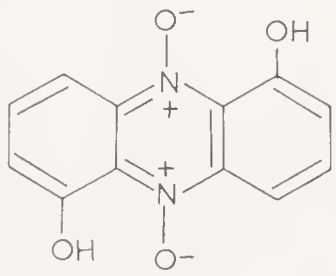

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iii. Alkoxyl and Aryloxy Groups

a. Hydrolysis to Hydroxy Compounds and Other Nucleophilic Displacements. α- and γ-Methoxy, -ethoxy, and -benzyloxy groups on *N*-oxide rings are readily hydrolysed to give the corresponding hydroxy *N*-oxide under acidic or basic conditions; this reaction is a nucleophilic displacement on the activated heterocyclic nucleus. Examples are collected in Table 4.09.

* See addendum in the Appendix.

Table 4.09. Hydrolysis of Ring Alkoxyl Groups in *N*-Oxides

Ring system	Reagent	Group hydrolyzed	Substituents unaffected	Yield, %	References
Pyridine 1-oxide	HCl	2-benzyloxy	—	ca. 68	49JA67, 51USP2540218
	(?)	4-benzyloxy	—	—	45JJ(5/6A)1
	HCl	6-benzyloxy	2-methyl	58	54JA3168
	HCl	2-ethoxy	—	(data)	48J1864, 49J2091, 50JG26
	BzCl	2-ethoxy	—	see note[a]	61JJ574
	HCl	2-ethoxy	3- and 4-methyl	—	49J2091
	NaOH	4-methoxy	2-methyl	70	59R981
	H_2SO_4	4-methoxy	2,6-dimethyl	70	68J(B)866
Quinoline 1-oxide	HCl	2-ethoxy	4-methyl	—	49J2091, 50JG26
Pyradazine 1-oxide	NaOH	4- and 5-methoxy	3,6-dimethyl	70–80	62JJ1208, 63CT337
	NaOH	5-methoxy	—	72	68CT142
Cinnoline 1-oxide	NaOH	4-methoxy	—	87	64CT619
Quinazoline 1-oxide	H_2O (100°) or 50% AcOH (reflux)	4-alkoxy and -phenoxy	—	48–63	59CT152
	(?)	2-ethoxy	7-methyl	—	52G513
	NaOH[b]	4-methoxy	—	74	64CT43
Purine 3-oxide	NaOH	6-methoxy	—	—	69BJ750
Quinoxaline 1-oxide	$AlCl_3$	5-methoxy	2,3-dimethyl	—	56J2058
1,2,4-Triazine 2-oxide	HCl	3-methoxy and -phenoxy	5,6-diphenyl	74	66JO3914
1,2,4-Benzotriazine 1-oxide	NaOH	3-ethoxy	7-carboxy	65	66H651
Isopyrazole 2-oxide	H^+	4-methoxy	3,5,5-trimethyl	—	62JO2881

[a] 1-Benzoyloxy-2-pyridone obtained.

[b] Reaction occurs at 100°; no reaction occurs at 20°.

Table 4.10. Nucleophilic Displacement Reactions on Alkoxy and Phenoxy *N*-Oxides

Ring system	Reagent	Substituents		Yield, %	References
		Unaffected	Affected		
Pyridine 1-oxide	morpholine	—	4-PhO-, 4-(*p*-Me-C_6H_4-S-)	77, —	44PJ141
	$POCl_3$, PCl_5	—	4-MeO → Cl, 3-$CONH_2$ → CN, 2-H → Cl [a]	32	56JA214
Quinoline 1-oxide	morpholine, piperidine	—	4-PhO [b]	—	45JJ8
	PhMgBr	—	2-MeO	ca. 40	54AN1029
Acridine 10-oxide	NH_3, N_2H_4	6-Cl-2-MeO	9-PhO	ca. 25	59TU36
	amines (various)	—	9-PhO	—	60ZO3476
Pyridazine 1-oxide	NaOEt, NaOMe	—	3-MeO; 5-MeO	—	67JJ114
	N_2H_4	—	3-MeO; 5-MeO	30–55	63CT348, 63CT1059, 68JH513
Pyrimidine 1-oxide	NaOMe, NaOEt, NaSPh, piperidine	6-Me	4-PhO	(data)	59CT505
Quinazoline 1-oxide	N_2H_4	—	—	—	64CT43
1,2,4-Triazine 2-oxide	NH_3, $MeNH_2$, NH_2OH, $PhNH_2$	—	5,6-diPhO	(data)	66JO3914

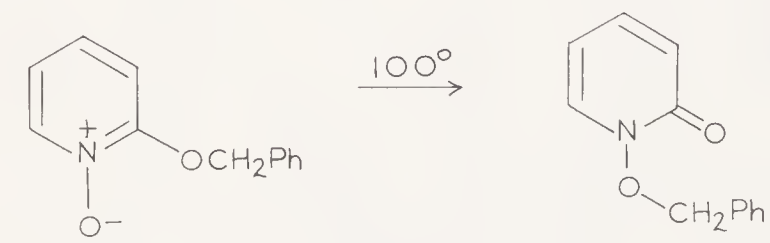
[a] 4-Methoxynicotinamide 1-oxide → 2,4-dichloronicotinonitrile.
[b] 4-Phenylthioquinoline 1-oxide reacts analogously.

The reaction fails, however, with 4-methoxy-2,6-dimethylpyridine 1-oxide (59R981). Among the β-alkoxy *N*-oxides, 3-ethoxypyrazine 1-oxide is readily hydrolysed (48J1859), but this must be considered a special case.

Other nucleophilic displacements have been carried out with alkoxy, and particularly with phenoxy, *N*-oxides. These reactions are summarized in Table 4.10. The reaction of 4-methoxypyridine 1-oxide with methoxide ions has been studied kinetically using ^{14}C-labelling methods (66JA1237). Ethoxy groups are frequently not replaced by amines [45JJ(9/10A)8], and sodium iodide in acetic acid does not effect demethylation of 4-methoxypyridine 1-oxide (61J3345).

b. Rearrangements. The alkyl moiety of alkoxy groups can rearrange from the oxygen atom linked to a ring carbon atom to the *N*-oxide oxygen atom.

Benzyloxy and allyloxy *N*-oxides readily rearrange to the corresponding *N*-substituted oxo derivatives in the pyridine (*194* → *195*) (64JO1650) and quinoline series (*196* → *197*) (58JJ613). At higher temperatures (140°), 2-methoxy- and 2-ethoxy-pyridine 1-oxide undergo a rearrangement similar to that shown in the scheme *194* → *195* (64JO1650); alkoxypyridazine 1-oxides rearrange analogously to give 1-alkoxypyridazinones (63CT1073; 65JJ344; 68CT1221). Recently it has been shown that the rearrangement of 2-allyloxypyridine 1-oxides to 1-allyloxy-2-pyridones is not of the Claisen type, and that only to a minor extent does rearrangement of the double bond take place; the major reaction is of the type *198* → *199*. However, a simultaneous Claisen rearrangement does occur to yield the 3-allyl derivative (e.g. *198* → *200*) (68JA4361). Similar conclusions have been reached by Japanese workers who showed that 2-cinnamyloxyquinoline 1-oxide rearranges to 1-cinnamyloxy-2-quinolone (68JJ661).



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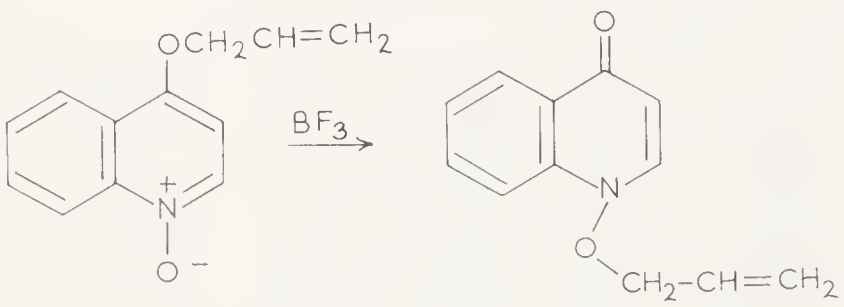

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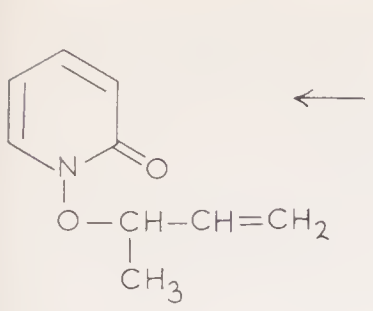

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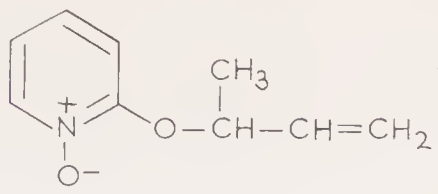

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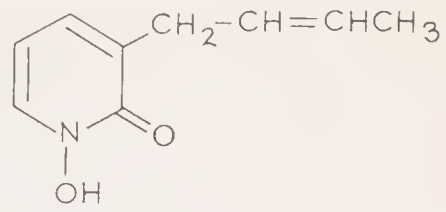

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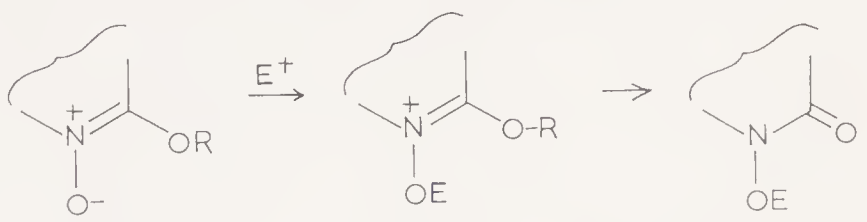
c. Other Reactions. The reaction of alkoxy *N*-oxides with electrophiles (E) at the *N*-oxide oxygen atom with subsequent loss of the alkyl group to yield *N*-(*O*-substituted) α- or γ-oxo heterocycles is related to the rearrangements just considered; cf. the sequence *201* → *203*. Thus, 2-ethoxy-pyridine 1-oxide and -quinoline 1-oxide react with primary and secondary alkyl halides to yield cyclic hydroxamic esters (cf. *204*), although the reaction between 4-ethoxypyridine 1-oxides and benzyl halides gives only benzaldehyde (66T25). 2-Ethoxypyridine 1-oxide reacts with acyl chlorides and sulphonyl halides to give 1-acyloxypyridones (*204*, R = COR or SO_2R), which are potential "activated esters" (cf. Section IV-4B) (65JA5186). Similarly, treatment of 2-ethoxyquinoline 1-oxide with acetobromoglucose yields 1-glucosyloxy-2-quinolone (65AP481), and alkoxypyridazine *N*-oxides are converted by alkyl or acyl halides into 1-alkoxy- or 1-acyloxy-pyridazinones (cf. *205* → *206*) (66JJ81; 68CT1244; cf. 66JJ314). The formation of *N*-acetoxy-α-oxo derivatives from α-alkoxyphthalazine *N*-oxides on treatment with acetic anhydride or acetyl chloride has also been reported (63JJ934).



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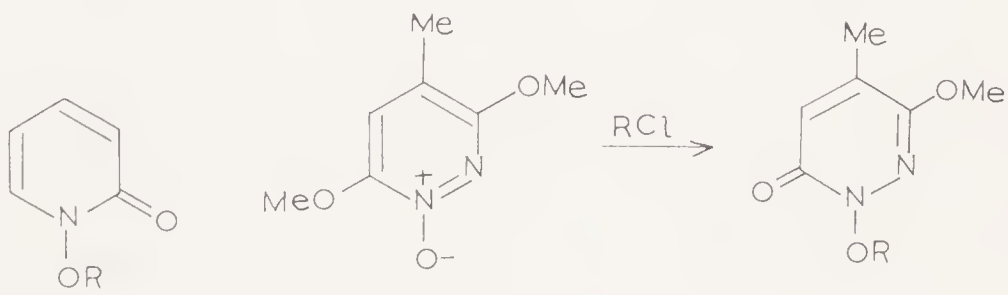

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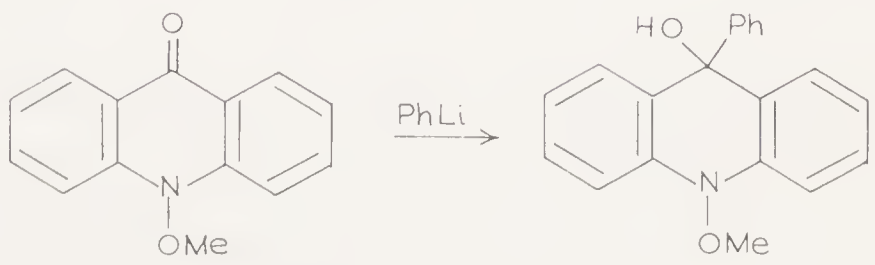


(207) (208)

Little is known about the reactions of *N*-alkoxy-oxo compounds (cf. Section II-4B); however, the reaction of phenyl lithium at the oxo group of 10-methoxyacridone (*207*) to give *208* (39CB1071) is of interest.

Benzyloxy groups attached to *N*-oxide rings may be selectively hydrogenolysed to yield the corresponding hydroxy *N*-oxides; catalytic reductions of this type are listed in Table 3.07 and discussed in Section III-2B.

C. NITROGEN-LINKED FUNCTIONAL GROUPS

i. Amino and Acylamino N-*Oxides*

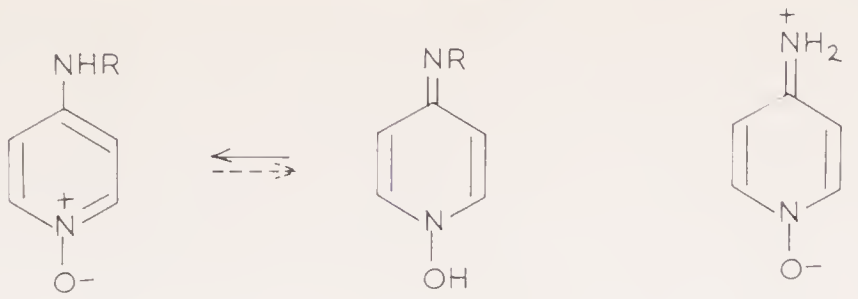
Amino *N*-oxides are important intermediates. They are obtained by the reduction of nitro *N*-oxides (Section IV-3Ciia), by the *N*-oxidation of suitably protected amino heterocycles (Section IV-3Cig), or by the nucleophilic displacement of nitro groups (Section IV-3Ciib) or halogen atoms (Section IV-3Ai).

Physical methods show that amino *N*-oxides exist predominantly in the amino tautomeric form. These compounds can be diazotized, and the diazonium derivatives undergo many of the standard reactions. Although acylation probably often involves initial attack at the *N*-oxide oxygen atom, the *N*-acyl derivatives are usually isolated. Amino *N*-oxides undergo a number of ring-closure reactions that provide synthetic routes to various bicyclic ring systems.

a. Tautomeric Structure. Gardner and Katritzky (57J191; 57J4375) showed by pK_a and ultraviolet spectral measurements that in aqueous solution 2- and 4-amino- and 2- and 4-methylamino-pyridine 1-oxides exist predominantly in the amino form (cf. *209*) rather than in the alternative imino form (cf. *210*); K_T values of ca. 10^8 are obtained. These conclusions are supported by the infrared spectra which show bands characteristic of amino and methylamino groups [57J4375; 59J3674; cf. 56ZP(7)123] and of the substituted pyridine rings (58J2192; 58J2195). For other work on the tautomerism of aminopyridine *N*-oxides, see references 53JJ140 and 55JA4445. Similar conclusions have been reached regarding the structures of 2-aminopyrroline 1-oxides (63SA1481) and aminobenzofuroxans [66J(C)971].

The tautomeric equilibria for amino *N*-oxides favour the amino forms considerably more than is the case for the corresponding amino heterocycles, when K_T values of ca. 10^4 are found. This behaviour is understandable from a consideration of the mesomeric possibilities (57J4375): canonical forms of type *211* are more favourable than those of type *212*, whereas forms of type *213* are less favourable than those of type *214*; cf. the discussion of the corresponding hydroxy compounds in Section IV-3Bia.

2- and 4-Acylaminopyridine 1-oxides also exist predominantly as such and not in the alternative imino forms (cf. *209* and *210*) (60J2937). This applies also to 2-acylaminoquinoxaline 1-oxides (66KG101).



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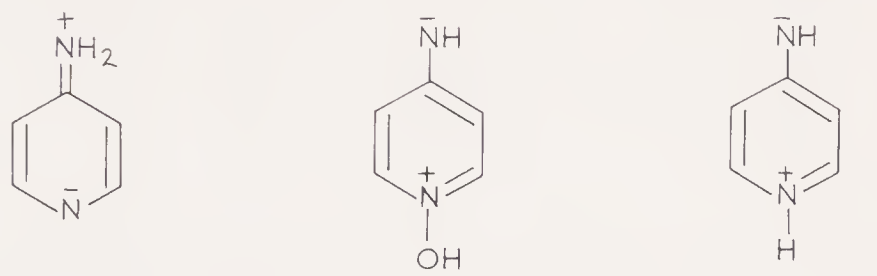
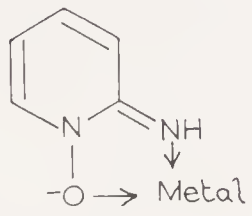


(212) (213) (214)

b. Chelate Complexes with Metals. 2-Aminopyridine 1-oxide was early shown to form metal complexes (56J2063), and these have been extensively investigated by Sigel, Brintziger, and Erlenmeyer (63H710; 63H712). The amino *N*-oxide can enter into complex formation as the neutral molecule, but in that case it is behaving like pyridine 1-oxide itself, i.e. as a monodentate ligand, and four or six moles of the amino *N*-oxide combine with one mole of a metal ion under the usual conditions (See Table 3.05).



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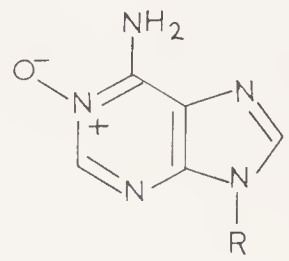

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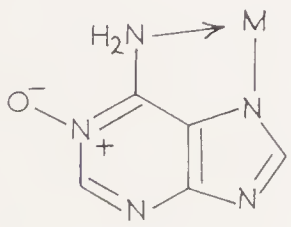

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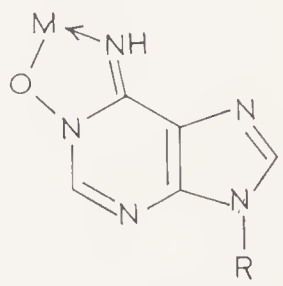


(218)

In the anionic form, amino *N*-oxides are bidentate ligands (*215*), and form very stable complexes with Cu(II) and Fe(III) (63H712). Although 2-aminopyridine 1-oxide itself is an extremely weak acid, the acidity is raised by 12 p*K* units on coordination with Cu(II) (63H712). Evidently, the blue colour formed by 2-aminopyridine 1-oxide and its 2-methylamino analogue in the

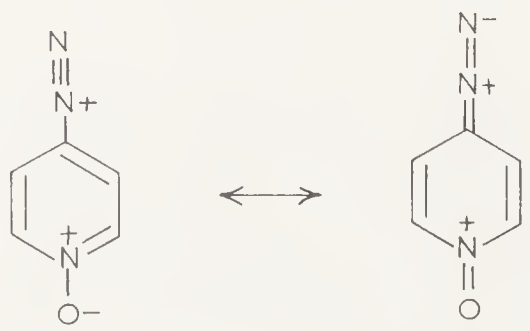
presence of Fe(III) is due to the anionic complex, since the colour is not observed with the 2-dimethylamino derivative (57J191).

2-Aminobenzothiazole 3-oxide (64CI368) and 2-aminopyrazine 1-oxide (51J932) also form blue ferric complexes. Complex formation by 1,10-phenanthroline 1-oxide has also been reported (65JO288). Adenine 1-oxide (*216*, R = H), adenosine 1-oxide (*216*, R = ribosyl), and the 1-oxide of adenylic acid complex with divalent ions (Mg, Fe, Co, Ba, Ni, Cu, Zn, and Mn) (60JA5642; 64H1701). Whereas the complexes derived from adenine 1-oxide are of the familiar type shown in structure *217*, those formed by the 1-oxides of adenosine and adenylic acid involve bonding with the *N*-oxide oxygen atom (*218*).

c. Diazotization of Amino Groups. Ochiai and Naito [45JJ(5/6A)3] found that 4-aminoquinoline 1-oxide yields, under normal conditions, a diazonium salt which undergoes many of the typical reactions of aryldiazonium cations; α- and γ-amino groups on *N*-oxides form diazonium cations which are considerably more stable than those derived from the corresponding amino-heterocycles; this is undoubtedly due to resonance stabilization in the *N*-oxides (cf. *219* ↔ *220*). However, the diazotization of most amino *N*-oxides proceeds less readily than that of anilines; thus, the mono-diazotization of 4,6-diaminoquinoline 1-oxide occurs preferentially at the 6-amino group [45JJ(5/6A)3].

Reactions involving diazotized amino *N*-oxides are summarized in Table 4.11. A diazonium salt has been prepared from 3-aminopyridine 1-oxide, but Sandmeyer replacement by a thiocyanato group could not be effected (56JO1077). The colorimetric determination of 4-aminoquinoline 1-oxide is based on diazotization and coupling reactions (64CT262).

d. Alkylation and Acylation of Amino N-*Oxides.* Amino *N*-oxides generally react with alkylating agents at an *N*-oxide oxygen atom, although the reaction of 4-aminoquinazoline 3-oxide with diazomethane affords a mixture of the 4-methylamino and the 3-methoxy derivatives (67JJ578). The *O*-alkylated products (*221*) are comparatively stable and behave similarly to the *O*-alkyl quaternary salts formed by other *N*-oxides; these alkylation reactions are discussed in Section III-1B2 and listed in Table 3.04. Spectroscopic evidence does indicate, however, that deprotonation of the amino group in the amino-*N*-alkoxy compounds occurs under alkaline conditions: *221* → *222* (57J4375); such products have been isolated in the purine series (66CI1598; 69CH458).

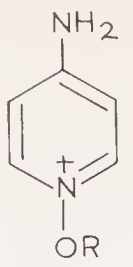


(219) (220)

Table 4.11. Groups Introduced into Rings Carrying an *N*-Oxide Function via Diazotization

Ring system	Position of amino group diazotized	Group introduced (% yield)	References
Pyridine 1-oxide	2,3,4,5, and 6	aryl (data)	45JJ(5/6A)1, 56AA(130)66-O, 61JO418[a]
	2	arylazo, various (data)	67JO1146
	2	azido	57JA678
	4	cyano (43–62)	45JJ(5/6A)1, 55JO1461, 58BF694
	4	halogeno	45JJ(5/6A)1, 61JJ1206, 65RC1045
	4	isothiocyanato[b] (data)	56JO1077
	2	1-naphthylazo, various (data)	57J191, 63MC646
	4	phenylazo, various (42–68)	61PC(13)58
Quinoline 1-oxide	4	hydrogen[c]	47JJ246
	2,3,4,5,6,7, and 8	arylazo	61JO2831
	4	cyano	45JJ(5/6A)3(B)
	4 and 6	halogeno	45JJ(5/6A)3(A), 45JJ(5/6A)3(B)
	3	hydrazino[d]	61JJ1743
	2	hydroxy	13GB3522
	4	(hydroxyazo dye)[e]	64CT262
Pyridazine 2-oxide	3	chloro	63CT269
Benzo[*c*]cinnoline 6-oxide	2 and 4	halogeno (46 and 44–65)	62J2454, 64J1265
Purine 1-oxide	6	hydrogen (27)[f]	65H433
	6	hydroxy	65H433, 66BJ633, 66JO966, 69CT1128
Pyrazine 1-oxide	3 and 5	bromo (8) and chloro (31)	66CT303
	4	chloro (55)	63CT337
	3	hydroxy	63G339
1,2,4-Benzotriazine 1-oxide	3	hydroxy (data)	49USP2489353, 59JO813, 59USP2911406

[a] 5,6-Dihydrobenzo[*f*]isoquinoline 2-oxide obtained from 4-amino-3-(2-phenethyl)pyridine 1-oxide.
[b] Attempted substitution with thiocyanate failed [45JJ(5/6A)1].
[c] Diazonium salt treated with NaH_2PO_2.
[d] Diazonium salt reduced with $SnCl_2$.
[e] Coupled with 2-hydroxy-6,8-naphthalenedisulphonic acid.
[f] Diazonium salt treated with NOCl; the diazonium salt also undergoes coupling reactions (60MI111).



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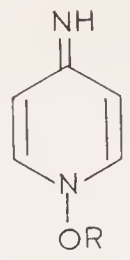

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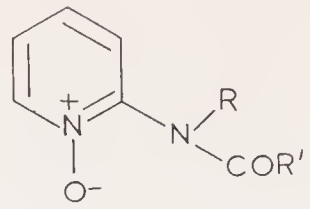

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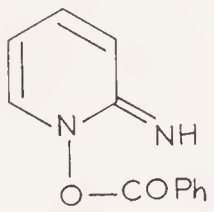

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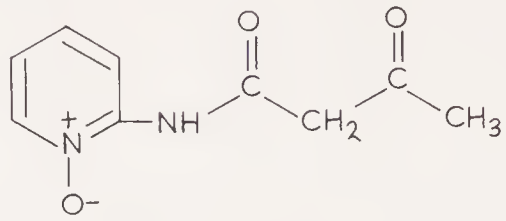

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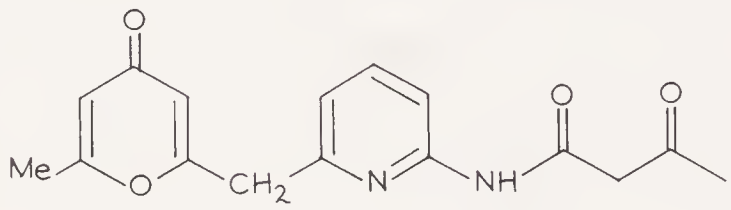

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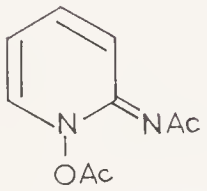

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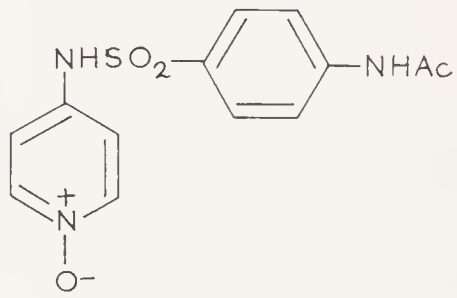


(229)

(230)

Jones and Katrizky (60J2937; cf. 57J191) showed that 2- and 4-amino- and 2- and 4-methylamino-pyridine 1-oxides undergo acetylation and benzoxylation to yield products acylated at the amino nitrogen atom (cf. *223*). However, in the case of 2-aminopyridine 1-oxide, a labile *O*-benzoate (*224*), which readily rearranges to the *N*-benzoyl derivative (cf. *223*), can be isolated (57J191). *N*-Acylation also occurs with ethyl chloroformate, phenyl isocyanate, diethyl oxalate, and 3,5-dinitrobenzoyl chloride (57J191). Diketene reacts with 2-aminopyridine 1-oxide to form the acetoacetamide *225*; reaction with excess ketene gives a product which has been formulated as *226* (64CT910). Benzoylation (and alkylation) of 2-aminopyrroline 1-oxide

Table 4.12. Acylation of Amino *N*-Oxides

Ring system	Site of acylation	Reagent	Other substituents	References
Pyridine 1-oxide	2- and 4-amino, 2- and 4-methylamino	Ac_2O, $ClCO_2Et$, PhNCO, $(CO_2Et)_2$, 3,5-diNO_2-C_6H_3-COCl	—	57J191, 60J2937
	2-amino	ketene	—	64CT910
	4-amino	KNCS	—	57JO984
	2-amino and 1-oxide[a]	Ac_2O	—	45JJ(5/6A)1, 49J133S, 54JA2785
Quinoline 1-oxide	4-amino	Ac_2O	—	44JJ(8A)6, 65JJ66
Pyridazine 1-oxide	6-amino	Ac_2O	3-methoxy	63CT114
Pyrazine 1-oxide	2-amino	—	3,5-dimethyl	51J932
Quinoxaline 1-oxide	2-amino	PhCOCl, MeOCOCl, CX_3COCl	—	66KG101
1,2,4-Triazine 2-oxide	3-amino	Ac_2O	5-phenyl	66JO3917
1,2,4-Benzotriazine 1-oxide	3-amino	—	—	49USP2489351
Pyrroline 1-oxide	2-amino	Ac_2O	5,5-dimethyl	63J5362
Benzothiazole 3-oxide	2-amino	Ac_2O	—	64CI368

[a] The product is a diacyl derivative.

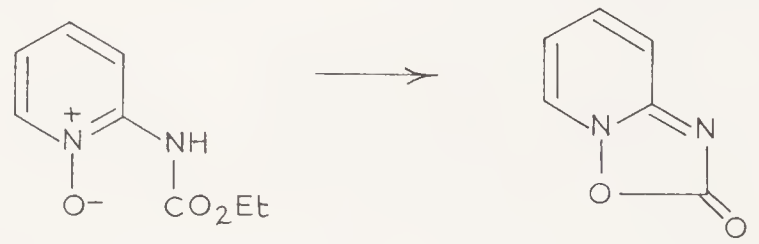
(*227*) occurs at the oxygen atom to give products of type *228*, which do not rearrange readily; however, acetylation gives the *N*-acetyl derivative (63J5632). References to analogous acylation reactions in other ring systems are given in Table 4.12.

Diacetylation of 2-aminopyridine 1-oxide gives the *O*,*N*-diacetyl derivative *229* (54JA2785; cf. 49J133S). The dibenzoylation of 4-aminopyridine 1-oxide proceeds analogously, and hydrolysis of the product yields the *N*-monobenzoyl derivative [45JJ(5/6A)1]. The analogous mono- and di-acetylated products of 4-aminoquinoline 1-oxide are known [44JJ(3A)6; cf. 65JJ66].

2-Aminopyridine 1-oxide is converted via treatment with acetylsulphanilyl chloride, and subsequent steps, into the sulphonamide drug, sulphapyridine 1-oxide (59BA203). 4-Aminopyridine 1-oxide has also been sulphonylated with *p*-acetamidobenzenesulphonyl chloride to give *230*, but the sulphonyl group is easily cleaved hydrolytically [45JJ(5/6A)1]. Sulphonamidopyridine 1-oxides are more acidic than the corresponding pyridines (58JO67).

e. Cyclization by Ring Closure at the N-*Oxide Oxygen Atom.* Reactions involving ring closure at a ring carbon atom of an amino *N*-oxide are considered in Section III-3Eiv under electrophilic attack on ring carbon atoms. Ring closures occurring at the *N*-oxide oxygen atom are considered in this section and those involving a substituent other than an amino group in the following one.

Pyridino-oxadiazolones (*232*), both unsubstituted and with a variety of ring substituents, were first prepared by Katritzky by pyrolysis of 2-ethoxycarbonylaminopyridine 1-oxides (*231*) (56J2063; 57J4385). Boyer *et al.* (57JA678) later obtained the same compounds by treatment of 2-aminopyridine 1-oxides with phosgene. Further pyridine derivatives (58H548), and the corresponding compounds in the quinoline (59JJ1063), isoquinoline (59JJ1063), and pyridazine series (62CT936) have been prepared similarly.



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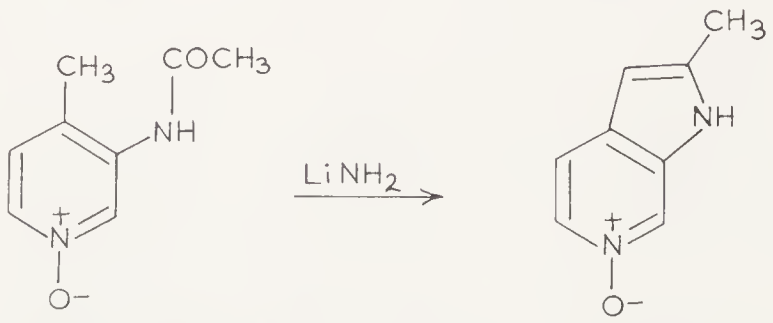

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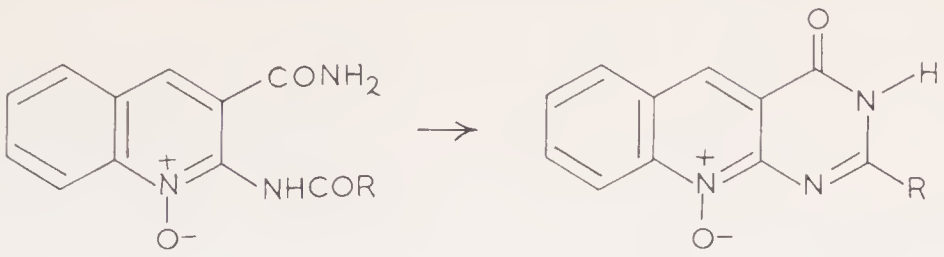

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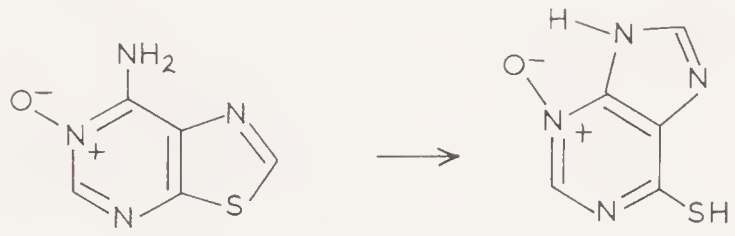

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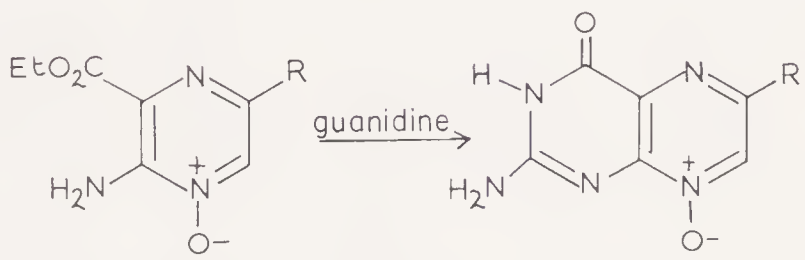


(239) (240)

f. Cyclization by Ring Closure onto a Substituent Attached to a Ring Carbon Atom. A miscellaneous group of reactions of this type has been reported; they are summarized in Table 4.13 and illustrated by structures *233* → *234*, *235* → *236*, *237* → *238*, and *239* → *240*.

g. Other Reactions. Amino *N*-oxides undergo many other reactions that are characteristic of aminobenzenes: they yield nitro compounds on oxidation, react with nitroso compounds to give azo derivatives, undergo Michael reactions, etc. These conventional reactions are summarized in Table 4.14.

Acylamino groups on *N*-oxide rings are readily hydrolysed to amino groups; indeed, many amino *N*-oxides are prepared in this way with the acyl group serving as a protecting group during the *N*-oxidation. Examples are given in Table 4.15.

Pyridino-oxadiazolones of type *241* behave in some ways like *O*-acylated *N*-oxides, and can be ring-opened by nucleophiles yielding ureas (*242*) with amines, urethanes (*243*) with alcohols, and amino compounds on hydrolysis (56J2063; 58H548). Similar studies in the quinoline series have been reported (59JJ1063).

Sugar residues may be hydrolytically cleaved from *N*-glycosidoamino *N*-oxides (64MC204).

Table 4.13. Ring Closure onto a Substituent to Give a New Heterocyclic *N*-Oxide

Starting *N*-oxide	*N*-Oxide produced	Reaction Scheme	Yield, %	References
7-Aminothiazolo[5,4-*d*]pyrimidine	purine 1- or 3-oxide	237 → 238	60	63MC825
5,6-Diaminopyrimidine	pteridine 1-oxide	—	76	65JO408
5,6-Diaminopyrimidine	purine 3-oxide	—	44	65JO408
5,6-Diaminopyrimidine	8-azapurine 3-oxide	—	78	65JO408
2-Acetamido- or -benzamido-quinoline-3-carboxamide	pyrimido[4,5-*b*]quinoline 10-oxide	235 → 236	63	53JO1755, cf. 56JA5108
2-Amino-3-ethoxycarbonylpyrazine	pteridine 8-oxide	239 → 240	60–71	68JA2424
3-Acetamido-4-picoline	6-azaindole 6-oxide	233 → 234	5	60JO2242

Table 4.14. Miscellaneous Reactions of Amino *N*-Oxides

Reaction	Ring system	Reagent	Position of amino group	Other substituents	References
$NH_2 \rightarrow NO_2$	pyridine 1-oxide	H_2SO_5	2	various alkyl	57JA3565
$NH_2 \rightarrow NO_2$	pyridine 1-oxide	AcO_2H	2′[a]	—	61CC2516
$NH_2 \rightarrow N{=}N\text{-}Ar$	pyridine 1-oxide	ArNO/KOH	2	—	59G1843
$NH_2 \rightarrow \text{-}N{=}N\text{-}$[b]	Δ^1-pyrroline 1-oxide	$K_3Fe(CN)_6$ + NaOH	2	5,5-dimethyl	65J1224
$NHCH_2CO_2H \rightarrow$ sydnone	pyridine 1-oxide	HNO_2, then Ac_2O	3	—	60AA(137)71-O
$NH_2 \rightarrow NHCH_2CO_2H$	pyridine 1-oxide	$OCHCO_2Et/H_2$	3	—	60AA(137)71-O
$NHMe \rightarrow N(Me)CH_2CH_2CN$	benzodiazepine 4-oxide	$HCONMe_2/CH_3CN$/Triton B	2	—	62USP3051701

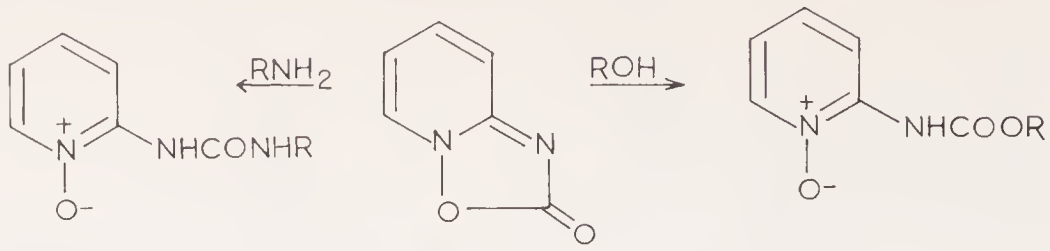
[a] 2-(2-Aminophenyl)pyridine 1-oxide.

[b] 2,2′-Azo- Δ^1, $\Delta^{1'}$-pyrroline 1,1′-dioxide is formed.

Table 4.15. Amino *N*-Oxides Prepared by Successive *N*-Oxidation and Hydrolysis of the Acylamino Heterocycles

Ring system	Acylamino group	*N*-Oxidizing reagent	Other substituents	Hydrolytic agent	References
Pyridine 1-oxide	2-acetamido	H_2O_2–AcOH	6-H and -Me	NaOH	54JA2785
	3-acetamido	H_2O_2–AcOH	H, 4-Me, 2,6-diMe	NaOH, H_2SO_4	60JO1716, 60JO2242, 63RC273
	4-acetamido	H_2O_2–AcOH	3-β-phenethyl	H_2SO_4	61JO418
	2,6-diacetamido	H_2O_2–AcOH	—	NaOH	54JA2785
	2-(*p*-acetamidobenzene-sulphonamido)	H_2O_2–AcOH	—	see note [a]	58JO67, 59USP2881166
	3- and 4-benzamido	H_2O_2–AcOH	—	NaOH	60T(9)194
	2-ethoxycarbonylamino	H_2O_2–AcOH	—	NaOEt-EtOH	57J191
	2-ethoxycarbonylamino	H_2O_2–AcOH	5-Me, 6-Me, 4,6-diMe	HCl	57J4385
	4-(*p*-ethoxybenzamido)	H_2O_2–AcOH	—	HCl	60J1511
Quinoline 1-oxide	2-acetamido	H_2O_2–AcOH	—	K_2CO_3	59JJ1063
	2-, 3-, 5-, and 6-acetamido	H_2O_2–AcOH	—	—	56AA(130)66-O
	4-diacetylamino	$PhCO_3H$	2- and 6-C_7H_{15}, 7-Cl	NaOH	56J3079
	2-ethoxycarbonylamino	H_2O_2–AcOH	—	HCl	57J4385
Isoquinoline 2-oxide	1-acetamido	H_2O_2–AcOH	—	HCl	59JJ1063
Pyrazine 1- and 4-oxide	2-acetamido	H_2O_2–AcOH	—	HCl	68KG725

[a] Acid (HCl) hydrolysis gives 2-aminopyridine 1-oxide, and basic hydrolysis yields the 2-(*p*-aminobenzenesulphonamido) analogue.



ii. Nitro Compounds

Of the remaining nitrogen-linked functional groups, by far the most important is the nitro group. Ochiai's discovery of the ready availability of 4-nitropyridine 1-oxide was perhaps the greatest single factor in opening up *N*-oxide chemistry. Many other nitro *N*-oxides are easily prepared by direct nitration (Sections III-3B and III-3C), and some can be obtained by oxidation of amino *N*-oxides (see Table 4.14). Reduction of nitro *N*-oxides can be accomplished in a variety of ways and nucleophilic replacement of the nitro group is also important synthetically.

a. Reduction. Many different products can be obtained by the reduction of nitro *N*-oxides. Catalytic reductions of *N*-oxides, including the nitro *N*-oxides, are listed in Table 3.07 and discussed in Section III-2B. Chemical reductions which lead to loss of the *N*-oxide function are treated in Sections III-2C to III-2G: the usual products are amino-heterocycles [which can, for example, be formed by catalytic reduction (Section III-2B) or dissolving metals (Section III-2F)] or nitro-heterocycles [which are produced by reduction with trivalent phosphorus compounds (Sections III-2Di–iv)], but azo-compounds and hydrazo-compounds have also been occasionally obtained (see Table 3.19).

Chemical reductions in which the *N*-oxide function is unaffected are recorded in Table 4.16, from which it is apparent that good selectivity can be obtained by use of the appropriate chemical reducing agents. Phenylhydrazine, and more recently photochemical reduction with ethanol, has been used for the preparation of hydroxyamino *N*-oxides. A mixture of zinc and acetic acid is often used as the reducing agent to obtain azoxy-bis *N*-oxides ($2NO_2 \rightarrow N{=}N^+\text{-}O^-$), whereas a wide variety of mild reducing agents can be used to prepare azo-bis *N*-oxides ($2NO_2 \rightarrow N{=}N$). Hydrazo-bis *N*-oxides have been obtained on reduction with hydrazine or stannous chloride ($2NO_2 \rightarrow NHNH$). Reduction of nitro *N*-oxides to amino *N*-oxides is usually achieved catalytically (see Table 3.07 and Section III-2B), but ammonium sulphide, stannous chloride, and hydrazine have also been utilized.

Comparative studies on the rate of reduction of 2,6-dimethyl-4-nitropyridine and its 1-oxide by ammonium sulphide, stannous chloride, etc., show that the presence of an *N*-oxide group decreases the rate of reduction of the nitro group (65RC709).

Table 4.16. Chemical Reduction of Nitro *N*-Oxides with Retention of the *N*-Oxide Function

Reduction product of nitro group	*N*-oxide[a]	Reducing agent	Position of nitro group reduced	Substituents unaffected[b]	Yield, %	References
-NHOH	pyridine	$PhNHNH_2$	4	—	(data)	63CT1084, 63AI19
	pyridine	ascorbic acid	4	—	—	69JJ67
	pyridine	*hv*–EtOH	4	—; 2- and 6-Me	—	66TL4729
	pyridine	$PhNHNH_2$	4	2-, 3-, and 2,6-di-Me	95–97	65AI17
	quinoline	biological[c]	4	see note[d]	—	62CT1221
	quinoline	$NaBH_4$	4	—	25	65CT1103
	quinoline	$PhNHNH_2$	4	—; Me (various)	(data)	63AI19, 67CT1
-NO=N-	pyridine	N_2H_4–Cu	4	—	—	58JJ248, 65CR51
	pyridine	Zn–AcOH	4	—	—	43JJ186
	pyridine	Zn–AcOH	4	2-Me	—	47JJ158
	pyridine	N_2H_4–Pt/C	4	3-Me	—	58CI1089
	pyridine	Zn–AcOH	4	3-Me	(data)	56CT174
	pyridine	Zn–AcOH	4	2,6-diMe	47	56CT174
	quinoline	$PhNHNH_2$	4	6-alkyl	(data)	69CT544
-N=N-	pyridine	liq. NH_3	4	—	"poor"	55JJ286
	pyridine	alc. NH_3	4	—	see note[e]	43JJ265
	pyridine	NH_4OH–H_2S	4	—	see note[f]	43JJ186
	pyridine	As_2O_3–NaOH	4	—	see note[g]	52R1145

[a] 1-Oxides unless otherwise indicated.
[b] Substituents, in addition to the *N*-oxide function, which are not affected.
[c] Reduction by microorganisms.
[d] 4-Aminoquinoline also obtained.
[e] Small amount of 4-aminopyridine 1-oxide formed.
[f] If reduction is carried in a "boiling solution," 4-aminopyridine 1-oxide is formed.
[g] Some 4,4′-azopyridine mono-*N*-oxide also formed.

Table 4.16. Chemical Reduction of Nitro *N*-Oxides with Retention of the *N*-Oxide Function—*continued*

Reduction product of nitro group	*N*-oxide[a]	Reducing agent	Position of nitro group reduced	Substituents unaffected[b]	Yield, %	References
-N=N-	pyridine	$PhCH_2NH^2$	4	—	—	43JJ265
cont'd.	pyridine	electrons[h]	4	—	—	45JJ429
	pyridine	liq. NH_3 + NH_4Cl	4	2-Me	"poor"	55JJ286
	pyridine	N_2H_4–Cu	4	2-Me	—	58JJ248, 58JJ1194, 65CR51
	pyridine	NH_4OH–H_2S	4	2- and 3-Me	— and 75	47JJ158, 56CT174
	pyridine	$SnCl_2$–HCl or –NaOH	4	2-Me	see note[i]	47JJ158, 52R1145
	pyridine	Zn–AcOH	4	2-Me	—	47JJ158
	pyridine	$NaNO_2$–NaOH	4	3- and 2,6-di-Me	(data)	56CT174
	pyridine	NH_4OH–H_2S	4	2,6-diMe	48[j]	56CT174
	pyridine	$NaBH_4$	4	2,6-diMe	—	62JO1665
-NHNH-	pyridine	N_2H_4–liq. NH_3	4	—	(data)	55JJ286
	pyridine	$SnCl_2$–HCl	4	—	—	43JJ186
	quinoline	$(NH_4)_2S$	4	—	—	43PJ574, 44JJ206

[h] Electrolytic reduction.
[i] 4-Amino-2-picoline also formed when reduction is effected by $SnCl_2$-HCl.
[j] Small amount of 4-aminolutidine also formed.

Table 4.16. Chemical Reduction of Nitro *N*-Oxides with Retention of the *N*-Oxide Function—*continued*

Reduction product of nitro group	*N*-oxide[a]	Reducing agent	Position of nitro group reduced	Substituents unaffected[b]	Yield, %	References
-NHNH-, *cont'd.*	quinoline	$N_2H_4 \cdot H_2O$–Cu	4	2-H and -Me	(data)	60JJ1573
	quinoline	$SnCl_2$–HCl	4	—	—	43PJ574, 44JJ206
	quinoline	Zn–AcOH	4	—	—	43PJ574, 44JJ206
$-NH_2$	pyridine	NH_3–H_2S	4	—	see note[k]	43JJ186
	pyridine	N_2H_4–Cu	4[l]	—	—	58JJ248, 65CR51
	pyridine	N_2H_4	4	2-H or -Me	—	58JJ248
	quinoline	biological[c]	4	—	see note[m]	62CT1221
	quinoline	$(NH_4)_2S$	4	—	—	44JJ206
	benzo[*c*]cinnoline[o]	$N_2H_4 \cdot H_2O$–Ni(R)[n]	5	—	68	62J2454
	quinoline	$Na_2S_2O_4$	4	—	—	43PJ574, 44JJ206
	quinoline	$SnCl_2$	3	4-OH-2-Me	see note[d]	21CB1067
	quinoline	Fe	4	2-Ph	—	65JJ66
	phenanthridine	$SnCl_2$–HCl	3(?) and 7	9-H and -aryl	42–54	50J703

[k] If reaction is carried out at low temperatures, 4,4′-azopyridine 1,1′-dioxide is formed.
[l] The intermediate azoxy 1,1′-dioxide can be isolated.
[m] 4-Hydroxyaminoquinoline 1-oxide and 4-aminoquinoline also formed.
[n] Raney nickel.
[o] Benzo[*c*]cinnoline 1-oxide.

b. Nucleophilic Replacement of the Nitro Group in Nitro N-*Oxides.* The nitrite anion is a good leaving group from sp^2-hybridized carbon atoms: it is superior to a chloride ion by a factor of ca. 1000 [66J(B)1058]. Since the first experiments by Ochiai in the early 1940's, a great many examples of the nucleophilic replacement of nitro groups *alpha* or *gamma* to an *N*-oxide function have been reported. However, attempts to effect replacement of the nitro group in 3-nitropyridine 1-oxides have failed [45JJ(3A)6; 60JO1716], and although nitro groups *beta* to the *N*-oxide function in nitropyridazine *N*-oxides undergo replacement (63CT342), these are activated by the second heterocyclic nitrogen atom. In most cases, 5- and 6-nitroquinoline 1-oxide are also unreactive (51JJ297), but the 2-nitro group in the phenazine 10-oxide *244* is replaced by an ethoxyl group on refluxing with sodium ethoxide (56CT117).

Reactions involving nucleophilic replacement of a nitro group in nitro *N*-oxides with retention of the *N*-oxide function are collected in Table 4.17; in many other nucleophilic replacement reactions, simultaneous reduction of the *N*-oxide group occurs, as is described in Sections III-2D to III-2F. Nucleophilic replacement reactions with halogeno-nitropyridine 1-oxides, in which either the nitro group or the halogen atom is replaced, are discussed in Section IV-3Aii.

Many of the reaction conditions involve acid catalysis: addition of a proton or another electrophile at the *N*-oxide oxygen atom enhances the reaction rate. Table 4.17 gives examples of the replacement of nitro groups by bromo (reagent: hydrogen bromide or acetyl bromide), chloro (hydrogen chloride or acetyl chloride), hydroxy (various reagents: if acid anhydrides are used the product is a 1-acyloxy-4-oxo compound), alkoxy (alkoxide ion), and amino groups (amines). An interesting recently reported example is the replacement of a nitro group by hydride ions (H^- from $NaBH_4$) (65CT1103). These nucleophilic replacements of nitro groups are of great synthetic importance.

Johnson [66J(B)1058] has carried out a kinetic investigation of the displacement of nitro groups in mono-nitropyridine 1-oxides by ethoxide ions; the entropies and energies of activation both decrease in the order $2 > 4 > 3$, but the influence of the entropy term is such that the rates at 20° also decrease in the same order ($2 > 4 > 3$). He has reported a similar study on the displacement with piperidine [66J(B)1062]. Semiquantitative measurements indicate that 4-nitropyridine 1-oxide is more susceptible to nucleophilic displacement than 4-nitropyridine (47JJ56). The kinetics of the nucleophilic replacement of a 4-nitro group in various quinoline 1-oxides have also been measured (63CT785): displacement rates are faster than for 4-nitropyridine 1-oxide and for 4-nitroquinoline. The rates of nucleophilic attack by ethoxide ions on substituted 4-nitroquinoline 1-oxides have been correlated with *sigma* constants and also with their carcinogenic activity (69CT987). Comparison of the reactions in both the pyridine 1-oxide (47JJ61) and quinoline

Table 4.17. Nucleophilic Replacement of a Nitro Group with Retention of the *N*-Oxide Function

Group replacing nitro group	*N*-Oxide[a]	Reagent	Position of nitro group replaced	Substituents unaffected	Yield, %	References
H	quinoline	$NaBH_4$	4	—	9	65CT1103
Br	pyridine	HBr–AcOH; HBr	4	—	70–80	51R581, 56JO1077
	pyridine	AcBr	4	3-CO_2H	—	63CB266
	pyridine	AcBr	4	2,5-diMe	95	67R655
	pyridine	AcBr	4	2,6-diMe	—	65RC1045
	pyridine	48% HBr	4	2-Me	ca. 63	48JJ126, 59PC(9)164
	pyridine	(?)	4	3-Me	—	55JJ292
	quinoline	30% HBr, $POBr_3$	4	—	ca. 60	51JJ297, 56JJ1337
	quinoline	48% HBr	4	6-Me	67	59WZ93
Cl	pyridine	AcCl, HCl, $POCl_3$	4	see note[b]	57–80	44PJ141, 45JJ70, 47JJ56, 51R581, 56J2404, 60TU24
	pyridine	AcCl, HCl	4	2-alkyl	ca. 70	48JJ126, 59WZ187, 60JJ339, 60PC(11)22, 65J2096
	pyridine	AcCl	4	3-alkyl (various)	ca. 75	55JJ292, 56JA214, 60J4953
	pyridine	AcCl, HCl–MeOH	4	3-CO_2H[c]	—	56JA214, 63CB266
	pyridine	AcCl, HCl, $POCl_3$	4	2,6- and 3,5-diMe	82–85	45JJ6, 60J4953, 62JO1665, 65RC1045
	pyridine	AcCl, HCl	4	2,3,6-tri- and 2,3,5,6-tetra-Me	61–92	59J1312, 60J4953

[a] These compounds are 1-oxides unless otherwise indicated.
[b] With $POCl_3$, 2,4-dichloropyridine is also formed (45JJ70).
[c] 3-Carboxy → 3-methoxycarbonyl.

Table 4.17. Nucleophilic Replacement of a Nitro Group with Retention of the *N*-Oxide Function—*continued*

Group replacing nitro group	*N*-Oxide[a]	Reagent	Position of nitro group replaced	Substituents unaffected	Yield, %	References
Cl, *cont'd.*	pyridine	HCl	4	2-CO_2H	—	59CB155
	pyridine	HCl	4	2-CN[d]	76	61RC463
	pyridine	HCl	4	2-Me	70	60PC(11)22
	2,2′-bipyridyl	HCl	4,4′	—	—	55JJ733
	2,2′-biquinolyl	AcCl	4,4′	—	—	66JH170
	quinoline	AcCl, HCl	4	2-Me	—	59EGP16921, 57CM388, 61ZC84, 63JJ348
	quinoline	AcCl	4	2-Ph	—	65JJ66
	quinoline	AcCl	4	2-Br[r]	63 (77)	68JJ656
	quinoline	HCl, $POCl_3$	4	—	ca. 95[e]	45JJ70, 51JJ297
	quinoline	HCl	4	6-CO_2H	58	60JJ339
	quinoline	HCl	4	Cl and Me (various)	—	67CT1
	quinoline	HCl	4	6-Me	91	59WZ93, 60AF1029
	quinoline	HCl	4	2-(*p*-MeO-C_6H_4)CH=CH	70	62PC(18)175
	quinoline	20% HCl	4	2-Me-8-NO_2	63	51JJ1078
	quinoline	HCl	4	6-NO_2	52	51JJ297
	quinoline	HCl	4	5-NO_2-6-substituted	54–78	51JJ297
	pyridazine	AcCl	3 and 4	—	65–80	63CT83, 63CT342
	pyridazine	AcCl, BzCl	4	3-OMe[f]	—	66JJ314
	pyridazine	AcCl, HCl	5	6-OMe-3-Me	—	63CT29
	pyridazine	AcCl, HCl	5	3- and 3,6-di-Me	see note[g]	63CT29, 63CT1511, 64CT228

[d] Hydrolyzed to the corresponding 2-carboxylic acid.
[e] 2,4-Dichloro- and 4-chloro-2-hydroxy-quinoline reported to be formed also (45JJ70).
[f] 6-Methoxy → 6-oxo and 1-oxide → 1-acetoxy or 1-benzoyloxy.
[g] 4-Chloro-3,6-dimethylquinoline 1-oxide (12%) and 4-chloro-3-methylquinoline-6-carboxaldehyde oxime (38%) also reported to be formed (63CT1511).

Table 4.17. Nucleophilic Replacement of a Nitro Group with Retention of the *N*-Oxide Function—*continued*

Group replacing nitro group	*N*-Oxide[a]	Reagent	Position of nitro group replaced	Substituents unaffected	Yield, %	References
Cl, *cont'd.*	cinnoline	HCl	4	3-OMe	—	63CT1527
	cinnoline	HCl	4	5-NO_2	94	64CT1090
	o-phenanthroline	PCl_3	4	—	64	65JO288
OH	2,2′-bipyridyl	30% H_2SO_4	4,4′	—	—	55JJ733
	pyridine	15% NaOH,[h] NaOH–H_2O_2, HCl[i]	4	—	—	51R581, 52R745
	pyridine	(?)	4	3-Me	—	55JJ292
	quinoline	Ac_2O, 40% H_2SO_4	4	—	ca. 70[j]	51JJ297, 57CT56
	quinoline	40% H_2SO_4	4	3- and 6-Br and -Cl	ca. 56	51JJ213, 51JJ297
	quinoline	40% H_2SO_4	4	6-Br-5-NO_2	37	51JJ297
	quinoline	40% H_2SO_4	4	2-Me	64	51JJ297
	quinoline	40% H_2SO_4	4	8-NO_2	44	51JJ297
	quinoline	NaOH	4	2-CO_2H	57	61PC(13)58
	acridine	H^+	9	—	—	60J3367
	pyridazine	Ac_2O	4	—	—	65JJ344
	imidazole[j]	H_2O	4	2-substituted	see note[k]	58LA(615)108
O-Alkyl	pyridine	NaOR,[l] R′OH,[m] NaOR–ROH[n]	4	—	23–70	43JJ265, 45JJ(5/6A)1, 47JJ61, 48JJ139, 51R581

[h] 4,4′-Azopyridine also formed; formation of azo compounds not observed if hydrogen peroxide present.

[i] 3-Chloro-4-hydroxypyridine 1-oxide (20%) also formed.

[j] With acetic anhydride, 4-hydroxyquinoline 1-oxide (6 parts), *N*-acetoxy-3-nitro-4-quinoline betaine (3 parts), and 4-hydroxy-3-nitroquinoline (1 part) also formed.

[k] Imidazole 3-oxide; 4,4′-dinitroglycosine 3,3′-dioxide.

[l] R = methyl, ethyl, butyl, and diethylaminopropyl.

[m] R′ = isopropyl, piperidino.

[n] With PhOH-MeOH, 2 parts 4-methoxy and 1 part 4-phenoxy obtained (47JJ61). With NaOPh-EtOH, 4-phenoxy is major product and 4-ethoxy minor product (48JJ139). With NaOBu-EtOH, 4-butoxy is major product and 4-ethoxy minor product (48JJ139).

Table 4.17. Nucleophilic Replacement of a Nitro Group with Retention of the *N*-Oxide Function—*continued*

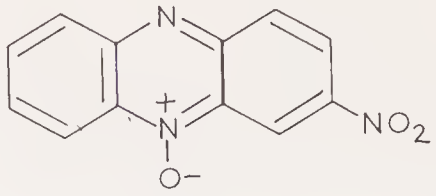
Group replacing nitro group	*N*-Oxide[a]	Reagent	Position of nitro group replaced	Substituents unaffected	Yield, %	References
O-Alkyl, *cont'd.*	pyridine	NaOR (various)	4	2-CO_2H	43–92	61PC(13)58
	pyridine	$NaOCH_2Ph$, NaOMe	4	3-CO_2H	77–81	56JA214, 60JA3141, 63CB266
	pyridine	$NaOCH_2Ph$, NaOMe	4	2-Me	80	58CB2194, 60JJ875
	pyridine	$NaOCH_2Ph$	4	3-Me	—	55JJ292
	2,2′-bipyridyl	NaOEt	4	—	65	58JA2745
	pyridine	NaOEt, NaOMe	4	2,6-diMe	—	45JJ6, 51JJ156
	pyridine	NaOMe	4	2,5-dialkyl	—	60JJ875
	pyridine	NaOMe	4	2- and 3-halogeno	—	61RC475, 62RC1465
	quinoline	NaOEt, NaOMe	4,5, and 6	—	—	43JJ280, 45JJ8, 51JJ297
	quinoline	NaOMe	5	3-Br	—	51JJ297
	2,2′-biquinolyl	NaOMe	4,4′	—	—	66JH170
	pyridazine	NaOMe	3 and 4	H and 3,6-diOMe	(data)	62CT643, 62JJ253, 63CT342, 66JJ1124
	pyridazine	NaOMe	4	3,6-di-OMe and -Me	(data)	60CT368, 64CT228
	pyridazine	NaOMe	6	3-OMe-4-Me	—	62JJ1005
	pyridazine	NaOMe	4 and 5	3-OMe and -Me	(data)	62JJ253, 63CT29, 64CT228
	pyridazine	NaOMe	4	6-Me	(data)	62JJ253
	pyridazine	NaOMe	4	3,6-diOMe	—	68CT1221
	cinnoline	NaOMe	3	—	ca. 95	63CT268, 64CT1090
	cinnoline	NaOMe	4	3-OMe	—	63CT1527

Table 4.17. Nucleophilic Replacement of a Nitro Group with Retention of the *N*-Oxide Function—*continued*

Group replacing nitro group	*N*-Oxide[a]	Reagent	Position of nitro group replaced	Substituents unaffected	Yield, %	References
O-Alkyl, *cont'd.*	phenazine[o]	NaOEt, NaOMe, KOEt	3	—	see note[o]	56CT117, 61JJ861
O-Allyl	pyridine	CH_2=CH-CH_2ONa	4	—	73	66CB368
O-Aryl	pyridine	$NaOCH_2Ph$	4	3-CO_2H	—	63CB266
	2,2′-bipyridyl	$NaOCH_2Ph$	4,4′	—	—	55JJ733
	pyridine	NaOPh, PhOH-ROH[n]	4	—	—	43JJ265
	pyridine	NaO-C_6H_4-CH_3(*p*)	4	2-CO_2H	20	61PC(13)58
S-Alkyl	quinoline	see note[p], NaH + RSH	4	—	—	53JJ946, 66JO939
	quinoline	$NaSCH_2CH(NH_2)CO_2H$	4	—	—	68JJ665
S-Linked	quinoline	thiamine	4	—	—	68JJ1103
S-Aryl	pyridine	Na-S-aryl	4	—	65	44PJ141
	2,2′-bipyridyl	Na-S-aryl	4	—	36	67J(B)106
	quinoline	Na-S-aryl	4	—	—	45JJ(9/10A)8
SH	quinoline	thioglycolic acid	4	H, 7-Cl, 2-Me, 6- and 8-NO_2	70–80	63CT785
-NHOH	pyridine	$(NH_4)_2S$	4	3-CO_2H	52	60JA3141
$-NHNH_2$	pyridine	N_2H_4	4	3-CO_2H	22[q]	60JA3141
-NHPh	pyridine	$PhNH_2$	4	3-CO_2H	—	64AJ1399
piperidino	pyridine	$C_5H_{11}N$ + *hν*	4	—	—	64P213
	quinoline	$C_5H_{11}N$	4	—	—	45JJ(9/10A)8
morpholino	pyridine	C_4H_9NO	4	—	"poor"	44PJ141
	quinoline	C_4H_9NO	4	—	—	45JJ(9/10A)8

[o] Phenazine 5-oxide. With NaOMe yield is 50%; with NaOEt yield is "poor."
[p] Cysteine or $HSCH_2CO_2Na$ at pH 7.2.
[q] 4-Aminonicotinic acid 1-oxide (7%) also formed.
[r] 2-Br(Cl) → 2-oxo.

1-oxide series (48JJ139) indicates that the replacement of a nitro group by small alkoxyl groups is easier than replacement by larger groups.



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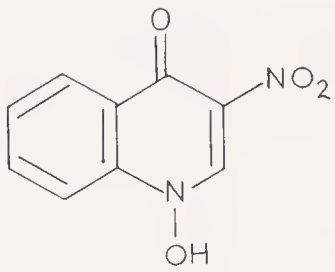

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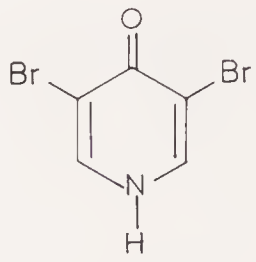

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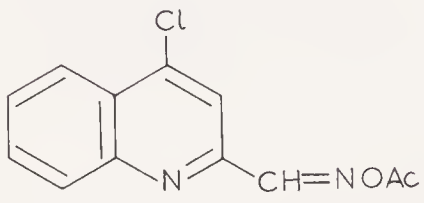

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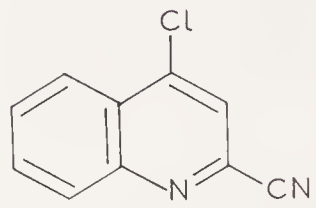

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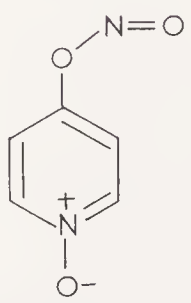


(249)

The nitrous acid formed in these nucleophilic replacement reactions, unless it is removed, sometimes reacts with the products. Thus, 4-nitroquinoline 1-oxide and acetic anhydride yield 1-hydroxy-3-nitro-4-quinolone (*245*) and its 1-acetoxy analogue, but if dimethylaniline is added to the reaction mixture, it traps the nitrous acid, and only 1-hydroxy-4-quinolone is formed (52JJ767). At high temperatures, 4-nitropyridine 1-oxide reacts with hydrobromic acid to give 3-mono- and 3,5-di-bromo-4-pyridone (*246*) as by-products by successive hydrolysis, reduction, and bromination (51JJ591). With acetyl chloride, 2-methyl-4-nitroquinoline 1-oxide yields the 2-oxime *247* and the 2-nitrile *248* by reaction of the acetyl nitrile with the α-methyl group (cf. Section IV-2Biiid). 2-Chloro-4-nitroquinoline 1-oxide reacts with

acetyl chloride to give, after treatment with sodium bicarbonate, 1-acetoxy-4-chloro-2-quinolone (68JJ656).

Recently, it has been reported that replacement of the nitro group in 4-nitropyridine 1-oxide by piperidine is strongly catalysed by light [64P213; 67J(B)15], and there is evidence that free-radical replacement of the nitro group is easy (68JJ1487).

c. Other Reactions of Nitro N-*Oxides.* Irradiation of 4-nitropyridine 1-oxides in hydroxylic solvents in the presence of oxygen yields 4-hydroxypyridine 1-oxides: the reaction is considered to involve photoisomerization to a nitrite intermediate (*249*) (67CT356). In the absence of oxygen, 4-hydroxyaminopyridine 1-oxides are also formed with unhindered compounds (for references see Table 4.16). Later work indicates that both these processes may proceed by a common intermediate (68BJ1769). If 4-nitroquinoline 1-oxides are irradiated 4-hydroxy-2-quinolones are obtained (67TL775). Free radical formation during irradiation of 4-nitroquinoline 1-oxides is discussed in Section III-5Bii.

An attempt to carry out the von Richter reaction with 4-nitropyridine 1-oxide failed (56JO934). According to the available abstract, the reaction of ammonia with 4-nitroquinoline 1-oxide yields the "8-nitro analogue", a highly improbable end-product (54JJ699).

iii. Other Nitrogen-linked Functional Groups

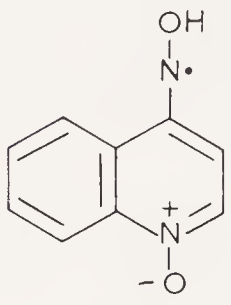
The methods of preparation and the reactions of hydrazino, hydroxyamino, nitroso, azido, azoxy, azo, and hydrazo *N*-oxides resemble those of the correspondingly substituted heterocycles.

a. Hydrazino N-*Oxides.* Hydrazino *N*-oxides are converted by nitrous acid into azido compounds (61JJ1743; see also references quoted for azido compounds in Section IV-3Ciiid). Hydrazino *N*-oxides also react readily with carbonyl compounds to form hydrazones, and with β-dicarbonyl compounds to give pyrazoles (see, e.g., references 57RC847 and 63CT1059).

b. Hydroxyamino N-*Oxides.* 4-Hydroxyaminopyridine 1-oxide can be reduced to 4-aminopyridine 1-oxide, and oxidized by permanganate to the 4-nitroso *N*-oxide or by peracetic acid to the 4-azoxypyridine 1-oxide; self-condensation in the presence of potassium hydroxide gives 4-azopyridine 1-oxide (60G903). Reduction to 4-aminopyridine is also possible (60JA3141) and has been accomplished catalytically (see Section III-2B). 4-Hydroxyamino-2,6-dimethylpyridine 1-oxide can be converted into the corresponding azo- and azoxy-bis *N*-oxides (62CC2146); Italian workers have carried out the same transformations and have also oxidized the compound to the 4-nitroso analogue (62G1138). Ochiai and Mitarashi have reported similar reactions for several substituted 4-hydroxyaminopyridine 1-oxides and for 3-hydroxyaminoquinoline 1-oxide (65AI17). 4-Hydroxyaminoquinoline 1-oxide undergoes analogous transformations (61JJ1743; 65JJ69); in addition,

this compound is converted by mild oxidation into a stable free radical (66AG323) which probably has the structure *250*, based on ESR measurements on isotopically labelled species (67BJ62). Free radical production is inhibited by ascorbic acid (67CT220). For the colorimetric estimation of 4-hydroxyaminoquinoline 1-oxide, see reference 64CT262. 6-Hydroxyaminopurine 3-oxide reacts with ammonia to yield the azoxy derivative (69MC717).*

c. Nitroso N-*Oxides.* 4-Nitrosopyridine 1-oxide shows reactions typical of the nitroso group (67G1569). In the pyrimidine *N*-oxide series, nitroso groups can be reduced to amino groups with sodium dithionite ($Na_2S_2O_4$) (65JO408); for other reactions, see reference 67JO3689.



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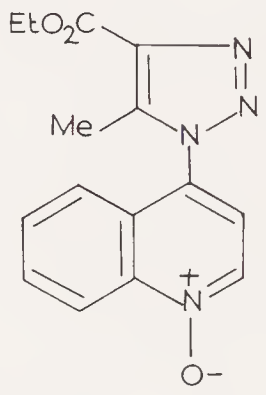


(251)

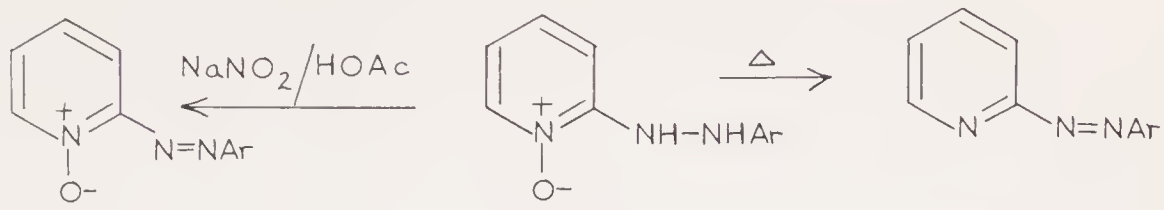
d. Azido N-*Oxides.* The reactions of 2- and 4-azido-pyridine and -quinoline 1-oxides have been studied by Itai and Kamiya (61CT87; 62CT471; 62CT669). On photolysis they yield nitrogen and the corresponding azo compounds; in an oxygen-containing atmosphere, azoxy derivatives are also formed. Nucleophilic displacement of the azido group by methoxyl or hydroxyl groups occurs readily. The azido group also reacts with several active methylene compounds to yield the corresponding amino *N*-oxide by nitrogen elimination and hydrogen abstraction: with acetoacetic ester, however, the triazole derivative *251* is formed.

Itai and Kamiya have also studied 3- and 6-azido- (63CT348) and 4- and 5-azido-pyridazine 1-oxide (63CT1059). These derivatives display reactions similar to those of their pyridine analogues. For parallel work on 3-azidoquinoline 1-oxides, see reference 61JJ1743.

e. Azoxy, Azo, and Hydrazo N-*Oxides.* Azoxy *N*-oxides may be converted successively into azo and hydrazo *N*-oxides by catalytic reduction: these reactions are included in Table 3.07 and discussed in Section III-2B. Arylhydrazino *N*-oxides (cf. *252*) are readily reoxidized to arylazo *N*-oxides (*253*) (55G1148; 55G1508). Heating arylhydrazinopyridine *N*-oxides (*252*) causes elimination of water to give the corresponding azopyridine (*254*) (56G705). Phenylazo derivatives (*253*, Ar = Ph) react with hydrogen bromide in an oxidation–reduction reaction to yield (bromophenyl)hydrazino-

* See addendum in the Appendix.

pyridine 1-oxides (55G1508). For rearrangements of azopyrroline 1-oxides, see reference 66J(C)382.*



(253) (252) (254)

D. SULPHUR-LINKED FUNCTIONAL GROUPS

α- and γ-Mercapto *N*-oxides are tautomeric with *N*-hydroxy α- and γ-thiones, and the available evidence indicates that these compounds all exist mainly in the thione form. As expected, most of their chemical reactions involve electrophilic attack at the sulphur atom. *N*-Hydroxy thiones are usually prepared by nucleophilic displacement reactions on the corresponding halogeno compounds (Section IV-3Ai), frequently via thiouronium salts (Section IV-3Div).

Alkylthio *N*-oxides, which are readily available by nucleophilic displacement reactions (Section IV-3Ai), are converted by the usual oxidative methods into sulphoxides and sulphones. Sulpho *N*-oxides show many of the reactions typical of sulphonic acids, but some of the derived sulphonamides undergo interesting rearrangements.

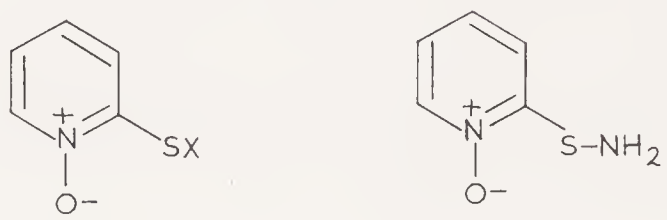
i. N-*Hydroxy Thiones* (*Mercapto* N-*Oxides*)

The tautomerism of *N*-hydroxy thiones with α- and γ-mercapto *N*-oxides (cf. *255* ⇌ *256*) has been the subject of some controversy, although it is now clear that the thione forms predominate. The mercapto form was originally considered to be preferred in the pyridine series (50JA4362), but it has been shown by Jones and Katritzky, using ultraviolet spectroscopy and p*K* measurements, that the 1-hydroxypyridine-2- and -4-thione forms predominate (by relatively small factors) in aqueous solution (60J2937; cf. 67TT745). It was later claimed that infrared spectral data indicated predominance of the mercapto form (62JO304), but this claim was subsequently withdrawn (62JO4718). The tautomeric equilibrium for mercaptopyridines lies much further to the side of the pyridine-thiones than does that for the corresponding *N*-oxides. This difference is plausible for exactly the same reasons as those discussed in Section IV-3Bia for the oxygen analogues. 9-Mercaptoacridine 10-oxide has been shown by physical methods to coexist with a comparable amount of 10-hydroxythioacridone (66T3227; [68RR1511).

* Imino *N*-oxides; see addendum in the Appendix.

(255) (256)

1-Hydroxypyridine-2-thione is alkylated (60USP2922793; 60USP2932647; 62JO304), acylated (60USP2922792; cf. 56USP2758116), sulphenylated (60USP2922790), phosphonylated (60USP2922791), ethoxycarbonylmethylated (65PP659), and thiocarbamoylated (60USP2940978) on the sulphur atom to give derivatives of type *257*. However, with acetobromoglucose, a mixture of *S*- and O-derivatives is obtained (69R241). It is a fairly strong acid (pK_a 4.67) and forms many salts (56USP2742393). *N*-Hydroxy α-thiones are chelating agents and form stable complexes with metal ions (64AC2485; 64JN1277); certain of these complexes show fungicidal activity (62USP-3027371). The bacteriocidal activity of 1-hydroxypyridine-2-thione is probably also due to its chelating ability (56J3684). 9-Mercaptoacridine 10-oxide also undergoes *S*-alkylation (68RR1511).*



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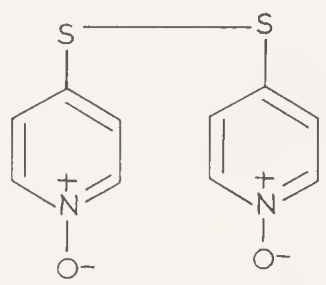


(259)

1-Hydroxypyridine-4-thione is oxidized by chlorine in good yield to 4-chlorosulphonylpyridine 1-oxide (55CT38; 60AQ395); the 2-thione reacts similarly (65PP659). With chloroamine, 1-hydroxypyridine-2-thione yields the sulphenamide *258* (65IC1716). *N*-Hydroxy thiones are readily oxidized to disulphide di-*N*-oxides; thus, compound *259* can be prepared by treatment of 1-hydroxypyridine-4-thione with hydrogen peroxide (49JJ542). 6-Amino-1-hydroxypurine-2-thione yields the sulphonic acid on oxidation by hydrogen peroxide, and the methylthio derivative on methylation (67JO1151).

Several 6-mercaptopurine 3-oxides are converted into the corresponding 6-halogenopurine 3-oxide by treatment with chlorine or bromine: these

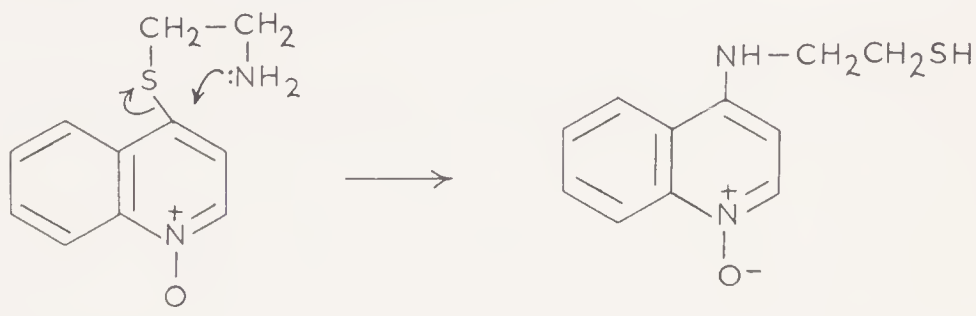
* See addendum in the Appendix.

reactions presumably involve initial oxidation and nucleophilic displacement of the sulphur function (69JO2157). For other reactions of *N*-hydroxypurine thiones, see reference 65ME1900.*

ii. Alkyl- and Aryl-thio Compounds, Sulphinyl and Sulphonyl Groups

Alkylthio [60PC(11)22; 61JJ612] and arylthio *N*-oxides (60JJ1145) are readily oxidized to the corresponding sulphonyl compounds (cf. 68CT1390). 2-Benzylthiopyridine 1-oxide on treatment with perbenzoic acid is converted successively into the corresponding sulphinyl and sulphonyl compounds [66LA(695)77]. 4-Phenylthioquinoline 1-oxide undergoes nucleophilic displacement of the thiophenate group with amines [45JJ(9/10A)8]. Intramolecular nucleophilic replacements of *S*-alkyl groups of type *260* → *261* have been studied by Hamana and Kumada (68JJ665), and some intermolecular analogues were also reported (68JJ672).

Sulphonyl and sulphinyl groups can undergo nucleophilic substitution. Thus, in the quinoline 1-oxide (68CT1390), quinoxaline *N*-oxide (57J3236), and furoxan series (64J904), the alkylsulphonyl group can be displaced by hydroxide ions: the sequence *262* → *264* illustrates the good leaving ability of the methylsulphinyl group (63JO2560). 4-Methylsulphonylquinoline 1-oxide is also converted into the 4-hydroxy analogue under acid-catalysed conditions by 40% sulphuric acid, and undergoes nucleophilic displacement with hydrazine and other nitrogen nucleophiles (68CT1390). The methylsulphonyl group has been utilized in nucleophilic displacement reactions in the purine 3-oxide series (69BJ750).



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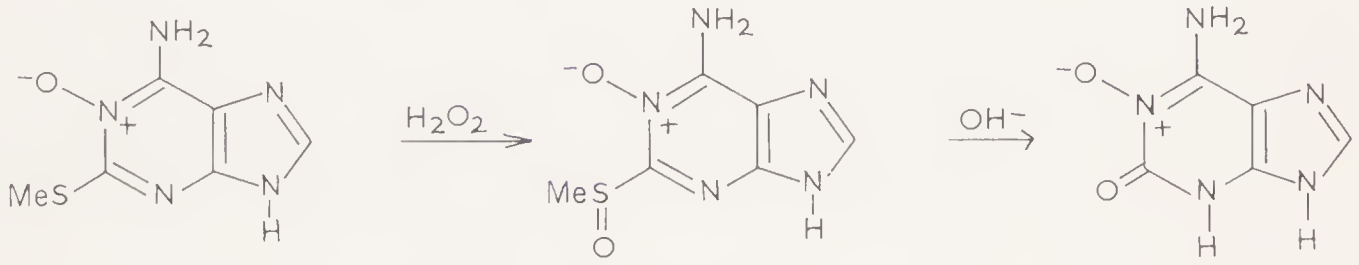


(262) (263) (264)

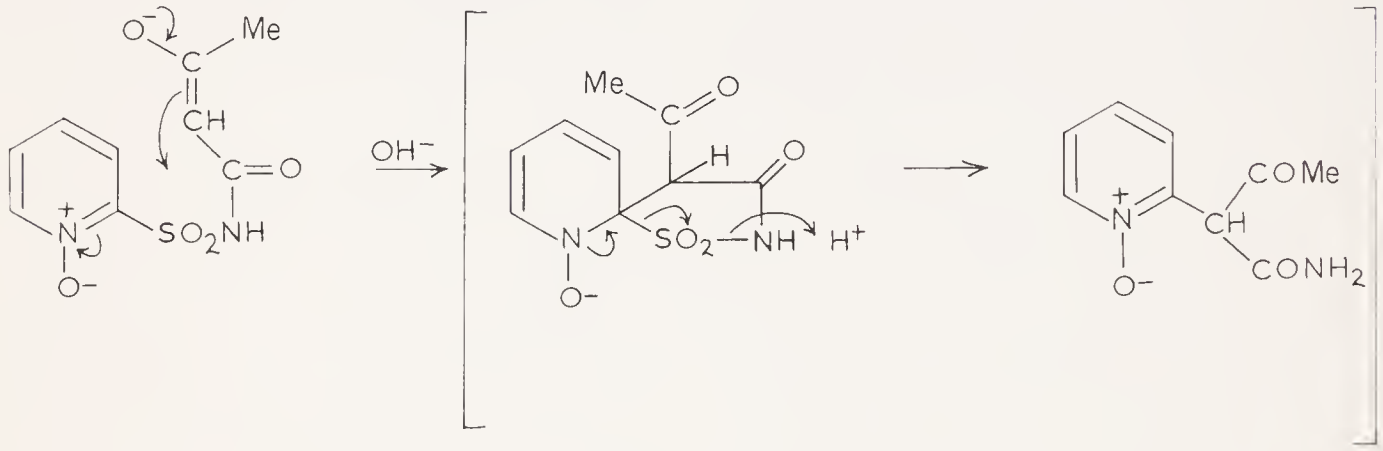
Attempts to effect rearrangement of 2- and 4-benzylthiopyridine 1-oxide to the analogous 1-benzyloxypyridine-thiones have failed (60J2937), which is in contrast to the successful rearrangement of the benzyloxy analogues (Section IV-3Biiib).

* See addendum in the Appendix.

iii. Sulpho and Aminosulphonyl Groups

The *N*-oxides of 2-, 3-, and 4-pyridinesulphonic acid are stable compounds: no evidence was found for rearrangement of the 4-isomer to the 3-derivative at 250° in oleum with added mercuric sulphate (cf. Section III-3Eii) (62JO-1329; cf. 58CI1559). The 1-oxide of sodium 4-pyridylsulphonate and its substituted derivatives give 4-cyanopyridine 1-oxides on fusion with potassium cyanide (61JJ917), and can also be converted by conventional methods into chlorosulphonylpyridine 1-oxides, which with amines and hydrazines yield the corresponding sulphonamides and sulphonylhydrazides (55CT38; 60AQ395). In the purine 3-oxide series, a 6-sulphonate group (—SO_3Na) has been displaced by hydroxylamine to yield 6-hydroxyaminopurine 3-oxide although other attempted nucleophilic replacements failed (69MC717). Analogous displacements with ammonia, hydroxide ion, and methoxide ion also succeeded (69JO2153).

N-Acylated-2- and -4-sulphonamidopyridine 1-oxides with an active methylene group adjacent to the carbonyl group rearrange under alkaline conditions: *265* → *268*, *269* (55CT38). The reaction proceeds as far as 2-carboxymethylpyridine 1-oxide (*269*) on heating, but the intermediate pyridino-isoxazolone (*268*) can be isolated at low temperatures (64CT595). *N*-Oxides with a side chain of the type -$SO_2NHCOCH_2Ph$ react similarly (64CT588), and the reaction has been studied kinetically (64CT601).



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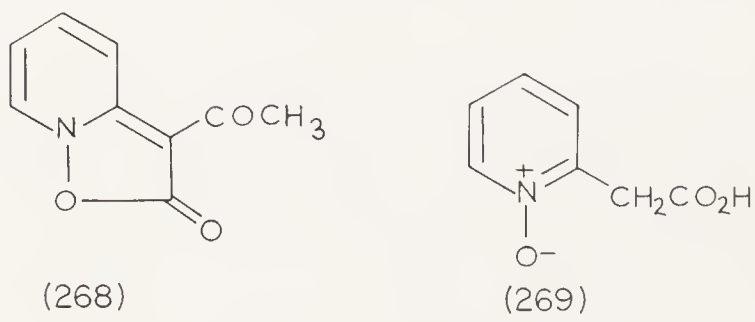
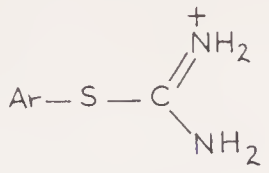


(268) (269)

iv. Other Sulphur-linked Functional Groups

The *N*-oxides of pyridyl- and quinolyl-isothiouronium salts (cf. *270*) have been used as intermediates for the preparation of *N*-hydroxy thiones; the latter compounds are readily formed by hydrolysis of the isothiouronium salts (49JJ542; 50JA4362; 60JO850); see also Section IV-3Ai.

Thiocyanato groups attached to heterocyclic *N*-oxides (cf. *271*) can be converted into mercapto, methylthio, and sulphide groups by standard reactions (61JJ1151). The sulphenamide *N*-oxide *258* reacts with pyridine-2-aldehyde to form *272*; both *258* and *271* form complexes with metal ions (65IC1716).



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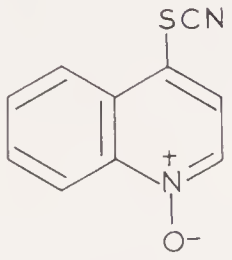

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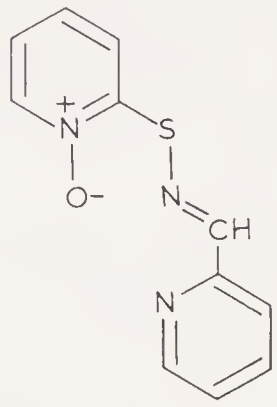


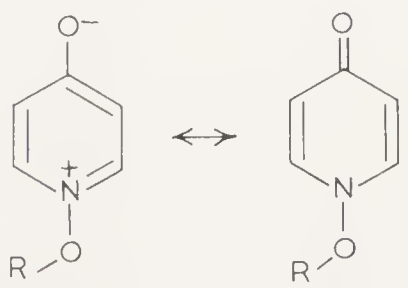
(272)

E. OTHER FUNCTIONAL GROUPS ATTACHED TO RING CARBON ATOMS

Chloromercuripyridine 1-oxides are converted into bromopyridine 1-oxides on treatment with bromine (58R340); similar reactions are known for the quinoline analogues (55JJ490).

4. Substituents Attached to an *N*-Oxide Oxygen Atom

Compounds containing substituents attached to an *N*-oxide oxygen atom are, strictly speaking, derivatives of *N*-hydroxy cations rather than of the *N*-oxides themselves. These compounds can be subdivided into two classes: cationic compounds, and those in which another substituent in the formal *N*-(substituent-oxy) cation carries a negative charge, thereby often giving rise to neutral molecules (cf. *273* ↔ *274*). Of the *N*-(substituent-oxy) cations, the *N*-alkoxy derivatives are the only important compounds. Many other derivatives are mentioned in passing in the sections dealing with electrophilic attack at an *N*-oxide oxygen atom (Sections III-1B, III-1C).



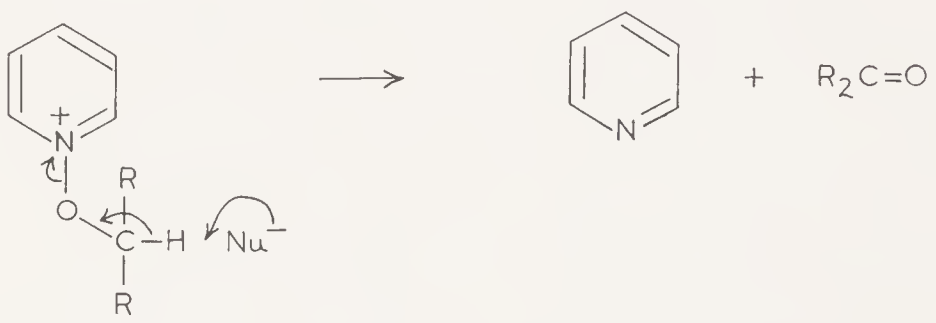
(273) (274)

A. *N*-ALKOXY CATIONS

Nucleophiles can react at the alkoxy group of *N*-alkoxy cations in either of two ways: to give a carbonyl compound and the deoxygenated base (*275* → *276*), or to effect dealkylation thereby freeing the *N*-oxide group (*277* → *278*). In addition two other reactions are known: nucleophilic reactions on α- or γ-ring carbon atoms can lead either to the elimination of OR and the formation of a substituted heterocycle, or to ring opening. These latter possibilities are discussed in detail under nucleophilic attack at ring carbon atoms. The factors influencing the pathway actually followed in reactions with different nucleophiles are discussed in reference 69T4291 : the hard/soft character of the nucleophile is clearly important, as is the ability to activate an adjacent hydrogen atom to removal as a proton after the nucleophile itself has added to the ring carbon atom.

i. Formation of Carbonyl Compounds and Deoxygenated Bases

This reaction has been suggested as a method both for preparing aldehydes (57JO1135), including α-ketoaldehydes (64JJ287), and, in combination with a preliminary reaction with ethyl bromoacetate, of deoxygenating *N*-oxides [59AA(135)76-O]. Successful applications of the reactions are recorded in Table 4.18, but failures are also known (59JO1632). Reaction of pyridine 1-oxide with bromomalonic ester yields the ester *279* by subsequent combination of the intermediate mesoxalic ester (formed by a process of type *280*) with unreacted bromomalonic ester (65RO1130). With alkali, the azo derivative *281* first loses a proton to give the anhydro derivative *282*; on heating *282* gives formaldehyde and 2-(*p*-hydroxyphenylazo)pyridine (67JO1146). The reaction of benzyl chloride with pyridine 1-oxide to form the aldehyde is apparently catalysed by epoxides; see reference 66NK978.



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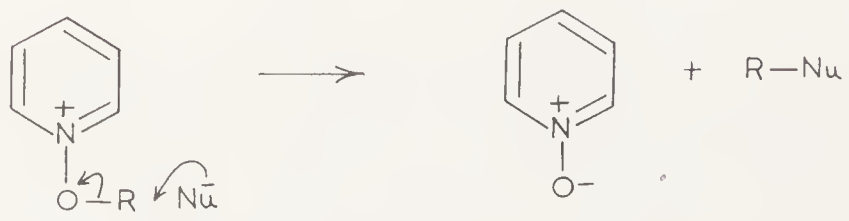

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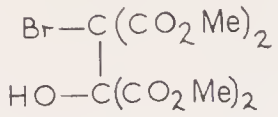

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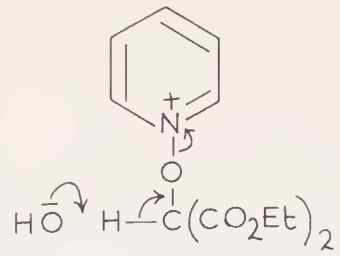

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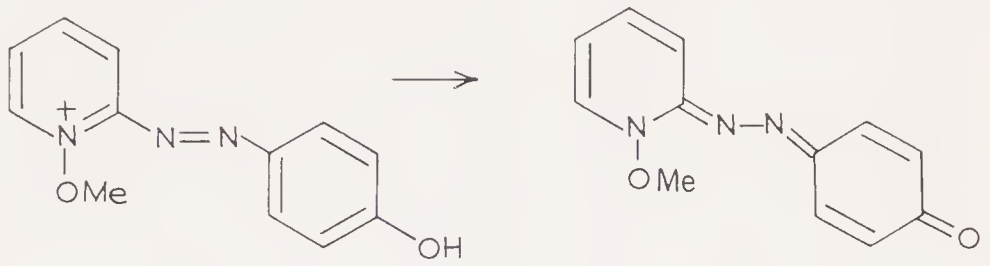

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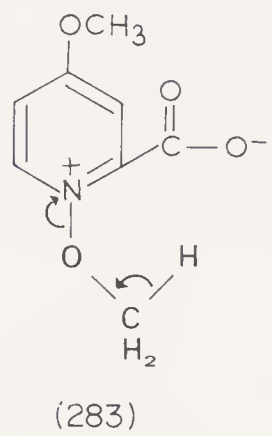


(283)

Recently, it has become apparent that this reaction is not nearly as simple as was first thought, and that extensive ring opening occurs (65T2205); this aspect is discussed in Section III-4Cib.

Profft and Steinke (61PC58) found that 2-carboxy-4-methoxypyridine 1-oxide is converted largely into 4-methoxypyridine by diazomethane, possibly via *283*.

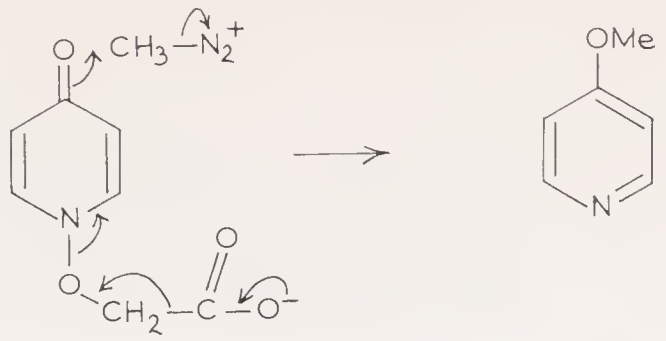
ii. Dealkylation of N-*Alkoxy Cations to Give* N-*Oxides*

1-Methoxypyridinium tosylate gives pyridine 1-oxide (15–56% yields) on treatment with sodium acetate, benzyl mercaptan, morpholine, aniline, hydroxylamine, semicarbazide, and phenylmagnesium bromide (59JO1836). However, reaction with ethoxide, hydroxide, and phenoxide ions yields only pyridine. The formation of *N*-oxides as by-products in the dealkylation has been reported by other investigators (61JO3802; 63JO1323), and recently a Russian group found that dealkylation is the major reaction observed on treating *N*-alkoxy cations with alcoholic hydrogen bromide (64ZO4191). Recently the factors influencing the occurrence of dealkylation for *N*-alkoxypyridinium, -quinolinium, and -isoquinolinium cations in contrast to other reaction paths have been discussed (69T4291).

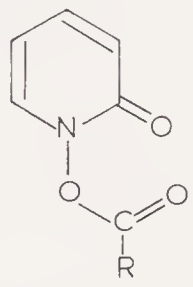
Table 4.18. Conversion of *N*-Alkoxy Cations into the Parent Heterocycle and a Carbonyl Compound

Ring system	*N*-Alkoxyl groups	Nucleophiles	Remarks	References
Pyridine	alkoxy[a]	TsO^-	benzophenone also formed	62JO317
	phenacyloxy	Br^-	—	64JJ287
	benzyloxy	Br^-	—	57JO1135
	butoxy	$n\text{-}C_8H_{17}S^-$	3- and 4-alkylthiopyridine also formed	63JO1320
	cyclic[b]	OH^-	2-vinylpyridine (85%)	58JA2217
	cyclopentenyloxy[c]	OH^-	cyclopentene-3,5-dione (13%)[d]	59JA4920
	ethoxy	Br^-, $n\text{-}PrS^-$, $n\text{-}C_8H_{17}S^-$	3- and 4-alkylthiopyridine also formed	44JJ210, 63JO1320
	ethoxycarbonylmethoxy[c]	Br^-	—	59AA(135)76-O
	methoxy	EtO^-, OH^-, I^-, PhO^-	—	43PJ574, 44JJ210, 56J2404, 59JO1836
Quinoline	methoxy	I^-	—	43PJ574, 44JJ210
Benzimidazole	methoxy	OH^-	—	66CT375

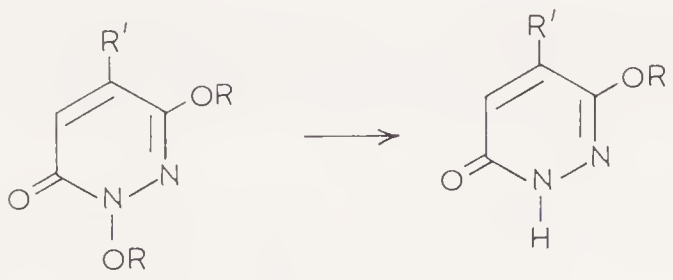
[a] R = (2,2-diphenyltetrahydro-3-furyl)methoxy.
[b] 2,3-Dihydro-4*H*-oxazino[2,3-*a*]pyridinium bromide.
[c] Salt of pyridine 1-oxide and *cis*-3,5-dibromocyclopentene.
[d] Isolated as dimer.



(284) (285)



(286)



(287) (288)

B. NEUTRAL *N*-ALKOXY DERIVATIVES

Relatively little is known about the reactions of compounds of this type, and their chemistry offers many opportunities for further investigation. 1-(Carboxymethoxy)-4-pyridone decomposes on treatment with diazomethane to yield carbon dioxide, formaldehyde, and 4-methoxypyridine (*284* → *285*) (58R331); evidently electrophilic attack at the oxygen atom in the 4-position is required, for with alkali, decomposition occurs to give glyoxalic acid (cf. Table 3.18). This reaction is not general for substituted pyridines (59R981).

1-Acyloxy-2-pyridones (*286*) are good acylating agents which combine crystallinity and stability with high reactivity; they are potentially applicable in peptide synthesis (65JA5186). 1-Alkoxypyridazinones of type *287* are decomposed by bases to the pyridazinones *288*. However, if the *O*-substituent (R in *287*) is $-CO_2Et$ or $-CH_2CH_2CO_2Et$, then decomposition to the free hydroxypyridazinone (*288*, R = R′ = H) occurs (68CT1244).

CHAPTER V

Bibliography

Introduction

References are designated by a number-letter code of which the first two digits denote the year of publication, the next one or two letters the journal, and the final digits the page number. Exceptionally, for journals of which more than one volume appears per year, the volume number is given in round brackets immediately after the journal letter code. A list of the journals to which the letter codes refer is given in Table 5.01, and a complementary key to the letter codes for specific journals appears in Table 5.02.

Most journals are assigned letter codes bearing obvious similarity to their titles. Patents are listed at the end of each year and are coded similarly, e.g. 60USP2922790 means United States Patent 2, 922, 790 (1960). Books, a few journals to which references are rarely made, and all other sources are coded MI (Miscellaneous) and listed under the relevant year of publication as 66MI1 etc.

Practically all sources have been checked in the original. Papers in Japanese have been covered using *Chemical Abstracts* and the English and/or German summaries frequently provided in the original journal; they have often been checked using Ochiai's book (67MIa). A few papers which have been covered using neither the original journal nor *Chemical Abstracts* are indicated by an asterisk.

Table 5.01. Letter Codes for Journal Titles

Code	Full Title
AA	Abstracts of Papers, American Chemical Society
AB	Analytical Biochemistry
AC	Analytical Chemistry
AF	Arzneimittel-Forschung
AG	Angewandte Chemie
AI	Annual Report of the ITSUU Laboratory (ITSUU Kenkyusho Nempo)
AJ	Australian Journal of Chemistry (formerly Australian Journal of Scientific Research)
AK	Arkiv för Kemi
AL	Atti della Accademia Nazionale dei Lincei, Rendiconti, Classe di Scienze Fisiche, Matematiche e Naturali
AM	Acta Medica Scandinavica
AN	Annali di Chimica (Rome)
AP	Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft
AQ	Anales de la Real Sociedad Española de Física y Química (Madrid)

Code	Full Title
AR	Academie de la Republique Populare Romîne
AS	Acta Chemica Scandinavica
AT	Atti della Accademia della Scienze di Torino
AY	Archives of Biochemistry and Biophysics
B	Biochemistry
BA	Bulletin de l'Academie Polonaise des Sciences, Serie des Sciences Chimiques
BB	Bulletin des Sociétés Chimiques Belges
BC	Biochemical Journal
BD	Bulletin of the Chemical Society of Belgrade (Glasnik Hemiskog Drustva, Beograd)
BF	Bulletin de la Société Chimique de France
BG	Berichte der Bunsengesellschaft für Physikalische Chemie [Zeitschrift für Electrochemie (ZE) up to 1962]
BH	Bulletin of the National Institute of Hygienic Sciences (Tokyo)
BJ	Bulletin of the Chemical Society of Japan
BK	Bunkô Kenkyû (Journal of the Spectroscopical Society of Japan)
BR	British Journal of Pharmacology and Chemotherapy
BS	Bollettino Scientifico della Facoltà di Chimica Industriale di Bologna
CA	Chemical Abstracts
CB	Chemische Berichte
CC	Canadian Journal of Chemistry
CD	Coordination Chemistry Reviews
CF	Ceskoslovenská Farmacie
CH	Chemical Communications
CI	Chemistry and Industry (London)
CM	Chemische Techniek (Berlin)
CN	Cancer Research
CO	Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences
CP	Journal de Chimie Physique et de Physicochimie Biologique
CR	Chemical Reviews
CT	Chemical and Pharmaceutical Bulletin (Tokyo) [formerly Pharmaceutical Bulletin (Tokyo)]
CW	Chemisch Weekblad
CX	Acta Crystallographica
CZ	Collection of Czechoslovak Chemical Communications
DA	Doklady Akademii Nauk SSSR (Proceedings of the Academy of Sciences of the USSR)
DI	Dissertation Abstracts
F	Il Farmaco (Pavia) Edizione Scientifica
FE	Federation Proceedings
FT	Farmakologiya i Toksikologiya
G	Gazzetta Chimica Italiana
GA	Gann (The Japanese Journal of Cancer Research)

Code	Full Title
H	Helvetica Chimica Acta
IA	Izvestiya Akademii Nauk Armyanskoi SSR, Seriya Fiziko-Matematicheskikh Nauk
IC	Inorganic Chemistry
IE	Industrial and Engineering Chemistry
IJ	Indian Journal of Applied Chemistry
IM	Chimica e l'Industria (Milan)
IN	Inorganic and Nuclear Chemistry Letters
IS	Israel Journal of Chemistry
IU	Istanbul University Fen Fakultesi Mecmuasi
IZ	Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk (Bulletin of the Academy of Sciences of the USSR, Chemical Sciences Section)
J	Journal of the Chemical Society
JA	Journal of the American Chemical Society
JB	Journal of Biological Chemistry
JF	Journal of Fermentation Technology (Hakko Kogaku Zasshi)
JG	Journal of the Royal Technical College (Glasgow)
JH	Journal of Heterocyclic Chemistry
JI	Journal of the Indian Chemical Society
JJ	Journal of the Pharmaceutical Society of Japan (Yakugaku Zasshi)
JM	Journal of Molecular Spectroscopy
JN	Journal of Inorganic and Nuclear Chemistry
JO	Journal of Organic Chemistry
JR	Journal of Antibiotics (Tokyo)
JS	Journal of Pharmaceutical Sciences
JT	Journal of Chemical Physics
JX	Journal of Bacteriology
JY	Journal of Scientific and Industrial Research (India)
KG	Khimiya Geterotsiklicheskikh Soedinenii [Chemistry of Heterocyclic Compounds (USSR)]
KK	Kaguku no Kenkyu [Chemical Researches (Japan)]
KM	Kieler Milchwirtschaftliche Forschungsberichte
LA	Leibig's Annalen der Chemie
M	Monatschefte für Chemie
MA	Applied Microbiology
MC	Journal of Medicinal and Pharmaceutical Chemistry
ME	Methoden der Organische Chemie
MI	(Miscellaneous books and journals)
MO	Memoirs of the Osaka University of the Liberal Arts and Education. B. Natural Science
MR	Memoirs of the Institute of Scientific and Industrial Research, Osaka University
MS	Acta Pathologica et Microbiologica Scandinavica

Code	Full Title
N	Naturwissenschaften
NA	Nature
NK	Nippon Kagaku Zasshi (Journal of the Chemical Society of Japan, Pure Chemical Section)
NW	Chemical News
OM	Organic Mass Spectrometry
OP	Optics and Spectroscopy (USSR) (Translation of Optika i Spektroskopiya)
OS	Organic Syntheses
P	Proceedings of the Chemical Society
PC	Journal für Praktische Chemie
PH	Journal of Physical Chemistry
PI	Proceedings of the Indian Academy of Sciences
PJ	Proceedings of the Japanese Academy [Formerly Proceedings of the Imperial Academy (Tokyo)]
PN	Proceedings of the National Academy of Sciences of the USA
PP	Journal of Pharmacy and Pharmacology
PS	Proceedings of Society for Experimental Biology and Medicine
PY	Hoppe-Seyler's Zeitschrift für Physiologische Chemie
QR	Quarterly Reviews (London)
R	Recueil des Travaux Chimiques des Pays-Bas
RC	Roczniki Chemii
RD	Report of the Research Institute of Dental Materials, Tokyo Medical and Dental University
RL	Rendiconti dell'Instituto Lombardo di Scienze e Lettere
RO	Russian Journal of Organic Chemistry (Zhurnal Organicheskoi Khimii)
RR	Revue Roumaine de Chimie
RS	La Ricerca Scientifica
RU	Russian Chemical Reviews (Uspekhi Khimii)
RV	Reviews of Pure and Applied Chemistry
SA	Spectrochimica Acta
SC	Science
SE	Symposia on Enzyme Chemistry (Tokyo) (Koso Kagaku Shiumpoziumu)
SJ	Journal of the Spectroscopic Society of Japan
SP	Scientific Papers of the Institute of Physical and Chemical Research (Tokyo)
SR	Annual Report of the Shionogi Research Laboratory (Shionogi Kenkyusho Nempo)
SU	Suomen Kemistilehti
SY	Shizuoka Yakka Daigaku Kaigaku 5-Shunen Kinen Rombunshu (Collection of Papers Celebrating the Fifth Anniversary of Shizuoka College of Pharmacy)
T	Tetrahedron
TA	Trudy Fiziko-Teknicheskogo Instituta, Akademiya Nauk Uzbekskoi SSR

Code	Full Title
TC	Theoretica Chimica Acta (Berlin)
TF	Transactions of the Faraday Society
TL	Tetrahedron Letters
TT	Talanta
TU	Trudy Ural'skogo Politekhnicheskogo Instututa im. S.M. Kirova
UJ	Annales Scientifiques de l'University de Jassy
UK	Ukrainskii Khimicheskii Zhurnal
WC	Wiadomosci Chemiczne
WZ	Wissenschafteliche Zeitschrift der Technischen Hochschule Leuna-Merseburg
Z	Chemiker-Zeitung
ZB	Chemisches Zentralblatt
ZC	Zeitschrift für Chemie
ZE	Zeitschrift für Elektrochemie [from 1962 called Berichte der Bunsengesellschaft für physikalische Chemie (BG)]
ZK	Shika Zairyo Kenkyusho Hokoku
ZN	Zeitschrift für Naturforschung
ZO	Zhurnal obschei Khimii (Journal of General Chemistry U.S.S.R.)
ZP	Zeitschrift für physikalische Chemie (Frankfurter Ausgabe)
ZR	Zentralblatt für Bakteriologie, Parasitenkunde
	Patents
BP	British patent
GP	German patent
EGP	East German patent
FP	French patent
JP	Japanese patent
USP	United States of America patent

Table 5.02. Letter Codes for Journal Titles

Full Title	Code
Abstracts of Papers, American Chemical Society	AA
Academie de la Republique Populaire Romîne	AR
Acta Chemica Scandinavica	AS
Acta Crystallographica	CX
Acta Pathologica et Microbiologica Scandinavica	MS
Anales de la Real Sociedad Española de Física y Química (Madrid)	AQ
Acta Medica Scandinavica	AM
Analytical Biochemistry	AB
Analytical Chemistry	AC
Angewandte Chemie	AG

Full Title	Code
Annales Scientifiques de l'University de Jassy	UJ
Annali di Chimica (Rome)	AN
Annual Report of the Itsuu Laboratory (Itsuu Kenkyusho Nempo)	AI
Annual Report of the Shionogi Research Laboratory (Shionogi Kenkyusho Nempo)	SR
Applied Microbiology	MA
Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft	AP
Archives of Biochemistry and Biophysics	AY
Arkiv för Kemi	AK
Arzneimittel-Forschung	AF
Atti della Accademia Nazionale dei Lincei, Rendiconti, Classe di Scienze Fisiche, Matematiche e Naturali	AL
Atti della Accademia della Scienze di Torino	AT
Australian Journal of Chemistry (formerly Australian Journal of Scientific Research)	AJ
Berichte der Bunsengesellschaft für Physikalische Chemie [Zeitchrift für Electrochemie (ZE) up to 1962]	BG
Biochemical Journal	BC
Biochemistry	B
British Journal of Pharmacology and Chemotherapy	BR
Bollettino Scientifico della Facolta di Chimica Industriale di Bologna	BS
Bulletin de l'Academie Polonaise des Sciences, Serie des Sciences Chimiques	BA
Bulletin de la Société Chimique de France	BF
Bulletin des Sociétés Chimiques Belges	BB
Bulletin of the Chemical Society of Belgrade (Glasnik Hemiskog Drustva, Beograd)	BD
Bulletin of the Chemical Society of Japan	BJ
Bulletin of the National Institute of Hygienic Sciences (Tokyo)	BH
Bunkô Kenkyû (Journal of the Spectroscopical Society of Japan)	BK
Canadian Journal of Chemistry	CC
Cancer Research	CN
Ceskoslovenska Farmacie	CF
Chemical Abstracts	CA
Chemical Communications	CH
Chemical and Pharmaceutical Bulletin (Tokyo) [formerly Pharmaceutical Bulletin (Tokyo)]	CT
Chemical News	NW
Chemical Reviews	CR
Chemische Berichte	CB
Chemische Techniek (Berlin)	CM
Chemisch Weekblad	CW
Chemisches Zentralblatt	ZB
Chemistry and Industry (London)	CI
Chimica e l'Industria (Milan)	IM
Chemiker-Zeitung	Z

Full Title	Code
Collection of Czechoslovak Chemical Communications	CZ
Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences	CO
Coordination Chemistry Reviews	CD
Dissertation Abstracts	DI
Doklady Akademii Nauk SSSR (Proceedings of the Academy of Sciences of the USSR)	DA
Farmakologiya i Toksikologiya	FT
Federation Proceedings	FE
Gann (The Japanese Journal of Cancer Research)	GA
Gazzetta Chimica Italiana	G
Helvetica Chimica Acta	H
Hoppe-Seyler's Zeitschrift für Physiologische Chemie	PY
Il Farmaco (Pavia) Edizione Scientifica	F
Indian Journal of Applied Chemistry	IJ
Industrial and Engineering Chemistry	IE
Inorganic Chemistry	IC
Inorganic and Nuclear Chemistry Letters	IN
Israel Journal of Chemistry	IS
Istanbul University Fen Fakultesi Mecmuasi	IU
Izvestiya Akademii Nauk Armyanskoi SSR, Seriya Fiziko-Matematicheskikh Nauk	IA
Izvestiya Akademii Nauk SSSR, Otdelenie Khimicheskikh Nauk (Bulletin of the Academy of Sciences of the USSR, Chemical Sciences Section)	IZ
Journal of the American Chemical Society	JA
Journal of Antibiotics (Tokyo)	JR
Journal of Bacteriology	JX
Journal of Biological Chemistry	JB
Journal of Chemical Physics	JT
Journal of the Chemical Society	J
Journal de Chimie Physique et de Physicochimie Biologique	CP
Journal of Fermentation Technology (Hakko Kogaku Zasshi)	JF
Journal of Heterocyclic Chemistry	JH
Journal of the Indian Chemical Society	JI
Journal of Inorganic and Nuclear Chemistry	JN
Journal of Medicinal and Pharmaceutical Chemistry	MC
Journal of Molecular Spectroscopy	JM
Journal of Organic Chemistry	JO
Journal of the Pharmaceutical Society of Japan (Yakugaku Zasshi)	JJ
Journal of Pharmaceutical Sciences	JS
Journal of Pharmacy and Pharmacology	PP
Journal of Physical Chemistry	PH
Journal für Praktische Chemie	PC
Journal of the Royal Technical College (Glasgow)	JG

Full Title	Code
Journal of Scientific and Industrial Research (India)	JY
Journal of the Spectroscopic Society of Japan	SJ
Kaguku no Kenkyu [Chemical Researches (Japan)]	KK
Khimiya Geterotsiklicheskikh Soedinenii [Chemistry of Heterocyclic Compounds (USSR)]	KG
Kieler Milchwirtschaftliche Forschungsberichte	KM
La Ricerca Scientifica	RS
Liebig's Annalen der Chemie	LA
Memoirs of the Institute of Scientific and Industrial Research, Osaka University	MR
Memoirs of the Osaka University of the Liberal Arts and Education. B. Natural Science	MO
Methoden der Organische Chemie	ME
(Miscellaneous books and journals)	MI
Monatshefte für Chemie	M
Nature	NA
Naturwissenschaften	N
Nippon Kagaku Zasshi (Journal of the Chemical Society of Japan, Pure Chemical Section)	NK
Optics and Spectroscopy (USSR) (translation of Optika i Spektroskopiya)	OP
Organic Mass Spectrometry	OM
Organic Syntheses	OS
Proceedings of the Chemical Society	P
Proceedings of the Japanese Academy [formerly Proceedings of the Imperial Academy (Tokyo)]	PJ
Proceedings of the Indian Academy of Sciences	PI
Proceedings of the National Academy of Sciences of the USA	PN
Proceedings of the Society for Experimental Biology and Medicine	PS
Quarterly Reviews (London)	QR
Recueil des Travaux Chimiques des Pays-Bas	R
Rendiconti dell'Instituto Lombardo di Scienze e Lettere	RL
Report of the Research Institute of Dental Materials, Tokyo Medical and Dental University	RD
Reviews of Pure and Applied Chemistry	RV
Revue Roumaine de Chimie	RR
Roczniki Chemii	RC
Russian Chemical Reviews (Uspekhi Khimii)	RU
Russian Journal of Organic Chemistry (Zhurnal Organicheskoi Khimii)	RO
Science	SC

Full Title	Code
Scientific Papers of the Institute of Physical and Chemical Research (Tokyo)	SP
Shika Zairyo Kenyusho Hokoku	ZK
Shizuoka Yakka Daigaku Kaigaku 5-Shunen Kinen Rombunshu (Collection of Papers Celebrating the Fifth Anniversary of Shizuoka College of Pharmacy)	SY
Spectrochimica Acta	SA
Suomen Kemistilehti	SU
Symposia on Enzyme Chemistry (Tokyo) (Koso Kagaku Shiumpoziumu)	SE
Talanta	TT
Tetrahedron	T
Tetrahedron Letters	TL
Theoretica Chimica Acta (Berlin)	TC
Transactions of the Faraday Society	TF
Trudy Fiziko-Teknicheskogo Instituta, Akademiya Nauk Uzbekskoi SSR	TA
Trudy Ural'skogo Politekhnicheskogo Instututa im. S.M. Kirova	TU
Ukrainskii Khimicheskii Zhurnal	UK
Wiadomosci Chemiczne	WC
Wissenschafteliche Zeitschrift der Technischen Hochschule Leuna-Merseburg	WZ
Zeitschrift für Chemie	ZC
Zeitschrift für Elektrochemie [from 1962 called Berichte der Bunsengesellschaft für physikalische Chemie (BG)]	ZE
Zeitschrift für Naturforschung	ZN
Zeitschrift für physikalische Chemie (Frankfurter Ausgabe)	ZP
Zentralblatt für Bakteriologie, Parasitenkunde	ZR
Zhurnal obschei Khimii (Journal of General Chemistry U.S.S.R.)	ZO

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Appendix

ADDENDA

References which came to hand too late to be incorporated in the main text, and could not be easily added in proof, are briefly reported here. The material is arranged in parallel with the text, and footnotes have been added at appropriate places in the text directing attention to the addenda. In this way it has been possible to include work which appeared in the literature through March 1970. Literature citations are collected in the bibliography (Chapter V).

Page 13

A detailed discussion of the interpretation of the ultraviolet spectra of *N*-oxides by molecular orbital methods is now available (69TC244).

Page 18

* Table 1.08

(Pyridine 1-oxide)$HgCl_2$	—	69CX2029
[(Pyridine 1-oxide)$_2CuBr_2$]$_2$	—	70CH204
(Pyridine 1-oxide)$_2Cu(NO_3)_2$	—	69CX2046
(Pyridine 1-oxide)$_4Cu(BF_4)_2$	—	69CX(B)1595
Furoxan	3,4-(*p*-chlorobenzoyl)	70J(B)223
Benzodifuroxan	$=PPh_3$, $=O$	69J(C)2295

† Mass spectral data have recently been reported for cinnoline 1-, 2-, and 1,2-di-oxides: deoxygenation is a dominant path in the decomposition (69OM1265). For the spectra of 2*H*-1,4-benzoxazine and 2*H*-1,4-benzothiazine hydroxamic acids, see reference 70OM105.

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Table 2.01

Pyridine	1	6-H or -alkyl-2-bromo-3-hydroxy	*ca.* 70	69AS2075
	1	2- or 6-alkyl-3-hydroxy	64 or 80	69AS2075

Page 27				
Table 2.01				
Pyridine	1	4-azolyl [4-isoxazolyl-, 4-pyrazolyl-, 4-(1,2,4-oxadiazolyl)-, 4-oxazolyl- 4-thiazolyl-]	24–46	69MC945
Page 28				
Table 2.01				
Pyridine	1	2-(2,4-dinitrobenzyl)-, various	3–28	69BF4425
Page 29				
Table 2.01				
Pyridine	1	3- and 4-(α-phenyl)acetic acids	79 and 85	69JO4150
Page 32				
Table 2.01				
Quinoline	1	3- and 4-trifluoromethyl	81 and 68	69CT2335
Page 34				
Table 2.01				
* 1,6-Naphthyridine	1 or 6	—	(data)	69JJ1260
† 1,6-Phenanthroline	6	—	62	69CT1511
Page 36				
Table 2.01				
Pyrido[2,3-*d*]pyridazine	6 and 7	—	14 and 24	69AJ1745
Page 44				
Table 2.01				
Benzotriazole	3	1-(2-pyridyl)	50	69BB553

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Table 2.02

Quinoline	1	5-, 6-, or 7-tritio	—	69JJ1317

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Table 2.03

* Quinoline	1	2,3-ethylene	84	69JO4131
† 2*H*-1,4-Diazepin-2-one	4	1,3-dihydro-1-methyl-5,6-diphenyl	6	69MC914

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Table 2.04

Pyridine	1	bis(diethoxymethyl)-, various	51–85	69BF3655
[The $CH(OEt)_2$ groups are simultaneously hydrolyzed to give the corresponding diformyl derivatives.]				
	1	bis(diethoxydeuteromethyl)-, various	60–80	69BF3683

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Table 2.06

Quinoline	1	2-trifluoromethyl; reflux, 20 hr	51	69CT2335

Page 55

Table 2.07

* Acridine	10	9-chloro-tetrahydro	35	69JJ1305
† Benzothiazole	3	2-H and -methyl-6-chloro, -methoxy, -methyl, -nitro	2–41	69CT1598

Page 56

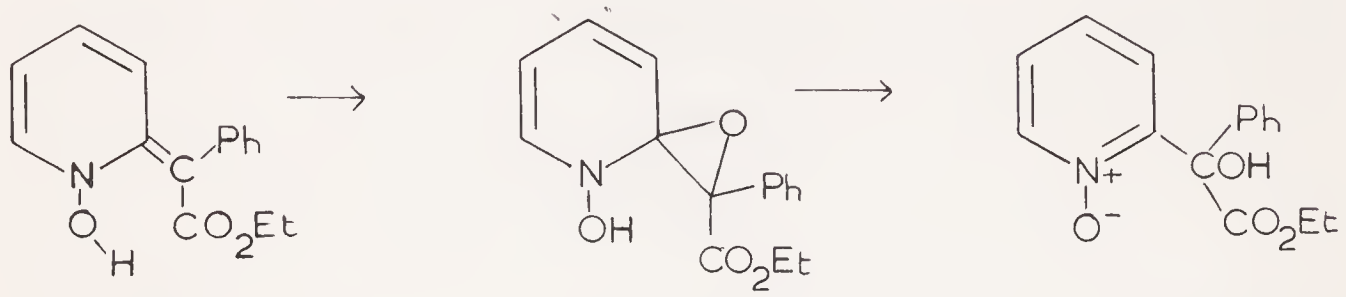
Cyclic azo coumpounds are oxidized by hydrogen peroxide to give *cis*-azoxy derivatives (69TL4643).

Page 58

Pertungstic acid has been used successfully to convert 1,6-naphthyridine and 1,6-phenanthroline into the corresponding 1,6-dioxides where conventional techniques failed (69CT1511).

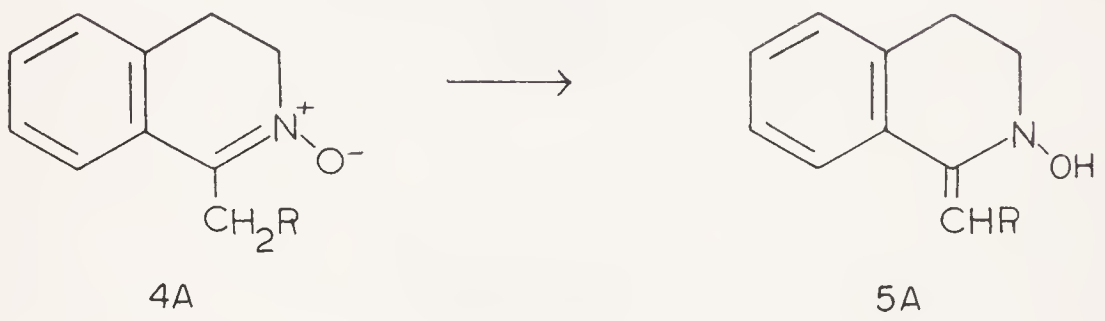
Page 62

* Recently it has been found that, in the *alpha*-position only, certain groups of type CHXY, where X and Y are electron-withdrawing substituents, are oxidized to C(OH)XY. The mechanism of this reaction is thought to involve epoxidation of a tautomeric form, e.g. *1A–3A* (69JO4150). A rather



1A 2A 3A

different type of reaction is the conversion of 1-alkyl-3,4-dihydroisoquinolines into the 1-alkylisoquinoline by peracid: this probably involves formation of the *N*-oxide *4A*, tautomerism into *5A*, and dehydration (70JM44).



4A 5A

† See reference 69LA(727)35 for further examples.

Page 65

Quinolines containing electron-withdrawing substituents in the 8-position are converted into oxindoles by peracid, probably via 3-hydroxylation (69CT2293).

Page 73

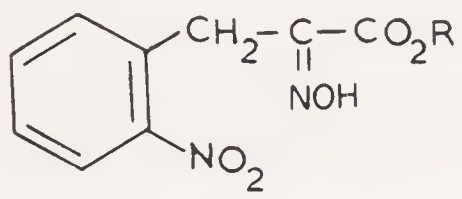
Such rearrangements have also been postulated to yield *intermediate N*-oxides (69CH1428).

Page 76

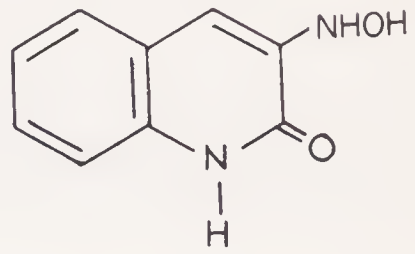
γ-Thiopyrones apparently undergo similar reactions (69JA4749).

Page 79

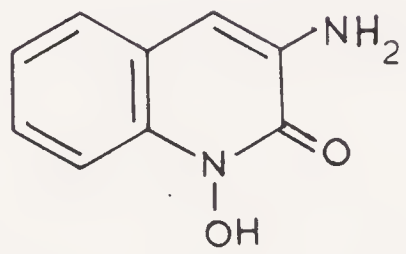
These reactions are not always as simple as was originally thought: the catalytic hydrogenation of *6A* was considered to give *8A* [67J(C)2446], but this product is now believed to be *7A*, whereas *8A* results from the reduction of *6A* with sodium borohydride and palladium-charcoal [69J(C)2207].



6A



7A



8A

Page 81

Table 2.12

$-CH_2C(CO_2Me)=NOH$	$NaBH_4$–Pd/C	3-amino	69J(C)2207

Page 84

Table 2.13

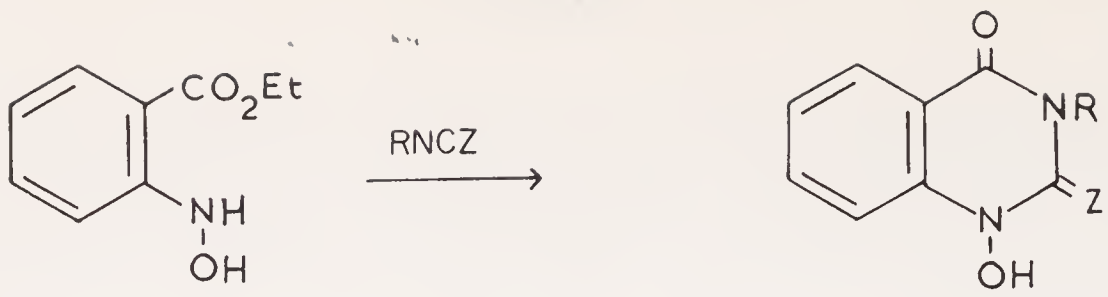
Benzo[*c*]cinnoline, various	5- and 5,6-di	H_2/Ni(R)	69JH523

Page 86

Ethyl acetoacetate and hydroxyurea yield 3-hydroxy-6-methyl-2,4-pyrimidinedione (70CI58).

Page 87

The hydroxyamino ester *9A* is converted into the quinazoline cyclic hydroxamic or thiohydroxamic acid *10A* (Z = O or S) as indicated (70CB82).



9A 10A

Page 90

Similarly, 3-methoxy-4(3*H*)-pteridinones have been prepared using *O*-methylhydroxylamine [69J(C)2777].

Page 91

Table 2.16

5-NH_2-4-CN-1-(2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)	$HC(OEt)_3$	adenosine 1-oxide derivative	—	69CT1128

Page 92

2-Amino-2-deoxy-D-glucose oxime reacts with glyoxal to yield 3-(D-*arabino*-tetrahydroxybutyl)pyrazine 1-oxide (69JO3842).

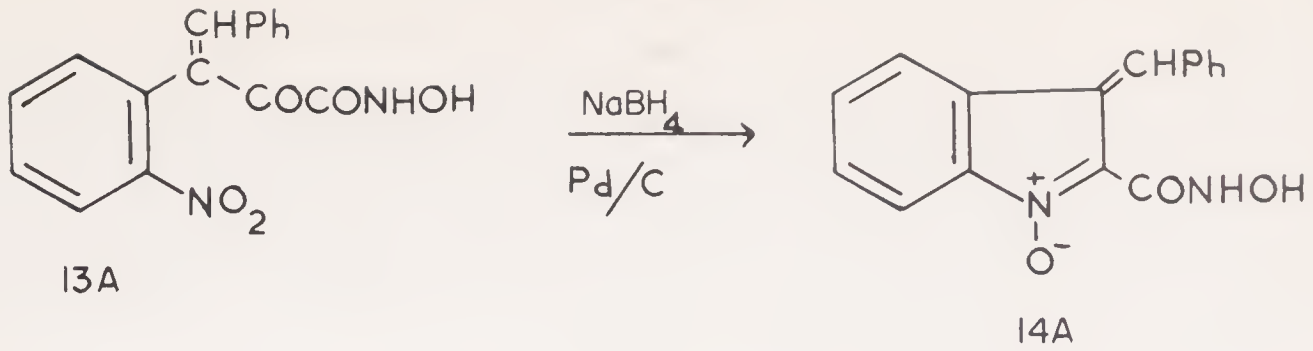
Page 93

The corresponding reaction, *11A* → *12A*, yields the 2-oxides of thiazolo[3,-2-*a*]pyrazinium salts [69J(C)2270].

11A 12A

Page 97

A further example of this reaction type has been reported: *13A* → *14A* [69J(C)2207]. For additional examples of the synthesis of isatogens from *o*-nitrotolans, see reference 69J(C)2453.



13A 14A

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For further examples, see references 69CB4177 and 69BJ3204.

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Table 2.24

p-Propenyl-anisole	HNO_2	3-*p*-methoxyphenyl-4-methylfuroxan	—	69J(C)1901

Page 129

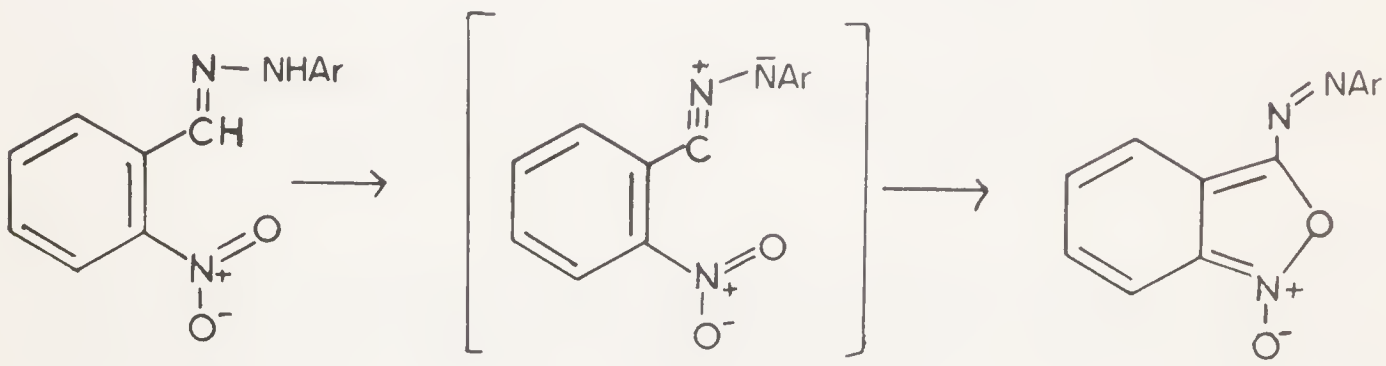
New examples of the photolytic ring closure of *N*-2,4-dinitrophenylamino acids and a detailed investigation of the reaction mechanism have been reported: 4-nitro-2-nitrosophenyl compounds are considered to be intermediates [69J(C)2127].

Page 132

It has more recently been shown, however, that the products described in reference 58CB1344 do *not* have structures of type *419*, rather they are 2,3,4,5,6,7-hexahydro-1-hydroxy-2,4-indolediones (69T4005).

Page 133

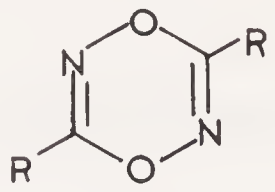
3-Arylazoanthranil 1-oxides (*17A*) are formed by lead tetraacetate oxidation of *o*-nitrobenzaldehyde phenylhydrazones (*15A*), probably via intermediate nitrile imides (*16A*) [69J(C)2587].



15A 16A 17A

Page 139

Some of the confusion in the literature has recently been clarified: *p*-chlorobenzonitrile oxide gives both products [69J(C)1901]. The dimerization of nitrile oxides to 1,2,4-oxadiazole 4-oxides is catalyzed by boron trifluoride, however an excess of catalyst yields a different dimer which is considered to have structure *18A* (69G165).



18A

Page 140

Table 2.31

p-Chlorobenzonitrile oxide	—	3,4-bis(*p*-chlorophenyl)	— 69J(C)1901

Page 141

Mixed dimerization of *p*-chloro- and *p*-methoxy-benzonitrile *N*-oxides gives all four possible products in nearly the quantities expected on a statistical basis for random reaction (70CH60).

Page 149

Table 3.03

Quinoline 1-oxide, 8-hydroxy 69JN3465

$k_{a_1} = 0{\cdot}0486$, determined by potentiometric titration

$k_{a_2} = 176\, k_w$, determined by solvent extraction methods

Page 157

Table 3.04

Pyridine 1-oxide	2- and 4-oximinomethyl	—	$ArSO_3^-$	69AP815
	2- and 4-oximinomethyl	—	$^-O_3S(CH_2)_nSO_3^-$	69AP822

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Pyridine 1-oxide is converted into the 1-*t*-butoxypyridinium ion (isolated as the perchlorate) by reaction with butyl chloride and silver perchlorate (69T4291).

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1,2,4-Oxadiazole 4-oxides form coordination complexes with boron trifluoride (69G165).

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Table 3.05

* Some analogous quinoline 1-oxide (QO) complexes with metal ions have been described: lanthanide complexes [$M(QO)_3Cl_3 \cdot H_2O$ and $M(QO)_4Cl_3 \cdot H_2O$] (69JN3181) and vanadium complexes [69J(A)1892]. Iron (III) complexes of pyridine 1-oxides have been studied by infrared spectroscopy (69JN3665).

† $M(PyO)_4X_2$	Cu	BF_4^-	—	X-ray	69CX(B)1595
‡ $M(PyO)_2X_2$	Cu	—	—	IR, μ	69IC1879, 69IC1886
	Zn	—	—	IR, μ, Λ	69J(A)1893
§ $M(PyO)X_2$	Co, Cu, Mn, Ni, Zn	trifluoro- and tri-chloro-acetates	methyl	IR, UV, μ, X-ray, refl.	69J(A)2892
	Cu	—	—	IR, μ	69IC1879, 69IC1886
	Hg	Br^-, Cl^-	2-, 3-, 4- and 2,6-d-methyl; 4-cyano	IR, μ	70J(A)378
	Mn, Ni	Cl^-	4-H, -OEt, -OMe	IR, μ, X-ray	69IC2559

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Table 3.05

$M(PyO)_2X_4$	V	F^-	4-nitro, -chloro, -methyl, and -methoxy	IR	69IN825

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Table 3.07

1,6-Naphthyridine 1- or 6-oxide	—	Ni(R)	—	—	69JJ1260

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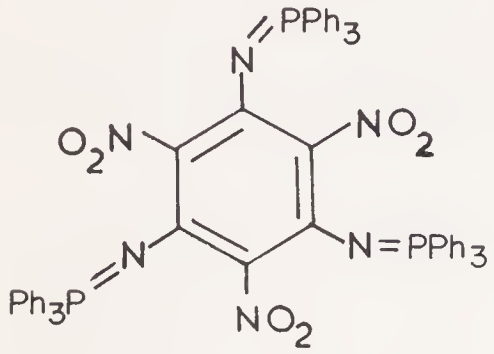
Table 3.07

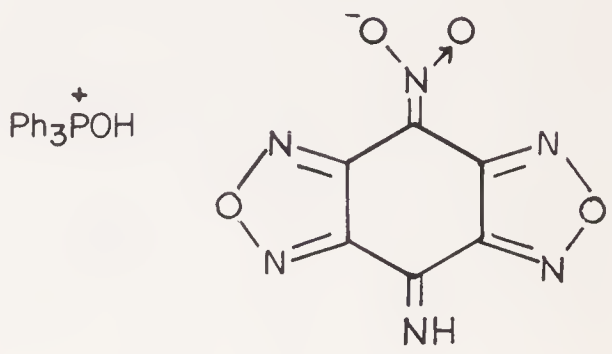
Imidazole 3-oxides	2,4,5-triaryl	Ni(R)	—	—	*ca.* 90	69CB4177

Page 197

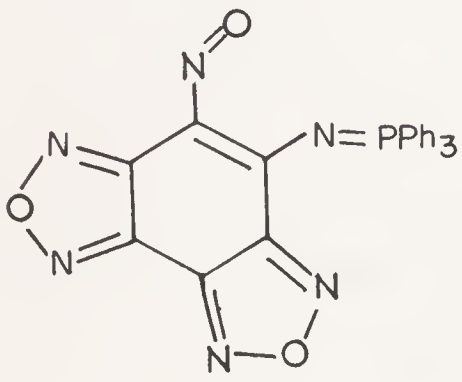
The complex reaction between benzotrifuroxan and triphenylphosphine yields, in addition to *77*, compounds *19A–22A*, the structures of which were obtained by X-ray methods [69J(C)2281; 69J(C)2285; 69J(C)2289; 69J(C)2292; 69J(C)2295]. Tentative mechanisms for the formation of these products have been reported [69J(C)2277].



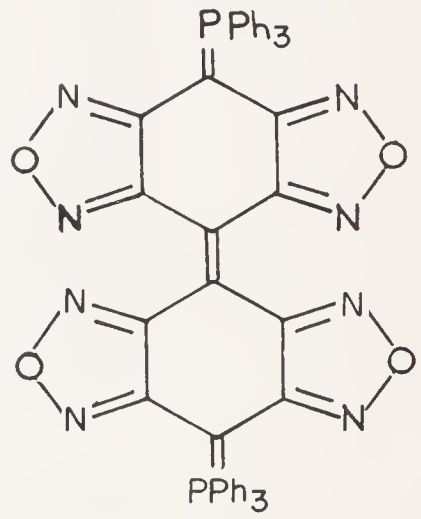
19A



20A



21A



22A

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Table 3.10

Benzofuroxan	PPh_3	—	"good"	69J(C)2277

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Table 3.11

Thiazolo[3,2-*a*]-pyrazinium 2-oxides	PBr_3	various	—	22–69	69J(C)2270

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Deoxygenation of *N*-oxides by dimethyl sulphoxide yields several by-products which are probably formed via intermediate radical species (69TL3619).

Page 215

Further work has been reported on the reactions of pyridine 1-oxide with alkoxyacetic, vinylacetic, and several arylacetic acid anhydrides by Rüchardt *et al.* (69CB3922), Koenig *et al.* (69T4875), and Cohen *et al.* (69JO2550). Detailed discussions of the various possible reaction mechanisms, new data including the results of ^{18}O-labelling, and the nature of the reaction products formed when, for example, ketenes are used in place of acid anhydrides are given. The overall position is still not completely clear, but all three groups are continuing their studies in this complex area.

Page 216

The enzymatic reduction of purine *N*-oxides by xanthine oxidase in the presence of an electron donor has been reported (69JB2498).

Page 226

Table 3.19

1,2,4-Oxadiazole 4-oxide	Zn–AcOH	2,5-di-phenyl	—	—	69G165

Page 230

Clear evidence for the formation of arene oxides in the photochemical reaction of pyridine 1-oxide with benzene and naphthalene has been reported (70TL457).

Page 234

Table 3.23

6-Alkyl-2-bromo-3-hydroxy	4	28%	45°C		69AS2075

Page 237

Table 3.24

2,3-Tetra-methylene	4	—	?	KNO_3–H_2SO_4	69JJ1305
5-, 6- or 7-Tritio	4	—	—	KNO_3–H_2SO_4	69JJ1317

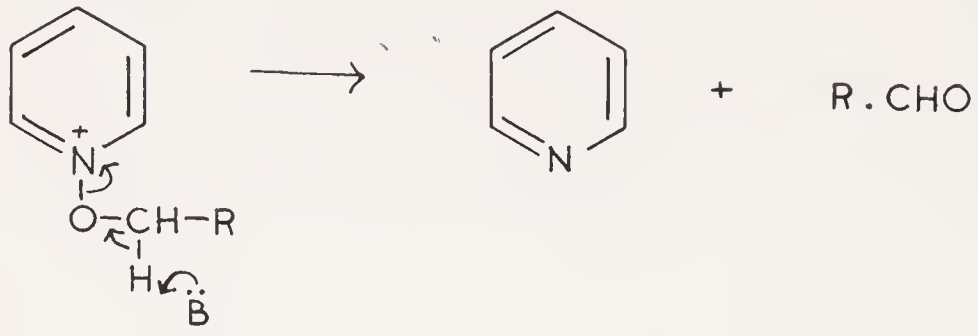
Page 249

Various substituted 3-hydroxypyridine 1-oxides are also brominated readily (69AS2075).

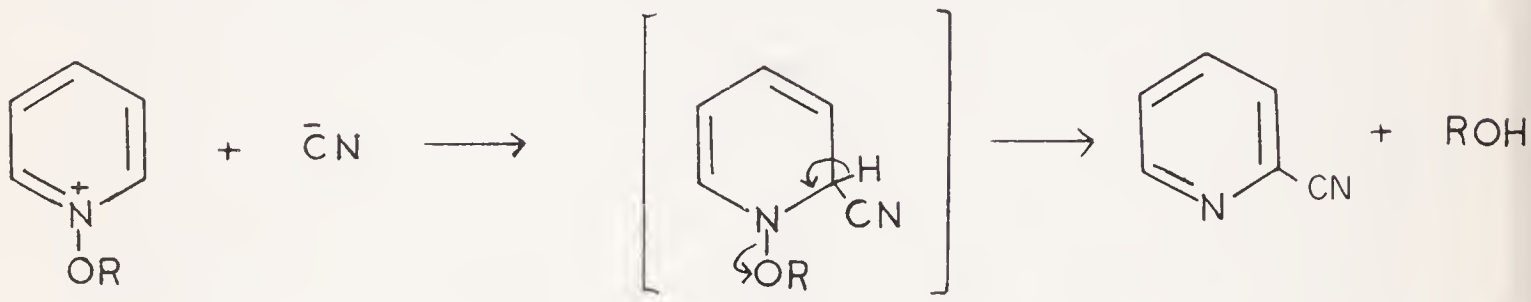
Page 258

1-Methoxypyridinium ion can react with nucleophiles in four different ways as shown in reaction paths A to D.

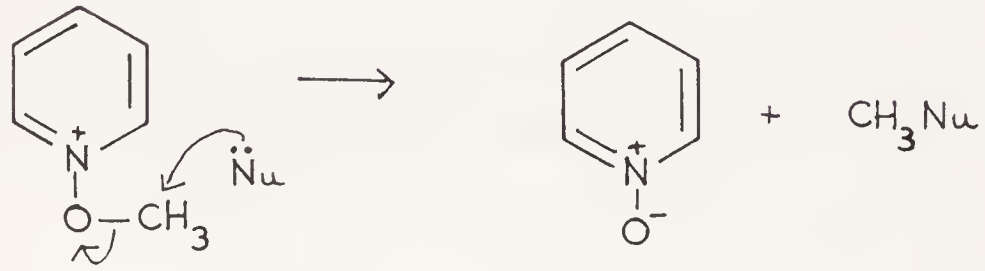
Path A



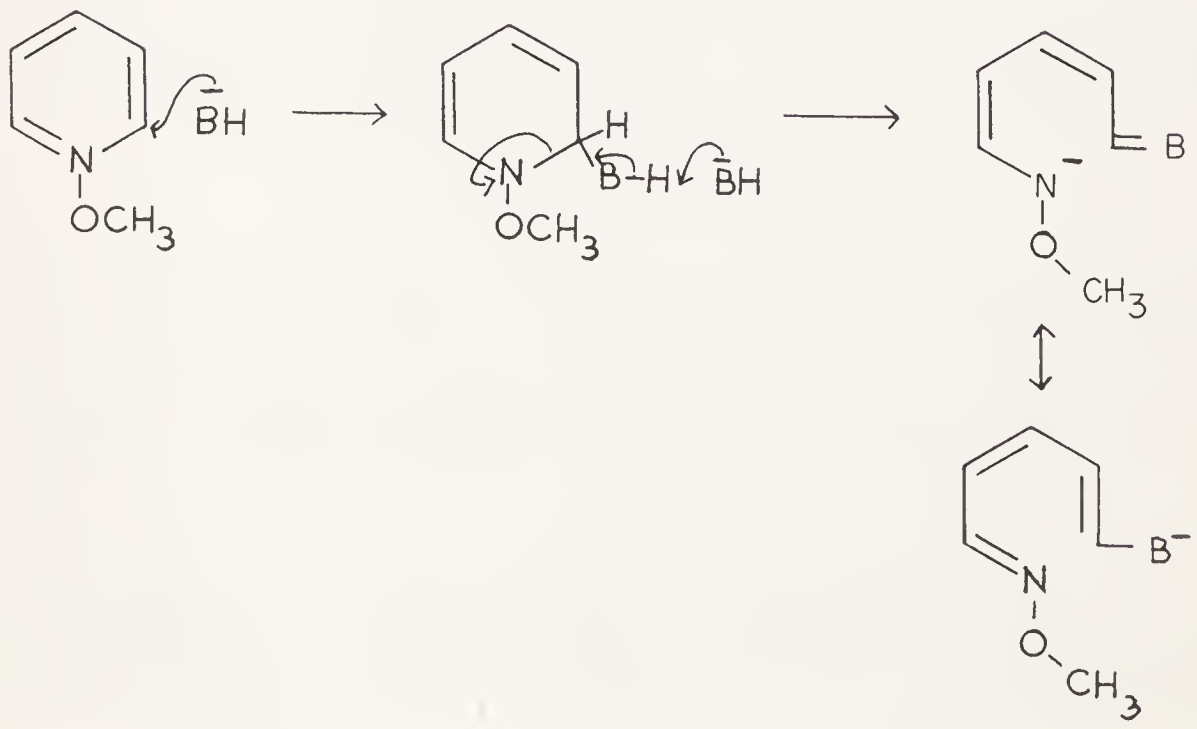
Path B



Path C



Path D



The nature of the nucleophile influences the choice of reaction path in the following four ways (69T4291). (*i*) Ring-opening by path D requires an acidic hydrogen attached to the nucleophilic centre. (*ii*) The "hardness" and "softness" of the nucleophile, as defined empirically by Pearson and Songstad (*J. Amer. Chem. Soc.*, 1967, **89**, 1827), or more rigorously by the MO method of Hudson and Klopman (68JA223), differentiates between path A, which involves attack at a hard hydrogen centre, and paths B or C which involve attack at relatively soft carbon centres. This expectation is broadly borne out as is shown in Table 3.28A where the results are arranged

Table 3.28A. Reaction Paths for Some Nucleophiles with *N*-Methoxypyridinium Salts

	Nucleophile	Solvent	Reaction path	Cross reference
	$S_2O_3^=$	water	C	III-4Dii
soft ↑	S-Alkyl	alkenethiol, ethanol	A + B + C	III-4Di
	SPh^-	ethanol	B + C (+A?)	III-4Di
	SO_2Ph^-	water, dimethylformamide	C	III-4Ciii
	SCN^-	methanol, ethanol–acetone	C	III-4Dii
	I^-	ethanol–acetone	C	III-4B
	CN^-	water, various buffers	B	III-4Fi
	Alkyl-MgBr	ether	B	III-4Fii
	Aryl-MgBr	ether	C?	III-4Fii
	N_3^-	water	C	III-4A
	NO_2^-	water, dimethylformamide	C	III-4A
	piperidine	none	D	III-4Eii
	morpholine	none	C	III-4Eii
	$ArNH_2$, ArNHMe	none	C	III-4Ei
	OAc^-	acetic acid	C	III-4C
	BH_4^-	water, borate buffer (pH 8)	B	III-4A
hard ↓	OMe^-	methanol	A	III-4C
	OPh^-	ethanol	A	III-4A
	OH^-	water	A + D	III-4Ci

in the order of decreasing softness of the nucleophile. (*iii*) Differentiation between attack at the 2- or 4-position is determined by subtle questions of kinetic versus thermodynamic control (R. N. Lindquist and E. H. Corders, *J. Amer. Chem. Soc.*, 1968, **90**, 1269) and other steric and mechanistic factors. (*iv*) Direct steric effects in the substrate, which are minimized in the *N*-methoxy series, are important with the *t*-butoxy compound and with derivatives carrying longer alkyl chains (59CT930).

For paths B or D, the initial step leading to the dihydropyridine intermediate is reversible whenever the entering nucleophile is also a good

leaving group. Such equilibria favour the reactants since the dihydro intermediates have not been detected. Certain quite strong nucleophiles such as iodide and azide anions react by path C. The initial reversible equilibrium is established, but the rate-determining loss of a proton from the dihydro intermediate is evidently too difficult in the absence of a strong activating effect, or of a strongly basic species, to assist in proton removal.

Successful path B reactions have been observed with only four types of nucleophiles, i.e. cyanide, mercaptide, and borohydride ions, and certain carbanions from Grignard reagents or active methylene compounds. For borohydride ions and the carbanions, the first step is reversible; the electron-withdrawing nature of the substituent group coupled with the pronounced basic nature of both nucleophiles assists the rate-determining deprotonation stage.

Page 273

Purine *N*-oxides can be enzymatically converted into the corresponding purin-8-ones by xanthine oxidase, that is they undergo oxidation at the 8-position with concomitant loss of the *N*-oxide function (69JB2494; 69JB2498; 69JB4072).

Page 278

For further work on the rearrangement of isatogens to anthranils, see reference 70J(C)242.

Page 279

The isolation of an intermediate in the tosyl chloride reaction, corresponding to that (*cf. 276*) isolated in the benzoyl chloride reaction, has been reported (69JJ756).

Page 282

Table 3.34

Quinoline 1-oxide	2-trifluoromethyl	4	33	69CT2335
	3-trifluoromethyl	2	77	69CT2335
	4-trifluoromethyl	2	74	69CT2335

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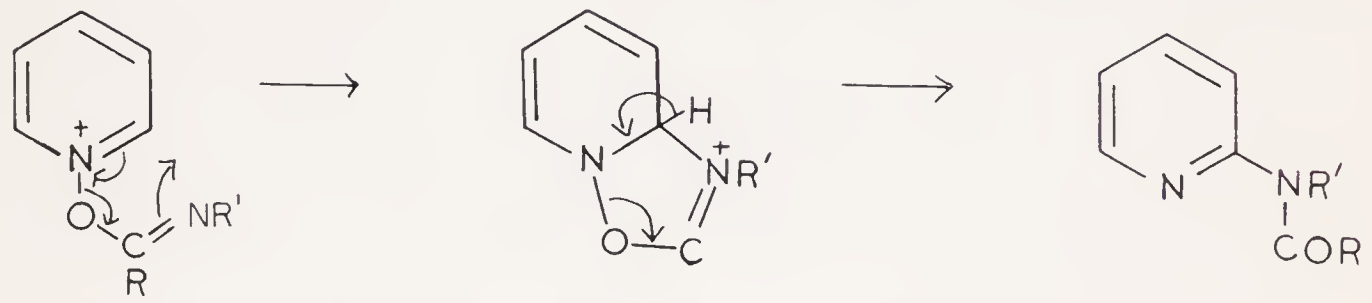
Further isotopic labelling experiments by Oae and his co-workers (69TL3559) show that rearrangement of 2-tosyloxy-1-isoquinolone proceeds mainly by a solvent-separated ion-pair mechanism. This conclusion is further substantiated by kinetic measurements of the reaction of substituted benzenesulphonyl chlorides with isoquinoline, which indicate that the rate-determining step is cleavage of the N-O bond. The effect of solvent is also discussed (69T5761): this work dispels initial doubts regarding the mechanism of this reaction.

Page 294

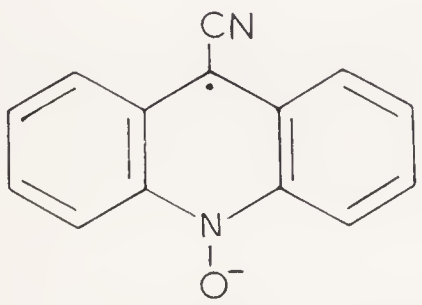
Abramovitch and Singer have reported that imidoyl chlorides react with *N*-oxides to yield *alpha*-substituted derivatives of type *25A* via intermediates *23A* and *24A*. The reaction, which is analogous to the reaction of *N*-oxides with acyl anhydrides (Section III-4C*ii*), is stated to be general and has obvious preparative importance (69JA5672).



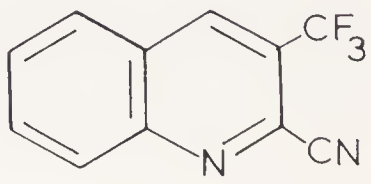
23A 24A 25A

Page 300

Cyanide ion will, exceptionally, add to free acridine 10-oxide and the adduct can be stabilized by air oxidation to yield the radical anion *26A* (70JO96). Similarly, 3-trifluoromethylquinoline 1-oxide yields the nitrile *27A* under mild conditions (69CT2335).



26A



27A

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Table 3.36

Quinoline 1-oxide	3-trifluoromethyl	2	69	69CT2335
	4-trifluoromethyl	2	51	69CT2335

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Table 3.40

Phenazine 10-oxide	2-nitro	$CH_2(CO_2Et)_2$	—	—	—	66G1630

(66G1630 S. Pietra and G. Casiraghi, *Gazz. Chim. Ital.*, 1966, **96**, 1630.)

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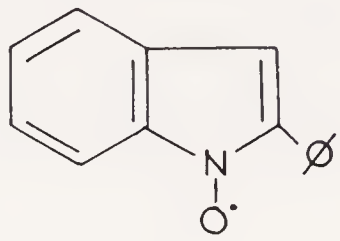
* Various biquinolyls formed by refluxing 4-nitroquinoline 1-oxide with 4-hydroxyquinoline 1-oxide in methanol for long periods are considered to arise by free radical reactions (69CT2178).

† Recent examples (69G885) include electron abstraction from 1-hydroxy-2-phenylindole by various azoxy and azo compounds, including pyridine 1-oxide derivatives, to yield a variety of products derived from dimerization or oxidation/reduction of the radical *28A*.



28A

Page 323

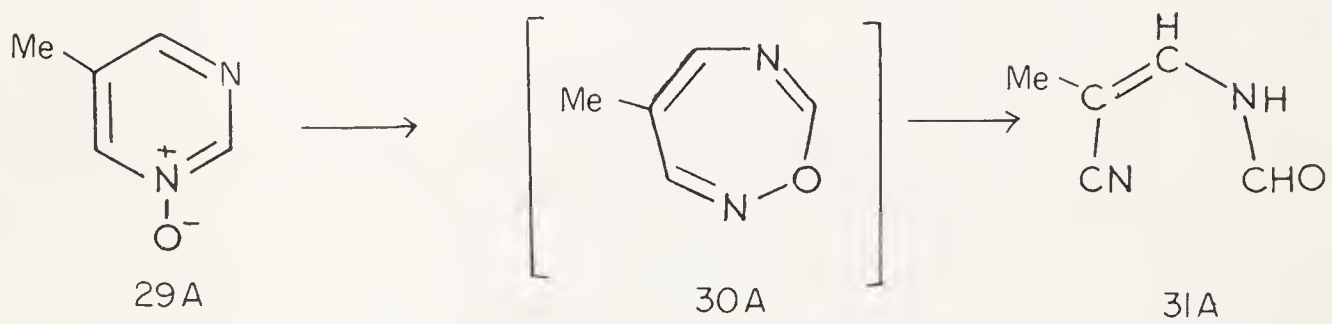
Recently support for the rearrangement of intermediates of type *455* into *456* in hydroxylic solvents and into *460* (followed by further reaction to give *459*) in non-hydroxylic solvents has been adduced from detailed studies of the photolysis of tetrahydroacridine 10-oxide (69CT1290) and of 3- and 4-phenylquinoline 1-oxide (69AS2149).

Page 325

The photolysis of 9-cyanoacridine 10-oxide yields four products: a mechanism similar to that discussed for quinoline 1-oxides has been proposed (69CT1294).

Page 326

5-Methylpyrimidine 1-oxide (*29A*) on irradiation in benzene yields (in addition to phenol and 5-methylpyrimidine) the nitrile *31A* which is considered to arise by isomerism of the oxadiazepine *30A* (69TL4899).



29A 30A 31A

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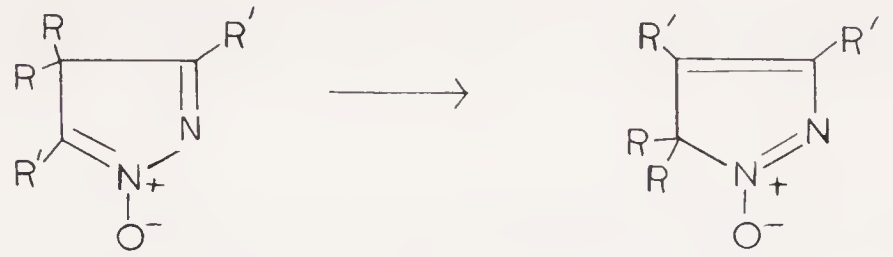
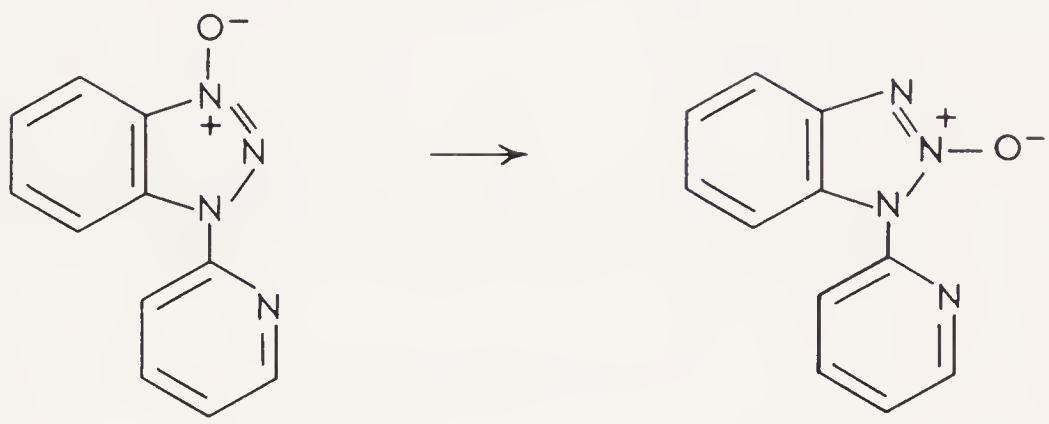
4*H*-Pyrazole 1-oxides undergo photochemical rearrangement to give the isomeric 5*H*-pyrazole 1-oxides (*32A* → *33A*) (70CH289). Hubert and

Anthoine have reported a very interesting isomerization of the benzotriazole 3-oxide *34A* to the isomeric 2-oxide (*35A*) on irradiation : some deoxygenation also occurs (69BB553).



32A 33A



34A 35A

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Many further examples of the reaction of benzofuroxans with enolate anions and related compounds have been reported; reaction also occurs with quinones to give phenazine 5,10-dioxides [69AG(E)596].

Page 336

A similar rearrangement of pteridine 5-oxides into purines has been reported, together with labelling experiments, which is consistent with a mechanism of type *561* → *564* [69AG(E)608].

Page 337

Molecular orbital calculations have been only partially successful in determining the position of the tautomeric equilibria arising from such spontaneous ring-opening reactions of unsymmetrical derivatives (69T4179).

Page 338

Further work which has appeared on the isomerization of furoxans clarifies anomalies in the literature concerning methyl-*p*-anisylfuroxan [69J(C)1901].

Page 340

It has been claimed that both tautomers of certain triarylimidazole 3-oxides can be isolated by recrystallization under controlled conditions (69CB4177). Recent chemical evidence (69BJ3204) for the conclusion that imidazole 3-oxides exist in the 1-hydroxyimidazole form is equivocal and the question remains open.

Page 342

Russian workers (69KG727) have used infrared spectral data to show that 2-aminoquinoxaline 1-oxide is protonated on the *N*-oxide oxygen atom in its salts, but that 2-aminoquinoxaline 4-oxide takes up the proton at the cyclic nitrogen atom in the 1-position. The amino group directs the proton addition, as might be expected.

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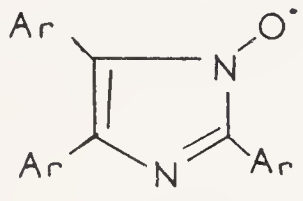
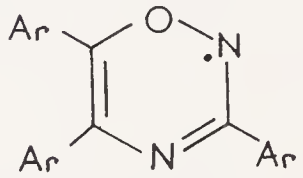
Imidazole 3-oxides (tautomeric with 1-hydroxyimidazoles) also yield free radicals (*36A*) by hydrogen abstraction; these rearrange to more stable radicals of type *37A* (70CB296).



36A



37A

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2-Lithiopyridine 1-oxides also react with sulphur and oxygen affording convenient synthetic routes to 1-hydroxy-2-pyridinethiones and 1-hydroxy-2-pyridones, respectively (69JH989).

Page 348

For π-complex formation between 4-nitroquinoline 1-oxide and phenol, see reference 69JJ994, and for complexes with methyl-benzenes and -anilines, see reference 69JJ1379. Pyridine 1-oxides form charge-transfer complexes with the silver salt of trinitromethane (69IZ2336).

Page 377

N-Oxides are deoxygenated by dimethyl sulphoxide to give the parent heterocycle together with by-products; for example, 4-benzylpyridine 1-oxide yields 4-benzylpyridine, 4-benzoylpyridine, and 1,2-diphenyl-1,2-di(4-pyridyl)ethane (69TL3619).

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Table 4.04

$-COCH_3 \rightarrow -COCH_2CH_2CO_2Et$	pyridine 1-oxide	2	69AP900

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2-Carboxypyridine 1-oxides form chelate complexes with trivalent boron atoms (69CB4025).

Page 383

2-Carboxy-6-methylpyridine 1-oxide yields 6-methyl-2-pyridone on treatment with acetic anhydride (69BJ3350).

Page 394

Table 4.06

Pyridine 1-oxide	2-Br	NaSR		—	70–80	69AS2075

Page 395

Table 4.06

Pyridine 1-oxide	4-Br	NaSPh	3-HO-2-SEt-6-Me	37	69AS2075

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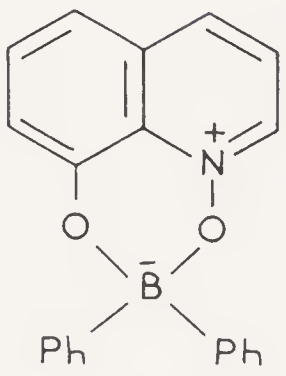
8-Hydroxyquinoline 1-oxide forms chelates, e.g. *38A*, with boron compounds (69CB4025).



38A

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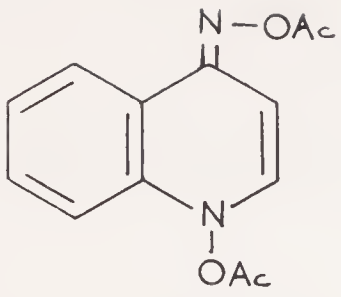
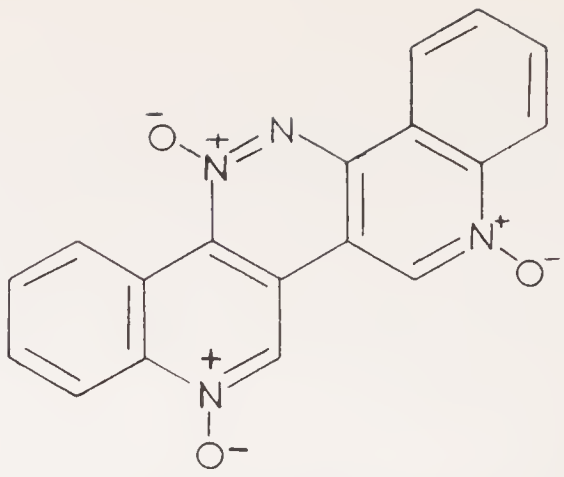
4-Hydroxyaminoquinoline 1-oxide forms the diacetyl derivative *39A* which undergoes ready homolysis of the N-O bonds to form free radicals (69CT1344). Further studies on the air oxidation of 4-hydroxyaminoquinoline 1-oxide indicate that the 4-nitroso analogue is formed as an intermediate (69CT2181); in alkaline solution pyridazino[3,4-*c*:5,6-*c*′]-biquinoline derivatives are formed, e.g. *40A*, probably via free radical intermediates (69CT2389).



39A



40A

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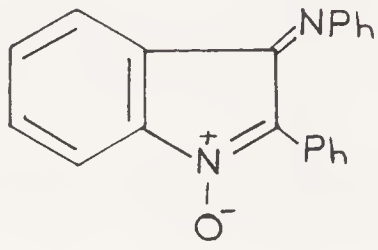
f. Imino N-*Oxides*

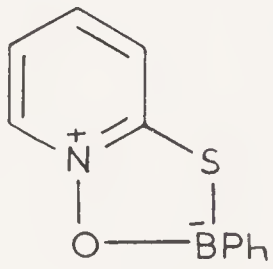
Imino *N*-oxides of type *41A* behave as strong hydrogen abstracting agents and can oxidize phenylhydrazines and other compounds (69AN315; 69G895).



41A

Page 444

1-Hydroxy-2-pyridinethione reacts with diphenylboronic acid to give the chelate compound *42A* (69N636).



42A

Page 445

1-Hydroxy-2-pyridinethiones react with sulphenyl chlorides to yield 2-(R-S-S)-PyO type compounds, the reactions of which have been studied [69LA(727)35].

Subject Index

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