PYRIDINE
AND
ITS DERIVATIVES

SUPPLEMENT
PART ONE

Edited by
R. A. Abramovitch
University of Alabama

AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS
NEW YORK • LONDON • SYDNEY • TORONTO

PYRIDINE AND ITS DERIVATIVES

SUPPLEMENT IN FOUR PARTS
PART ONE

This is the fourteenth volume in the series
THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS
A SERIES OF MONOGRAPHS
ARNOLD WEISSBERGER and EDWARD C. TAYLOR
Editors

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TO THE MEMORY OF

Michael

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

Arnold Weissberger

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Preface

Four volumes covering the pyridines were originally published under the editorship of Dr. Erwin Klingsberg over a period of four years, Part I appearing in 1960 and Part IV in 1964. The large growth of research in this specialty is attested to by the fact that a supplement is needed so soon and that the four supplementary volumes are larger than the original ones. Pyridine chemistry is coming of age. The tremendous variations from the properties of benzene achieved by the replacement of an annular carbon atom are being appreciated, understood, and utilized.

Progress has been made in all aspects of the field. New instrumental methods have been applied to the pyridine system at an accelerating pace, and the mechanisms of many of the substitution reactions of pyridine and its derivatives have been studied extensively. This has led to many new reactions being developed and, in particular, to an emphasis on the direct substitution of hydrogen in the parent ring system. Moreover, many new and important pharmaceutical and agricultural chemicals are pyridine derivatives (these are usually ecologically acceptable, whereas benzene derivatives usually are not). The modifications of the properties of heteroaromatic systems by *N*-oxide formation are being exploited extensively.

For the convenience of practitioners in this area of chemistry and of the users of these volumes, essentially the same format and the same order of the supplementary chapters are maintained as in the original. Only a few changes have been made. Chapter I is now divided into two parts, Part A on pyridine derivatives and Part B on reduced pyridine derivatives. A new chapter has been added on pharmacologically active pyridine derivatives. It had been hoped to have a chapter on complexes of pyridine and its derivatives. This chapter was never received and it was felt that Volume IV could not be held back any longer.

The decision to publish these chapters in the original order has required sacrifices on the part of the authors, for while some submitted their chapters on time, others were less prompt. I thank the authors who finished their chapters early for their forebearance and understanding. Coverage of the literature starts as of 1959, though in many cases earlier references are also given to present sufficient background and make the articles more readable. The literature is covered until 1970 and in many cases includes material up to 1972.

I express my gratitude to my co-workers for their patience during the course of this undertaking, and to my family, who saw and talked to me even less than usual during this time. In particular, I acknowledge the inspiration given me by the strength and smiling courage of my son, Michael, who will never know how much the time spent away from him cost me. I hope he understood.

R. A. ABRAMOVITCH

University, Alabama

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PYRIDINE AND ITS DERIVATIVES

SUPPLEMENT IN FOUR PARTS

PART ONE

This is the fourteenth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

CHAPTER IA

Properties and Reactions of Pyridines

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I. Introduction

The first edition of this series surveyed the rapid development of pyridine chemistry through 1959. Since that time, as in all fields of chemistry, the volume of the pyridine literature has expanded tremendously. This review treats some of the major advances in studies of the properties and reactions of pyridine derivatives since 1959. As in the first edition, this chapter emphasizes the differences between pyridine chemistry and benzene chemistry.

In the intervening decade or so, the greatest advances have probably been the development of various spectroscopic methods and the application of these techniques to more detailed studies of the physical properties of organic compounds, tremendously simplifying physical organic chemical investigations, as well as the discovery of new substitution reactions of this ring system. With these analytical techniques available, many more reaction mechanisms have been investigated more thoroughly than was ever possible before. This, in turn, has contributed greatly to the very rapid growth of pyridine literature. Equally significant is the fact that mechanistic and orientation studies are being carried out kinetically and quantitatively at an accelerated rate.

This chapter follows the general pattern set in the first edition, starting with a presentation of the physical properties of the pyridines, followed by a discussion of their chemical reactivity. The effect of the pyridine nucleus on the reactivity of functional groups is treated, and finally a brief discussion of free energy relationships in this system is given. No attempt at exhaustive coverage has been made; instead, references to articles reviewing the various topics discussed are given wherever possible.

The preparation and properties of the reduced pyridines are taken up in Part B of this chapter.

II. Physical Properties

1. Basicity

Most physical properties of pyridine derivatives reflect an interaction between substituents and the pyridine ring, and this is especially so of basicities and dipole moments.

Several groups have studied the effect on pK's of varying the substituent at a particular nuclear position (1–4) or the effect of changing the nature of the substituents (5, 6). The pK_a's of a series of 4-substituted nicotinic acid-1-oxides have also been measured (7). The ionization constants of substituted pyridines have been tabulated, and effects of substituents discussed (8) in terms of their mesomeric, inductive, and steric effects. Substituents at the 2- and 4-positions can influence the basic strength by stabilizing the conjugate acid through mesomeric and/or inductive electron release, or, vice versa, by destabilizing the conjugate acid through a *-M* or *-I* effect. The pK_a's of a series of 3-substituted pyridines were correlated with the σ-constants of the substituents (9) and these studies were extended (5, 10). Correlations of pK_a's of 2- and 4-styrylpyridines (11) and of 4-*R*-pyridinium ions (12) with substituent constants have also been reported. The pK_a's of some alkylpyridines are discussed in Chapter V.3.A.

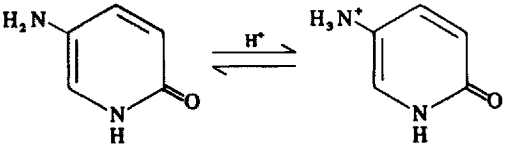
Clarke and Rothwell (13) found a linear relation between the pK_a of the base and the rate of formation of alkyl pyridinium salts. 2-Substituted pyridines gave a different line but with the same slope as that for the 3- and 4-substituted derivatives. This "*ortho*-effect" was not attributed to a steric effect *per se*, as originally suggested by Brown and Kanner (14) because of the small steric size of the proton. McDaniel and Özcan's reinvestigation (15) of 2,6-di-*tert*-butylpyridine supported this view, finding that the lowered pK_a was due to steric hindrance to solvation of the cations rather than to strain involving the bound proton. A similar conclusion was reached on the basis of the measurement of the heats of neutralization of pyridine, the picolines, and 2,6-lutidine, the values being extrapolated to infinite dilution (16) (*cf.* 17).

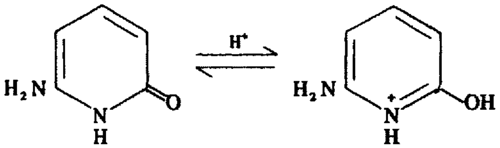
Jaffé and Doak (18) and later Jaffé (19) proposed a general equation relating the p*K* of substituted pyridine-1-oxides to the substituent constant σ^R of the group attached to the ring:

$$pK = (1.89 \pm 0.07)\sigma^R + 0.812$$

where σ^+ is used for mesomerically electron donating substituents, and σ^- for mesomerically electron withdrawing substituents. 2-Substituted pyridine-1-oxides have also received the Hammett treatment (20).

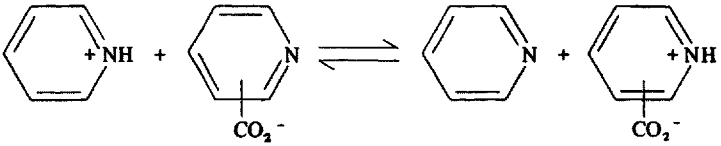
Ionization constants have provided a means of studying tautomeric ratios in substituted pyridines such as the amino- and hydroxypyridines (8, 21). From a consideration of the ionization constants and u.v. spectra of amino-2 (and 4)-pyridones and their *O*- and nuclear *N*-methyl derivatives it has been established that protonation of 3- and 5-amino-2-pyridone and 3,4-diamino-2-pyridone occurs first at the 3-(or 5)-amino group, but 4- and 6-amino-2-pyridone and 2- and 3-amino-4-pyridone are protonated first at the oxygen atom (22). First protonation of dimethylaminopyridines and their *N*-oxides occurs on the ring nitrogen (pyridines) or at the *N*-oxide oxygen (23).





Hammett correlations have been used (24) to evaluate the tautomeric equilibria in a number of 2-arylsulfonamidopyridines.

The proton transfer reactions:



have been studied (25), and it was concluded that the entropy change results largely from electrostatic effects, while ΔH^0 is a result of both electrostatic and conjugative effects.

A correlation was observed between the IR spectral shifts ($\Delta\nu$) due to hydrogen-bonding between methanol and a number of alkylpyridines (determined in an inert solvent) and the pK_a of the base. With other substituted pyridines the correlation was not as good (26). Steric hindrance of the basic site

$$\Delta\nu_{\mathrm{MeOH}} = 19.6\ \mathrm{p}K_a + 169\,(\mathrm{cm}^{-1})$$

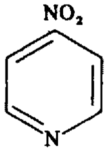
may influence pK_a more than $\Delta\nu$, and differences in solvation effects probably contribute to some of the scatter observed. Also, pK_a's were determined in water where resonance and inductive effects play a major role both in the unprotonated (but hydrogen-bonded) base and in its protonated form (also hydrogen-bonded). Since $\Delta\nu$ values were measured in CCl_4 solution, these are influenced by resonance and inductive effects in the hydrogen-bonded base only. If resonance effects differed markedly on going from unprotonated to the protonated form of a base than correlation of pK_a's with $\Delta\nu$ would not have been expected (26).

2. Dipole Moments

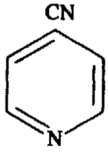
Molecular dipole moments are calculated as the vector sums of the bond moments of the various functional groups in a molecule, assuming no mesomeric interaction between the groups. To the extent that there is an interaction, the experimental dipole moment differs from a theoretical moment calculated on the basis of group moments determined from aliphatic compounds. Because the pyridine ring itself possesses a dipole moment—as opposed to benzene, which does not—mesomeric interactions are more common and more complex in this series.

The determination and application of the dipole moment data in the heterocyclic series, including pyridines and pyridine-1-oxides, have been surveyed (27).

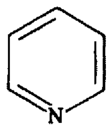
It has been shown previously that electron donating substituents interact with the pyridine ring to a greater extent than with the benzene ring (28). More recent and extensive determinations (29–32) tend to support this and strengthen the conclusion (28) that "electron attracting substituents interact only as much as with benzene if at all." In fact, a comparison of the moments of pyridine (**IA-1**), 4-nitropyridine (**IA-2**), and 4-cyanopyridine (**IA-3**) with those of their carbocyclic analogs (**IA-4** and **IA-5**, respectively) suggests that there may be even less interaction between these -M substituents and the ring in the pyridine series than in the benzene series (33). This is in accord with the finding that the π-electron ring current is larger for pyridine than for benzene (34) (*vide infra*); that is, a greater perturbation of the aromatic ring is needed to produce as great a degree of electron withdrawal in pyridine as in benzene.



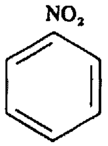
IA-2
1.7 D



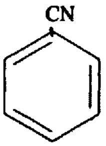
IA-3
1.65 D



IA-1
2.2 D



IA-4
3.97 D



IA-5
4.05 D

The dipole moments of some pyridine-1-oxides have been measured, and generally, these are found to be about 2 D larger than those of the corresponding amine (35). Dipole moments have been used to compare the electron accepting ability of the pyridine-1-oxide ring with that of nitrobenzene and **IA-1**, and have been correlated with substituent constants (32). The dipole moment of pyridine-1-oxide was calculated to be $\mu_{\text{tot}} = 4.78$ D from computed SCF-charge distributions in the ground S_0 state (36). This compares well with the experimentally found value $\mu_{\text{ex}} = 4.78 \pm 0.07$ D.

3. Spectroscopic Properties

In the first edition of this series a brief discussion of the use of ultraviolet and infrared spectroscopy in the elucidation of structural details of pyridine derivatives was given. In the last decade, the definition of spectroscopy has been expanded to include techniques which do not involve the absorption of light energy. In particular, nuclear magnetic resonance, mass, and to some degree, electron spin resonance spectrometry have been valuable additions to the pyridine chemist's "tool chest."

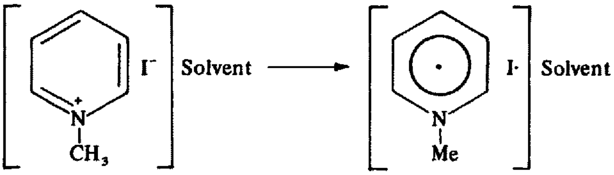
A. *Ultraviolet Absorption*

This topic has been discussed extensively by Schofield (8) who has tabulated the data for the free bases and the cation, anion, and zwitterion where these are applicable (see also Ref. 37). The ultraviolet and visible spectra of monocyclic azines contain a weak, but not forbidden, $n \rightarrow \pi^*$ transition which has no counterpart in carbocyclic compounds (38). The importance of this transition is dependent on the separation between the heteroatom and the potential conjugative substituent (39, 40) and on the nature of the substituents; thus the $n \rightarrow \pi^*$ transition is not observed for 2-bromopyridines because of the inductive effect exerted by the bromine atom (41). Systematic studies of the ultraviolet absorption characteristics of numerous pyridine derivatives have been carried out and summarized (8). The UV spectra of alkylpyridines are discussed further in Chapter V.I.3.B., those of pyridine-1-oxides in Chapter IV.II.8.

Numerous MO calculations have been carried out to predict transition probabilities and differences in energy levels in pyridine and pyridinium salts (42–44, and Ref. cited therein), and also to interpret $n \rightarrow \pi^*$ transitions (45).

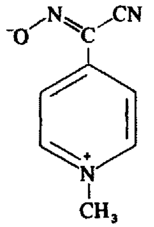
The application of UV spectroscopy to tautomerism of various pyridine derivatives has been very fruitful, since the electronic spectrum of a compound arises from its π-electron system which, to a first approximation, is unaffected by substitution of an alkyl group for a hydrogen atom. A comparison of the UV spectrum of a potentially tautomeric compound with the spectra of the alkylated forms of both tautomers often shows which is the predominant tautomer in the unalkylated species (for review, see Ref. 46). For example, equilibrium constants were derived from the p*H* dependency of the ultraviolet spectra of pyridoxine and pyridoxyl analogs in aqueous solution, thus providing information about the *in vivo* action of the biologically important but more complex compounds (47). The clear differences in the UV spectra of the thiopyridone-pyridyl sulfide tautomers have been described (48, 49).

The color of some heteroaromatic salts in solution and in the solid state has been attributed to charge-transfer transitions. In these cases, the more polarizable the anion the deeper is the color. The energies of the charge-transfer bands are related to the electron affinity of the cation, but not to the nucleophilic atom localization energies of the carbon atoms in the heterocyclic cation. This is in agreement with a delocalized model of the excited state for the charge-transfer transition (50):



The ultraviolet spectra of pyridine-1-oxides have been discussed in terms of hydrogen bonding and donor-acceptor behavior (51).

Since the ultraviolet maximum of pyridine-1-oxide is sensitive to solvent polarity, its use in determining "Z-values" for solvents has been advocated (52). Because of intramolecular charge transfer from oximate oxygen to the pyridinium ring, 1-methyl-4-cyanoformylpyridinium oximate (CPO) has two electronic absorption bands whose positions are measures of solvent polarity (53a). Intramolecular charge transfer phenomena have also been observed for several *N*-arylalkylpyridinium ions (54). The effect of solvents on the ultraviolet spectra of *N*-oxides has been discussed (53). Phosphorescence spectra, excitation


(CPO)

spectra, and the degree of polarization of 4-nitropyridine-1-oxide were recorded under degassed conditions at 77°K (55). The phosphorescence spectra show a blue shift in some alcohol solvents compared with those in ether, indicating hydrogen bonding interaction $\overset{+}{N}-\overset{-}{O}\cdots HOR$ in the protic solvents. The assignments and nature of excited states were compared with the results of PPP-SCF-MO-CI calculations. The π-π^* band appearing in the longest wavelength region has the character of an intramolecular charge transfer-band from the *N*-oxide group to the NO_2 group. The orbital electron distributions at the highest occupied (HOMO) and lowest vacant (LVMO) molecular orbitals were calculated (the charge transfer arises by one-electron transfer from the HOMO to the LVMO). Applications of the use of ultraviolet spectral data on *N*-oxides to the determination of pK_a values, intramolecular hydrogen bonding, charge transfer complexes, tautomerism of hydroxy-, amino-, and mercaptopyridine-1-oxides, among others, have been summarized (56).

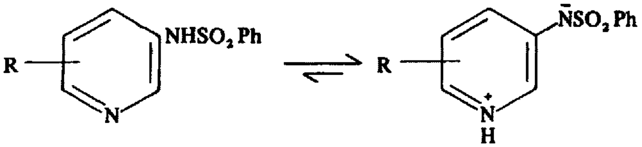
B. *Infrared Absorption*

As more and more compounds have been examined, correlations peculiar to pyridine ring substitution have become apparent. For example, correlations have been found for 2- and 3-substituted pyridines in the 600 to 650 cm^{-1} region; 4-substituted derivatives resemble their benzene analogs (57). In terms of the C-H out-of-plane bendings, pyridine may be treated as a monosubstituted benzene. Extending the analogy, a 2,3-disubstituted pyridine may be considered to be a 1,2,3-trisubstituted benzene, and two bands are indeed found at 813 to 769 and 752 to 725 cm^{-1} (58). Similarly, a 2,5-disubstituted pyridine shows the two expected bands at 828 to 813 and 735 to 724 cm^{-1} (58), characteristic of a 1,2,4-trisubstituted benzene. A distinction between 2,3- and 2,5-disubstituted pyridines was found in the C=C and C=N stretching vibration region (59): 2,3-disubstituted derivatives exhibit a band at 1578 to 1588 cm^{-1}, and 2,5-disubstituted derivatives one at 1599 to 1605 cm^{-1}, which is a useful correlation unless absorption by substituents obscures this region. Similarly, 3,5-bis(carbalkoxy)pyridines unsubstituted at C-4 exhibit two bands between 1540 to 1580 and 1590 to 1610 cm^{-1}, but those bearing a 4-substituent have only one band in the range of 1500 to 1700 cm^{-1} (60). Katritzky and Ambler (61) have surveyed and assigned the bands due to pyridine, pyridine complexes, salts, and *N*-oxides, as well as the influence of the nature and position of substituents upon the intensities of the characteristic modes of vibration. The IR spectra of alkylpyridines are discussed further in Chapter V.13.B.

Tautomeric equilibria and hydrogen bonding have been investigated extensively (61). Particular use has been made recently of the variation in the C=O (62) and C=N (63-65) stretching frequencies in tautomeric mixtures.

Infrared spectroscopy has been used to examine the extent of the mesomeric interaction between the *N*-oxide oxygen of pyridine-1-oxides and substituents (66-69). In one case, a lack of correlation was attributed to a coupling of absorption frequencies (70). In another instance, a correlation was found using corrected and derived σ values (69). The infrared spectra of pyridine-1-oxides is discussed further in Chapter IV.II.7.

The infrared spectra of a number of 3-benzenesulfonamidopyridines and *N*-sulfonyliminopyridinium ylides have been measured (71). The 3-sulfonamides exhibited two strong SO_2 bands in the normal range of 1320 to 1340 and 1160 to 1170 cm^{-1}. The NH stretching band appeared at 2880 to 2650 cm^{-1}, however, suggesting that the sulfonamides existed predominantly in the zwitterionic form in the solid state. In contrast to the sulfonamides, the



N-sulfonylimino ylides exhibited two strong bands due to SO_2 in the 1270 to 1285 and 1130 to 1140 cm^{-1} regions. The bathochromic shift may be due to the delocalization of the electron pair on the imino nitrogen onto the sulfonyl group, rather than toward the pyridine ring, so that back-donation may not be important in these ylides.

Assignments of the Raman bands have been made for a series of pyridines (72), picolines (73), and their *N*-oxides.

C. *Nuclear Magnetic Resonance Spectroscopy*

The application of NMR spectroscopy to pyridine chemistry has been discussed extensively (74–76) and is not covered in detail here. Reduced symmetry in pyridine (C_{2v} relative to D_{6h} for benzene) and electronic perturbations of the ring by the nitrogen atom cause unsubstituted pyridine, pyridine-1-oxide, and simple pyridinium salts to show three magnetically nonequivalent groups of protons. The order of absorption is H-2 $<$ H-4 $<$ H-3 for pyridine, H-2 $\ll$ H-4 $<$ H-3 for pyridinium salts, but H-2 $\ll$ H-3 $<$ H-4 for pyridine-1-oxide (77) (Table IA-1). The change in order for pyridine-1-oxide is due to mesomeric "back-donation" by the *N*-oxide function, increasing the electron density at C-4 relative to C-3 which can only be affected by the strong inductive withdrawal by the *N*-oxide (for more details, see Chapter IV.II.6).

TABLE IA-1. Chemical Shifts (δ) for Proton Resonances[a] of Pyridine, Pyridine-1-Oxide, and Pyridinium Ion in CCl_4[b]

	Pyridine	Pyridine-1-oxide	Pyridinium ion
H-2	8.53	8.10	8.83
H-3	7.19	7.28	8.19
H-4	7.58	7.08	8.73

[a] Adapted from Ref. 77.

[b] Pyridinium ion values from measurements of pyridines in 18 *N* D_2SO_4

The substitution pattern of a pyridine derivative can be determined from the observed spin-spin coupling pattern. The individual coupling constants (J_{ij}) fall