THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

PYRIDINE AND ITS DERIVATIVES

SUPPLEMENT PART TWO

Edited by

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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.

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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 by a nitrogen 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
June 1973

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CHAPTER IV

Pyridine-1-oxides

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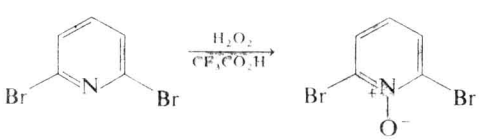
Since the early 1940s, Japanese workers (1), as well as den Hertog (2) in Holland and Colonna (3) in Italy opened up the field of pyridine-1-oxides. The chemistry of these compounds has been reviewed by Katritzky (4a, b), Shaw (5), Abramovitch and Saha (6), and Ochiai (7). For the most part, this chapter is a supplement to the one previously written by Shaw (5) in the 1961 edition of this series. Repetition occurs only for continuity.

I. Preparation

Pyridine-1-oxides may be prepared by the direct oxidation of pyridines with per-acids, or by the introduction or the exchange of substituents in the ring with retention of the *N*-oxide group already present. The latter method permits the synthesis of those *N*-oxides which are not available by direct oxidation, but this method is discussed separately under the appropriate section on the reactions of pyridine-1-oxides. Only a few pyridine-1-oxides have been prepared from nonpyridine precursors.

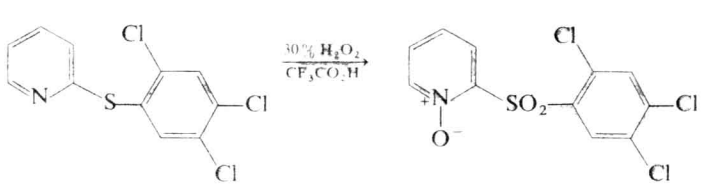
1. Direct Oxidation

Pyridine was first oxidized to the *N*-oxide with perbenzoic acid (8). Perphthalic acid (9) and hydrogen peroxide in glacial acetic acid (10) have also been used. Recently, it has been found that 2,6-dibromopyridine (**IV-1**) can be converted to its *N*-oxide (**IV-2**) with 30% hydrogen peroxide in trifluoroacetic acid in spite of the steric hindrance and the inductive effects of the bromine atoms which prevented *N*-oxidation with perbenzoic or peracetic acid (11). This reagent is also effective in the *N*-oxidation of 2,3,5,6-tetrachloropyridine and 2,3,4,5,6-pentachloropyridine (12), as well as



IV-1 **IV-2**

2-chloro-3-nitropyridine (13), and 2-bromo-5-chloropyridine (14). Using the reagent, 2-(2,4,5-trichlorophenylthio)pyridine (**IV-3**) was converted to the corresponding sulfone-1-oxide (**IV-4**) (15). Oxidation of pentachloropyridine



IV-3 **IV-4**

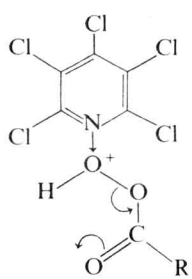
in trichloroperacetic acid at 50° for 5 hr yields the *N*-oxide (ca. 20%) and unreacted starting material (16, 17). Higher temperatures or longer heating caused deoxygenation until the concentration of *N*-oxide fell to ca. 10%.

Loss of oxygen was due to the presence of hydrogen peroxide since prolonged heating of the *N*-oxide in boiling trifluoroacetic acid had no untoward effect. This reaction could involve nucleophilic attack by the *N*-oxide on the peroxy acid, followed by loss of molecular oxygen from the intermediate *N*-peroxide (eq. IV-1) (17a).

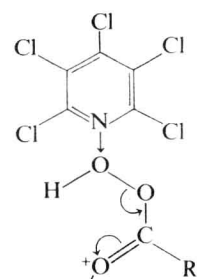
$$C_5H_5N^+—O^-\overset{+}{O}(H)—OCOR \longrightarrow C_5H_5N^+—O—OH + OCOR^- \xrightarrow{-RCO_2H}$$

$$C_5H_5N^+—O—O^- \longrightarrow C_5H_5N + O_2 \qquad \text{(IV-1)}$$

Pentachloropyridine-1-oxide was obtained in high yield (>80%) from the reaction of pentachloropyridine with a mixture of an organic peracid and concentrated sulfuric acid (17b). For best results, the substrate was dissolved in a mixture of sulfuric acid and acetic acid, and hydrogen peroxide, varying in strength from 30 to 90%, was added slowly with stirring at or below room temperature. The success of a mixture of peracid and sulfuric acid in oxidizing weakly basic nitrogen compounds is probably due to enhancement of the electrophilicity of the peroxidic oxygen through protonation of the acid which must ease the transfer of H^+ to the nucleophile, as indicated in **IV-5** and **IV-6** (17b). Substitution of polyphosphoric acid for sulfuric acid usually gave inferior results with these compounds (17b), but a mixture of polyphosphoric and peracetic acid was effective in the *N*-oxidation of 4-methoxytetrachloropyridine. In the presence of sulfuric acid, this compound suffers hydrolysis and gives the corresponding 4-hydroxytetrachloropyridine-1-oxide (17b).

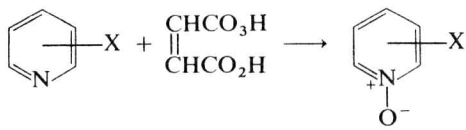


IV-5



IV-6

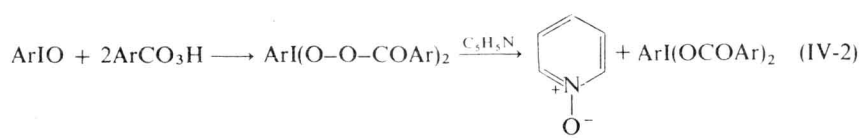
m-Chloroperbenzoic acid has been used for the *N*-oxidation of heterocyclic compounds (18a) and polyarylpyridines (18b). Monopermaleic acid has been shown to be effective in the oxidation of 2-chloro- (19a), 3-methoxy-, 3-fluoro-, and 3-mesylaminopyridine (**IV-7** (19b) to their *N*-oxides (**IV-8**).



IV-7 IV-8

3-Pyridyltetra-*O*-acetyl-β-D-glucopyranoside, 4-pyridyltetra-*O*-acetyl-β-D-glucopyranoside, and 4-pyridyl-β-D-glucopyranoside were converted to the *N*-oxides with perbenzoic acid (20). Vinylpyridines (21) and polyvinylpyridines (22a, b) are also oxidized with peracids to the *N*-oxides.

Recently, a new organic oxidant, (dibenzoyldioxyiodo)benzene, has been used for the preparation of pyridine-1-oxide (85%) in 30 min (eq. IV-2) (23). This reagent is obtained by the reaction of iodosobenzenes with substituted perbenzoic acids in chloroform-methanol (8:1) at 0°. A word of caution: (dibenzoyldioxyiodo)benzenes detonate at 80 to 120° and many spontaneously ignite or detonate upon manipulation in the solid state at room temperature; also manipulation with metal spatulas is not recommended (23).



The formation and properties of pyridine-1-oxides obtained by direct oxidation are given in Table IV-1.

TABLE IV-1. Preparation of Pyridine-1-oxides by Direct Oxidation

Pyridine (R)	Conditions	Properties	Yield (%)	Ref.
Pyridine	H_2O_2, AcOH, Δ, 6 hr	m.p. 66°	95–100	24
	H_2O_2, AcOH	m.p. 64–6°, b.p. 100–105°/1 mm		25
	$ArI(O_2COAr)_2$, 30 min		85	23
2,6-d_2	H_2O_2, AcOH	b.p. 130–131°/9 mm		26
Pyridine, HCl	(i) 50% H_2O_2, AcOH, tungstic acid (ii) conc. HCl		85	27
	(i) molybdic anhydride, 60°, 2 hr (ii) $Ca(OH)_2$ (iii) HCl			27
Pyridine-$^{14}C_2$, HCl	(i) 40% AcO_2H, <80°, 6 hr (ii) HCl	m.p. 180–181°		28

Table IV-1 (*Continued*)

Pyridine (R)	Conditions	Properties	Yield (%)	Ref.
2-Me	H_2O_2, AcOH	b.p. 124–125°/15 mm n_D^{20} 1.5910	84	25
	H_2O_2, AcOH, 1–1.5 hr	b.p. 120–125°/14 mm n_D^{20} 1.591		29
3-Me	H_2O_2, AcOH	m.p. 33–36° b.p. 150°/15 mm	81	25
	H_2O_2, AcOH, 1–1.5 hr	b.p. 150–153°/20 mm		29
4-Me	H_2O_2, AcOH	m.p. 184°	86	25
	H_2O_2, AcOH, 1–1.5 hr	m.p. 183.5–184°		29
4-Me, HCl	(i) 50% H_2O_2, 60°, 6 hr (ii) HCl		72.5	27
2,3-Me_2	30% H_2O_2, AcOH	b.p. 118°/4 mm		30
2,4-Me_2	H_2O_2, AcOH, 70°, 16 hr	b.p. 110°/1 mm	79	25
	30% H_2O_2, AcOH	b.p. 91°/0.3 mm		30
2,5-Me_2	H_2O_2	m.p. 53–58°		31
	30% H_2O_2, AcOH, 80–90°	m.p. 55–57°; picrate, m.p. 122.5°		32
	30% H_2O_2, AcOH, 80°, 10 hr	m.p. 55–57°; picrate, m.p. 122.4–124°		33
	30% H_2O_2, AcOH	b.p. 86°/0.3 mm		30
	30% H_2O_2, AcOH, 70–80°, 10 hr	m.p. 60°	80.5	34
2,6-Me_2	H_2O_2, AcOH, 1–1.5 hr	b.p. 120–123°/21 mm		29
	30% H_2O_2, AcOH	b.p. 107–108°/5 mm	76	35
	30% H_2O_2, phthalic anhydride		35	35
	H_2O_2, AcOH			36
3,4-Me_2	H_2O_2, AcOH, 70–80°, 18 hr	m.p. 138°	77.4	34
	H_2O_2, AcOH			37
4-*t*-Bu-2,5-Me_2	30% H_2O_2, AcOH, 80°, 10 hr	m.p. 77–78°; picrate, m.p. 122.4–124°		33
2,3,6-Me_3	30% H_2O_2, AcOH	m.p. 63°, b.p. 84°/0.2 mm; picrate, m.p. 97–98.5°		30
2,4,6-Me_3	30% H_2O_2, AcOH			30
3-*t*-Bu-2,4,6-Me_3	30% H_2O_2, AcOH, 70–80°	m.p. 120–121°, b.p. 168–170°/15 mm		38, 39
2-Et	H_2O_2, AcOH	b.p. 103–105°/3 mm; picrate, m.p. 134–137°		40
5-Et-2-Me	30% H_2O_2, AcOH	b.p. 120°/2 mm; picrate, m.p. 110°		35
2,6-Et_2		b.p. 120–127°/10 mm	57.8	41
2-Pr	H_2O_2, AcOH, 70°, 3 hr	b.p. 102°/2 mm		42
2,6-Pr_2		b.p. 135–139°/10 mm	57.3	41

Table IV-1 (*Continued*)

Pyridine (R)	Conditions	Properties	Yield (%)	Ref.
2,6-Bu_2		b.p. 162–164°/10 mm	57	41
2,6-Di-*n*-amyl		b.p. 180–183°/8 mm	59.5	41
2-$(CH_2)_7CH_3$		b.p. 140°/0.7 mm n_D^{20} 1.5220		43
2-Methyloctyl	30% H_2O_2, AcOH, cat. H_2SO_4, R.T.	b.p. 137–138°/0.1 mm n_D^{21} 1.5256; picrate m.p. 88–89°		44
2-$(CH_2)_8CH_3$	30% H_2O_2, AcOH, cat. H_2SO_4, R.T.	m.p. 39–40°, b.p 52°/1 mm n_D^{19} 1.5230; HCl, m.p. 85–86°; picrate, m.p. 77–78°		44
2-$(CH_2)_9CH_3$				43
2-$CH[(CH_2)_5CH_3]_2$				43
2-$(CH_2)_{11}CH_3$		m.p. 54–56°		43
2-$(CH_2)_{16}CH_3$	AcO_2H	m.p. 67–67.5°		43
	35% H_2O_2, AcOH, 78–80°, 12 hr	m.p. 70–72°		45
2-Tridecyl	BzO_2H in $CHCl_3$, 0.16 hr	m.p. 55–56°		43
3-Tridecyl	BzO_2H in $CHCl_3$, 0.16 hr	m.p. 54–55°		43
4-Tridecyl	H_2O_2, AcOH	m.p. 61–63°		43
3-Trimethylsilyl	H_2O_2, AcOH	b.p. 146°/6 mm; picrate, m.p. 107–108°		46
4-Et	AcO_2H	m.p. 106–109°	84	47
4-Heptadecyl	35% H_2O_2, AcOH, 75–80°, 12 hr	m.p. 31–32°		45
1,2-Di-(4-pyridyl)ethane		m.p. 236–238°		48
1,2-Di-(6-methyl-2-pyridyl)ethane	30% H_2O_2, AcOH, 70–80°, 3 hr	m.p. 183–185°		49
1,2-Di(4-ethoxy-3-pyridyl)ethane	AcO_2H			50
1,2-Di-(6-methyl-2-pyridyl)ethylene	30% H_2O_2, AcOH, 70–80°, 3 hr	m.p. 247.5–249°		49
1,3-Di-(2-pyridyl)propane	H_2O_2, AcOH	m.p. 212–213°; picrate, m.p. 138°	8	51
1,5-Di-(4-pyridyl)pentane		m.p. 218–220°		48
1,6-Di-(2-pyridyl)hexane		m.p. 140–141°		48
1,6-Di-(3-pyridyl)hexane		m.p. 186–188°		48
1,6-Di-(4-pyridyl)hexane		m.p. 241–244°		48
1-(2-Pyridyl)-6-(3-pyridyl)hexane		m.p. 108–110°		48
1-(2-Pyridyl)-6-(4-pyridyl)hexane·$\frac{1}{2}H_2O$		m.p. 135–137°		48
1,7-Di-(4-pyridyl)heptane		m.p. 152–154°		48
1,8-Di-(4-pyridyl)octane		m.p. 155.7°		48