PYRIDINE AND ITS DERIVATIVES

SUPPLEMENT PART FOUR

Edited by

R. A. Abramovitch

University of Alabama

AN INTERSCIENCE® PUBLICATION

JOHN WILEY & SONS

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TO THE MEMORY OF

Michael

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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.

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 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

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CHAPTER XIII

Pyridine Alcohols

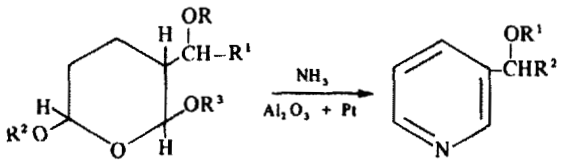
ELLIS V. BROWN

University of Kentucky, Lexington, Kentucky

I. Preparation

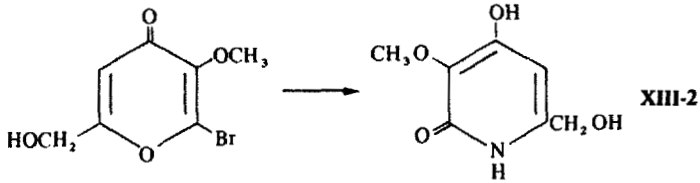
1. From Nonpyridine Starting Materials

Although pyrones have been heated with ammonia to give pyridines, 3-(1-alkoxyalkyl)pyridines recently have been prepared by heating 2,6-dialkoxy-3-(1-alkoxyalkyl)tetrahydropyrans with ammonia over aluminum oxide impregnated with platinum or palladium (1) **(XIII-1)**. 4-Hydroxy-6-hydroxymethyl-3-methoxy-2-pyridone was synthesized from 2-bromo-6-hydroxymethyl-3-

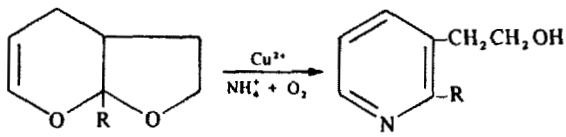


XIII-1

methoxy-4-oxo-4*H*-pyran and aqueous ammonia (2) **(XIII-2)**. 1,7-Dioxaindans **(XIII-3)** are converted to 2-(3-pyridyl)ethanols by oxygen and cupric ion in ammoniacal solution (3).



XIII-2



XIII-3

2. Oxidation of Side Chains

The picolines, 2-ethylpyridine and 4-isopropylpyridine, have been oxidized to the corresponding alcohols with air using various catalysts. The reaction is

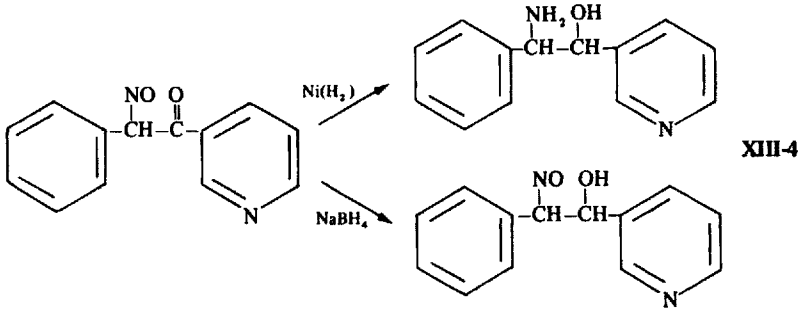
believed to proceed by a radical mechanism (4). The oxidation of alkylpyridines to alcohols by manganese dioxide-containing ores was deemed unprofitable because of the quantity of oxidizing agent needed (5).

3. Hydrolysis of Side-Chain Halides

2,6-Bis(chloromethyl)pyridine on acid hydrolysis produced the bis-alcohol, an intermediate in the preparation of polyurethanes (6).

4. Reduction of Aldehydes and Ketones

Pyridine aldehydes and ketones have been reduced to carbinols but recent papers deal with ketone reduction only. An interesting reducing agent used on a series of 4-pyridylmethyl ketones is tetramethylammonium borohydride (7). 3-Pyridyl 2-thiazolyl ketone was reduced by Raney nickel in acetic acid to the carbinol (8, 9). Lithium aluminum hydride was used to reduce 2-(α-bromophenacyl)pyridine to *threo*-1-phenyl-2-bromo-2-(2-pyridyl)ethanol (10), and the same procedure was used to prepare the corresponding chlorohydrin. 4-(Bromoacetyl)pyridine was also reduced to the halohydrin by sodium borohydride (11). Lithium aluminum hydride was also used to reduce 3-benzoyl-4-phenylpyridine to the carbinol (12). Sodium metal in liquid ammonia followed by the appropriate alkyl halide gave a series of phenylpyridylalkylaminocarbinols (13, 14) (see Table XIII-17). Hydrogenation of 4-acetylpyridine to the carbinol was effected by a palladium catalyst and hydrogen (15). Nitrosobenzyl pyridyl ketones were reduced by Raney nickel and hydrogen to the amino alcohols or by sodium borohydride to the nitroso alcohols (16) **(XIII-4)**.



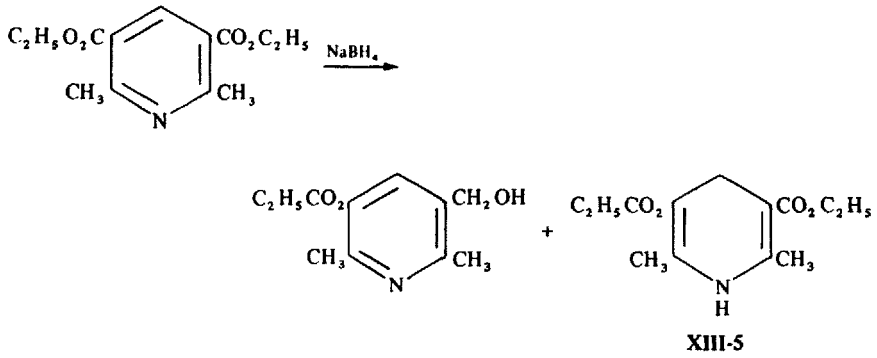
XIII-4

In vivo reduction of 3-acetylpyridine to 3-pyridinemethylcarbinol was effected by the rat (17). The adrenal glands of several species reduced 2-methyl-1,2-bis

(3-pyridyl)propanone to the alcohol, and the same change was brought about by sodium borohydride (18). Sodium borohydride was also used to prepare phenyl-2-pyridylcarbinol from an ozonolysis product (19).

5. Reduction of Acids and Esters

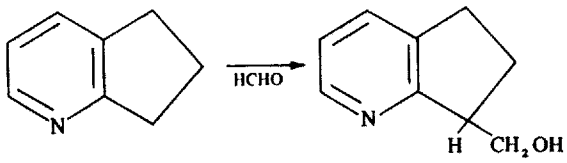
Pyridine esters were reduced with lithium aluminum hydride to the carbinols. Ethyl nicotinate, ethyl 4-methylnicotinate, ethyl 2,3-di-(2-pyridyl)propane-2-carboxylate, the corresponding butane, and many others were reduced in this way (20–23). Certain esters, such as diethyl pyridine-2,6-dicarboxylate, can be reduced with sodium borohydride (24–26) although there is the danger of nuclear reduction with this agent (26, 27) **(XIII-5)**.



XIII-5

6. Aldol Condensation of Alkylpyridines with Aldehydes

Methyl groups at the 2-, 4-, and 6-positions in pyridine undergo reaction with formaldehyde to give the carbinols and, in some cases, dihydric alcohols. For example, 5-ethyl-2-methylpyridine gives 5-ethyl-2-(2-hydroxyethyl)pyridine (28). 2,4-Lutidine gives a mixture of 2-(2-hydroxyethyl)-4-methylpyridine and 4-(2-hydroxyethyl)-2-methylpyridine, while collidine gives a mixture containing 2,4-dimethyl-6-(2-hydroxyethyl)pyridine (29). 2,6-Lutidine can react either at one or at both methyls (30). A number of industrial preparations of vinylpyridines start with various methylpyridines to give the carbinols (31–35). Arrhenius parameters and rate constants were determined for the formation and dehydration of 2-(2-hydroxyethyl)pyridine (36). Isopropenylpyridines were prepared from 2- and 4-ethylpyridine and formaldehyde through the 2-(2- or 4-pyridyl)propanols (37). A somewhat more novel reaction was the condensation of (2,3-pyrido)cycloparaffins with formaldehyde (38) **(XIII-6)**.



XIII-6

7. From Organometallic Compounds and Pyridine Aldehydes, Ketones, and Esters

2-Pyridine aldehyde has been treated with a number of substituted phenylmagnesium halides to give the corresponding carbinols (39, 40). Numerous 3-pyridyl ketones have been converted to carbinols by Grignard reagents (8, 12, 41–46) as have 4-pyridyl ketones. Several amino alcohols were prepared by treating 2- and 4-pyridyl aminoalkyl ketones with Grignard reagents (47, 48). From 2- and 4-benzoylpyridines with organomagnesium halides various tertiary alcohols were prepared and these were resolved (49). 2-(2-Carbethoxycyclopropyl)pyridine, 5-(2-carbethoxycyclopropyl)pyridine, and 4-(2-carbethoxycyclopropyl)pyridine were converted to carbinols by various Grignard reagents (50–52). Organosodium compounds gave carbinols with pyridine ketones (53). Pyrazinyllithium compounds have been used to prepare pyridylpyrazinylcarbinols (54).

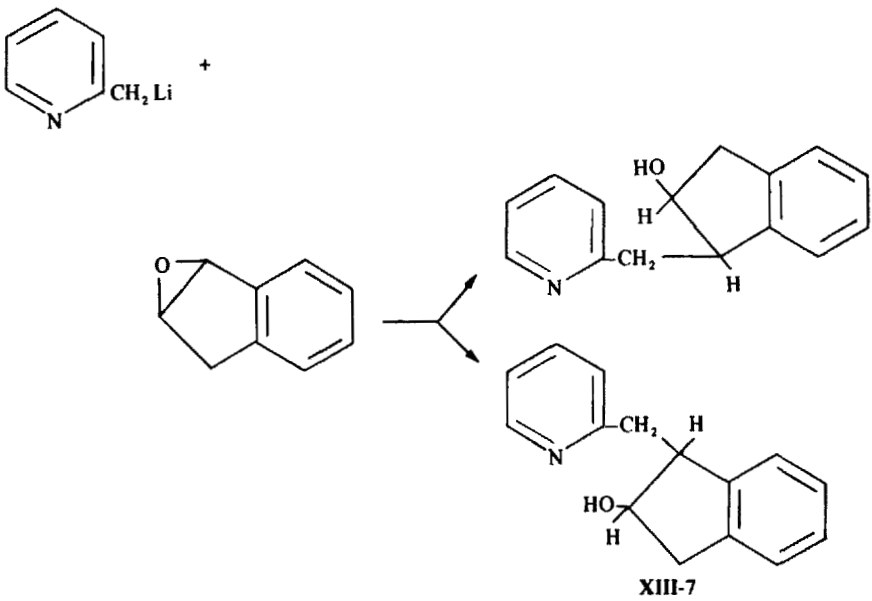
8. From Metallopyridine Compounds

Numerous alcohols have been prepared by the reaction of α-picolyllithium with various ketones (48, 53, 55–61). 2-Ethylpyridine (62), 2,4-lutidine, and 2,4,6-collidine (63) underwent lithiation at the 2-position, and this was followed by carbinol formation (29). 2-Picolyllithium reacted with acrylaldehyde (acrolein) to give the unsaturated carbinol (64). 2-Picolyllithium (65) and various alkylpyridines (66) with epoxides have given carbinols (**XIII-7**), but with chloromethyl methyl ether ethers were formed (67, 68) (**XIII-8**).

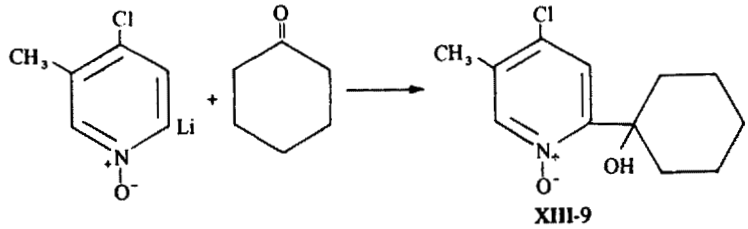
2-Benzylpyridine was converted to the organolithium compound and then treated with various ketones to form phenyl-2-pyridylcarbinols (69–71).

3-Picolylsodium reacted with formaldehyde to give the alcohol (70). The sodium and potassium derivatives of 3-benzylpyridine have been converted to carbinols by reaction with ketones (71, 72).

Organometallic derivatives of 4-picoline have been reacted with benzoyl chloride (73–75), with cyclohexanoyl chloride (76, 77), various esters (75, 78, 79) and ketones (53, 80) to give the 4-pyridylcarbinols. 4-Benzylpyridine lithium derivative has been reacted with ketones to give 4-pyridylcarbinols (70,

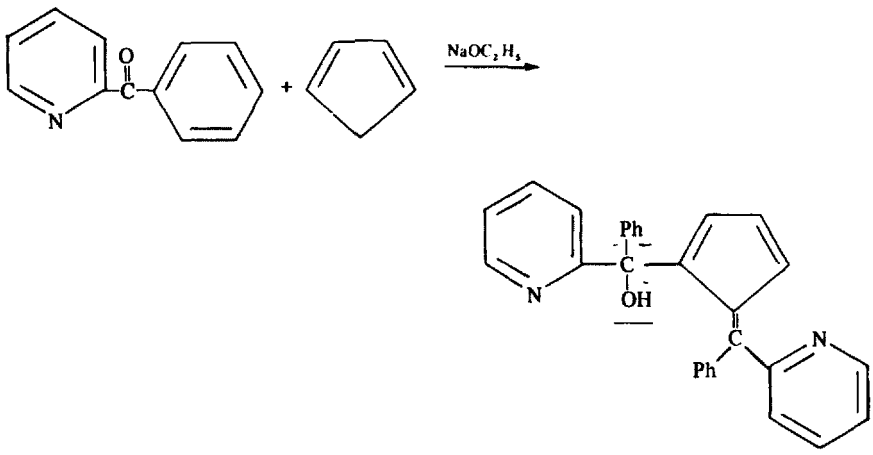


71). 2-Pyridyllithium and 3,4,5-trimethoxybenzophenone afforded the carbinol (81) and the 6-lithium derivative of 4-chloro-3-methylpyridine-1-oxide reacted with cyclohexanone to give the tertiary alcohol (**XIII-9**) (82) (see also Chapter



IV). Many ring-lithiated pyridines have given carbinols when treated with ketones (83–86). 5-Ethynyl-2-methylpyridine, when converted to a metalloacetylene derivative, reacted with ketones to give the ethynylcarbinols (87–89).

2-Pyridyl phenyl ketone reacted with sodium ethylate followed by cyclopentadiene to give α-phenyl-α-[6-phenyl-6-(2-pyridyl)-2-fulvenyl]-2-pyridinemethanol (**XIII-10**), as did the corresponding 3- and 4-pyridyl phenyl ketones (90–93).



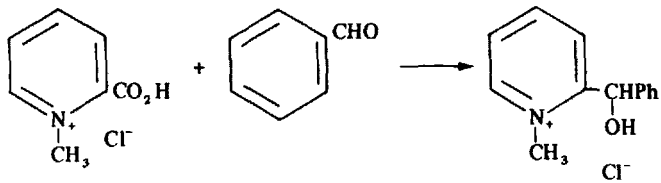
XIII-10

9. Aldol Condensation of Pyridine Aldehydes

Nitroethane reacts with all three pyridine aldehydes in the presence of secondary amines to give the corresponding nitrocarbinols (94). Pyridine aldehydes were condensed with the α-methylene group of several ketones using Amberlite IRS-400 in place of the conventional base (95).

10. Hammick Reaction

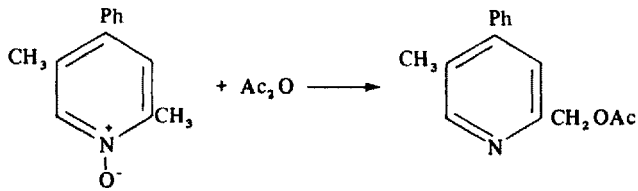
In an extension of the Hammick reaction sodium 2-pyridylacetate was decarboxylated in cyclohexanone, acetophenone, and benzaldehyde to give the respective alcohols (96). A biography and bibliography of Dalzill Lewellyn Hammick who died in 1966 has appeared (97). A reaction certainly related to the Hammick reaction is the decarboxylation of homarine chloride in aromatic aldehydes, such as benzaldehyde, to give 2-(α-hydroxybenzyl)-1-methylpyridinium chloride (**XIII-11**) (98).



XIII-11

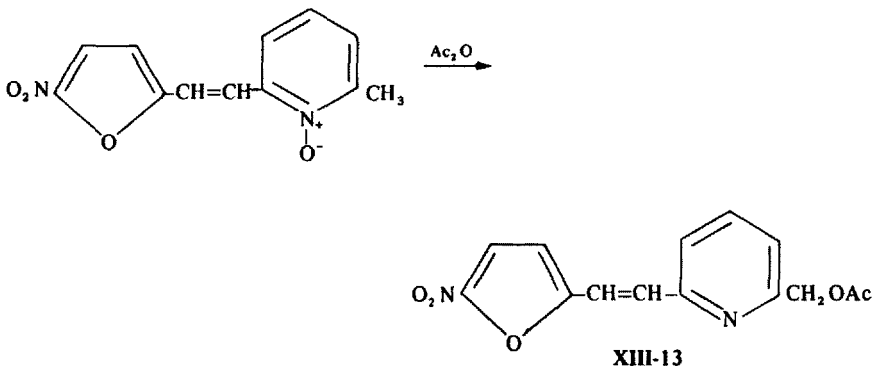
11. Rearrangement of Alkylpyridine-1-Oxides

The work on the rearrangement of 2-, 3-, and 4-alkylpyridine-1-oxides (see also Chapter IV) can be divided into synthetic efforts and mechanism studies. Along synthetic lines, 2-picoline-1-oxide has been converted to 2-pyridylcarbinol through its acetate (20, 99); 4-pyridylcarbinol was similarly prepared (20), as was 6-methyl-2-pyridylcarbinol (97). 2,4,6-Collidine-1-oxide rearranged in acetic anhydride to give 4,6-dimethyl-2-pyridylcarbinol and 2,6-dimethyl-4-pyridylcarbinol (100), while 2,5-dimethyl-4-phenylpyridine-1-oxide gave 5-methyl-4-phenyl-2-pyridylcarbinol through the acetate (101) (**XIII-12**). Both pyrindane-



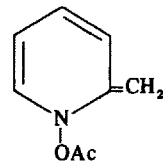
XIII-12

1-oxide (102) and some other (2,3-pyrido)cycloparaffin-1-oxides (38) have been rearranged to the carbinols. 4-Methoxy- and 4-ethoxy-2-picoline-1-oxide were converted to the 2-carbinols (103). 2-[2-(5-Nitro-2-furyl)vinyl]-6-methylpyridine-1-oxide was rearranged to the 6-carbinol acetate (**XIII-13**) (104).



XIII-13

Many papers have been written concerning the mechanism of this rearrangement and a very reasonable intermediate is **XIII-14**, an anhydro-base structure. There is discussion as to whether a radical pair or an ion pair is involved in the rearrangement. Oae and co-workers have used ^{18}O in the study of this reaction (105, 106). Many other workers have tried to distinguish between the ion pair



XIII-14

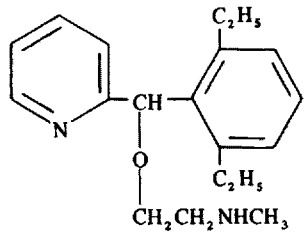
and radical pair mechanism (102–112). Rate constants and ^{18}O incorporation have been reported recently (113, 114). The problem has been reviewed in two articles and a book (115–117). Acetyl and benzoyl chlorides have been shown to convert 2-picoline-1-oxide to the corresponding carbinol esters (118) (for a more detailed treatment see Chapter IV).

12. Emmert-Asendorf Reaction

This reaction involves the condensation of a pyridine with a ketone in the presence of magnesium or magnesium amalgam to give a pyridyl alcohol. Recently a quantitative study of the reaction of pyridine and 3-picoline with cyclohexanone and 2-methylcyclohexanone and of pyridine with 4-*t*-butylcyclohexanone has been carried out (119).

II. Properties

The properties of pyridine alcohols are the expected ones for alcohols containing a tertiary amine group. A number of physiological activities have been reported for various compounds and are mentioned here. Pharmacological properties of benzylpyridylcarbinols have been reported (120). Psychopharmacological activity has been ascribed to *trans*-2-(4-pyridyl)-α,α-diphenylcyclopropanemethanol (50). 3-Pyridinemethanol diminishes circulating cholesterol and fatty acids in the blood (121, 122). The toxicity and distribution of 1-(3-pyridyl)ethanol in mice has been investigated using ^{14}C tagging (123). 2-{2,6-Diethyl-α-[2-(methylamino)-ethoxy]benzyl}pyridine **(XIII-15)** and its



XIII-15

carbamate have diuretic properties in rats (124). The blood levels of 2,6-pyridinemethanol bis(*N*-methylcarbamate) after different dosages has been reported (125). Of six pyridylalkylcarbinols tested for rat choleretic activity, 1-(2-pyridyl)propanol had the most rapid action, and 1-(3-pyridyl)butanol had the most prolonged activity (126). Hypotensive and spasmolytic activity has been reported for a series of 4-pyridylcarbinols carrying various amino groups (9). Antihelminthic properties have been ascribed to 2-(β-methoxyethyl)pyridine (127) and its pathological effects noted (128).

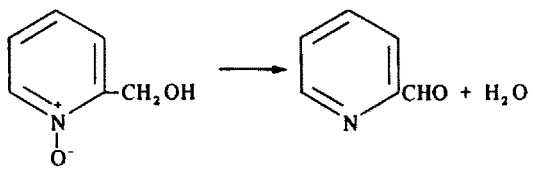
The optical rotations of a group of alkyl 2-, 3-, and 4-phenylcarbinols have been recorded (49, 129). The dissociation constants (pK_a alcohol-pK_a amine) of a group of 2-, 3-, and 4-pyridine alcohols have been measured (130). N.m.r. spectral data aided in the determination of the structure of 3-hydroxy-2-pyridinemethanol (131). Intramolecular hydrogen bonding in 2-(2-hydroxyethyl)- and 2-(3-hydroxypropyl)pyridine has been studied (132).

For other physical properties one should consult the tables at the end of this chapter. Some quaternary salts of 2-pyridinemethanol have been prepared (133). The kinetics of hydrolysis of 2-, 3-, and 4-pyridylmethylphosphates have been determined (134).

III. Reactions

1. Oxidation

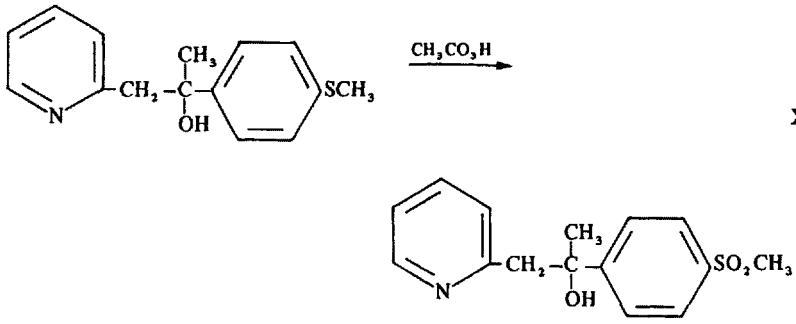
Oxidation of pyridine alcohols to aldehydes continues to be an important synthetic reaction and has been carried out recently by self-oxidation of the 1-oxides using phenylhydrazine (135) and by $PhCH{=}SO_2$ or sulfonate esters of the alcohols (136). The self-oxidation of 2-pyridinemethanol-1-oxide to the aldehyde by heating has been patented (137) **(XIII-16)**. An example of carbinol



XIII-16

to acid oxidation where a ring hydroxyl group is protected by benzylation followed by potassium permanganate oxidation has been reported (138, 139). 3-Pyridinemethanol has been oxidized biologically to nicotinic acid (140). Air oxidation in a basic medium converted 3-pyridyl-2-thiazolylcarbinol to the ketone (8, 141) and manganese dioxide oxidized methyl-4-pyridylcarbinol to

4-pyridyl methyl ketone (15). Surprisingly, a thioether linkage in a pyridinemethanol could be oxidized to the sulfone with hydrogen peroxide without affecting the alcohol (71) **(XIII-17)** and, in several cases, the pyridine ring

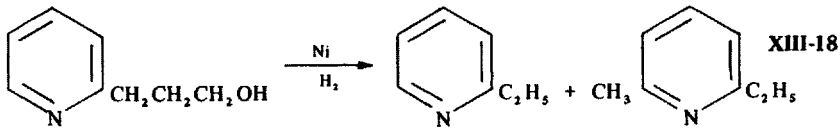


XIII-17

nitrogen of a pyridinemethanol has been converted to the 1-oxide using peracetic acid without oxidizing the alcohol (69, 142). 1-(α-Pyridyl)-3-butene-2-ol underwent the Oppenauer oxidation to the corresponding ketone (64).

2. Reduction

The reduction of pyridine alcohols to hydrocarbons takes place often with α-methylation, and this reaction **(XIII-18)** has been discussed by Reinecke and Kray (143-148). The more usual reduction is that of the pyridine ring to the



XIII-18

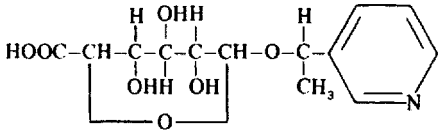
piperidine and this has been accomplished with a variety of reagents, that is, platinum and hydrogen (44, 71, 76, 146, 147), rhodium and hydrogen (148), sodium borohydride (26), and Raney nickel and hydrogen (148, 149).

3. Esterification and Etherification

Numerous esters of pyridine alcohols have been prepared by normal methods. Among esters synthesized recently are acetates (150, 151), camphorates (152),

succinates (153), salicylates (154), tartrates (155), 2-(2,4,5-trichlorophenoxy)-propionates (156), phenylcarbonates (157), α-(*p*-chlorophenoxy)isobutyrate (158), 2,2-dimethyl-3-(2-methylpropenyl)cyclopropylcarboxylates (159), xanthates (160), various sulfonates (136), phosphates (20, 160-163), thionphosphates (162, 164), and diphenylborinates (165). Carbamate derivatives of pyridine alcohols have been prepared for use as antiphlogistics (166-171). Thiocarbamates have also been reported (151, 172-175) as well as complexes with triphenylboron (176).

Ethers of pyridine alcohols are formed by the reaction between halogen containing compounds and the sodium alcoholates as well as from pyridine alcohols with other alcohols using catalysts (177-179). Many pyridine ethers are claimed to have biological properties (40, 41, 180, 181). The glucuronide of 3-pyridylmethylcarbinol **(XIII-19)** has been isolated from rat urine (17).



XIII-19

Bis(2-pyridylmethyl)ether has been rearranged by $NaNH_2$ to give 1,2-di-(2-pyridyl)ethanol (182).

4. Replacement of Hydroxyl Groups by Halogen

The carbinol group can be replaced by halogen directly using hydrogen halides or thionyl chloride (183), and esters of carbinols such as the acetates can be converted to halides by hydrogen halides (184).

5. Dehydration to Olefins

Dehydration of carbinols to olefins is a rather common reaction in the pyridine series, often with a view to making vinyl-type monomers. The reagents used include the following: hydrochloric or sulfuric acids (60, 76, 146, 185), thionyl chloride (76, 186), and phosphorus pentoxide (94). Heat alone has effected the dehydration in many cases (30, 31, 36, 37, 187) and also heat plus sodium hydroxide (188) or alumina (189). The acetate esters of pyridine alcohols can be dehydrated directly by heat (190). Pyridylcyclohexyl alcohols have been dehydrated and aromatized by heating in a mixture of acetic and sulfuric acid (83, 84, 86).