SOME STUDIES OF THE CHEMISTRY OF PYRIDINE-1-OXIDES

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by

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ABSTRACT

The generation of pyridyl-1-oxide carbanions and their subsequent condensation with electrophilic reagents is described. The intermediate carbanions react with bromine and chlorine to give 2,6-dihalopyridine-1-oxides, with sulfur to give biologically active 1-hydroxy-2-pyridinethiones, with oxygen to give 1-hydroxy-2-pyridones, with benzyl bromide to yield 1-benzyloxy-pyridinium bromide, with epoxides to form polymers, with acetaldehyde and cyclohexanone to give secondary and tertiary alcohols, respectively, and with Schiff bases to yield secondary amines. A series of bases, other than n-butyllithium, were examined for their ability to generate the pyridyl-1-oxide carbanions. Dehydration and polymerization of some 2-pyridyl alkanol-1-oxides gave poly-(2-vinylpyridine-1-oxide).

In vitro pharmacological testing results are given for some of the sulfur compounds prepared.

The following new compounds were prepared and characterized:

6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide

6,6'-dibromo-2,2'-dipyridyl-1-oxide

6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1-oxide

2,6-dibromo-4-methylpyridine-1-oxide

6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1,1'-dioxide

6,6'-dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide

2,6-dibromo-3,4-dimethylpyridine-1-oxide

2,6-dichloro-3,4-dimethylpyridine-1-oxide

4-chloro-1-hydroxy-3-methyl-6-pyridinethione

2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)disulfide

3,4-dimethyl-1-hydroxy-2-pyridinethione

3,4-dimethyl-1-hydroxy-6-pyridinethione

3,4-dimethyl-1-hydroxy-2-sulfhydro-6-pyridinethione

1-hydroxy-2-(2',4'-dinitrophenylthio)-4,5-dimethyl-6-pyridinethione

3,4-dimethyl-1-hydroxy-2-pyridone

3,4-dimethyl-1-hydroxy-6-pyridone

1-benzyloxy-3,4-dimethylpyridinium bromide

1-benzyl-3,4-dimethylpyridinium bromide

2,6-di-(1-hydroxyethyl)pyridine-1-oxide

2,6-bis-(α-anilinobenzyl)pyridine-1-oxide

2,6-bis-(α-anilinobenzyl)-3,4-dimethylpyridine-1-oxide

2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide

3-methyl-4-(1-hydroxycyclohexylmethyl)pyridine-1-oxide

Zinc salts of:

- 4-chloro-1-hydroxy-3-methyl-6-pyridinethione
- 3,4-dimethyl-1-hydroxy-2-pyridinethione
- 3,4-dimethyl-1-hydroxy-6-pyridinethione
- 3,4-dimethyl-1-hydroxy-2-sulfhydro-6-pyridinethione

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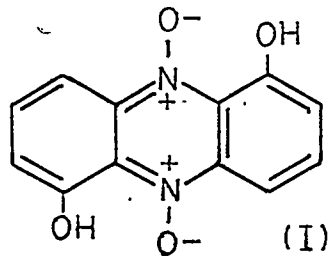
1.0.0.0.0 INTRODUCTION

In 1940 Linton (1) reported that the dipole moment of pyridine-1-oxide (4.24 D) was much lower than calculated from the group moment of the N-oxide function and the moment of pyridine. To explain this observation he concluded that pyridine-1-oxide must be a resonance hybrid of several canonical structures some of which exert a back donation of electrons from the oxygen to pyridine. Ochiai (2) then predicted that electrophilic substitution of pyridine-1-oxide should occur in the 2- and 4-positions. This assumption was confirmed by nitration of pyridine-1-oxide which gave 4-nitropyridine-1-oxide in good yield, together with a small amount of 2-nitropyridine. It was also observed (2) that the nitro group in the 4-position of pyridine-1-oxide was very reactive, being easily displaced by nucleophilic reagents and very susceptible to reduction. These early studies provided a new method for the synthesis of 4-substituted pyridine-1-oxides and opened up the field of pyridine-1-oxide chemistry. The chemistry of pyridine-1-oxides has gradually been developed and several reviews on this subject have now been published (3-6).

1.1.0.0.0 Pharmacological properties of some pyridine-1-oxide derivatives

The first sign of interest in the pharmacological properties of pyridine-1-oxides probably came with the isolation of iodinin (I) in 1938 from Chromobacterium iodinum, a compound exhibiting strong antibacterial activity (7). However little attention was paid to this



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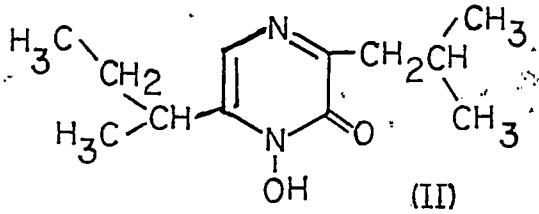
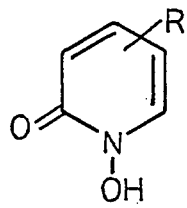


(II)

class of compounds until aspergillic acid (II), a mold metabolite from Aspergillus flavus (8) was characterized as a cyclic hydroxamic acid (9). The structure of aspergillic acid has since been fully elucidated by Dutcher and Wintersteiner (9,10), Newbold and Spring (11), and Dunn et al. (12). Aspergillic acid is highly inhibitory in vitro to the growth of gram positive and gram negative organisms (13,14) and to M. tuberculosis (15). Its toxicity is so severe, however, that it cannot be used for therapeutic purposes. Aspergillic acid has served as a model for the synthesis of structurally related hydroxamic acids since simpler hydroxamic acids

unrelated to pyrazine also possess antibacterial activity (10).

In the pyridine series Newbold, Spring, and others (11,16) synthesized 1-hydroxy-2-pyridones (III) and found that these compounds exhibit a marked antibacterial activity. Similarly, Shaw (17) synthesized 2-, 3-, and 4-hydroxypyridine-1-oxides and found that only 1-hydroxy-2-pyridones possess significant antibacterial activity. Shaw and co-workers (18) also synthesized



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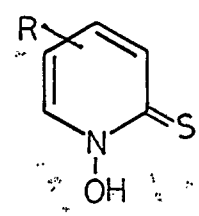
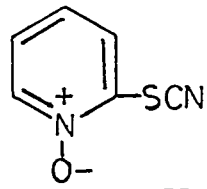


(IV)

some 1-hydroxy-2-pyridinethiones (IV). The in vitro antibacterial test results showed that these cyclic thiohydroxamic acids had a greater antibacterial activity than the corresponding 1-hydroxy-2-pyridones.

The Chas. Pfizer Company has taken out a patent (19) for the use of 2-mercaptopyridine-1-oxide derivatives in which the mercapto-hydrogen has been replaced by an imidazolinyl or tetrahydropyrimidinyl group. These compounds are useful as anti-infection agents and in the treatment of superficial mycoses.

Leonard and his co-workers have shown that 2-thiocyanatopyridine-1-oxide (V) and its 4-nitro derivative (20) at low concentrations exhibit a broad spectrum of activity against bacteria and fungi.



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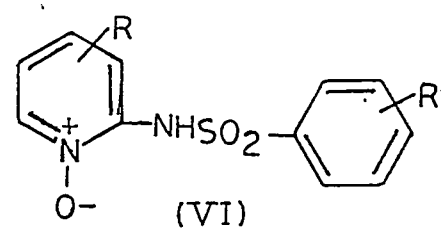
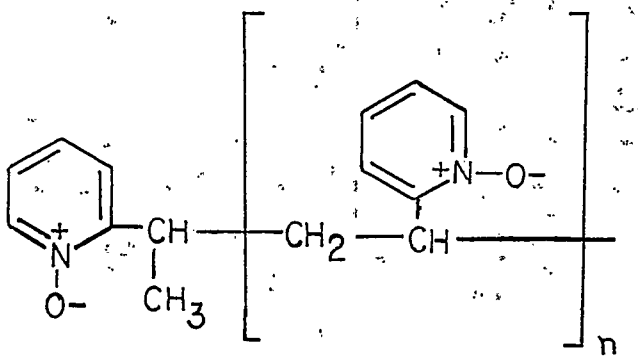


(VI)

Childress and Scudi (21) reported that 2-(sulfanilamido)pyridine-1-oxide and its methyl homologs (VI) possess potent antimicrobial activity.

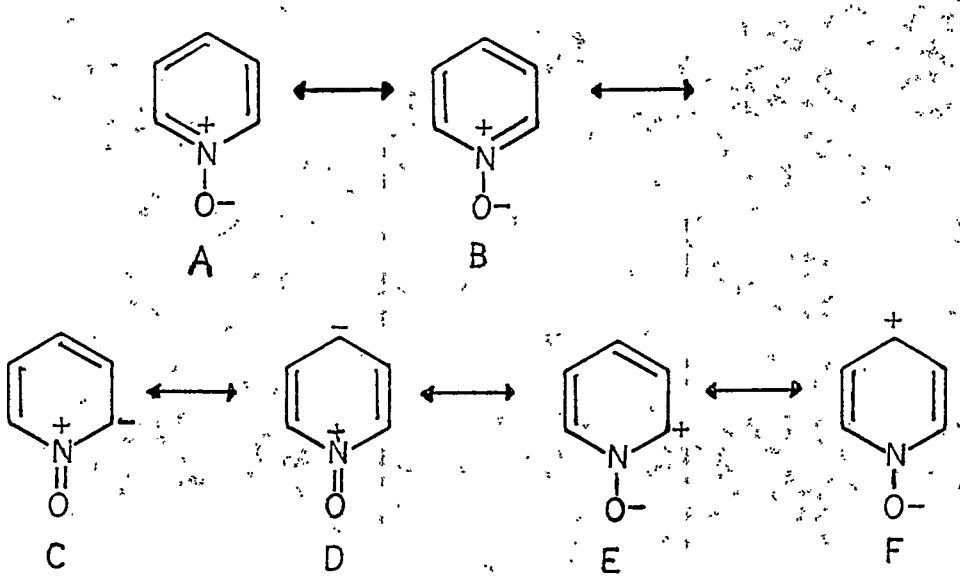
Holt and co-workers (22-24) reported that poly-(2-vinylpyridine-1-oxide) (VII) of molecular weight greater than 50,000 is chemotherapeutically active against the pathogenic effects of silica in animals. The mechanism by which silica exerts its fibrogenic action is unknown but it is postulated that monosilicic acid may be produced by dissolution of silica in phagocytic cells exerting a cytotoxic action. If this is so, the protective action of poly-(2-vinylpyridine-1-oxide) may be due to the interaction of silicic acid with this polymer.



(VII)

1.2.0.0.0 Properties of pyridine N-oxides

Pyridine-1-oxide is considered to be a resonance hybrid of various canonical structures (VIII A-F).



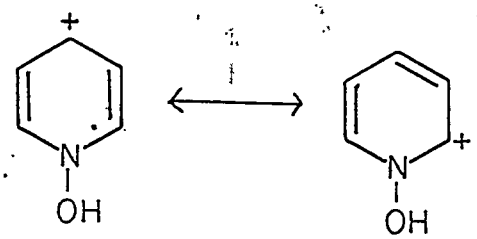
(VIII)

Linton (1) found the dipole moment of pyridine-1-oxide to be much lower than calculated which indicates contributions from structures C and D. The lone pair electrons of the oxygen atom in pyridine-1-oxide must be conjugated

with the electron sextet of the pyridine ring. Contributions from structures C and D would also tend to stabilize the amine oxide structure making it resistant to reduction and make it susceptible to electrophilic substitution at the 2- and 4-positions.

Participation of structures E and F would result in a lowering of the electron density at C-2 and C-4 which would enhance nucleophilic attack at these positions.

N.m.r. studies (6,72) showed that changes in the position of the chemical shifts of H_4 and H_3 in pyridine-1-oxides probably reflect the change in π-electron densities at these centers. Proton resonances of substituted pyridine-1-oxides in various solvents suggest that the contributions of C and D are significant in aprotic solvents while in acid solution such as trifluoroacetic acid pyridine-1-oxide will exist as the conjugate acid (VIII G,H).



G (VIII) H

These facts illustrate the change in electronic structure which pyridine-1-oxides undergo with change in

the nature of the solvent. The change in electron densities at the various positions such as the inversion of the relative orders of the π-electron densities at the 3- and 4-positions in going from aprotic to highly protic solvents indicate that the mesomeric effect of the N-oxide group is easily changed and that it has both electron-withdrawing (-M) and electron-donating (+M) ability. This paradox of activation toward nucleophilic and electrophilic attack by the pyridine-1-oxide structure can be resolved if one recalls that it is not only the electron distribution in the isolated molecule which determines the rates of substitution reactions, but also the extent to which the molecule is polarized by the approaching reagent. The N-oxide function is remarkable in that it is strongly polarizable in both directions.

The pK_a value (6) for pyridine-1-oxide (0.79) is much lower than that of pyridine (5.29). This fact further indicates that there is interaction between the N-oxide group and the pyridine ring depicting contributions from C and D which result in a decreased negativity of the oxygen atom and a decrease in the affinity for hydrogen ion, consequently a lower pK_a.

Pyridine-1-oxides are weak bases and often undergo reaction as the $\geqslant\overset{+}{N}$-O-substituted pyridinium ion (6) including the hydroxypyridinium ion. In $\geqslant\overset{+}{N}$-O-substituted

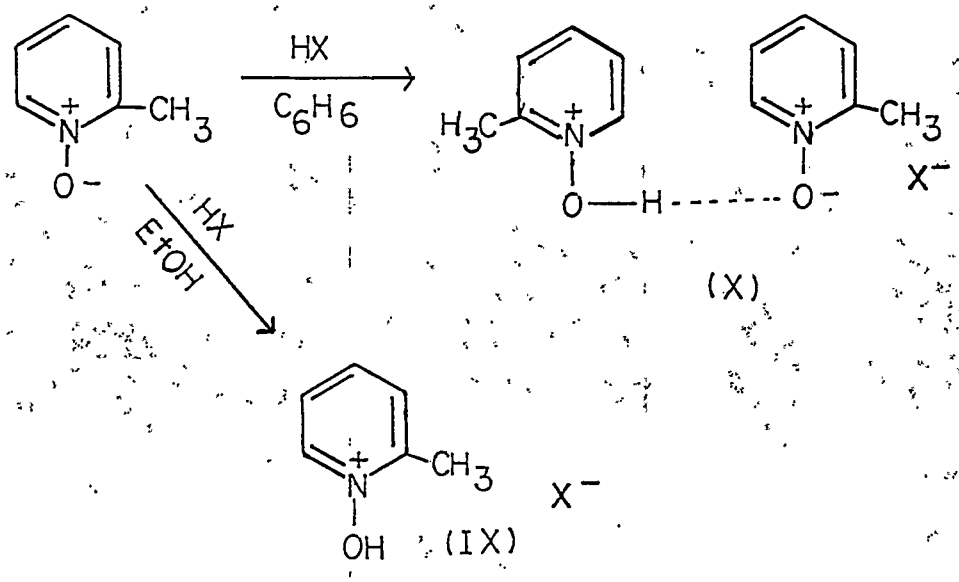
compounds the electronegativity of the oxygen increases and the back donation of electrons from oxygen to the ring is inhibited. Contributions from structures G and H now become larger. Physical data (6) have shown that the properties of $\geq\overset{+}{N}$-O-substituted compounds are similar to $\geq\overset{+}{N}$-substituted pyridinium ion. In these systems the electron density of the pyridine ring is decreased, making it more difficult for electrophilic substitution to occur. If it does occur it should take place at C-3. In contrast, this system would favor nucleophilic attack at C-2 and C-4, these being the centers of lowest electron density.

1.3.1.0.0 Electrophilic addition to the N-oxide group

The oxygen atom in pyridine-1-oxides undergoes addition of protons, metals, Lewis acids, alkyl or aryl halides, alkyl sulphonates and acyl halides.

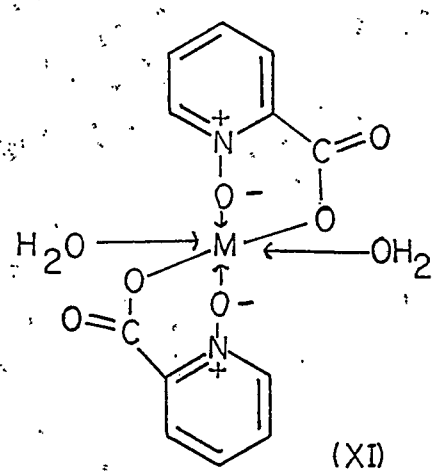
Pyridine-1-oxide forms stable crystalline salts with strong acids. The hydrochloride, hydrobromide, perchlorate, and picrate salts have been used extensively in the purification and characterization of pyridine-1-oxides. Vozza (25) has shown that the nature of the hydrohalide salt formed may be solvent dependent. Addition of a hydrogen halide to 2-picoline-1-oxide in

ethanol yields a normal (1:1) hydrohalide (IX) while an abnormal (2:1) salt (X) was obtained in benzene.



Pyridine-1-oxides react with Lewis acids such as sulfur trioxide and boron trifluoride to give addition compounds (6). Intermolecular hydrogen bonding between 4-nitropyridine-1-oxides and phenols (26) gives molecular compounds in 1:1, 2:1 and 1:2 molar ratios.

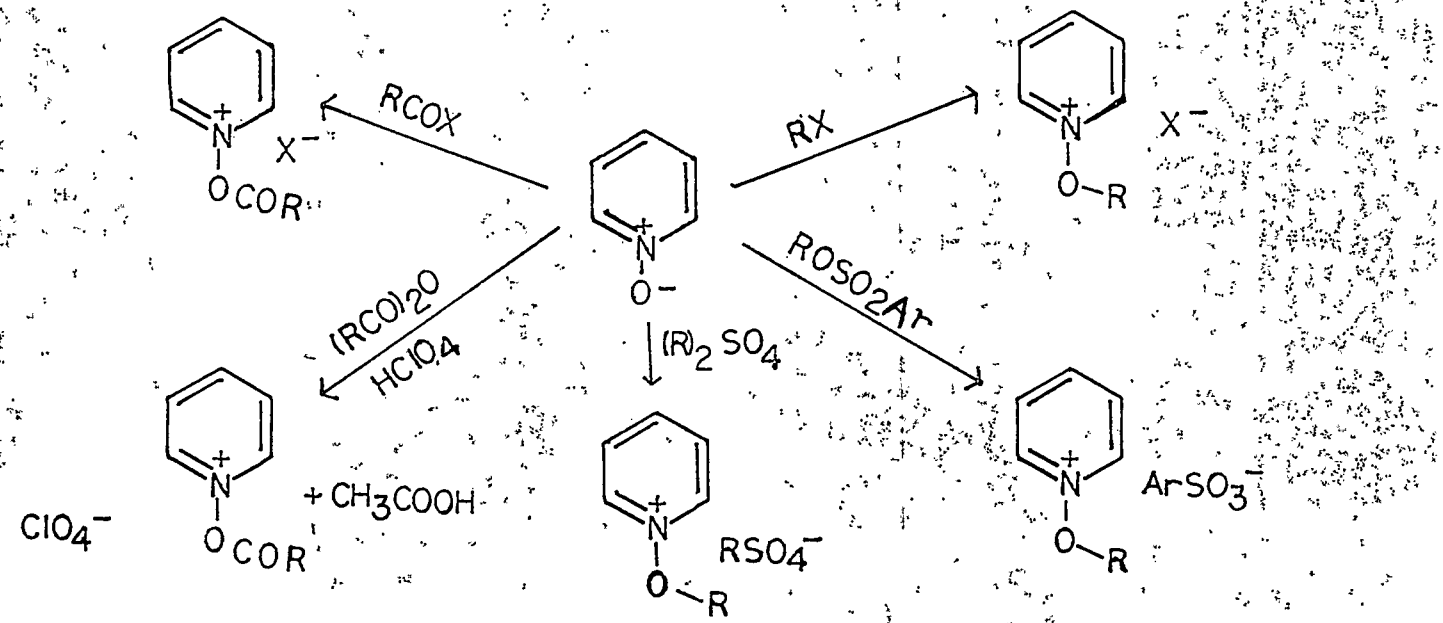
Coordination of the oxygen atom in pyridine-1-oxides to metal ions gives complex metallic salts (27), as illustrated below (XI).



(XI)

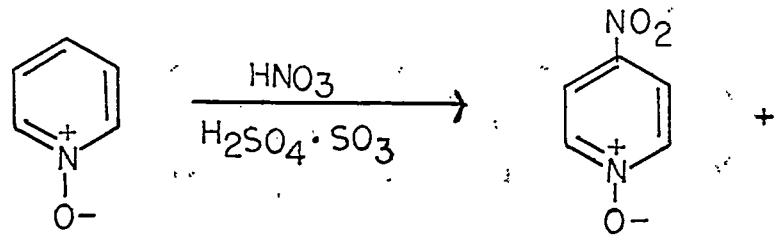
M: Mn^{II}, Fe^{II}, Co^{II}, Ni^{II}, Cu^{II}, Mg^{II}.

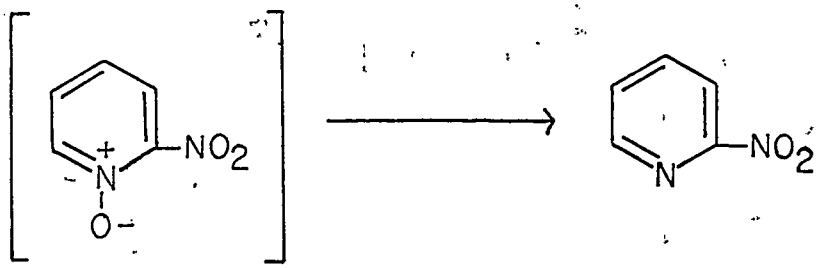
Finally, pyridine-1-oxides undergo electrophilic addition to the oxygen atom by alkyl or aryl halides, dialkylsulfates, alkylsulphonates to give the respective alkyl or aryloxypyridinium salts, and by acyl halides or acid anhydrides to give the acyloxypyridinium salts (6) as illustrated below.



1.3.2.0.0 Electrophilic substitution at carbon

Charge distribution and localization energy calculations (28) predict that electrophilic substitution of pyridine-1-oxide should occur primarily at the C-2 position. In actual practice there is almost exclusive attack at C-4. Nitration of pyridine-1-oxide with potassium nitrate in concentrated sulfuric acid containing fuming sulfuric acid (6) at 90° yields 4-nitropyridine-1-oxide in yields as high as 90% together with a small amount of 2-nitropyridine. den Hertog and co-workers (29) obtained 4-nitropyridine-1-oxide in



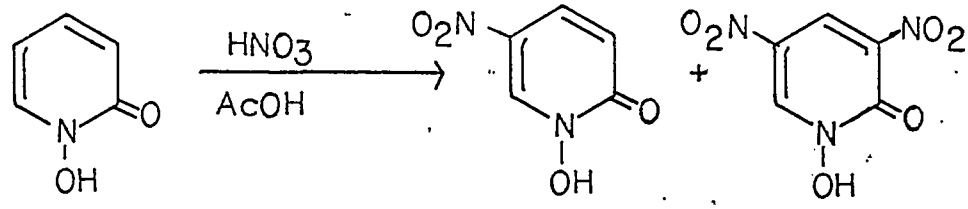


80-90% yield by heating pyridine-1-oxide with fuming nitric acid in concentrated sulfuric acid at 90°. When reaction temperatures are raised above 110° the yield

of 2-nitropyridine increases slightly and the yield of 4-nitropyridine-1-oxide decreases as the yield of 4-nitropyridine increases. The predominant attack at C-4 has been attributed to the remarkable polarizability of the N-oxide bond which results in a major contribution from structure VIII D in the species going to the transition state and to the powerful inductive effect of the N-oxide function which would decrease the electron density at C-2 making it less susceptible to electrophilic attack. The steric effect of the oxygen atom upon the approaching electrophile is probably not sufficient to account for the lack of attack at C-2. Moodie and co-workers have reported (30) that nitration of pyridine-1-oxide occurs on the free base.

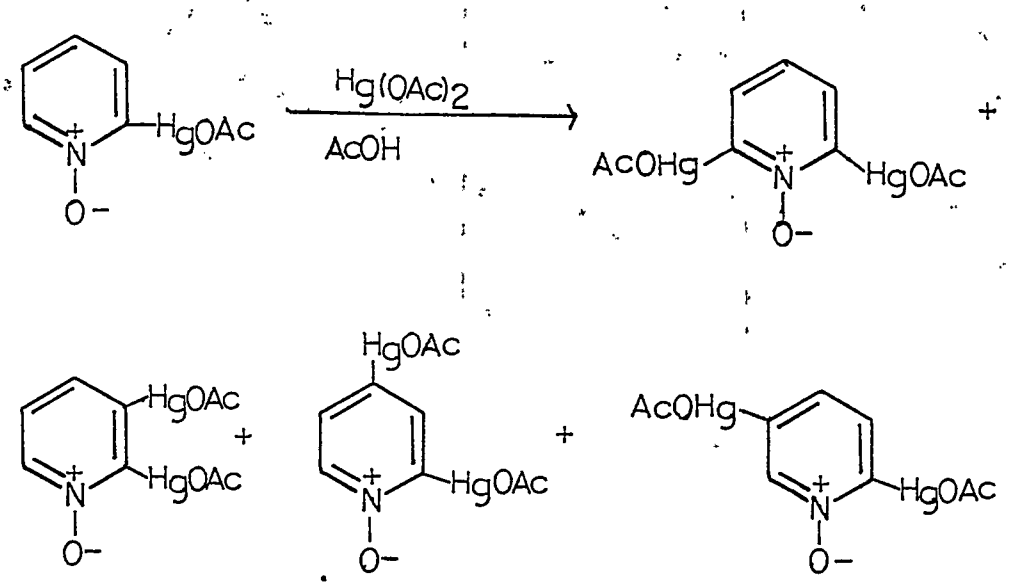
In electrophilic substitution of substituted pyridine-1-oxides the directive influence of the N-oxide group exceeds that of all but the most powerful o:p-directing substituents (5,6). In nitration experiments the 4-nitro product is obtained in high yield. However, nitration of 2-hydroxypyridine-1-oxide with nitric acid in acetic acid at 0° gave 1-hydroxy-5-nitro-2-pyridone (60-70%), while under more vigorous conditions the 3,5-dinitro product was obtained (31). These results are further evidence for the existence of the

1-hydroxy-2-pyridone structure which is the species undoubtedly undergoing nitration.



In contrast to the nitration of pyridine-1-oxide, acid-catalyzed hydrogen exchange has been reported (32) to take place on the conjugate acid of the base (VIII, G and H). In the conjugate acid exchange occurs at C-3 which is the center of highest electron density.

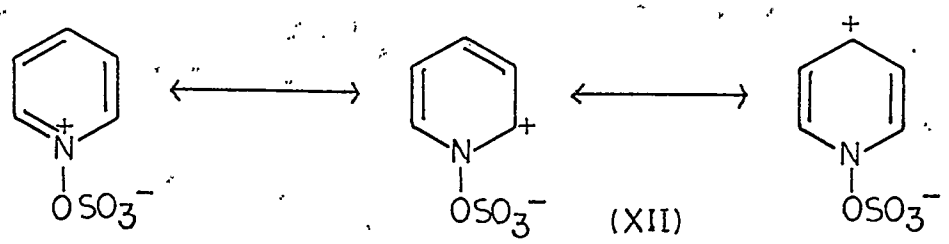
It was originally reported (33) that mercuration of pyridine-1-oxide with mercuric acetate in glacial acetic acid at 130° gave the 4-substituted acetoxy-mercury product. van Ammers and den Hertog (34,35) showed that this assumption was incorrect and that acetoxymercuration occurs first at C-2 and that some of the 2-substituted product undergoes further reaction to yield disubstituted products.



In contrast to the marked polarizability of the N-oxide function in nitration the polar effect is very small in bromination. den Hertog and co-workers (36) found that although the reaction did not take place when pyridine-1-oxide was heated with excess bromine in 90% sulfuric acid at 200°, addition of silver sulfate gave a 10% yield of 2- and 4-bromopyridine-1-oxide in a ratio of 1:2. Bromination in 65% fuming sulfuric acid gave 3-bromopyridine-1-oxide (37).

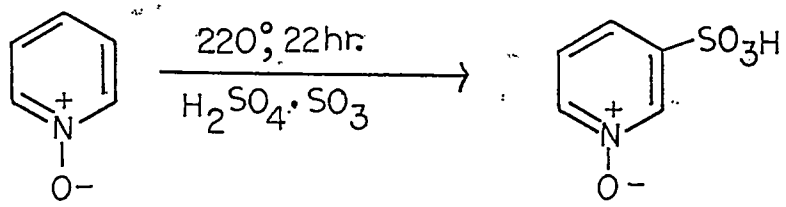
The exclusive attack at C-3 has been explained (5,6) on the assumption that in fuming sulfuric acid a stable adduct is formed between pyridine-1-oxide and

sulfur trioxide (XII), which results in deactivation of the 2-, 4-, and 6-positions toward electrophilic attack.



(XII)

Evans and Brown (38) prepared pyridine-1-oxide-3-sulphonic acid by heating pyridine-1-oxide in 20% fuming sulfuric acid at 220-240° with a catalytic amount of mercuric sulfate.



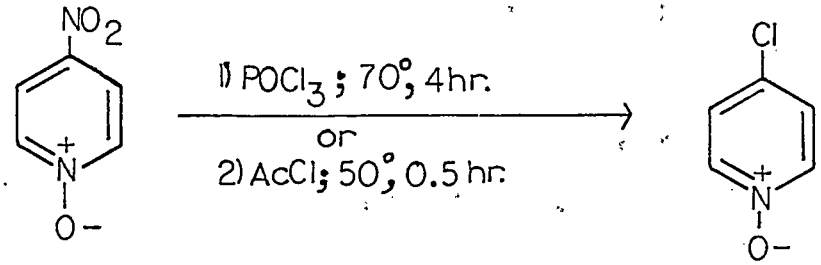
These results suggest that there is no activation by the N-oxide function towards sulfonation. Substitution at C-3 is probably due to the formation of the pyridine-1-oxide-sulfur trioxide adduct.

1.4.1.0.0 Nucleophilic displacement in substituted pyridine-1-oxides

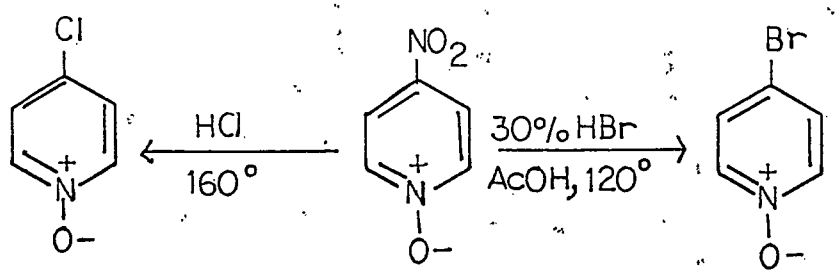
A nitro group ortho or para to the N-oxide group is very reactive towards nucleophilic displacement and is

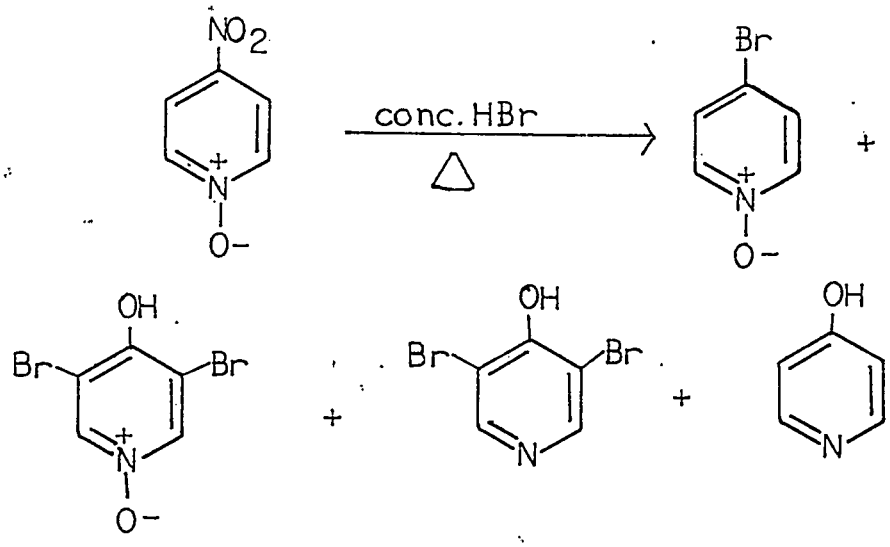
known to undergo easy substitution by halogens, alkoxyl, aryloxyl, arylthio, and hydroxyl groups (6).

Reaction of 4-nitropyridine-1-oxide (2) with acetyl chloride or phosphorous oxychloride under mild conditions gave the 4-chloro product in high yields. Brown

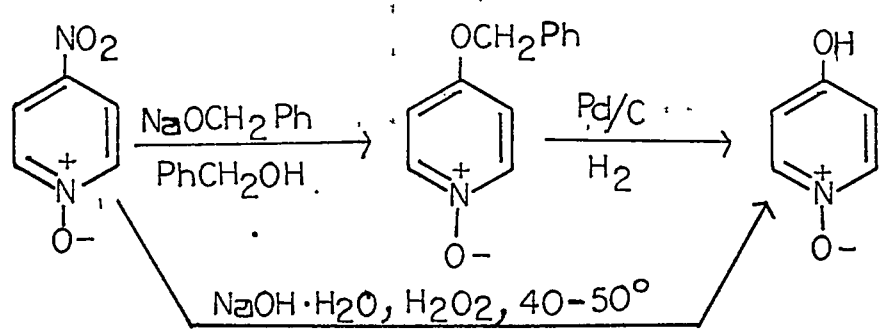


later reported (68) that treatment of 2-nitropyridine-1-oxide with acetyl chloride in the cold proceeds smoothly to give the 2-chloro derivative and that this reaction was faster than that of 4-nitropyridine-1-oxide. den Hertog and Combé (39) found that the 4-nitro group in 4-nitropyridine-1-oxide underwent substitution by halogen when heated with hydrochloric or hydrobromic acid. The reaction with concentrated hydrobromic acid was also accompanied by side reactions such as hydrolysis, bromination of the 3-position and deoxygenation.

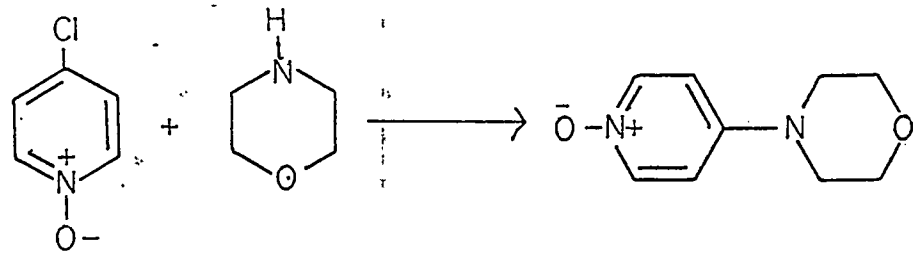




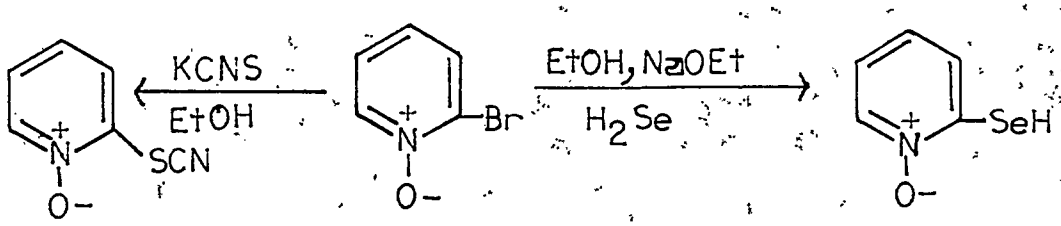
Ochiai and his co-workers (2) prepared 4-hydroxypyridine-1-oxide by treatment of 4-nitropyridine-1-oxide with sodium phenylmethylate followed by catalytic reduction of the 4-benzyloxy product with a palladium-charcoal catalyst. den Hertog and Combé (40) obtained the same product by warming 4-nitropyridine-1-oxide with sodium hydroxide while adding hydrogen peroxide to prevent reduction by the sodium nitrite produced in the reaction. Sodium nitrite acts as a reducing agent (6) to give some 4,4'-azopyridine-1,1'-dioxide as well.



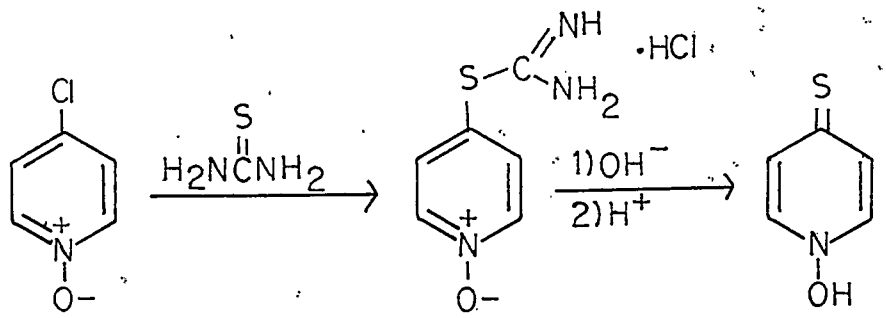
Halogen atoms ortho or para to the N-oxide group in pyridine-1-oxide are readily substituted by nucleophilic reagents. Nucleophilic substitution of a nitro group in pyridine-1-oxide with an amine does not proceed smoothly. When the nitro group is replaced by a halogen atom and then reacted with an amine the reaction proceeds favourably. Thus, reaction of 4-chloropyridine-1-oxide with morpholine in a sealed tube at 130-140° yields 4-morpholinopyridine-1-oxide (2).



Leonard and Wajngurt (41) prepared 2-thiocyanatopyridine-1-oxide from 2-bromopyridine-1-oxide while Mautner and his co-workers (42) prepared the 2-selenol of pyridine-1-oxide.

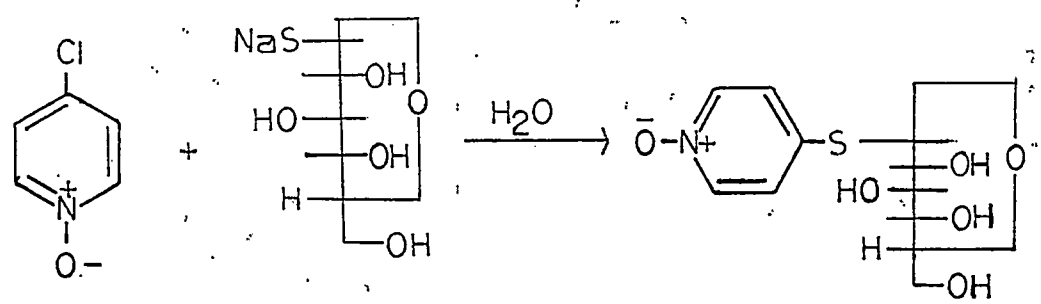


Numerous reports have appeared in the literature describing the reactions of 2- and 4-halopyridine-1-oxides with sulfur containing compounds. Itai (43) synthesized 1-hydroxy-4-pyridinethione by reaction of 4-chloropyridine-1-oxide with thiourea to give the isothiouronium salt which was then decomposed with base.



1-Hydroxy-2-pyridinethione has been prepared from 2-bromopyridine-1-oxide and thiourea in an analogous reaction (18,44). Reaction of 2-halopyridine-1-oxides with alkali sulfides (18,45,46) has also been used extensively in preparing 1-hydroxy-2-pyridinethiones.

Wagner and co-workers (47) have shown that 2- or 4-halopyridine-1-oxides react with thioglucosides. For example, 4-chloropyridine-1-oxide reacts with sodium-1-thio-β-D-glucopyranoside to give 4-(β-D-glucopyranosylthio)pyridine-1-oxide as shown below.



Finally, treatment of 2-halopyridine-1-oxides with aqueous acid (48) or aqueous sodium hydroxide (18) yields 1-hydroxy-2-pyridones.

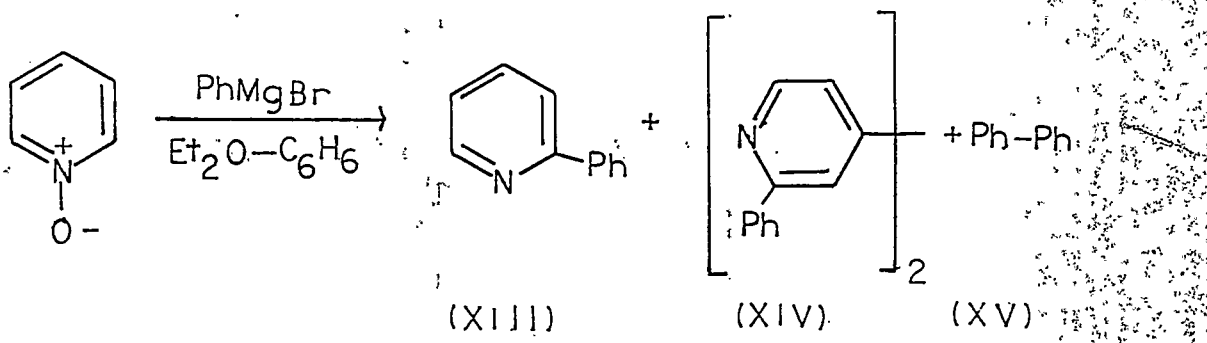
1.4.2.0.0 Nucleophilic substitution by organometallic compounds

Pyridine-1-oxides are very susceptible to nucleophilic attack at C-2 and C-4 probably due to contributions from structures VIII E and F.

These nucleophilic reactions may be viewed as electrophilic attack of the metal ion on the oxygen of the N-oxide group together with or followed by attack at the 2-position by the nucleophile, and then elimination of metal hydroxide from the adduct to give the deoxygenated product.

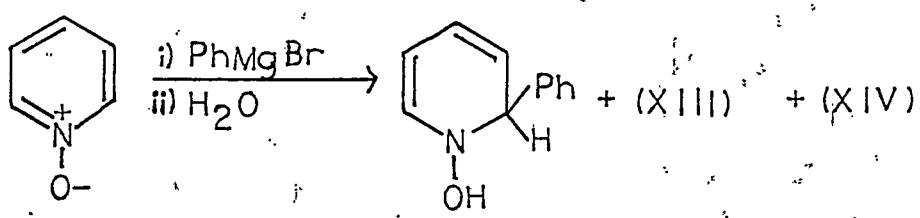
Colonna (49) reported that the reaction of phenylmagnesium bromide with pyridine-1-oxide in ether gave a

low yield of 2-phenylpyridine (XIII). When Ochiai and Arima (50) repeated this same reaction using benzene-ether as the solvent 2,2'-diphenyl-4,4'-bipyridyl (XIV) (4%), and biphenyl (XV) were isolated in addition to 2-phenylpyridine (XIII) (13%). More recently it was



(XIII) (XIV) (XV)

reported (51) that the same reaction in tetrahydrofuran gave a high yield of 1-hydroxy-2-phenyl-1,2-dihydro-pyridine (XVI), together with small amounts of 2-phenyl-pyridine (XIII), and 2,2'-diphenyl-4,4'-dipyridyl (XIV).

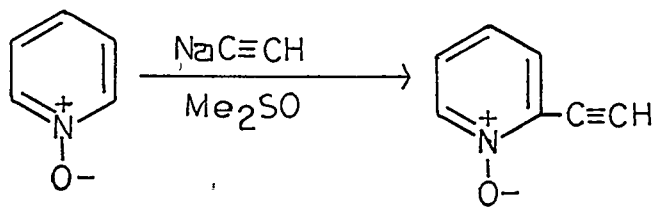


60-80%
(XVI)

Abramovitch, Giam, and Poulton (99) have shown that phenyllithium reacts readily with pyridine-1-oxide to

give 2-phenylpyridine (XIII), and a number of unidentified products.

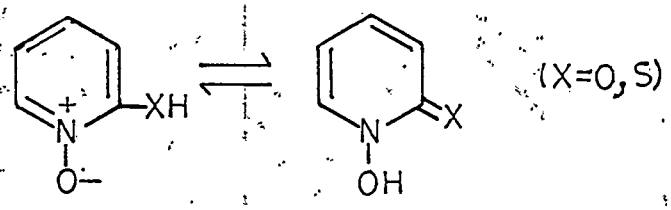
Blumenthal (53) prepared 2-ethynylpyridine-1-oxide in 91% yield from the reaction of pyridine-1-oxide and sodium acetylide in dimethyl sulfoxide at room temperature. 2-Ethynylpyridine-1-oxide is useful as a



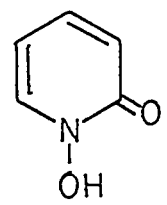
precursor to vinyl compounds and as a stabilizer for chlorinated hydrocarbon solvents.

1.5.0.0.0 The tautomerism of 2-mercapto- and 2-hydroxypyridine-1-oxides

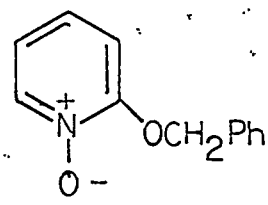
2-Substituted pyridine-1-oxides, in which the substituent atom adjacent to the ring carries a proton, are potentially tautomeric.



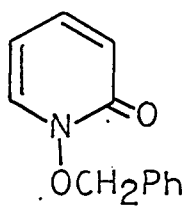
Shaw (17) examined the ultraviolet spectrum of N-hydroxy-2-pyridone (XVII), and compared it to those of 2-benzyloxypyridine-1-oxide (XVIII), N-benzyloxy-2-pyridone (XIX), and 3-hydroxypyridine-1-oxide (XX).



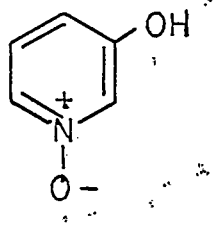
(XVII)



(XVIII)



(XIX)



(XX)

Shaw concluded that 2-hydroxypyridine-1-oxide exists as the N-hydroxy-2-pyridone tautomer since its ultraviolet spectrum [($\lambda_{max.}^{EtOH}$ mμ (ε): 228 (7200), 305 (4600)] was the same as that of N-benzyloxy-2-pyridone and similar to that of 2-pyridone [($\lambda_{max.}^{EtOH}$ mμ (ε): 227 (7300), 300 (5000)]. 2-Pyridone is itself considered to be in the lactam rather than in the hydroxypyridine form (54,55). The maxima at 260 mμ for 2-benzyloxypyridine-1-oxide and at 263 mμ for 3-hydroxypyridine-1-oxide are apparently related to the N-oxide configuration. No tautomeric structure compared to that of a hydroxamic acid can be formulated for these latter two compounds. Gardner and Katritzky (56) have also reported that 2-hydroxypyridine-1-oxide exists mainly as

N-hydroxy-2-pyridone and that it is strongly intramolecularly hydrogen bonded. Chemical evidence (31) also supports the pyridone tautomer since nitration of 2-hydroxypyridine-1-oxide proceeds readily to the 5-nitro, and 3,5-dinitro products depending on the reaction conditions used. In contrast, nitration of pyridine-1-oxide occurs almost exclusively at C-4 (29).

Similarly, in the 2-mercaptopyridine-1-oxide system Jones and Katritzky (57) reported on the basis of basicity measurements, ultraviolet and infrared spectral data that the 1-hydroxy-2-pyridinethione tautomer predominates over the 2-mercaptopyridine-1-oxide structure by a factor of about 52.

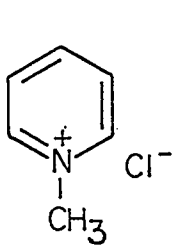
1.6.0.0.0 Base-catalyzed deprotonation and ring metallation of pyridine-1-oxides

Considerable attention has recently been directed to base-catalyzed hydrogen-deuterium exchange in pyridine-1-oxides. These studies have been initiated to study the effect of the N-oxide function on the position and rate of exchange and the mechanism by which deprotonation occurs.

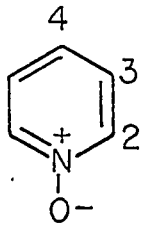
Abramovitch, Vinutha, and Singer (58) reported the rates of base-catalyzed hydrogen-deuterium exchange of 3-bromopyridine-1-oxide in $NaOD-D_2O$ to be in the order

of 2- > 6- > 4- >> 5. A similar study (59) with 3-chloropyridine-1-oxide showed the same order of reactivity; exchange at C-2 being 100 times faster than at C-6 which in turn was 100 times faster than exchange at C-4, while exchange at C-5 was not detected. In an earlier publication (60) Kawazoe and co-workers reported that H-D exchange of pyridine-1-oxide in alkaline medium occurred most readily at C-2 and C-6 and that N-methylpyridinium iodide was completely deuterated by 3% NaOD-D_2O when heated at 190° for three hours. These authors also reported that deuteration of pyridine-1-oxide or N-methylpyridinium iodide did not occur in 96% D_2SO_4 at 220°.

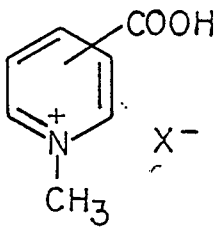
Recently Zoltewicz and his co-workers (61,62) reported that the kinetic data for the H-D exchange in a $D_2PO_4^-$-DPO_4^{2-} buffer of N-methylpyridinium chloride (XXI), and pyridine-1-oxide (XXII) are very similar to the known relative rates (63) of decarboxylation of the isomeric N-methylpyridinium carboxylates (XXIII). These



(XXI)



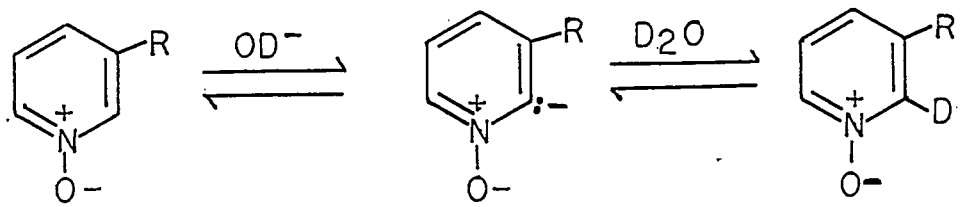
(XXII)



(XXIII)

decarboxylation reactions presumably involve the intermediate formation of carbanions. The relative rates of decarboxylation of these N-methylpyridinium carboxylates (XXIII) at C-2, 3, and 4 are 1600, 2.8, and 1, respectively, while H-D exchange of pyridine-1-oxide for positions 2, 3, and 4 are 1500, 10, and 1. These results suggest that a carbanion intermediate is involved in H-D exchange since the relative reactivities of the corresponding positions in these three molecules are quantitatively similar.

These results also indicate that pyridine-1-oxides undergo hydrogen exchange by simple deprotonation reactions and that the positional reactivity is determined primarily by the inductive effect of the N-oxide group and to a lesser degree by the halogen substituent.

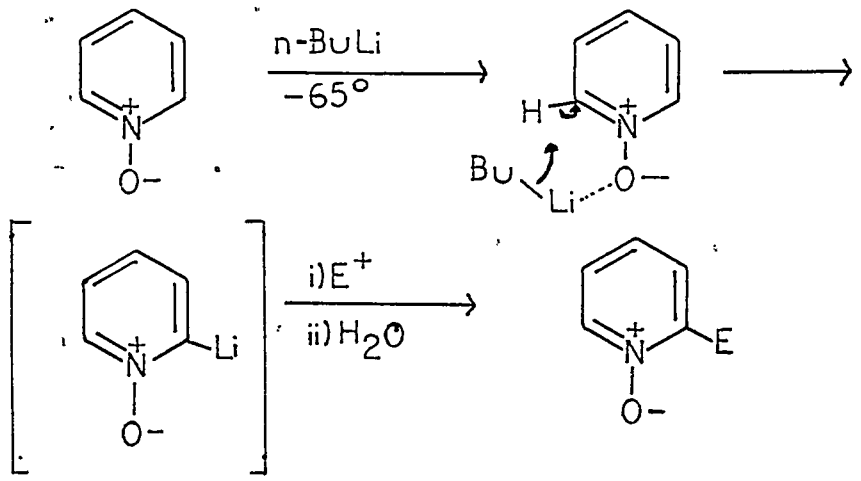


The deuteroxide ion abstracts a proton from C-2 to give the carbanion which then abstracts a deuteron from the solvent.

Howe and Ratts (64) and Boekelheide and Lehn (65) generated the N-methylpyridinium ion carbanion and

pyridine-1-oxide carbanion from their corresponding 2-carboxylates using the Hammick reaction.

Recently Abramovitch and co-workers (66,67) generated and trapped pyridylcarbanion-1-oxides in non-protic solvents. Treatment of pyridine-1-oxide in a non-protic solvent with n-butyllithium gave the carbanion which can be trapped with electrophilic reagents. A proposed mechanism for this reaction is the formation of a co-ordinate bond between lithium and the pair of electrons on the oxygen and the abstraction of the C-2 proton by the butyl carbanion to give the 2-pyridyl-carbanion-1-oxide. Condensation of the pyridylcarbanion-1-oxide with an electrophile yields the substituted product in which the N-oxide function is retained. These are the first reports describing the trapping of a 2-pyridylcarbanion-1-oxide generated as a result of nuclear proton abstraction.



2.0.0.0.0 OBJECTS OF RESEARCH

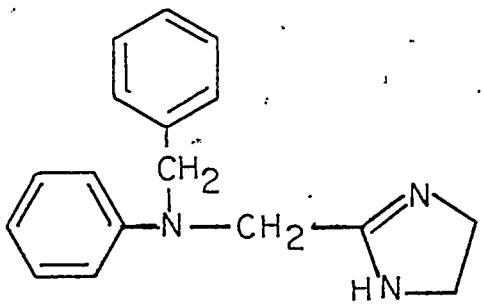
Kinetic studies (58,59) of the base-catalyzed H-D exchange of 3-halopyridine-1-oxides showed the rates of exchange to be in the order of 2 > 6 > 4 >> 5. A similar study (62), showed the rates of deuterium-hydrogen exchange for deuterated pyridine-1-oxide at C-4, C-3,5, and C-2,6 to be 1, 10, and 1500 respectively. It was postulated (58) that base-catalyzed deprotonation occurs first at C-2 to give the 2-pyridylcarbanion-1-oxide which then abstracted a deuteron from D_2O to give 2-deuteriopyridine-1-oxide. Abramovitch and co-workers (66,67) showed this mechanism to be correct by generating the carbanion in a non-protic solvent and subsequently trapping the pyridylcarbanion-1-oxide with a suitable electrophile. Thus, this appeared to be a new general method for the introduction of substituents into the 2-position of pyridine-1-oxides. It was therefore of interest to examine the scope and synthetic versatility of this reaction. This method was to be used in the preparation of halopyridine-1-oxides. Some of these compounds are structurally related to the most powerful herbicides and pesticides now available.

It seemed likely that a new method of preparing cyclic hydroxamic acids might be developed. Reaction of

lithiopyridine-1-oxides with molecular oxygen and sulfur to give the pharmacologically interesting 1-hydroxy-2-pyridones and 1-hydroxy-2-pyridinethiones was to be studied.

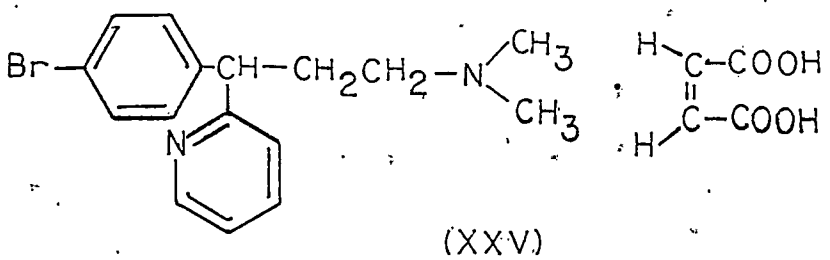
The reaction of lithiopyridine-1-oxides with epoxides to give pyridylalkanol-1-oxides was worthy of investigation. Dehydration and polymerization of these alcohols would provide a route to substituted polyvinylpyridine-1-oxides which are useful in the treatment of silicosis (22-24), and could possibly be used in the production of artificial membranes and plastics due to their wetting characteristics.

Application of this method to the preparation of secondary amines from Schiff bases was to be explored. These pyridylamine-1-oxides have a structural similarity to some antihistamines (69) such as 2-(N-benzylanilinomethyl)-2-imidazoline phosphate (Antistine phosphate) (XXIV), and 2-[p-bromo-α-(2-dimethylaminoethyl)benzyl]-pyridine maleate (Dimetane) (XXV).



·H_3PO_4

(XXIV).



(XXV)

Finally it appeared necessary to examine the effectiveness of other bases to generate the 2-pyridyl-carbanion-1-oxide so that the reaction conditions could be modified in order to increase its scope and versatility.

3.0.0.0.0 DISCUSSION

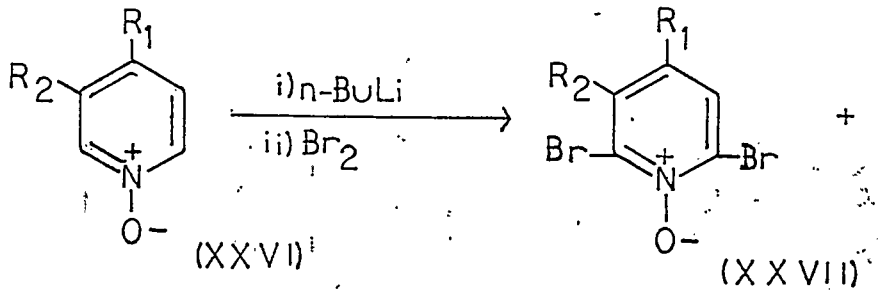
3.1.0.0.0 Reactions of 2-lithiopyridine-1-oxides

The pyridyl-1-oxide carbanions were generated *in situ* by the addition of n-butyllithium to a solution or suspension of the pyridine-1-oxide in tetrahydrofuran at -65° or in ether on warming to room temperature under an atmosphere of nitrogen. The lithiopyridine-1-oxide was then treated with a suitable electrophile.

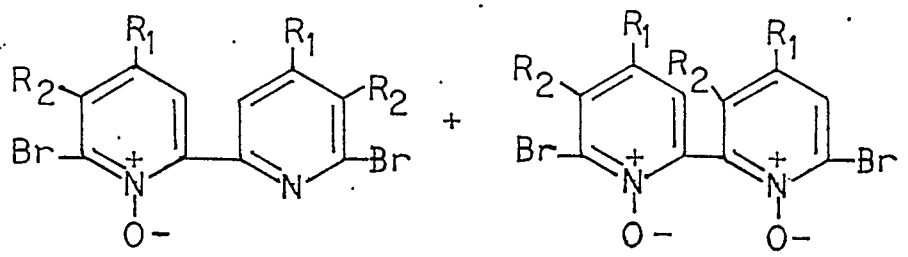
3.1.1.0.0 Reactions with halogens to give halopyridine-1-oxides

The reaction of lithiopyridine-1-oxides with bromine gave a variety of dihalogenated products (Table 1). Treatment of the lithium derivative of pyridine-1-oxide (XXVI, R_1=R_2=H) at -65° with an excess of bromine gave 2,6-dibromopyridine-1-oxide (XXVII, R_1=R_2=H, 3.1%), 6,6'-dibromo-2,2'-dipyridyl-1-oxide (XXVIII, R_1=R_2=H, 6.2%), and 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (XXIX, R_1=R_2=H, 8.2%).

The formation of the 2,6-dibromo product (XXVII) suggests the possible intermediacy of the 2,6-dilithio intermediate (XXX). Alternatively, 2-lithiopyridine-1-oxide (XXXI) could abstract a proton from C-6 in a

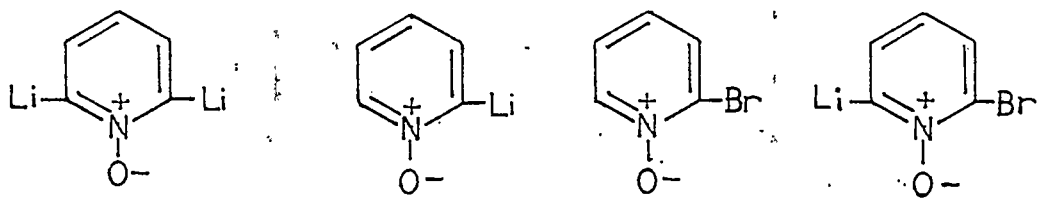


(XXVI) (XXVII)



(XXVIII) (XXIX)

molecule of 2-bromopyridine-1-oxide (XXXII) to give 2-bromo-6-lithiopyridine-1-oxide (XXXIII) which can then react to give the 2,6-disubstituted product (XXVII).



(XXX) (XXXI) (XXXII) (XXXIII)

The presence of a bromine atom at the 2-position in 2-bromopyridine-1-oxide (XXXII) may increase the acidity of the C-6 proton making hydrogen abstraction by 2-lithiopyridine-1-oxide (XXXI) more facile at this site. However this process is unlikely since no unreacted pyridine-1-oxide was recovered. One would also expect

any excess n-butyllithium present at the beginning of the reaction to react very quickly with bromine thus preventing any further hydrogen abstraction from pyridine-1-oxide. The presence of 2,6-dilithiopyridine-1-oxide (XXX) is therefore plausible.

The structure of 2,6-dibromopyridine-1-oxide (XXVII) was confirmed by examination of its infrared, n.m.r., and mass spectra. The infrared spectrum of this compound shows the presence of an $\overset{+}{N}\text{-}O^{-}$ group (1255 cm^{-1}) (81). The n.m.r. spectrum in deuterochloroform exhibited a 2 H doublet ($J_{3,4} = J_{4,5} = 8$ Hz) at τ2.36 due to C_3-H, C_5-H, and a 1 H triplet ($J_{3,4} = J_{4,5} = 8$ Hz) at τ3.08 due to C_4-H.

Aromatic N-oxides can readily be recognized by mass spectrometry since they form abundant fragments arising from the loss of an oxygen atom (97, 104). The abundance of the $(M-16)^{+\cdot}$ ion usually ranges from 15-40%. The molecular ions are usually major peaks for aryl halides and the loss of a halogen atom gives rise to the most abundant ion when the ring contains no alkyl group larger than methyl. It appears that mass spectrometry is a useful technique for the identification and structure determination of aryl halides (105).

The mass spectrum of 2,6-dibromopyridine-1-oxide exhibited a parent ion at m/e 251 ($C_5H_3Br_2NO^{+}$) in

agreement with the calculated molecular weight (for ^{79}Br). In addition, there were also (M+2) and (M+4) peaks at m/e 253 (base peak) and m/e 255 due to ^{81}Br. The isotope peaks of bromine-containing compounds are uniquely discernible through their doublet character associated with the approximately 1:1 ratio of the ^{79}Br and ^{81}Br isotopes. Consequently they have a particular diagnostic value. The remainder of the spectrum could be accounted for as illustrated in Scheme 1. The molecular ion at m/e 251 ($C_5H_3Br_2NO^+$) can undergo two fragmentations. An (M-79) peak at m/e 172 ($C_5H_3BrNO^+$) arises from loss of a bromine atom. This fragment ion can then undergo consecutive fragmentations to give an ion at m/e 144 ($C_4H_3BrN^+$) by loss of CO, an ion at m/e 117 ($C_3H_2Br^+$) by loss of HCN, and an ion at m/e 38 ($C_3H_2^+$) by loss of the second atom of bromine. Although the fragment ion at m/e 172 is present in less than 2% abundance it appeared necessary to postulate this ion in order to explain the presence of ions at m/e 144, 117 and 93 respectively. The loss of bromine from the molecular ion is an expected fragmentation (105), and it is known (97) that bromotropones eliminate CO and/or bromine. The ions at m/e 144 and 117 were complemented by ions at m/e 146 and 119 respectively due to ^{81}Br. Alternatively, the fragment ion at m/e 172 ($C_5H_3BrNO^+$) can lose a bromine

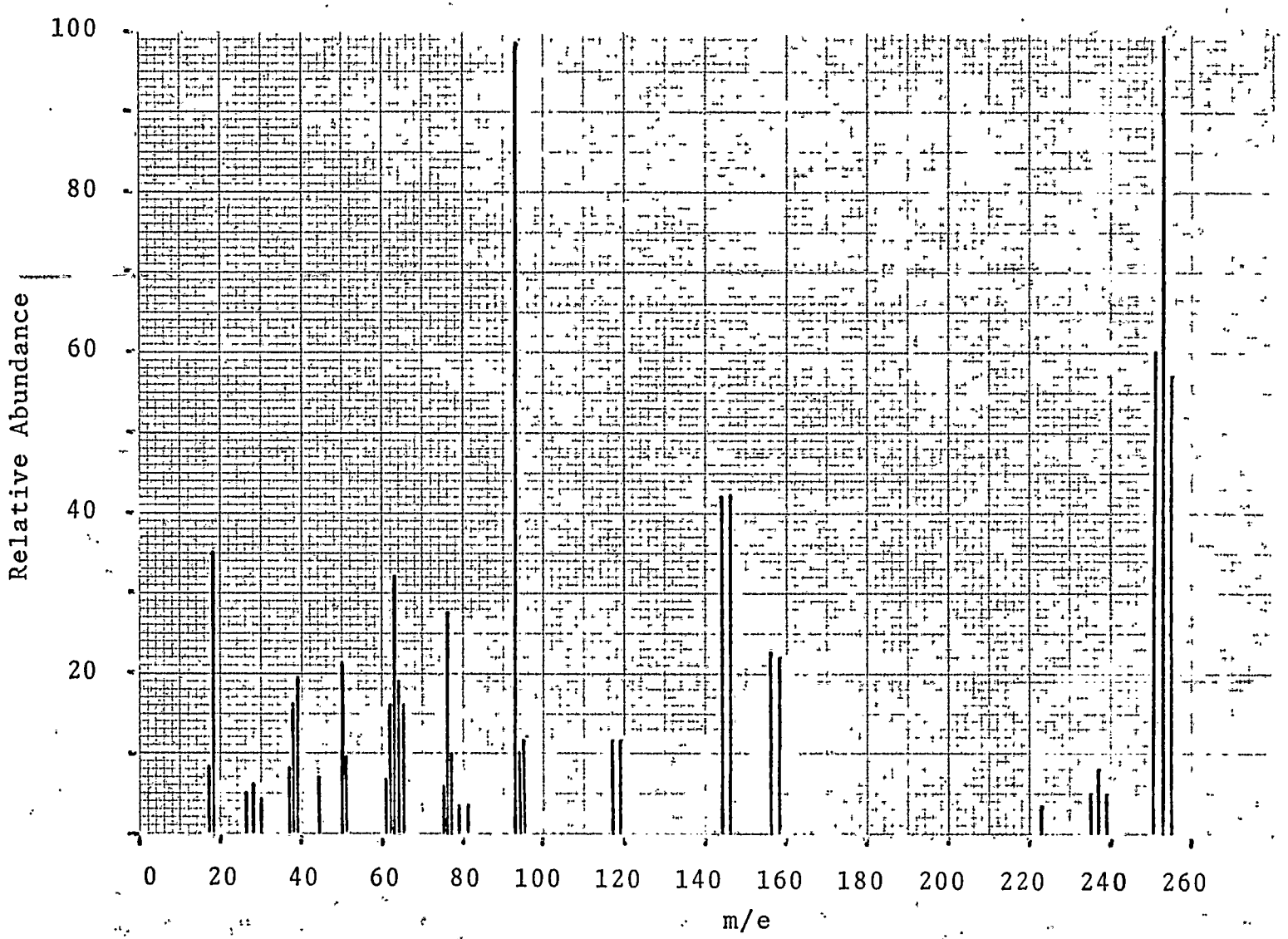
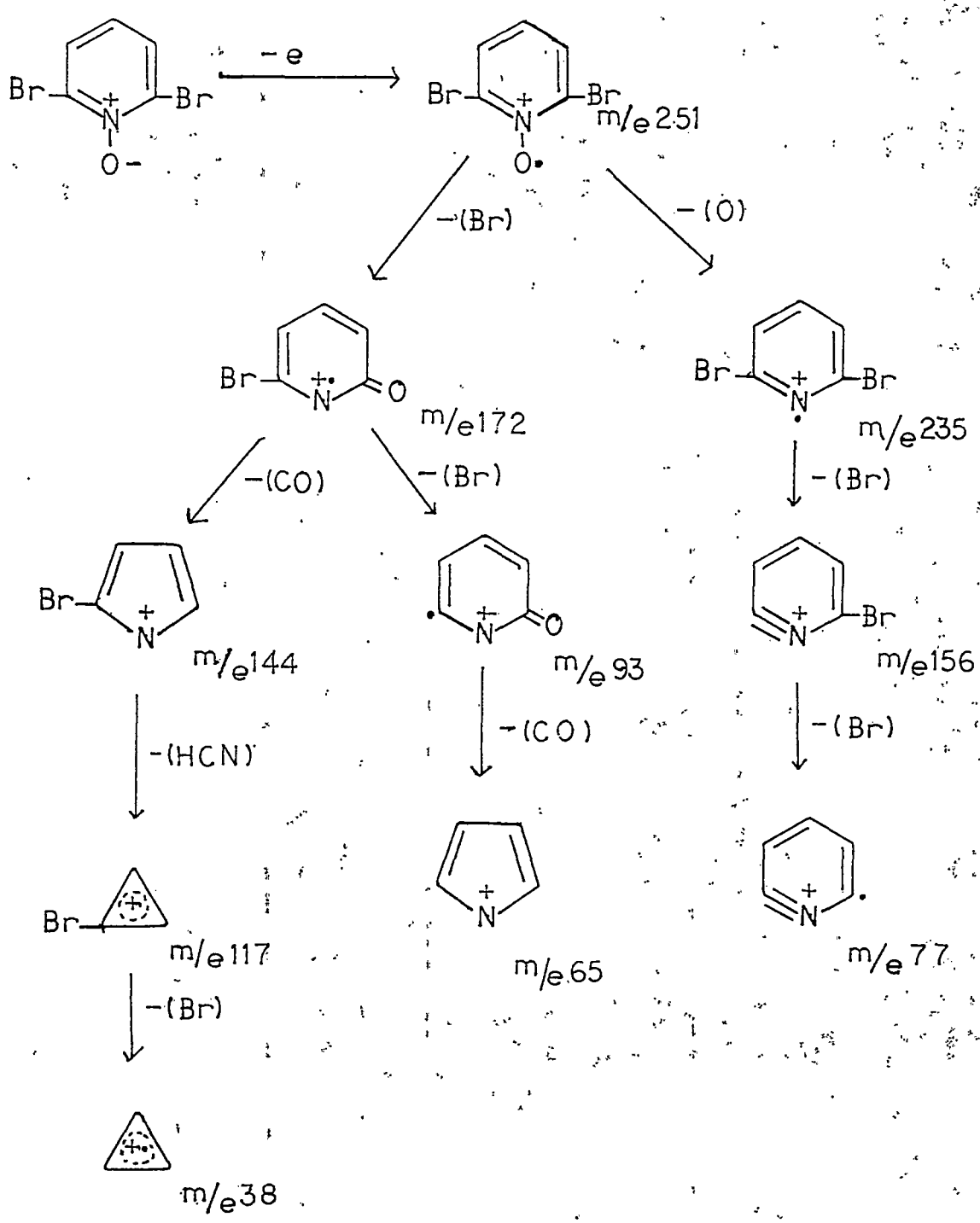


Figure 1.--Mass spectrum of 2,6-dibromopyridine-1-oxide (70 eV)

SCHEME 1

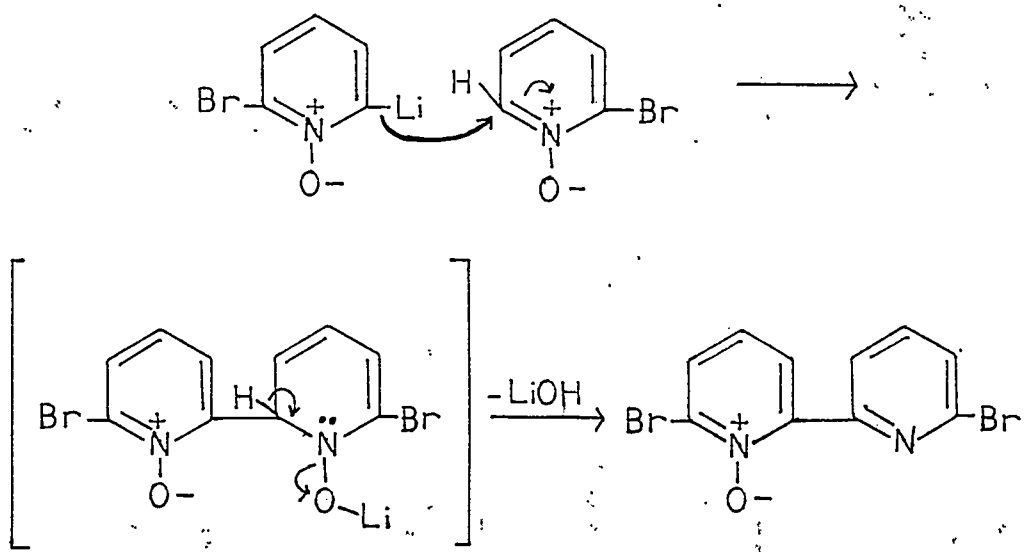

Br
Br
N
O
-e
m/e 251
-(Br)
-(O)
m/e 172
-(CO)
-(Br)
m/e 235
-(Br)
m/e 144
m/e 93
m/e 156
-(HCN)
-(CO)
-(Br)
m/e 117
m/e 65
m/e 77
-(Br)
m/e 38

atom to give an ion at m/e 93 ($C_5H_3NO^+$) which in turn could lose CO to give an ion at m/e 65 ($C_4H_3N^+$). The molecular ion at m/e 251 ($C_5H_3Br_2NO^+$) could also undergo consecutive fragmentations to give ions at m/e 235 ($C_5H_3Br_2N^+$) due to the loss of an oxygen atom, m/e 156 ($C_5H_3BrN^+$) due to the loss of a bromine atom, and then to m/e 77 ($C_5H_3N^+$) due to the loss of the second bromine atom. The ions at m/e 235 and 156 were complemented by ions at m/e 237, 239 and 158 respectively due to the presence of ^{81}Br. This appears to be a characteristic fragmentation pattern for the other 2,6-dihalogenated pyridine-1-oxides also prepared (Table 1).

The formation of 6,6'-dibromo-2,2'-dipyridyl-1-oxide (XXVIII) can be envisaged as a nucleophilic addition of 2-lithio-6-bromopyridine-1-oxide to 2-bromopyridine-1-oxide, and then elimination of lithium hydroxide from the adduct (XXXIV) to give the deoxygenated product (XXVIII).

This observation is in agreement with a report by Abramovitch, Giam, and Poulton (99) that phenyllithium reacts readily with pyridine-1-oxide to yield 2-phenylpyridine as one of the products.

The structure of 6,6'-dibromo-2,2'-dipyridyl-1-oxide was consistent with its infrared, n.m.r., and mass spectra. The infrared spectrum revealed the presence of



(XXXIV) (XXVIII)

an $\overset{+}{N}$-O^- group (1265 cm^{-1}) (81). The n.m.r. spectrum exhibited a 1 H quartet ($J_{4',5'}$ = 8 Hz; $J_{3',5'}$ = 1 Hz) at τ0.98 due to the C_5'-H, a 1 H quartet ($J_{4,5}$ = 8 Hz; $J_{3,5}$ = 2 Hz) at τ1.73 due to the C_5-H, a 1 H quartet ($J_{3,4}$ = 8 Hz; $J_{3,5}$ = 2 Hz) at τ2.25 due to the C_3-H, a 1 H doublet (J = 8 Hz) at τ2.35 due to the C_4'-H, a 1 H quartet ($J_{3',4'}$ = 8 Hz; $J_{3',5'}$ = 1 Hz) at τ2.48 due to the C_3'-H, and a 1 H triplet (J = 8 Hz) at τ2.85 due to the C_4-H. The mass spectrum exhibited a parent peak at m/e 328 in agreement with the calculated molecular weight (for ^{79}Br). There were also (M+2) and (M+4) peaks at m/e 330 and m/e 332, which indicate the presence of

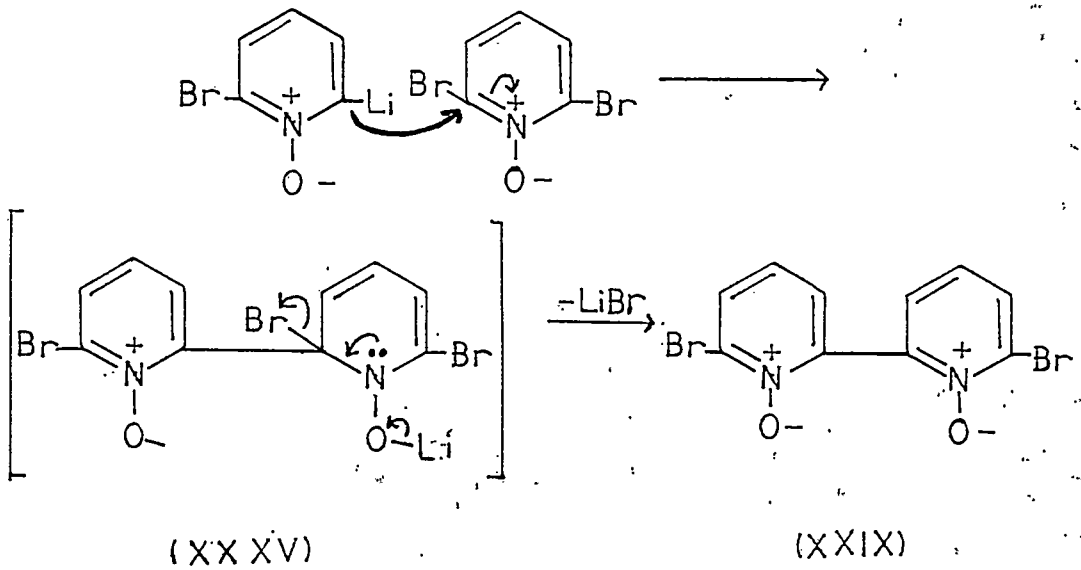
TABLE 1

Reaction of the lithium derivatives of 4-substituted and 3,4-disubstituted pyridine-1-oxides with halogens at -65°

(XXVI) R_1	R_2	Solvent	Removal of excess halogen	% Products XXVII	XXVIII	XXIX
a) With bromine						
H	H	THF-ether	- -	3.1	6.2	8.2
		THF-ether	Phenol	4.0	- -	4.1
		HMPT-ether	- -	0.8	- -	1.15
Me	H	THF	- -	4.6	18.1	12.7
Me	Me	THF	$Na_2S_2O_3$	12.8	- -	4.3
		THF	Phenol	23.3	- -	1.6
		THF	i) Phenol and ii) then N_2 gas	8.9	- -	2.4
b) With chlorine				XXXIX		
H	H	THF	- -	4.5		
Me	Me	THF	Phenol	8.8		

two bromine atoms, as well as an (M-16) fragment ion ($C_{10}H_6Br_2N_2^+$) due to the loss of an oxygen atom.

The formation of 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (XXIX) can be viewed as a nucleophilic addition of 2-bromo-6-lithiopyridine-1-oxide to 2,6-dibromopyridine-1-oxide to give the intermediate (XXXV) which can eliminate lithium bromide to yield XXIX.



(XXXV) (XXIX)

The infrared, n.m.r., and mass spectral data, and elemental analyses were in agreement with this structure. The infrared showed the presence of an $\overset{+}{N}$-O- group (1265 cm^{-1}) (81). The n.m.r. spectrum in deuteroacetic acid exhibited a 2 H multiplet at τ2.30-2.55 due to the C_5-H, C_5'-H, and a 4 H multiplet at τ2.60-2.85 due to the C_3-H, C_3'-H, C_4-H, and C_4'-H. The mass spectrum

exhibited a molecular ion at m/e 344 in agreement with the calculated molecular weight (for ^{79}Br), (M+2) and (M+4) peaks at m/e 346 (base peak) and m/e 348 due to ^{81}Br and an (M-17) peak at m/e 327 ($C_{10}H_5Br_2N_2O^+$) presumably due to the loss of a hydroxyl group.

The absence of 2-bromopyridine-1-oxide as one of the reaction products was rather surprising. It seemed possible that the monosubstituted product was undergoing further bromination on warming the reaction mixture to room temperature to give the disubstituted product (XXVII). The reaction of lithiopyridine-1-oxide with bromine was repeated, except that phenol was added to remove any unreacted bromine, before the reaction mixture was allowed to warm up to room temperature. Using this procedure 2,6-dibromopyridine-1-oxide (XXVII, $R_1=R_2=H$, 4.0%) and 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (XXIX, $R_1=R_2=H$, 4.1%) were obtained. Neither 6,6'-dibromo-2,2'-dipyridyl-1-oxide (XXVIII, $R_1=R_2=H$) nor 2-bromopyridine-1-oxide (XXXII) were detected in this experiment.

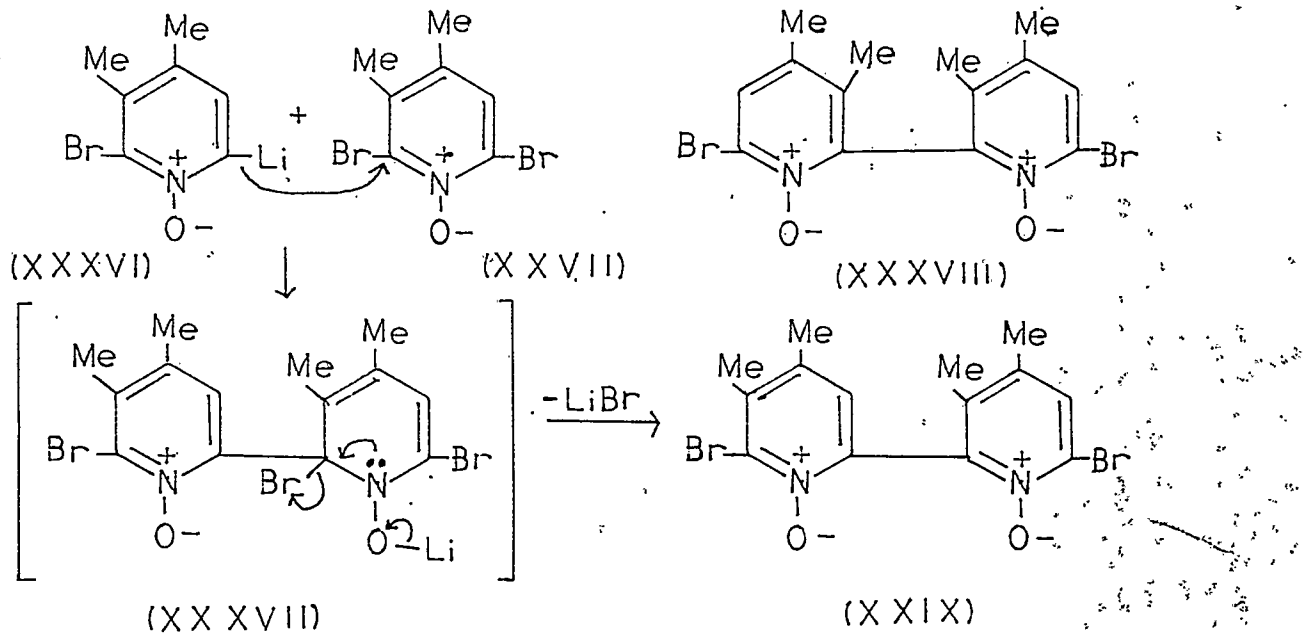
When the reaction was repeated using ether-hexamethylphosphoramide (40:3 v/v) as the solvent rather than tetrahydrofuran-ether (1:1 v/v) as above, 2,6-dibromopyridine-1-oxide (0.8%) and 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (1.15%) were obtained.

It was previously proposed that 2-bromopyridine-1-oxide (XXXII) undergoes nucleophilic addition at C-2 by 2-lithio-6-bromopyridine-1-oxide (XXXIII) to give the adduct (XXXIV) which can then eliminate lithium hydroxide to yield XXVIII. If this mechanism is correct the absence of 2-bromopyridine-1-oxide can be rationalized since this process would remove 2-bromopyridine-1-oxide from the reaction mixture.

The reaction of lithio-4-methylpyridine-1-oxide with bromine gave 6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1-oxide (XXVIII, $R_1=CH_3$, $R_2=H$, 18.1%), 2,6-dibromo-4-methylpyridine-1-oxide (XXVII, $R_1=CH_3$, $R_2=H$, 4.6%) and 6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1,1'-dioxide (XXIX, $R_1=CH_3$, $R_2=H$, 12.7%) (Table 1). The structures assigned to these compounds are consistent with their infrared, n.m.r., and mass spectra, and elemental analyses. The reaction of the lithium derivative of 3,4-dimethylpyridine-1-oxide gave two products, whether or not the excess bromine was removed prior to warming up to room temperature (Table 1). 6,6'-Dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide (XXIX, $R_1=R_2=CH_3$) and 2,6-dibromo-3,4-dimethylpyridine-1-oxide (XXVII, $R_1=R_2=CH_3$) were separated as above and were identified through their infrared, n.m.r., and mass spectra and elemental analyses.

The structure of 6,6'-dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide (XXIX, $R_1=R_2=CH_3$) was confirmed by its n.m.r. spectrum which exhibited a 1 H singlet at τ2.50 due to C_5'-H, a 1 H singlet at τ2.88 due to C_3-H, and 4 methyl singlets at τ7.58, 7.74, 7.82, and 8.04 respectively, the areas of the latter being in the ratio of 3:3:3:3. If a symmetrical product such as XXXVIII (or its isomer) had been formed the n.m.r. spectrum would be expected to show only one 2 H absorption due to the pyridine β-protons and only two methyl peaks instead of four. This product undoubtedly arises from nucleophilic addition of the monolithiated product (XXXVI) to 2,6-dibromo-3,4-dimethylpyridine-1-oxide (XXVII, $R_1=R_2=CH_3$) to give the intermediate adduct (XXXVII) which eliminates lithium bromide to give XXIX ($R_1=R_2=CH_3$). This observed orientation is consistent with the known directive effect of a 3-methyl group upon the addition of organolithium compounds to pyridines (83).

In a control experiment (5.2.1.4.0), treatment of 3,4-lutidine-1-oxide with bromine under the usual reaction conditions did not give any halogenated products. Mosher and Welsh (84) reported that bromination of pyridine-1-oxide could not be effected at 110° in the presence of iron powder. In separate experiments where

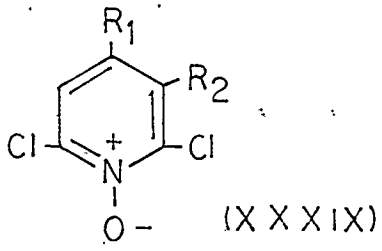


the amounts of n-butyllithium and/or bromine were decreased no monobromo products were obtained. This is therefore further evidence for the intermediacy of the dianion XXX.

The reaction of lithiopyridine-1-oxide with chlorine gave 2,6-dichloropyridine-1-oxide. The infrared spectrum revealed the presence of an $\overset{+}{N}$-O^- function (1265 cm^{-1}) while the n.m.r. spectrum in deuterochloroform exhibited a 2 H doublet ($J_{3,4} = J_{4,5} = 8$ Hz) at τ2.56 due to C_3-H and C_5-H, and a 1 H triplet ($J_{3,4} = J_{4,5} = 8$ Hz) at τ2.92 due to C_4-H. The mass spectrum showed a molecular ion at m/e 163 (for ^{35}Cl), (M+2) and (M+4) peaks at m/e 165 and m/e 167 due to the ^{37}Cl isotopic cluster and

a fragment ion at m/e 147 ($C_5H_3Cl_2N^+$) due to the loss of an oxygen atom. The remainder of the fragmentation pattern was similar to that depicted for 2,6-dibromopyridine-1-oxide in Scheme 1.

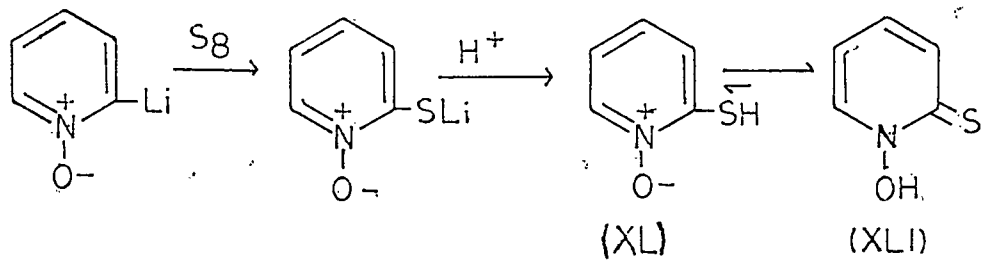
The anion of 3,4-lutidine-1-oxide was treated with chlorine gas to give 2,6-dichloro-3,4-dimethylpyridine-1-oxide (Table 1). The infrared, n.m.r. and mass spectra, and elemental analysis were consistent with this structure. In the reactions with chlorine none of the bimolecular products were isolated.



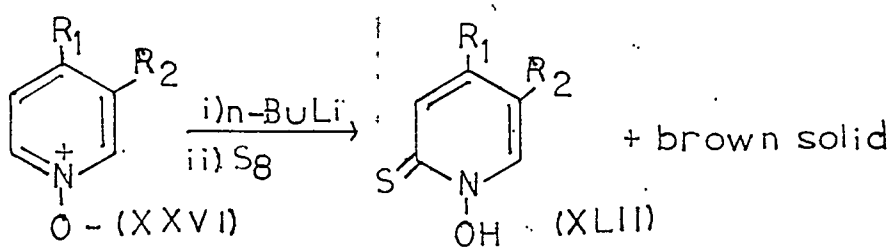
(XXXIX)

3.1.2.0.0 Reactions with sulfur to give 1-hydroxy-2-pyridinethiones

A general method of preparing cyclic thiohydroxamic acids has been developed which involves the direct introduction of sulfur into the ring by the thiation of lithiopyridine-1-oxides. The existence of this tautomerism (XL ⇌ XLI) has already been discussed (1.5.0.0.0) and it has been shown (57) that the cyclic thiohydroxamic structure (XLI) predominates over the mercaptopyridine-1-oxide tautomer (XL) by a factor of 52.



Treatment of the lithium derivative of pyridine-1-oxide (XXVI, R_1=R_2=H) with sulfur in tetrahydrofuran at -65° gave 1-hydroxy-2-pyridinethione (XLII, R_1=R_2=H, 7.9%) (Table 2) and a brown plastic-like solid.



The infrared spectrum of 1-hydroxy-2-pyridinethione revealed the presence of an N-OH group (2650 cm^{-1}) (81, 100), and the n.m.r. spectrum showed a 1 H octet ($J_{5,6}$ = 7 Hz; $J_{4,6}$ = 1.5 Hz; $J_{3,6}$ = 0.75 Hz) at τ1.93 due to C_6-H, a 1 H octet ($J_{3,4}$ = 8.5 Hz; $J_{3,5}$ = 1.75 Hz; $J_{3,6}$ = 0.75 Hz) at τ2.37 due to C_3-H, a 1 H octet ($J_{3,4}$ = 8.5 Hz; $J_{4,5}$ = 7 Hz; $J_{4,6}$ = 1.50 Hz) at τ2.74 due to C_4-H, a 1 H sextet ($J_{5,6}$ = 7 Hz; $J_{4,5}$ = 7 Hz; $J_{3,5}$ = 1.75 Hz) at τ3.23 due to C_5-H, and a 1 H singlet at τ-1.6 due to the OH proton (disappears on addition of D_2O). This compound was identical (I.R. and n.m.r.) with an authentic sample prepared as described under 5.5.3.0.0.

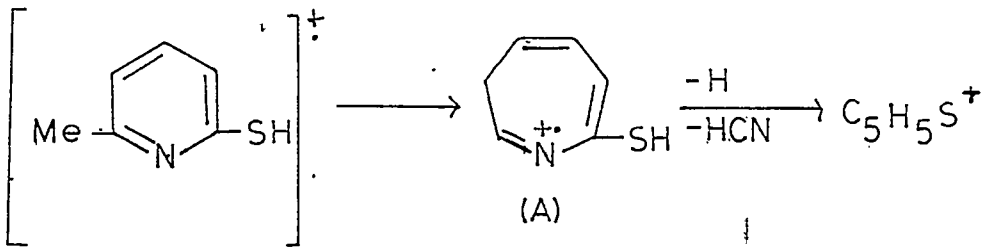
Since mercaptans are very susceptible to oxidation one may expect the brown solid obtained in this reaction to consist of disulfide or polymeric disulfide moieties. It is known (85) that disulfides can be reduced quantitatively with lithium aluminum hydride. However, when this solid was subjected to reduction no change was observed. Further attempts to separate and characterize this substance did not yield any identifiable product.

When the same reaction was repeated at room temperature with ether as the solvent, the same 1-hydroxy-2-pyridinethione (XLII, R_1=R_2=H, 10.1%) (Table 2) was obtained.

Reaction of the lithium derivative of 4-methyl-pyridine-1-oxide (XXVI, R_1=CH_3, R_2=H) with sulfur gave 1-hydroxy-4-methyl-2-pyridinethione (XLII, R_1=CH_3, R_2=H, 38.7%) (Table 2). This structure is consistent with its infrared, n.m.r., and mass spectra.

There does not appear to be any study on the mass spectra of cyclic thiohydroxamic acids in the literature, but by analogy with the 1-hydroxy-2-pyridone nucleus, the direct loss of O and OH from the molecular ion would be expected (103). The fragmentation of 2-pyridinethione and 2-alkylthiopyridines induced by electron impact have been studied and the principal fragmentation pathways have been elucidated with the aid of deuterium labelling

(101). The most important fragmentation of 2-pyridinethione is the loss of CS from the molecular ion to give the pyrrole molecular ion at m/e 67 ($C_4H_4NH^+$). The composition of this ion has been confirmed by high-resolution mass measurement. Two other important fragmentations are the loss of SH, and loss of H followed by HCN from the molecular ion. In the case of 2-methylpyridine-6-thiol it is postulated that ring expansion occurs to give an ion (A), which then loses H followed by HCN as illustrated below.



(A)

The mass spectrum of 1-hydroxy-4-methyl-2-pyridinethione could be accounted for as illustrated in Scheme 2. The parent ion at m/e 141 could undergo consecutive fragmentations (Path 1) to give fragment ions at m/e 97 ($C_5H_7NO^+$) by loss of CS, m/e 80 ($C_5H_6N^+$) by loss of OH, and m/e 53 ($C_4H_5^+$) by loss of HCN. Alternatively, the molecular ion at m/e 141 could lose OH to give an ion at m/e 124 ($C_6H_6NS^+$) (Path 2) which can eliminate CS to give an ion at m/e 80 ($C_5H_6N^+$). The molecular ion loses an oxygen atom to give a fragment ion at m/e 125 ($C_6H_7NS^+$) which can eliminate CS (Path 3) to give an ion at m/e 81

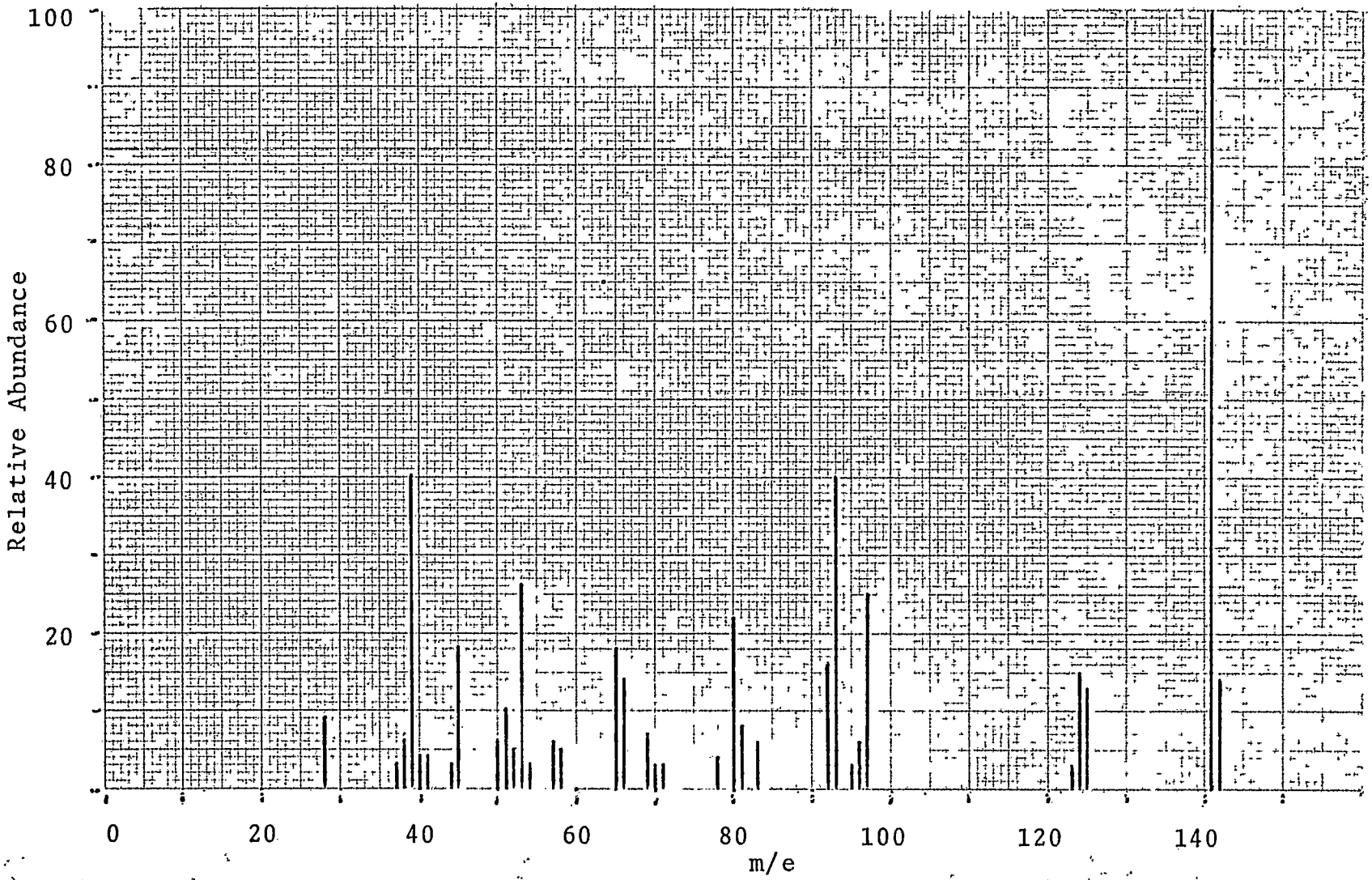
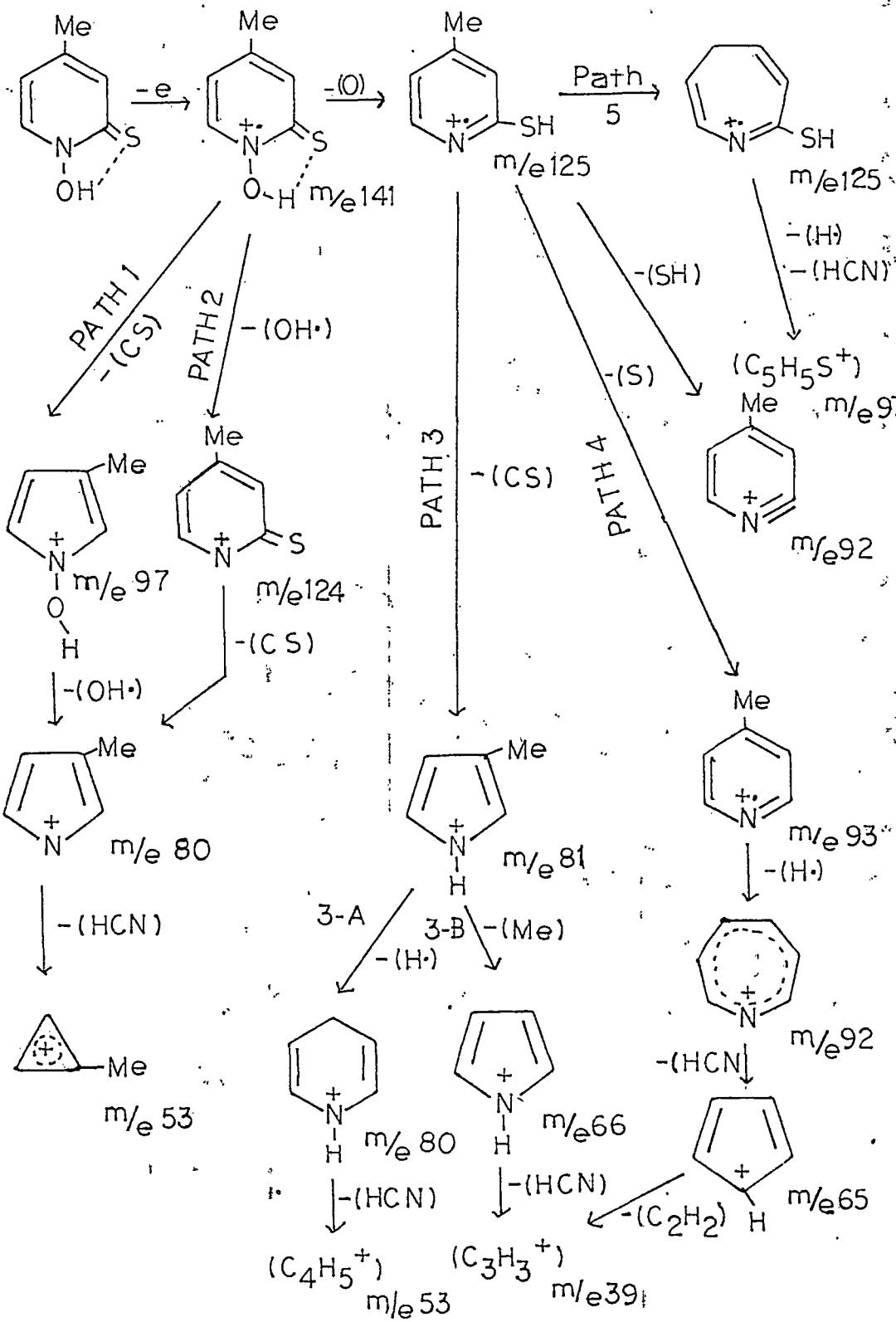


Figure 2.--Mass spectrum of 1-hydroxy-4-methyl-2-pyridinethione (70 eV)

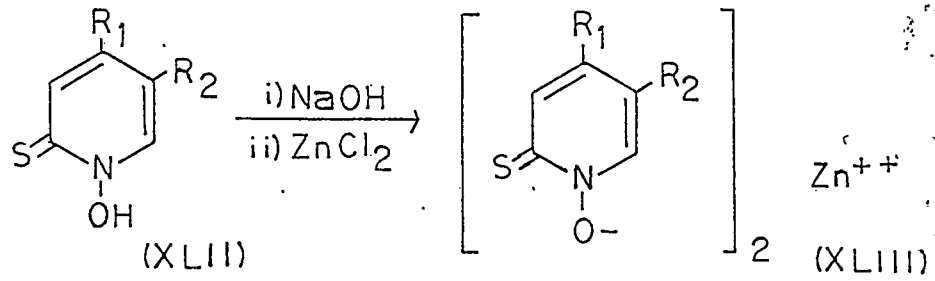
SCHEME 2


Me
-e
-(O)
Path 5
SH
m/e125
m/e141
PATH 1
-(CS)
PATH 2
-(OH·)
-(SH)
-(H·)
-(HCN)
-(S)
(C5H5S+)
m/e97
m/e92
PATH 3
-(CS)
PATH 4
m/e124
-(CS)
-(OH·)
m/e 97
m/e 80
m/e 81
m/e 93
-(H·)
3-A
3-B
-(Me)
-(HCN)
m/e 53
m/e 80
m/e66
m/e65
-(C2H2)
(C4H5+)
m/e 53
(C3H3+)
m/e39

($C_5H_7N^+$); this can fragment further by Path 3-A to give a fragment ion at m/e 80 ($C_5H_6N^+$) by loss of a hydrogen atom and an ion at m/e 53 ($C_4H_5^+$) by loss of HCN, or by 3-B to give an ion at m/e 66 ($C_4H_4N^+$) by loss of a methyl group, and then m/e 39 ($C_3H_3^+$) by loss of HCN. The fragment ion at m/e 125 ($C_6H_7NS^+$) can also undergo consecutive fragmentations (Path 4) to give a fragment ion at m/e 93 ($C_6H_7N^+$) due to the loss of sulfur, an ion at m/e 92 ($C_6H_6N^+$) due to loss of a hydrogen atom, an ion at m/e 65 ($C_5H_5^+$) due to loss of HCN, and an ion at m/e 39 ($C_3H_3^+$) due to loss of C_2H_2. The fragment ion at m/e 125 ($C_6H_7NS^+$) can also lose SH as described previously to give an ion at m/e 92 ($C_6H_6N^+$) or can rearrange (Path 5) and then eliminate H followed by HCN to give an ion at m/e 97 ($C_5H_5S^+$) as described above.

The anion from 4-chloro-3-methylpyridine-1-oxide (XXVI, R_1=Cl, R_2=CH_3) was treated with sulfur to give 4-chloro-1-hydroxy-3-methyl-6-pyridinethione (XLII, R_1=Cl, R_2=CH_3, 11.45%) (Table 2), and another product which was resistant to reduction with lithium aluminum hydride. Further attempts to purify and characterize this product failed. The infrared, n.m.r. and mass spectra of 4-chloro-1-hydroxy-3-methyl-6-pyridinethione were consistent with its structure. Purification of this compound proved to be rather difficult as it was very

unstable and tended to decompose quite vigorously. Cyclic thiohydroxamic acids form chelates readily, consequently 1-hydroxy-4-chloro-3-methyl-6-pyridinethione (XLII, R_1=Cl, R_2=CH_3) was characterized as its zinc complex (XLIII, R_1=Cl, R_2=CH_3, 86%). The structure of XLIII



(XLII) (XLIII)

(R_1=Cl, R_2=Me) was confirmed through its mass spectrum and elemental analyses. The mass spectrum exhibited a molecular ion peak at m/e 414 (for ^{35}Cl) and the chlorine isotopic cluster peaks at m/e 416 and m/e 418, and a peak at m/e 398 due to the loss of an oxygen atom.

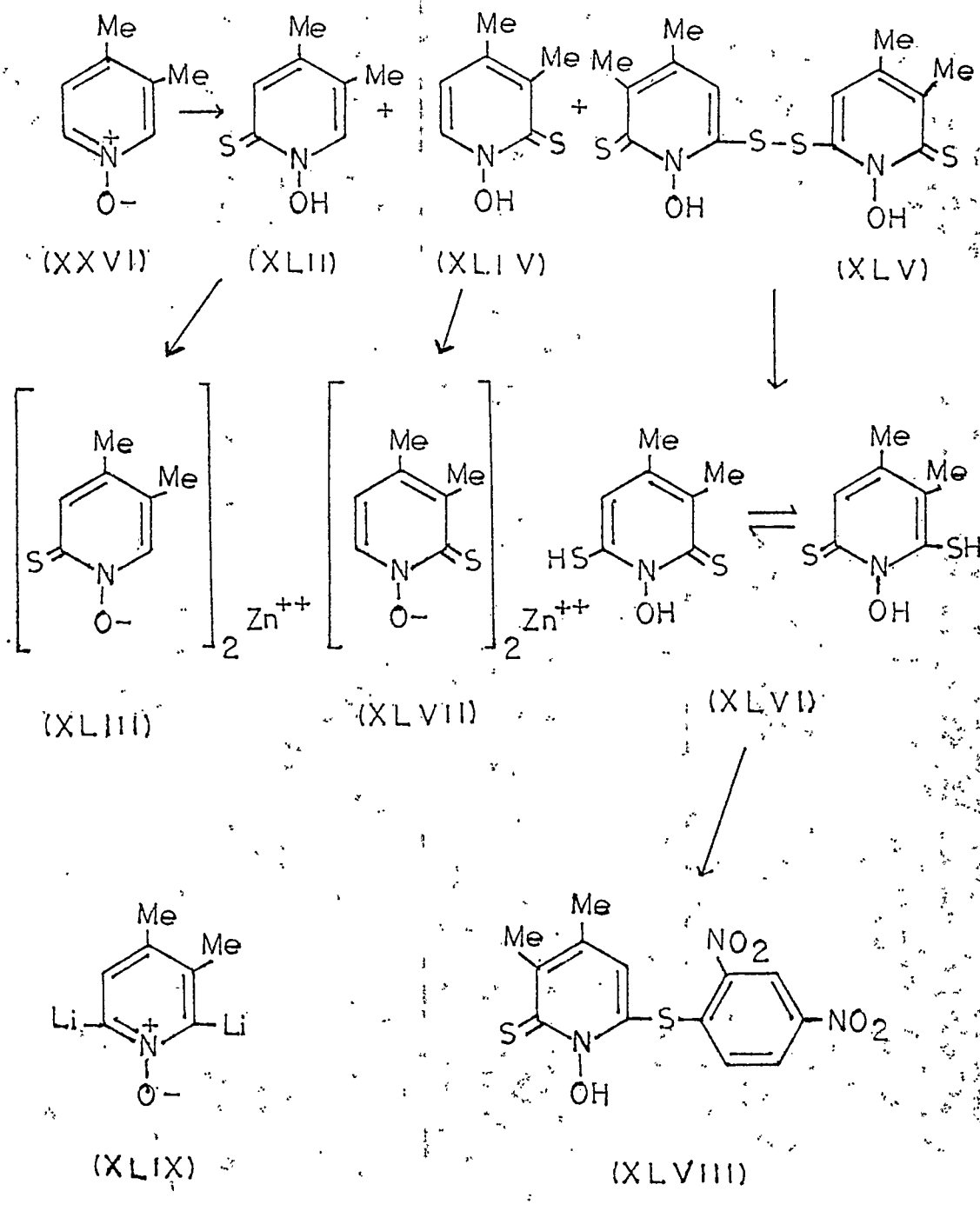
Treatment of the lithium derivative of 3,4-dimethylpyridine-1-oxide (XXVI, R_1=R_2=CH_3) in tetrahydrofuran at -65° with sulfur gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (XLII, R_1=R_2=CH_3, 24.1%), 1-hydroxy-3,4-dimethyl-2-pyridinethione (XLIV, R_1=R_2=CH_3, 12.5%), and 2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)-disulfide (XLV, 37.4%) (or its isomer LII) (Table 2).

The empirical composition of the disulfide (XLV) was deduced from the elemental analysis, molecular weight determination (osmometer) and by characterization of its

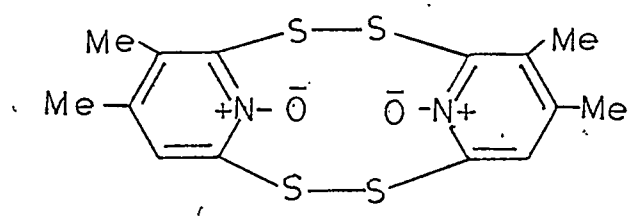
TABLE 2

Reaction of the lithium derivatives of some pyridine-1-oxides with sulfur

(XXVI)				% Products		
R_1	R_2	Solvent (temp °C)	Source of Sulfur	XLII	XLIV	XLV
H	H	THF (-65°)	S_8	7.9	- -	- -
		Ether (25°)	S_8	10.1	- -	- -
Me	H	THF (-65°)	S_8	38.7	- -	- -
Cl	Me	THF (-65°)	S_8	11.45	- -	- -
Me	Me	THF (-65°)	S_8	24.1	12.5	37.4
		Ether (25°)	S_8	7.3	7.9	21.1
		THF (-65°)	S_2Cl_2	7.5	4.6	- -
		Ether (25°)	C_2H_4S	11.0	7.7	- -


(XXVI)
(XLII)
(XLIV)
(XLV)
(XLIII)
(XLVII)
(XLVI)
(XLIX)
(XLVIII)

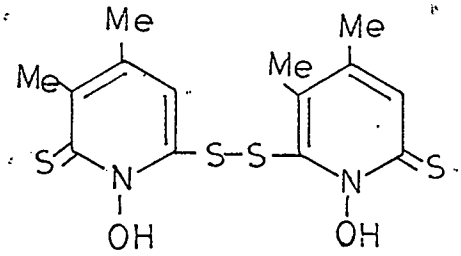
reduction product (XLVI). The molecular weight determination of XLV was carried out using an osmometer since disulfides are very susceptible to cleavage upon electron bombardment in the mass spectrometer. The experimental value of 378 agrees well with the calculated molecular weight (372) for XLV. A cyclic structure (L) could also be postulated on the basis of the molecular weight determination and isolation of 3,4-dimethyl-1-hydroxy-2-sulfhydro-6-pyridinethione (XLVI) after reduction with lithium aluminum hydride. However this structure cannot be considered since the elemental analysis does not support this structure. The infrared spectrum exhibited a hydrogen bonded N-OH group (2350 cm^{-1}) (81, 100).



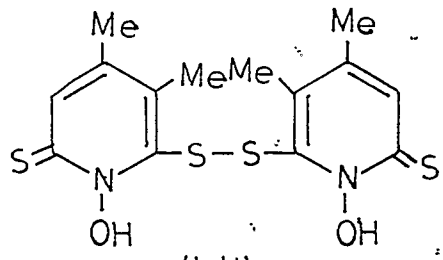
(L)

The n.m.r. spectrum of XLV in deuteropyridine exhibited a 2 H singlet at τ2.94 due to two pyridine protons and two 6 H singlets at τ7.50 and 8.1, respectively, due to two types of methyl groups.

These n.m.r. chemical shifts eliminate the unsymmetrical structure (LI) since one would expect two 1 H singlets for the β-protons and four 3 H singlets for the



(LI)



(LII)

four methyl groups had this structure been the correct one. On the basis of these results the orientation of the methyl groups is uncertain and two symmetrical structures are possible (XLV or LII).

The formation of XLV (or LII) is further evidence of possible 2,6-dimetalation and the intermediacy of XLIX.

Reduction of XLV with lithium aluminum hydride gave 3,4-dimethyl-1-hydroxy-2-sulfhydro-6-pyridinethione (XLVI) in quantitative yield. This can exist in two tautomeric modifications: formulation (XLVI) is consistent with the infrared, n.m.r. and mass spectra, and elemental analyses. The infrared spectrum showed a sulfhydro group (2350 cm^{-1}) (81). The n.m.r. spectrum in deuterochloroform exhibited a broad 2 H singlet at τ1.32 due to two acidic hydrogens which exchange readily with D_2O, a 1 H singlet at τ3.32 due to the C_5-H, and two 3 H singlets at τ7.75 and 7.81, respectively, due to the aromatic methyl groups. The mass spectrum exhibited a molecular ion at m/e 187 which is in agreement with the

calculated molecular weight, a fragment ion at m/e 171 due to the loss of an oxygen atom, and a fragment ion at m/e 170 presumably due to the loss of a hydroxyl group. In the solid state XLVI may exist as a mixture of the two possible isomeric structures while in solution a tautomeric equilibrium may exist (86). If hydrogen exchange in solution is indeed exceedingly rapid what one may see in the n.m.r. spectrum is a time averaged signal of the two possible structures (XLVI). An alternative possibility is that XLVI may exist as 2,6-disulfhydro-3,4-dimethylpyridine-1-oxide.

Treatment of the sodium salt XLVI with 2,4-dinitrochlorobenzene gave a 2,4-dinitrophenylsulfenyl derivative (XLVIII) for which two isomeric structures can again be written (uncertainty about which tautomer has reacted). The structure assigned to this product (XLVIII) (or its isomer) is consistent with its mass spectrum and elemental analysis. The mass spectrum shows a parent peak at m/e 353 and peaks at m/e 336 ($C_{13}H_{10}N_3O_4S_2^+$) and m/e 337 ($C_{13}H_{11}N_3O_4S_2^+$) due to the loss of an hydroxyl group and an oxygen atom respectively.

The isolation of 1-hydroxy-3,4-dimethyl-6-pyridinethione (XLII, $R_1=R_2=CH_3$) and 1-hydroxy-3,4-dimethyl-2-pyridinethione (XLIV, $R_1=R_2=CH_3$) in 24.1 and 12.5% yields, respectively, suggests that metalation occurs

preferentially at the least hindered α-carbon. This observation would also be predicted on the basis of the relative acidities of the α-protons. The 3-methyl group in 3,4-lutidine-1-oxide would decrease the acidity of the C_2-H more than that of C_6-H, making base-catalyzed deprotonation more favorable at C-6.

The sodium salts of the cyclic thiohydroxamic acids XLII (R_1=R_2=CH_3) and XLIV (R_1=R_2=CH_3) reacted readily with zinc chloride to give their respective zinc salts XLIII (R_1=R_2=CH_3) and XLVII, which were identified through their mass spectra and elemental analyses.

Reaction of the lithio derivative of 3,4-lutidine-1-oxide in ether at 25° with sulfur gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (7.3%), 1-hydroxy-3,4-dimethyl-2-pyridinethione (7.9%) and 2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyl-6,6'-dipyridinethione)disulfide (or LII) (21.1%) (Table 2).

The lithio derivatives of 3,4-lutidine-1-oxide were also treated with other sulfur-containing reagents. Reaction of lithio-3,4-lutidine-1-oxide in tetrahydrofuran at -65° with sulfur monochloride gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (7.5%) and 1-hydroxy-3,4-dimethyl-2-pyridinethione (4.6%). Treatment of lithio-3,4-lutidine-1-oxide in ether at 25° with ethylene

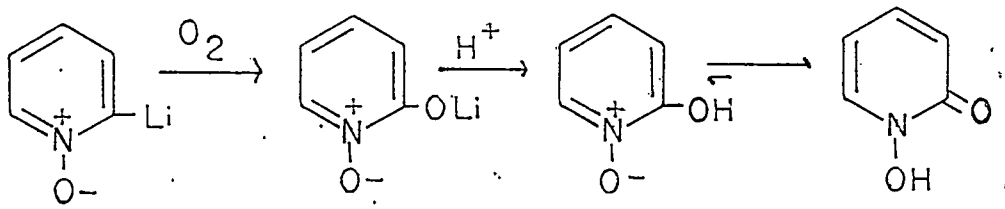
sulfide gave XLII (R_1=R_2=CH_3) and XLIV (R_1=R_2=CH_3) in 11.0 and 7.7% yields, respectively (Table 2).

Treatment of the sodium salt of 1-hydroxy-3,4-dimethyl-6-pyridinethione with 2,4-dinitrochlorobenzene did not yield the desired 2,4-dinitrophenylthioether. Likewise, reaction of the sodium salt of 1-hydroxy-3,4-dimethyl-6-pyridinethione with o-nitrochlorobenzene failed to give any of the expected o-nitrophenyl derivative. The starting materials were recovered in both reactions. Acetylation of 1-hydroxy-3,4-dimethyl-6-pyridinethione with acetic anhydride gave at least six major products which were not investigated further. The presence of six products is not unreasonable since alkylpyridine-1-oxides are known to undergo several reactions which yield rearranged products, depending on the position of the alkyl substituent (4-6).

All of the cyclic thiohydroxamic acids prepared gave the characteristic purple color with ferric chloride.

3.1.3.0.0 Reactions with oxygen to give 1-hydroxy-2-pyridones

A method of preparing cyclic hydroxamic acids has been developed which involves the direct introduction of oxygen into the ring by the oxygenation of lithiopyridine-1-oxides.



(LIII) (LIV)

The existence of this tautomerism (LIII ⇌ LIV) has been discussed (1.5.0.0.0) and it has been shown (17, 31, 56) that 2-hydroxypyridine-1-oxide (LIII) exists mainly as the 1-hydroxy-2-pyridone tautomer (LIV).

Treatment of the anion of pyridine-1-oxide (XXVI, $R_1=R_2=H$) with oxygen failed to yield any of the desired 1-hydroxy-2-pyridone (LIV). However reaction of the lithio derivative of 4-methylpyridine-1-oxide (XXVI, $R_1=CH_3$, $R_2=H$) with molecular oxygen gave 1-hydroxy-4-methyl-2-pyridone (LV, 12.7%). The infrared spectrum of this compound showed an N-OH group (2550 cm^{-1}) (81, 100). The n.m.r. spectrum exhibited a 1 H doublet ($J_{5,6}$ = 7 Hz) at τ2.42 due to C_6-H, a 1 H doublet ($J_{3,5}$ = 2 Hz) at τ3.56 due to C_3-H, a 1 H quartet ($J_{5,6}$ = 7 Hz; $J_{3,5}$ = 2 Hz) at τ3.90 due to C_5-H, a 3 H singlet at τ7.82 due to C_4-CH_3, and a 1 H singlet at τ-2.08 due to the hydroxyl group. The latter peak disappears on the addition of D_2O.

Several authors (103, 104) have mentioned that prominent first-generation fragment ions from cyclic

hydroxamic acids arise at $(M-16)^+$ and $(M-17)^+$ due to the expulsion of an oxygen atom and loss of a hydroxyl radical, respectively. The fragmentation of 2-pyridone and alkylpyridones induced by electron impact has been studied (101) and the principal fragmentation pathways have been determined with the aid of deuterium labelling. The most prominent fragmentation of 2-pyridone is the loss of CO to give the pyrrole molecular ion ($C_4H_4NH^+$). Fragmentations involving the loss of OH, and loss of H followed by HCN from the 2-pyridone molecular ion are scarcely detectable.

The mass spectrum of 1-hydroxy-4-methyl-2-pyridone could be accounted for as illustrated under Scheme 3. The molecular ion at m/e 125 ($C_6H_7NO_2^+$) can lose CO (Path 1) to give a fragment ion at m/e 97 ($C_5H_7NO^+$) which can eliminate a hydroxyl group to give an ion at m/e 80 ($C_5H_6N^+$). This can then lose HCN to give a fragment ion at m/e 53 ($C_4H_5^+$). Alternatively, the fragment ion at m/e 97 ($C_5H_7NO^+$) can lose an oxygen atom to give an ion at m/e 81 ($C_5H_7N^+$). The molecular ion at m/e 125 ($C_6H_7NO_2^+$) can also under consecutive fragmentations to give ions at m/e 109 and m/e 81 due to the loss of an oxygen atom and then CO respectively.

It has been reported (101) that loss of H followed by HCN from 2-pyridone is scarcely detectable. The loss

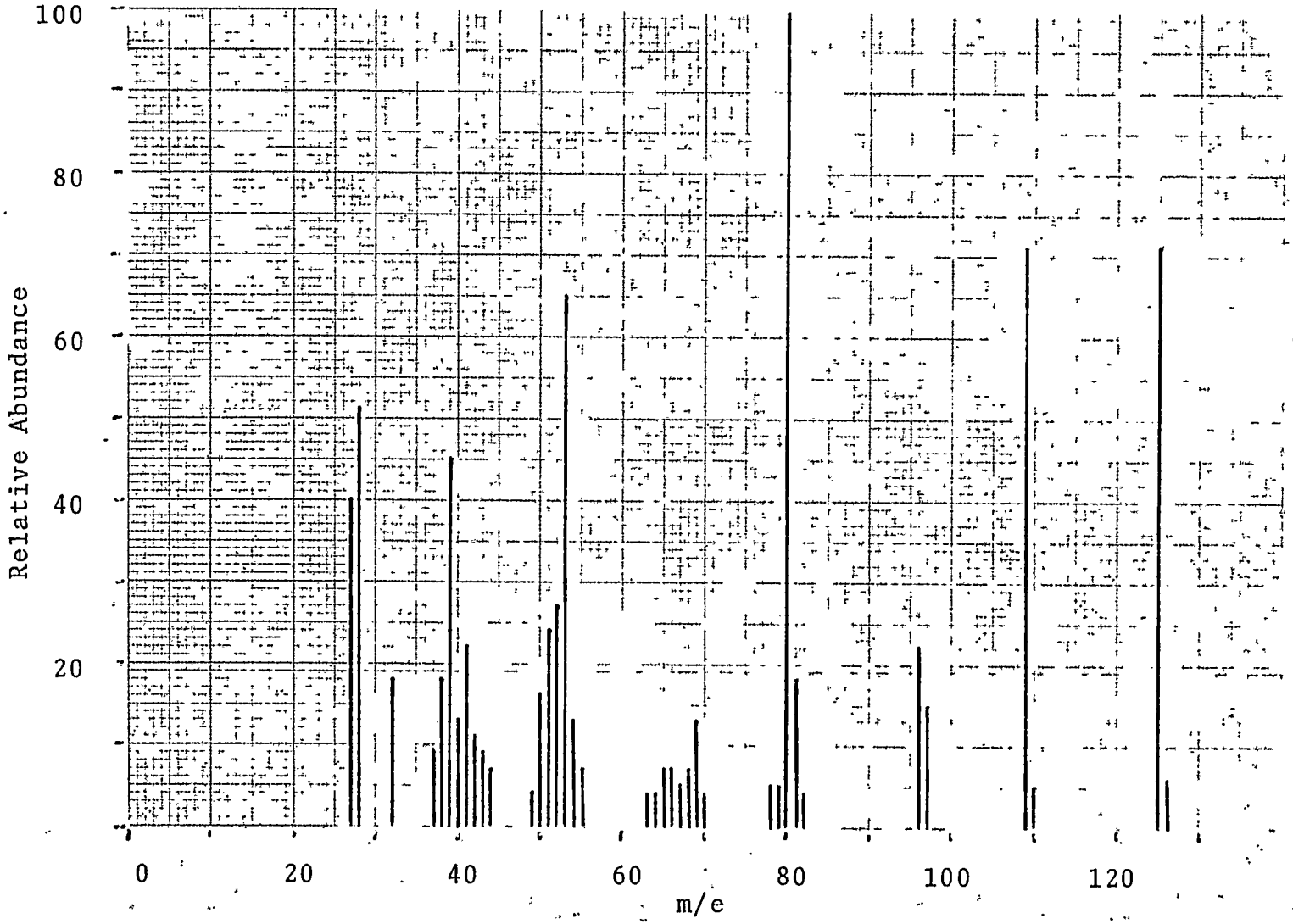
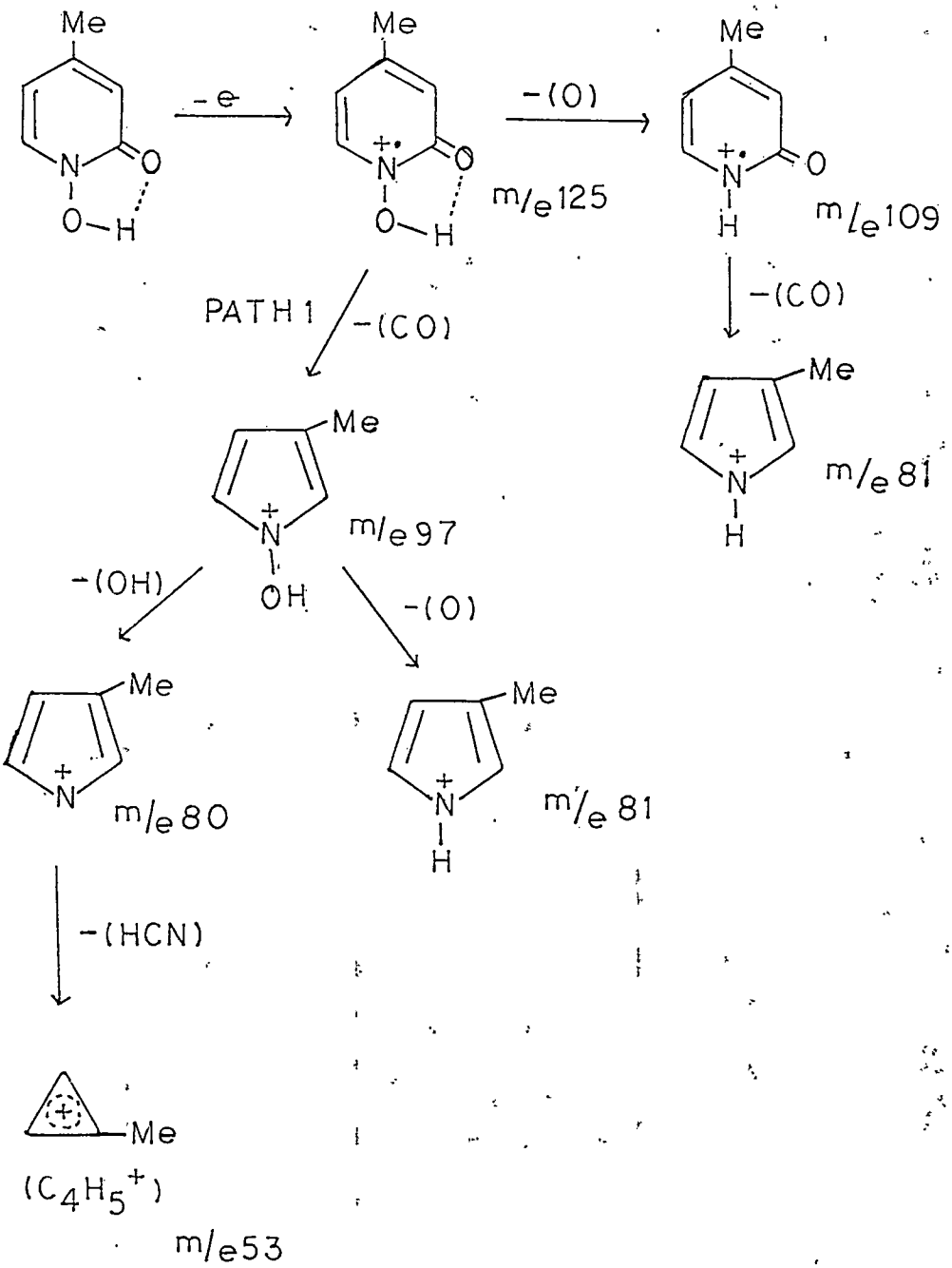


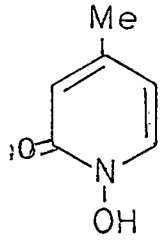
Figure 3.--Mass spectrum of 1-hydroxy-4-methyl-2-pyridone (70 eV)

SCHEME 3

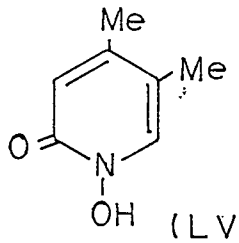

Me
-e
-(O)
m/e125
m/e109
PATH 1
-(CO)
-(CO)
m/e97
m/e81
-(OH)
-(O)
m/e80
m/e81
-(HCN)
Me
(C4H5+)
m/e53

of HCN from the fragment ion at m/e 80 appears to be an important fragmentation in this case.

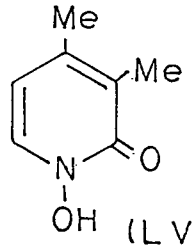
Treatment of the lithio derivative of 3,4-dimethylpyridine-1-oxide (XXVI, $R_1=R_2=CH_3$) with molecular oxygen gave 1-hydroxy-3,4-dimethyl-6-pyridone (LVI, 13.9%) and 1-hydroxy-3,4-dimethyl-2-pyridone (LVII, 10%). The infrared, n.m.r. and mass spectra, and elemental analyses were consistent with these structures.



(LV)



(LVI)



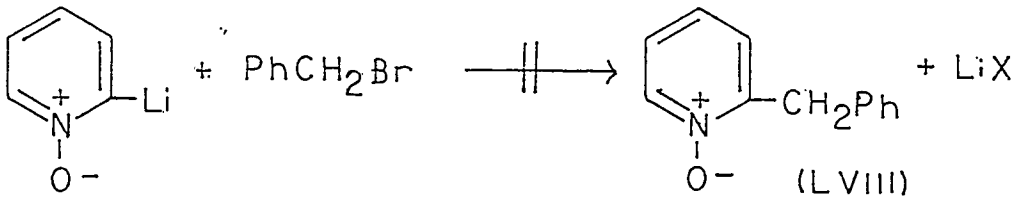
(LVII)

These cyclic hydroxamic acids gave the characteristic red color with ferric chloride.

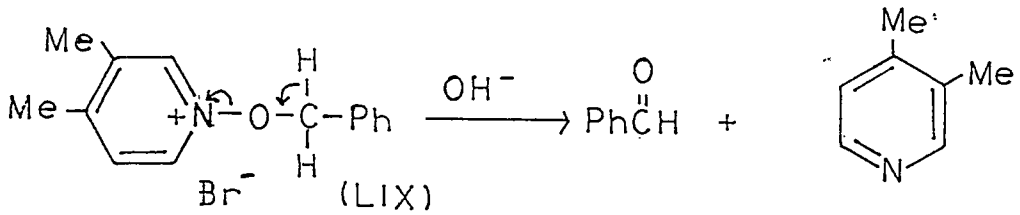
3.1.4.0.0 Reaction with benzyl bromide

The reaction of alkyl and arylhalides with organolithium reagents is generally a convenient method of alkylation or arylation (87, 88). It was hoped that the reaction of 2-pyridyl-1-oxide carbanions and benzyl bromide would yield 2-substituted benzylpyridine-1-oxides (LVIII).

In a control reaction, treatment of 3,4-lutidine-1-oxide with benzyl bromide (5.2.4.1.0), in the absence of n-butyllithium, gave 1-benzyloxy-3,4-dimethylpyridinium



bromide (LIX, 75.4%), and a yellow oil which was shown to consist of benzaldehyde, 3,4-lutidine and benzyl bromide. 3,4-Lutidine and benzaldehyde probably arise from alkaline decomposition of 1-benzyloxy-3,4-dimethyl-pyridinium bromide (LIX). The pH of the reaction mixture

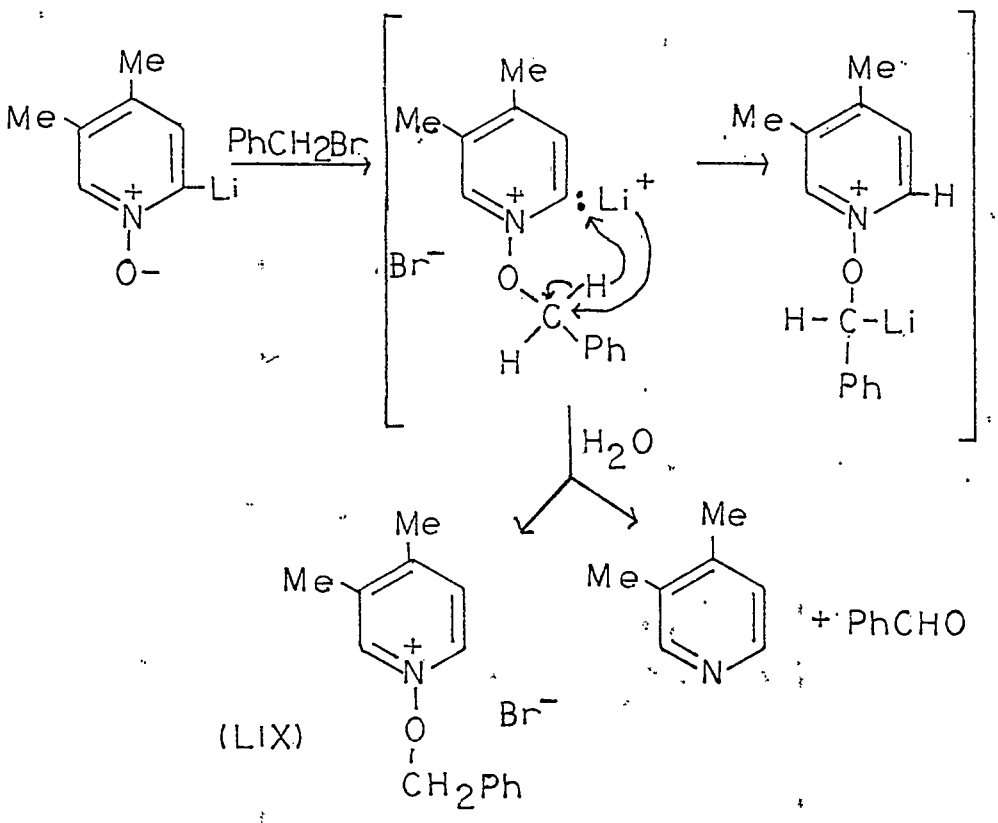


was adjusted to 10 before extraction in order that the conditions would be identical with those reactions where n-butyllithium was used. Feely, Lehn, and Boekelheide (89) prepared quaternary salts of amine oxides by heating the appropriate pyridine-1-oxide and benzyl bromide in acetonitrile, and reported that alkaline decomposition of 1-benzyloxypyridinium salts is both an excellent method for preparing aromatic aldehydes and a convenient way of deoxygenating pyridine-1-oxides. This control reaction mentioned above illustrates the ease with which electrophilic addition of benzyl bromide to the N-oxide group of 3,4-lutidine-1-oxide takes place.

The structure assigned to 1-benzyloxy-3,4-dimethylpyridinium bromide is consistent with its n.m.r. spectrum and elemental analyses. The n.m.r. spectrum in deuterium oxide (internal TMS capillary) exhibited a 1 H doublet ($J_{2,6}$ = 2 Hz) at τ0.86 due to C_2-H, a 1 H quartet ($J_{5,6}$ = 7 Hz; $J_{2,6}$ = 2 Hz) at τ0.96 due to C_6-H, a 1 H doublet ($J_{5,6}$ = 7 Hz) at τ1.96 due to C_5-H, a 5 H multiplet at τ2.32 due to the phenyl group, a 2 H singlet at τ4.17 due to the methylene group, and two 3 H singlets at τ7.22 and 7.32 respectively, due to the aromatic methyl groups.

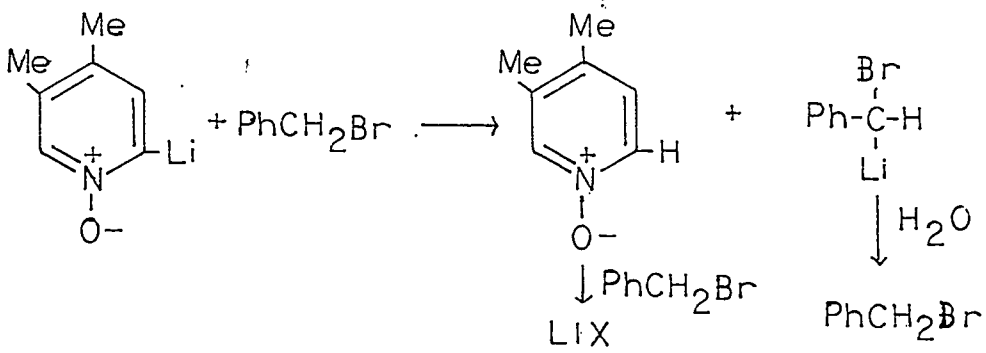
Addition of benzyl bromide (1 equiv.) to the lithium derivative of 3,4-lutidine-1-oxide (5.2.4.0.0.d) during a three-minute interval, followed by a further reaction time of one minute and then quenching with 18% hydrochloric acid, gave 1-benzyloxy-3,4-dimethylpyridinium bromide (LIX, 26.7%) and an oil which on distillation gave a mixture of benzaldehyde, 3,4-lutidine and benzyl bromide, as shown by separation and collection of the three components by gas-liquid chromatography, and 3,4-lutidine-1-oxide (21.8% recovery). The 3,4-lutidine-1-oxide may have resulted from decomposition of 1-benzyloxy-3,4-dimethylpyridinium bromide (LIX) on distillation. It is more likely to be unreacted starting material due to the short reaction time. No evidence of carbon alkylation was obtained.

Addition of benzyl bromide (5.2.4.0.0.a, b, and c) to a dark brown solution of lithiopyridine-1-oxide resulted in a rapid discharge of the brown color of the 3,4-dimethylpyridyl-1-oxide carbanion. The rapid disappearance of the brown color and formation of 1-benzyloxy-3,4-dimethylpyridinium bromide (LIX), benzaldehyde and 3,4-lutidine may be explained in two ways. A very rapid electrophilic attack by benzyl bromide on the oxygen of the N-oxide group followed by intramolecular hydrogen-lithium exchange would explain the loss of the



brown coloration and account for three of the products isolated in the reaction.

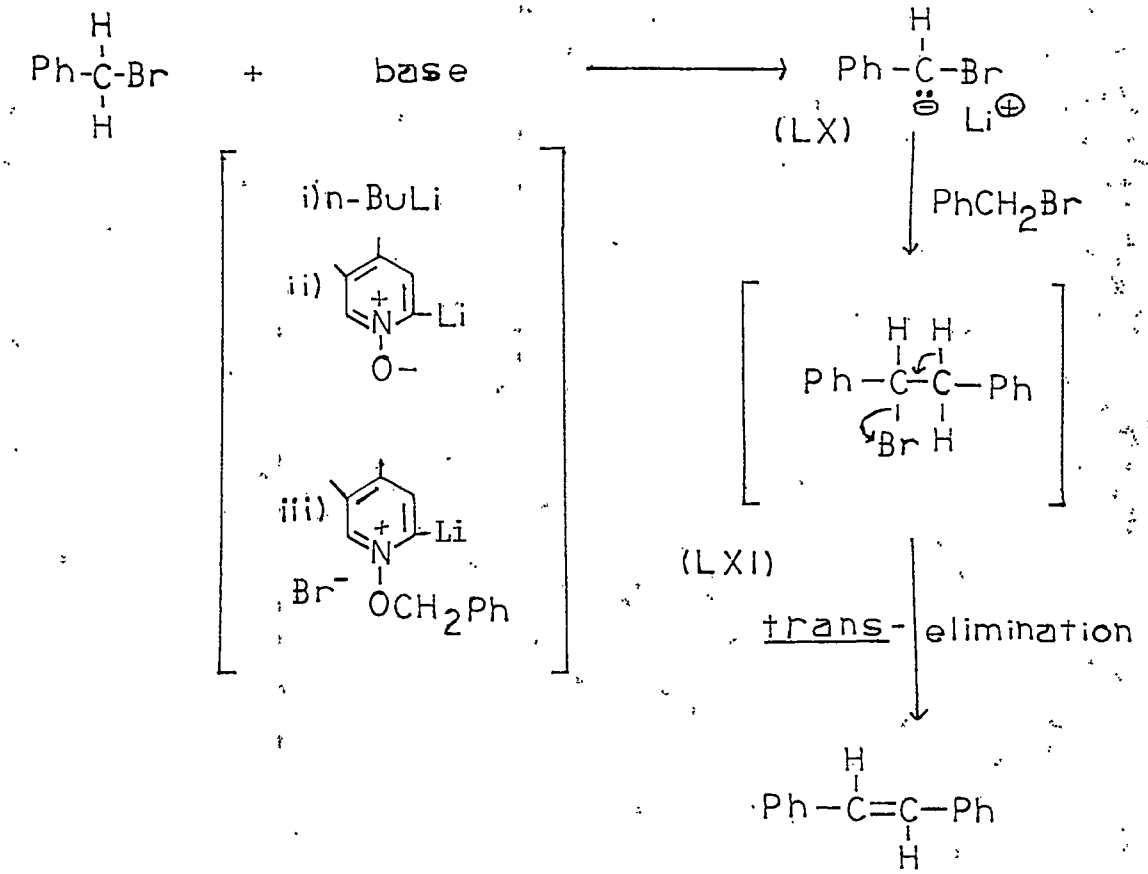
Alternatively, rapid intermolecular hydrogen-lithium exchange between benzyl bromide and lithio-3,4-lutidine-1-oxide would also result in the discharge of the brown color. This mechanism would also rationalize the



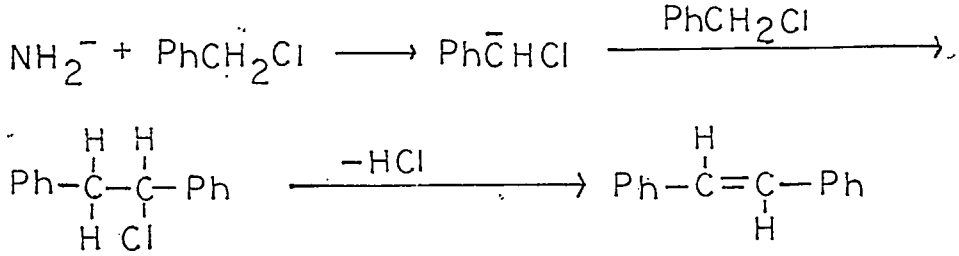
presence of 3,4-lutidine-1-oxide and benzyl bromide. It is possible that both of the above processes are occurring simultaneously.

The reaction of lithio-3,4-lutidine-1-oxide was repeated using both one (5.2.4.0.0.b) and two equivalents (5.2.4.0.0.a) of benzyl bromide. In both experiments benzaldehyde, 3,4-lutidine, 3,4-lutidine-1-oxide and trans-stilbene were obtained after the reaction mixture was separated by column chromatography, fractional distillation and gas-liquid chromatography of the distillate. However, in the first reaction (5.2.4.0.0.b) benzyl bromide was not detected by gas-liquid chromatography when the distillate was examined.

Benzyl bromide is a Lewis acid possessing two active hydrogens. Consequently, base-catalyzed hydrogen abstraction may occur to give LX, which could react with more benzyl bromide to give the adduct (LXI). Trans-elimination of hydrogen bromide from the adduct (XLI) would then give trans-stilbene.



This mechanism appears reasonable since it has been reported (87, 90-92) that amide ion in liquid ammonia readily converts benzyl chloride into stilbene.



Treatment of 3,4-lutidine-1-oxide with one equivalent of n-butyllithium and then with one equivalent of benzyl bromide (5.2.4.0.0.c) gave a colorless oil after distillation. Gas-liquid chromatography of the oil gave rise to benzaldehyde, 3,4-lutidine and benzyl bromide in the ratio (not molar) of 2.4 : 1.1 : 9.4 as calculated from the relative areas under the curves.

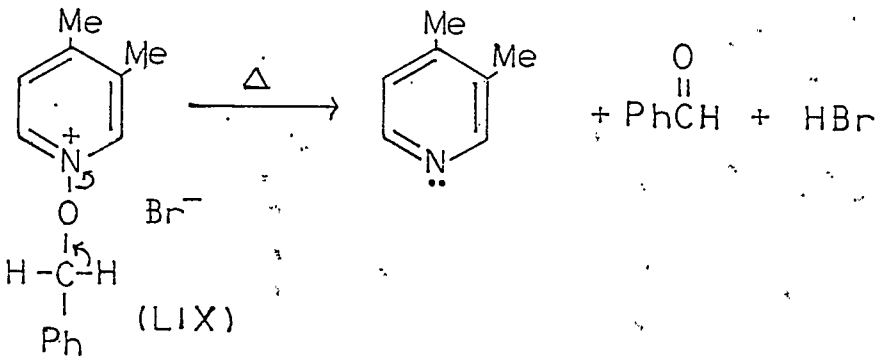
The distillates obtained after distillation of the reaction products were analyzed by gas-liquid chromatography as described in the individual reactions and the ratio (not molar) of benzaldehyde : 3,4-lutidine : benzyl bromide was calculated from the relative areas under their curves. These ratios bear very little significance since it was shown (5.2.4.1.0) that benzaldehyde and 3,4-lutidine may arise from alkaline decomposition of 1-benzyloxy-3,4-dimethylpyridinium bromide in the work-up procedure. It was also shown that 1-benzyloxy-3,4-dimethylpyridinium bromide decomposes thermally in the injector port of the gas chromatograph (5.2.4.2.0.c) to benzaldehyde, 3,4-lutidine and benzyl bromide and on distillation (5.2.4.2.0) to benzaldehyde, 3,4-lutidine,

benzyl bromide and 3,4-lutidine-1-oxide. However, it is significant that no χ-benzyl-3,4-dimethylpyridines were detected.

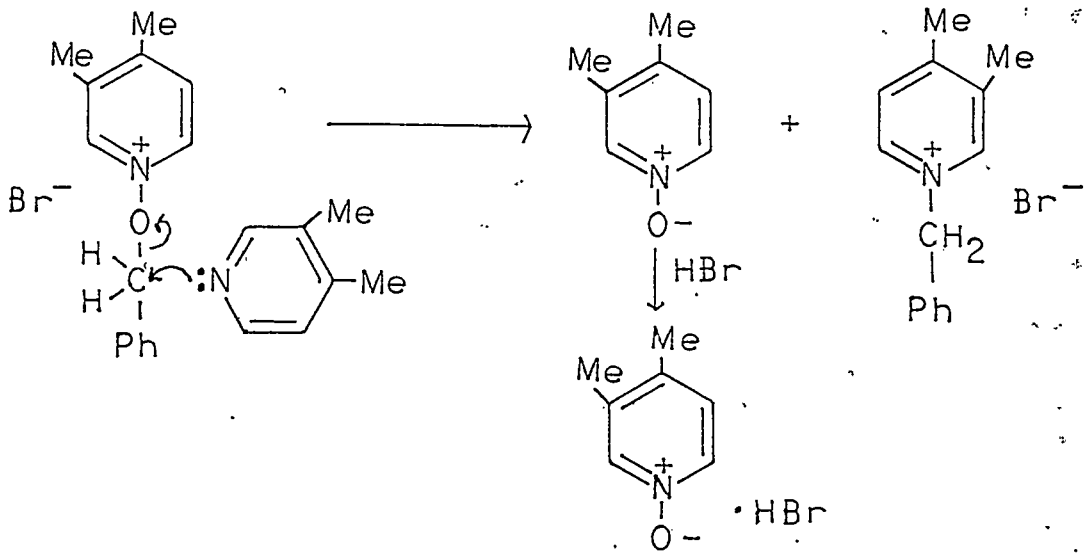
Repeated attempts to purify the reaction products by thin-layer and in most cases by column chromatography failed. No evidence was obtained which would indicate the presence of 2-benzyl-4,5-dimethylpyridine-1-oxide or of 2-benzyl-4,5-dimethylpyridine in any of the above reactions. These results suggest that electrophilic attack at the carbanionic site did not occur.

A solution of 1-benzyloxy-3,4-dimethylpyridinium bromide in tetrahydrofuran was boiled under reflux for 240 hr. (5.2.4.2.0.b). Fractional crystallization and column chromatography of the product gave unchanged 1-benzyloxy-3,4-dimethylpyridinium bromide (20%), 3,4-lutidine-1-oxide hydrobromide (23%), 1-benzyl-3,4-dimethylpyridinium bromide (11.3%) and a yellow oil which did not contain nitrogen.

If the bromide ion is a sufficiently strong base to remove one of the acidic methylene protons from 1-benzyloxy-3,4-dimethylpyridinium bromide (LIX), then LIX could give rise to 3,4-lutidine and benzaldehyde as shown in the scheme below.

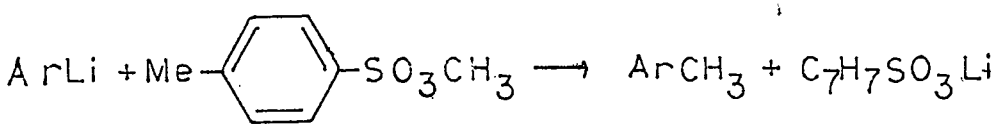


(LIX)

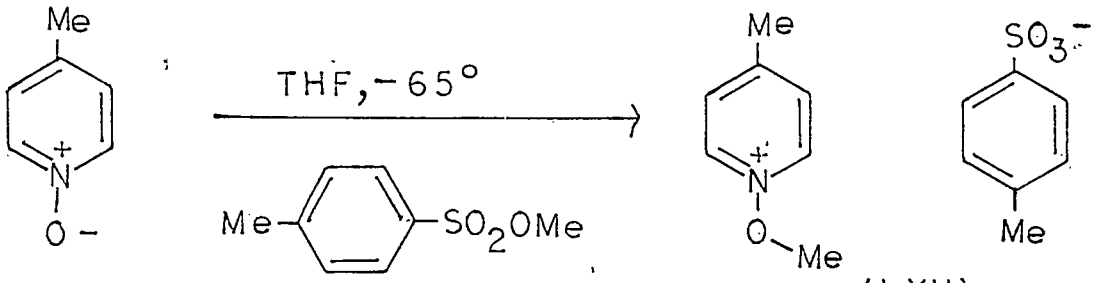


Nucleophilic attack on LIX by 3,4-lutidine could then give 3,4-lutidine-1-oxide and 1-benzyl-3,4-dimethyl-pyridinium bromide. No rearranged product other than 1-benzyl-3,4-dimethylpyridinium bromide was detected.

Methyl p-toluenesulfonate is known to be a powerful methylating reagent and reaction with organolithium reagents gives the corresponding methylated product (93).



Before any extensive studies involving the reaction of lithiopyridine-1-oxides with methyl p-toluenesulfonate were undertaken a control reaction, in the absence of n-butyllithium, was carried out using the reaction conditions to be used later.



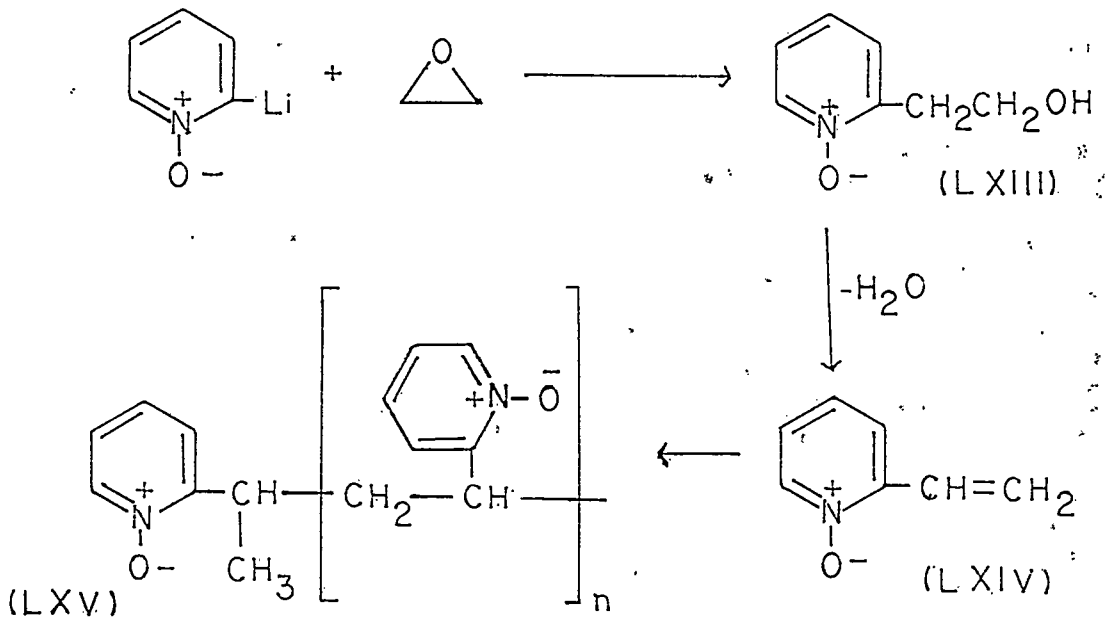
(LXII)

The isolation of 1-methoxy-4-methylpyridinium toluene p-sulfonate (LXII, 87%) prompted us to abandon this course since electrophilic addition to the N-oxide group was occurring in a manner similar to that discussed previously in the case of benzyl bromide. Katritzky (75) prepared metho p-toluenesulfonates of pyridine-1-oxides by heating the appropriate pyridine-1-oxide and methyl p-toluenesulfonate in the absence of solvent at 110° for 5 hr.

3.1.5.0.0 Reactions with epoxides to give polymers

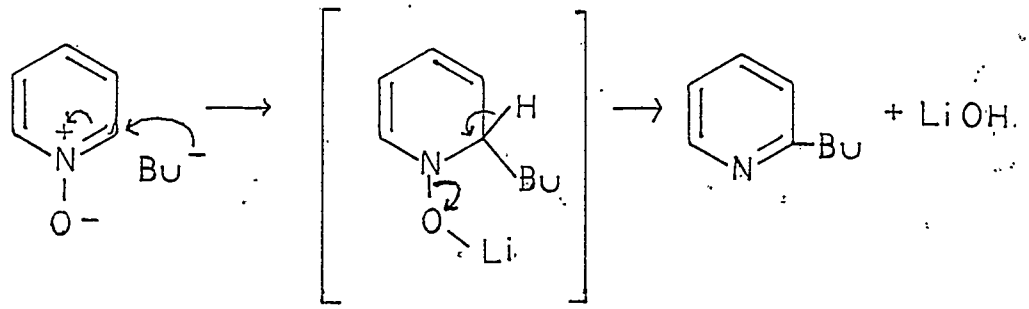
The reaction of organolithium reagents with epoxides is a convenient method for the synthesis of alcohols (94-96).

It was anticipated that 2-lithiopyridine-1-oxides would react readily with epoxides to yield 2-substituted alcohols (LXIII). Dehydration of the 2-pyridylalkanol-1-oxides (LXIII) would give 2-vinylpyridine-1-oxides (LXIV) which, on polymerization, would yield poly-(2-vinylpyridine-1-oxide) (LXV) as outlined below.



Treatment of the lithio derivative of pyridine-1-oxide in tetrahydrofuran at -15° with a five molar excess of ethylene oxide (5.2.6.1.0.a) gave 2-n-butylpyridine (9.5%) and a mixture of pyridine-1-oxide and a higher molecular weight product which could not be resolved by column chromatography. The n.m.r., i.r., and mass

spectra of 2 n-butylpyridine were identical with those of an authentic sample. 2-n-Butyllithium probably arises from nucleophilic addition of n-butyllithium to the 2-position in pyridine-1-oxide to give the adduct (LXVI) which can eliminate lithium hydroxide as illustrated below.



(LXVI)

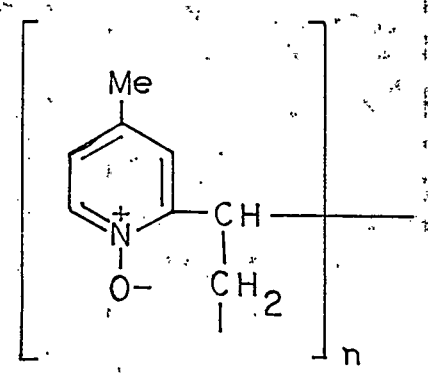
The mass spectrum of the mixture mentioned above exhibited an ion at m/e 95 ($C_5H_5NO^+$) (base peak) which can be attributed to the molecular ion of pyridine-1-oxide and a fragment ion at m/e 79 ($C_5H_5N^+$) due to the loss of an oxygen atom from the molecular ion. Other less abundant ions due to the higher molecular weight product occurred at m/e 106 (18), 109 (15), 122 (11), 155 (15), 156 (37), and 170 (8). A fragment ion at m/e 121 ($C_7H_7NO^+$) due to 2-vinylpyridine-1-oxide which is found in the mass spectrum of 2-(2'-pyridyl)ethanol-N-oxide (M-18) was not present. The infrared spectrum of this mixture exhibited all those absorptions present in

pyridine-1-oxide as well as bonds at 2960, 2930 and 2875 cm^{-1} which indicate the presence of aliphatic methyl and methylene stretching vibrations. The n.m.r. spectrum showed a 2 H multiplet at τ1.74 due to C_2-H, C_6-H, a 3 H multiplet at τ2.66 due to C_3-H, C_4-H, C_5-H, a broad 1 H singlet at τ4.76 due to -C<u>H</u>-, a broad 2 H singlet at τ6.3 due to -C<u>H</u>$_2$-, and a broad 2 H singlet at τ7.14 probably due to a -C<u>H</u>$_2$- group.

Pyridine-1-oxide probably arises by hydrogen abstraction, either from tetrahydrofuran, ethylene oxide or perhaps both. In a control experiment treatment of ethylene oxide with <u>n</u>-butyllithium did not yield an ethylene oxide polymer.

Similar results were obtained when the reaction was repeated using ether as solvent at -15° (5.2.6.1.0.b) or ether as solvent at 25° (5.2.6.1.0.c).

Reaction of the 4-methylpyridyl-1-oxide carbanion with ethylene oxide in ether at 25° (5.2.6.2.0.c) for 2 hr. gave an elastic-like hygroscopic solid. When a molecular weight determination ($CHCl_3$) was performed on the reaction product using an osmometer, a value corresponding to a molecular weight of 812 was obtained. This molecular weight corresponds to a value of n = 6, should the polymer have a structure similar to that of poly-(4-methyl-2-vinylpyridine-1-oxide) (LXVII) shown below.



(LXVII)

When the same reaction was repeated (5.2.6.2.0.b) with a reaction time of 10 hr., the reaction product exhibited a molecular weight ($CHCl_3$) of 1866 as determined from the osmetric measurement. This molecular weight corresponds to n = 14 for the poly-(4-methyl-2-vinylpyridine-1-oxide) structure (LXVII).

A portion of the reaction product was purified by dissolution in acetone and then reprecipitation by addition of ether. The n.m.r. spectrum of this purified product exhibited a 2 H multiplet at τ1.4-2.2 due to C_6-H, a 2 H multiplet at τ2.5-3.5 due to C_3-H, C_5-H, a complex 4 H multiplet at τ5.5-6.6 probably due to -C<u>H</u>-, -C<u>H</u>$_2$-, and complex multiplets at τ7.0-9.3 probably due to -C<u>H</u>$_2$- and -C<u>H</u>$_3$. The integral could not be measured accurately, consequently these values are subject to question. No structure was assigned to either of these polymers since the substitution pattern cannot be interpreted on the basis of the spectral results. The structure may be complicated further by the presence of

cross-linked polymers, since 2,6-disubstituted products have been isolated in the case of bromination, chlorination and reaction with sulfur.

The reaction of 3,4-dimethylpyridyl-1-oxide carbanion in tetrahydrofuran at -65° (5.2.6.3.0.a) with ethylene oxide did not proceed and 3,4-lutidine-1-oxide was recovered almost quantitatively. When the same reaction was carried out in ether at 25° (5.2.6.3.0.c) and a reaction time of 16 hr., two products were obtained from column chromatography. Elution with ether-methanol (2:1 v/v) gave a viscous yellow oil, b.p. 140°/0.075 mm. (83.3% calc'd as $C_9H_{13}NO_2$). The infrared spectrum (film) showed the presence of an hydroxyl group (3325 cm^{-1}) and an $\overset{+}{N}$-O^- group (1260 cm^{-1}) (81).

The n.m.r. spectrum exhibited a 2 H multiplet at τ1.86-2.12 due to C_6-H, a 2 H multiplet at τ2.84-3.12 due to C_3-H, C_5-H, a 2 H singlet at τ5.20 due to OH protons (disappear on addition of D_2O), a 2 H triplet ($\underline{J}$ = 6 Hz) at τ6.10 due to -$C\underline{H}_2$-, a broad 2 H singlet at τ6.40 due to -$C\underline{H}$- or -$C\underline{H}_2$-, a 2 H triplet ($\underline{J}$ = 6 Hz) at τ6.70 due to -$C\underline{H}_2$-, a 2 H triplet ($\underline{J}$ = 6 Hz) at τ6.80 due to -$C\underline{H}_2$-, and four 3 H singlets at τ7.74, 7.76, 7.79, and 8.06 respectively due to four types of aromatic methyl groups. On the basis of this n.m.r. evidence one could postulate that this product consists of a mixture of

2-(4,5-dimethyl-2-pyridyl)ethanol-1-oxide and 2-(3,4-dimethyl-2-pyridyl)ethanol-1-oxide. The mass spectrum exhibited an ion at m/e 167 ($C_9H_{13}NO_2^+$) which could be attributed to the molecular ion of either alcohol mentioned above and a fragment ion at m/e 149 ($C_9H_{11}NO^+$) due to the loss of water from the molecular ion. It is known (97) that alcohols often do not exhibit a molecular ion, but rather an (M-18) peak due to the loss of water. The elemental analyses were not consistent with this postulate however. Consequently, no conclusion could be reached concerning the composition of this oil which would satisfy all the results.

Elution with methanol gave an elastic-like solid which was purified by dissolution in ethanol and reprecipitation by addition of ether. The n.m.r. spectrum of a chloroform solution exhibited a broad 1 H singlet at τ1.98 due to C_6-H, a broad 2 H singlet at τ2.94 due to C_3-H, C_5-H, a broad 5 H singlet at τ6.12 due to -C<u>H</u>-, a broad 12 H singlet at τ6.34 due to -C<u>H</u>-, -C<u>H</u>$_2$-, and a 16 H multiplet at τ7.74 probably due to the aromatic methyl groups. No structure was assigned to this product but the n.m.r. spectral data suggests that this may be a 2,6-disubstituted polymer.

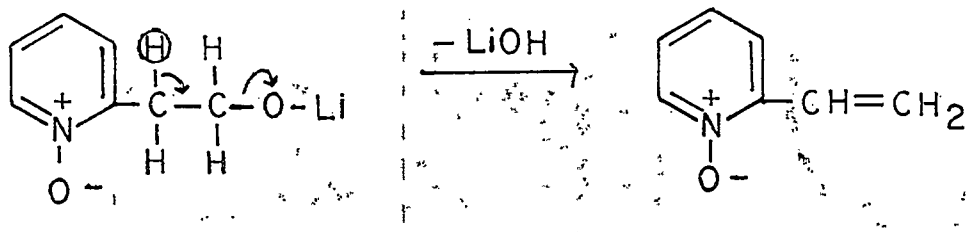
A portion of the reaction product from the above experiment was stirred in the presence of concentrated

sulfuric acid for 30 min. at room temperature to give an elastic-like solid identical (I.R. and n.m.r.) with the product eluted above with methanol. Subsequent work in this laboratory has shown that 2-(2'-pyridyl)ethanol-N-oxide is not dehydrated in the presence of concentrated sulfuric acid at room temperature. This evidence implies that the oil eluted from the column above with ether-methanol (2:1 v/v) is not a mixture of the two postulated alcohols.

The reaction of lithio-3,4-lutidine-1-oxide with ethylene oxide in ether at 25° for 2 hr. (5.2.6.3.0.d) gave a hygroscopic solid (2.2 g.) which was purified by dissolution in acetone and reprecipitation by addition of ether. A molecular weight determination ($CHCl_3$) on the yellow solid obtained after purification (0.5 g.) gave a value corresponding to a molecular weight of 2222 while the oil which did not precipitate on the addition of ether exhibited a molecular weight of 311.

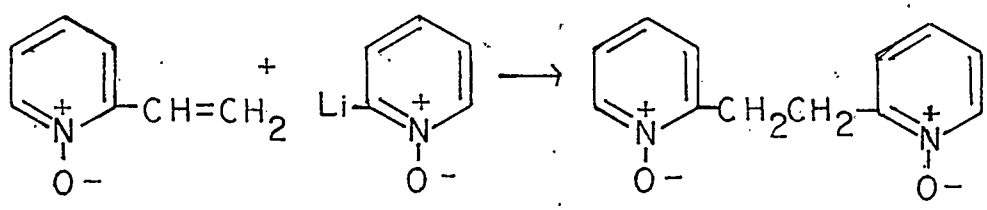
Reaction of the 3,4-dimethylpyridyl-1-oxide carbanion in ether at 25° with an 8 molar excess of ethylene oxide for 18 hr. (5.2.6.3.0.f) gave a product (2.2 g.) which was purified as mentioned above to give a product (0.9 g.), identical (I.R.) to the material eluted with methanol under (5.2.6.3.0.b). This material had a molecular weight of 1215 (osmetric determination).

The reaction of 2-picolyllithium with ethylene oxide (95) proceeds readily to give 3-(2-pyridyl)propan-1-ol (44-50%). Lewis and Raphael (96) reported that 2-lithioanisole reacts readily with ethylene oxide at room temperature to give 2-(2'-ethan-1-ol) anisole (72%). Earlier Cristol and his co-workers (94) obtained methylbenzylcarbinol (58) as the sole product from the reaction of phenyllithium and propylene oxide at room temperature. Recently Meyers and his colleagues (98) have reported that reaction of the lithium salt of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-(4 H)oxazine with epoxides gives the corresponding alcohols in high yields. In the four examples cited above, the authors do not report the presence of vinylic or polymeric products. However the reaction of lithiopyridine-1-oxides with ethylene oxide becomes more complicated due to the presence of an acidic hydrogen in the primary reaction product (LXVIII). Elimination of lithium hydroxide would give the corresponding 2-vinylpyridine-1-oxide



(LXVIII)

which can undergo self-condensation to yield poly-(2-vinylpyridine-1-oxide), particularly in the presence of strong base. Holt and Lindsay (24) reported that vinylpyridines polymerize almost quantitatively in the presence of n-butyllithium. Furthermore, it has been shown in this laboratory (5.4.4.0.0) that 2-vinylpyridine-1-oxide polymerizes on standing at room temperature and in the presence of n-butyllithium to yield poly-(2-vinylpyridine-1-oxide). It has been reported (82) that 2-vinylpyridine-1-oxide reacts readily with nucleophiles. The reaction conditions used in this study appear to be appropriate for the reaction of 2-vinylpyridine-1-oxide with 2-lithiopyridine-1-oxide. However it is quite



unlikely that much 2-lithiopyridine-1-oxide will be present since an excess of ethylene oxide was used, unless the elimination of lithium hydroxide from LXVIII is very much faster than reaction of lithiopyridine-1-oxide with ethylene oxide.

Previous results in this laboratory have shown that 2,6-dimetalation of pyridine-1-oxide does occur. The presence of 2,6-disubstituted primary reaction products

could, therefore, give rise to cross-linked polymers with complicated structures.

In the earlier experiments, a solution of ethylene oxide was added slowly to a solution of the lithiopyridine-1-oxide. Since a base is required to abstract the acidic proton from LXVIII it was decided to use "inverse addition," a method whereby a solution of the lithiopyridine-1-oxide is added dropwise to a large excess of the epoxide. Consequently, there should be a large excess of the epoxide present at all times and the intermediate LXVIII might not eliminate lithium hydroxide to give 2-vinylpyridine-1-oxide unless the reaction of lithiopyridine-1-oxide with the epoxide is much slower than the elimination process.

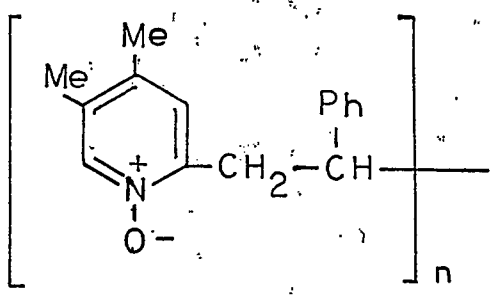
Using the inverse addition procedure a solution of the 3,4-dimethylpyridyl-1-oxide carbanion was added dropwise to a 4 molar excess of ethylene oxide. The reaction product was chromatographed on an alumina column to give 3,4-lutidine-1-oxide (38% recovery) and a yellow oil identical (I.R. and n.m.r.) with the material eluted under 5.2.6.3.0.b with ether-methanol (2:1 v/v). Recovered 3,4-lutidine-1-oxide undoubtedly arises from hydrogen abstraction since lithiation would be complete under these conditions.

The reaction of the lithium derivative of 3,4-lutidine-1-oxide with cyclohexene oxide failed to proceed under a variety of conditions (5.2.6.4.0.a, b, and c).

Reaction of lithio-3,4-lutidine-1-oxide with styrene oxide in ether at room temperature (5.2.6.5.0.a) gave a product which exhibited a molecular weight of 653 (osmetric determination of a chloroform solution). The infrared spectrum revealed the presence of an $\overset{+}{N}$-O^- group (1260 cm^{-1}) (81). There was no absorption in the 3200-3500 cm^{-1} region which is indicative of hydroxyl absorption. The n.m.r. spectrum exhibited a broad 2 H singlet at τ2.12 due to C_2-H, a complex 6 H multiplet at τ2.86 due to C_3-H, C_6H_5-, a 3 H multiplet at τ6.6 due to -C<u>H</u>-, -C<u>H</u>$_2$-, and a 6 H multiplet at τ7.86 due to C_3-CH_3, C_4-CH_3. The mass spectrum exhibited the highest mass at m/e 316, approximately one-half the molecular weight obtained from the osmetric determination, which suggests that this material is cleaving upon electron bombardment.

A portion of the reaction product was chromatographed on an alumina column (5.2.6.5.0.a). The major fraction of the product was eluted as a sharp band suggesting the presence of one major product (LXIX, n = 3). However there was a minor fraction before and after the main component which may be due to lower (LXIX, n = 2) and higher (LXIX, n = 4) molecular weight materials of

similar empirical composition. The results obtained would support a structure similar to LXIX shown below where n = 3 (n = 1; m.w. = 225).

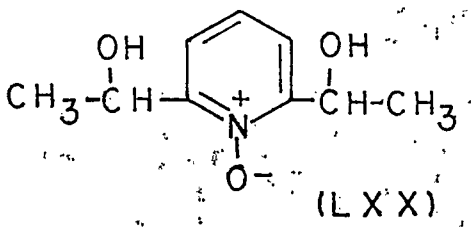


(LXIX)

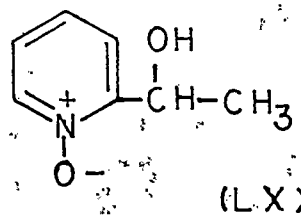
The above reaction was repeated (5.2.6.5.0.b) using the inverse addition method to give a product identical (I.R.) with that obtained in the previous reaction (5.2.6.5.0.a). Again most of the product was eluted as a sharp band on column chromatography. The infrared spectrum was identical with that obtained as under 5.2.6.5.0.a.

3.1.6.0.0 Reaction with acetaldehyde to give secondary alcohols

Reaction of lithiopyridine-1-oxide with acetaldehyde gave 2,6-di-(1-hydroxyethyl)pyridine-1-oxide (LXX, 30.1%) and 2-(1-hydroxyethyl)pyridine-1-oxide (LXXI, 36.3%).



(LXX)



(LXXI)

The structures assigned to these compounds are consistent with their infrared, n.m.r., and mass spectra, and elemental analyses.

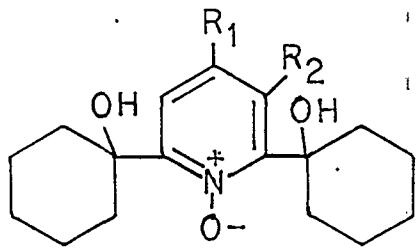
The infrared spectrum of 2,6-di-(1-hydroxyethyl)-pyridine-1-oxide (LXX) showed the presence of a hydrogen-bonded OH group (3350 cm^{-1}) and an $\overset{+}{N}$-O^{-} group (1240 cm^{-1}) (81). The mass spectrum did not exhibit a parent ion at m/e 183 ($C_9H_{13}NO_3^{+}$) but it did show an ion at m/e 165 ($C_9H_{11}NO_2^{+}$) due to the loss of water from the molecular ion, this being a characteristic feature of many alcohols (97). The n.m.r. spectrum exhibited a 3 H singlet at τ2.56 due to C_3-H, C_4-H, and C_5-H, a 2 H singlet at τ4.18 due to the hydroxyl groups (disappear on addition of D_2O), a 2 H quartet (J = 6.5 Hz) at τ4.76 due to -C<u>H</u>-CH_3, and a 6 H doublet (J = 6.5 Hz) at τ8.47 due to -CH-C<u>H</u>$_3$.

3.1.7.0.0 Reactions with cyclohexanone to give tertiary alcohols

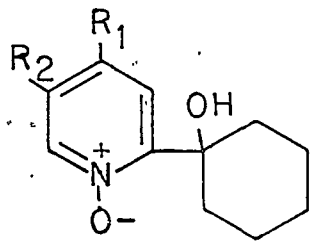
During the course of this study it was observed that reaction of pyridyl-1-oxide carbanions with some electrophilic reagents did not occur at -65°. The reaction of pyridyl-1-oxide carbanions with cyclohexanone was known (67) to proceed smoothly to give the corresponding alcohols in reasonable yields. This reaction was, therefore,

chosen as a model reaction with which to examine the stability and reactivity of the pyridyl-1-oxide carbanion in ether solution at room temperature. It was thus found that the pyridyl-1-oxide carbanions could be generated from a cold (-65°) suspension of the pyridine-1-oxide in ether containing two equivalents n-butyllithium on warming to room temperature over a period of 20 min. before reaction with the ketone.

This led to 2,6-di-(1-hydroxycyclohexyl)pyridine-1-oxide (LXXII, R_1=R_2=H, 36.5%) and 2-(1-hydroxycyclohexyl)-pyridine-1-oxide (LXXIII, R_1=R_2=H, 12.5%).



(LXXII)



(LXXIII)

Treatment of 4-methylpyridyl-1-oxide carbanion with cyclohexanone at room temperature gave 2,6-di-(1-hydroxycyclohexyl)-4-methylpyridine-1-oxide (LXXII, R_1=CH_3, R_2=H, 24.9%) and 2-(1-hydroxycyclohexyl)-4-methylpyridine-1-oxide (LXXIII, R_1=CH_3, R_2=H, 19.8%).

Lithio-3,4-lutidine-1-oxide and cyclohexanone gave 2,6-di-(1-hydroxycyclohexyl)-3,4-dimethylpyridine-1-oxide

(LXXII, $R_1=R_2=CH_3$, 15.6%) and 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (LXXIII, $R_1=R_2=CH_3$, 56.3%).

The structures assigned to these compounds are consistent with their infrared and n.m.r. spectra, and m.p. of the known compounds (66, 67).

The results obtained above are generally superior to those obtained (66, 67) when the same reactions were carried out at -65° as shown in Table 3. In contrast,

TABLE 3

Reactions of the lithium derivatives of substituted pyridine-1-oxides with cyclohexanone

N-oxide of	Solvent	% Products LXXII	LXXIII
Pyridine	Ether (-65°)*	- -	7.4
	THF-ether (-65°)*	14.8	4.6
	Ether (25°)	36.5	12.5
4-Methylpyridine	THF (-65°)*	27.3	21.1
	Ether (25°)	24.9	19.8
3,4-Dimethyl-pyridine	THF (-65°)*	12.1	38.7
	Ether (25°)	15.6	56.3

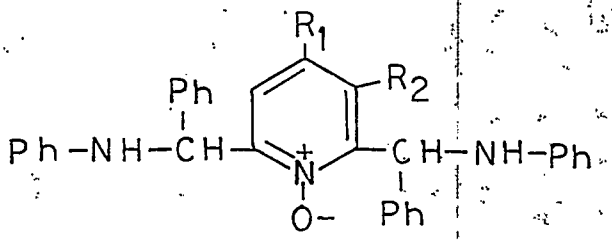
*Results previously reported (67).

the yields of cyclic thiohydroxamic acids were usually inferior when the reactions were carried out at room temperature using ether as the solvent (Table 2). This

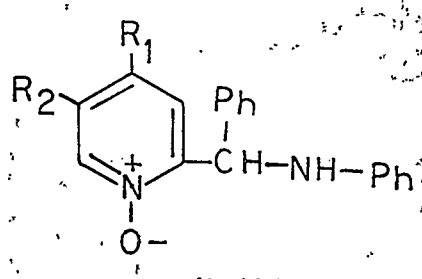
does appear to be a useful method of generating the pyridyl-1-oxide carbanions since some reactions which do not proceed in tetrahydrofuran at -65° (5.2.6.0.0) proceed readily under these conditions.

3.1.8.0.0 Reaction with Schiff bases to give secondary amines

The reaction of organolithium reagents with Schiff bases is a convenient method of preparing substituted amines (102). Treatment of 3,4-dimethylpyridyl-1-oxide carbanion in tetrahydrofuran at -65° with N-benzylideneaniline (5.2.9.2.0.a) gave 2,6-bis-(α-anilinobenzyl)-3,4-dimethylpyridine-1-oxide (LXXIV, $R_1=R_2=CH_3$, 61.8%) and 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (LXXV, $R_1=R_2=CH_3$, 12.1%) (Table 4).



(LXXIV)

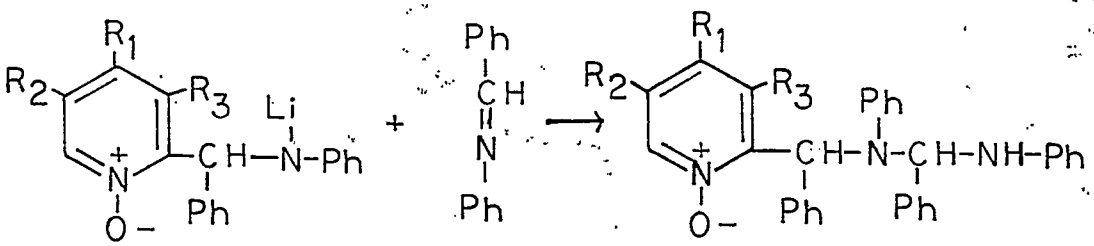


(LXXV)

The structures assigned to these compounds are consistent with their infrared, n.m.r., and mass spectra, and elemental analyses.

The infrared spectrum of 2,6-bis-(α-anilinobenzyl)-3,4-dimethylpyridine-1-oxide (LXXIV, $R_1=R_2=CH_3$) showed the presence of an NH group (3350 cm^{-1}) and an $\overset{+}{N}\text{-}O^-$ group (1255 cm^{-1}) (81). The n.m.r. spectrum exhibited a complex 15 H multiplet at τ2.55-3.15 due to C_5-H, and 14 aromatic protons, a complex 6 H multiplet at τ3.25-3.70 due to 6 aromatic protons, a 2 H singlet at τ3.89 due to -CH-, a 2 H singlet at τ5.49 due to -NH- (disappears on addition of D_2O) and two 3 H singlets at τ7.77 and 7.89 respectively, due to the aromatic methyl groups.

One could also postulate structures LXXVI ($R_1=R_2=CH_3$, $R_3=H$ or $R_1=R_3=CH_3$, $R_2=H$) as alternative ones for this compound. These, however, do not agree with the



(LXXVI)

n.m.r. spectrum since there were no resonances downfield of τ2.55. The C_6-H in 2-substituted-4,5-dimethylpyridine-1-oxides invariably appears at τ1.85-2.10 in solution. The C_6-H in 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (LXXV, $R_1=R_2=CH_3$) gave rise to a peak at τ2.02. The presence of two NH protons also supports structure LXXIV ($R_1=R_2=CH_3$).

The mass spectrum of (LXXIV) did not exhibit a parent ion peak at m/e 485 ($C_{33}H_{31}N_3O^+$) but did show a fragment ion at m/e 469 ($C_{33}H_{31}N_3^+$) due to loss of an oxygen atom (97, 104), and an ion at m/e 468 ($C_{33}H_{30}N_3^+$) due to loss of an oxygen and hydrogen atom. Aromatic secondary amines show an (M-1) ion due to loss of a hydrogen atom (106). The remainder of the mass spectrum could be accounted for as shown under Scheme 4. The molecular ion at m/e 485 ($C_{33}H_{31}N_3O^+$) can expel the anilinium ion ($C_6H_5NH_2^+$) to give an ion at m/e 93 (base peak) which can lose an H atom to give an ion at m/e 92 ($C_6H_5NH^+$), or HCN and then an H atom to give an ion at m/e 65 ($C_5H_5^+$). The fragment ion at m/e 469 ($C_{33}H_{31}N_3^+$) could lose a phenyl radical to give an ion at m/e 392 ($C_{27}H_{26}N_3^+$), or $C_6H_5NH^+$ to give an ion at m/e 377 ($C_{27}H_{25}N_2^+$). Alternatively, the ion at m/e 469 can give rise to ions at m/e 287 ($C_{20}H_{19}N_2^+$) and at m/e 182 ($C_{13}H_{12}N^+$). The fragment ion at m/e 182 ($C_{13}H_{12}N^+$) can then undergo further fragmentation as shown under Scheme 4, Path 1.

The mass spectrum does not support LXXVI (R_1=R_2=CH_3, R_3=H; R_1=R_3=CH_3, R_2=H) since the expected fragment ions at m/e 363 and m/e 273 due to $PhCH=\dot{\overset{+}{N}}(Ph)CH(Ph)NHPh$ and $Ph\dot{\overset{+}{N}}=CH(Ph)NHPh$ respectively, were absent. The

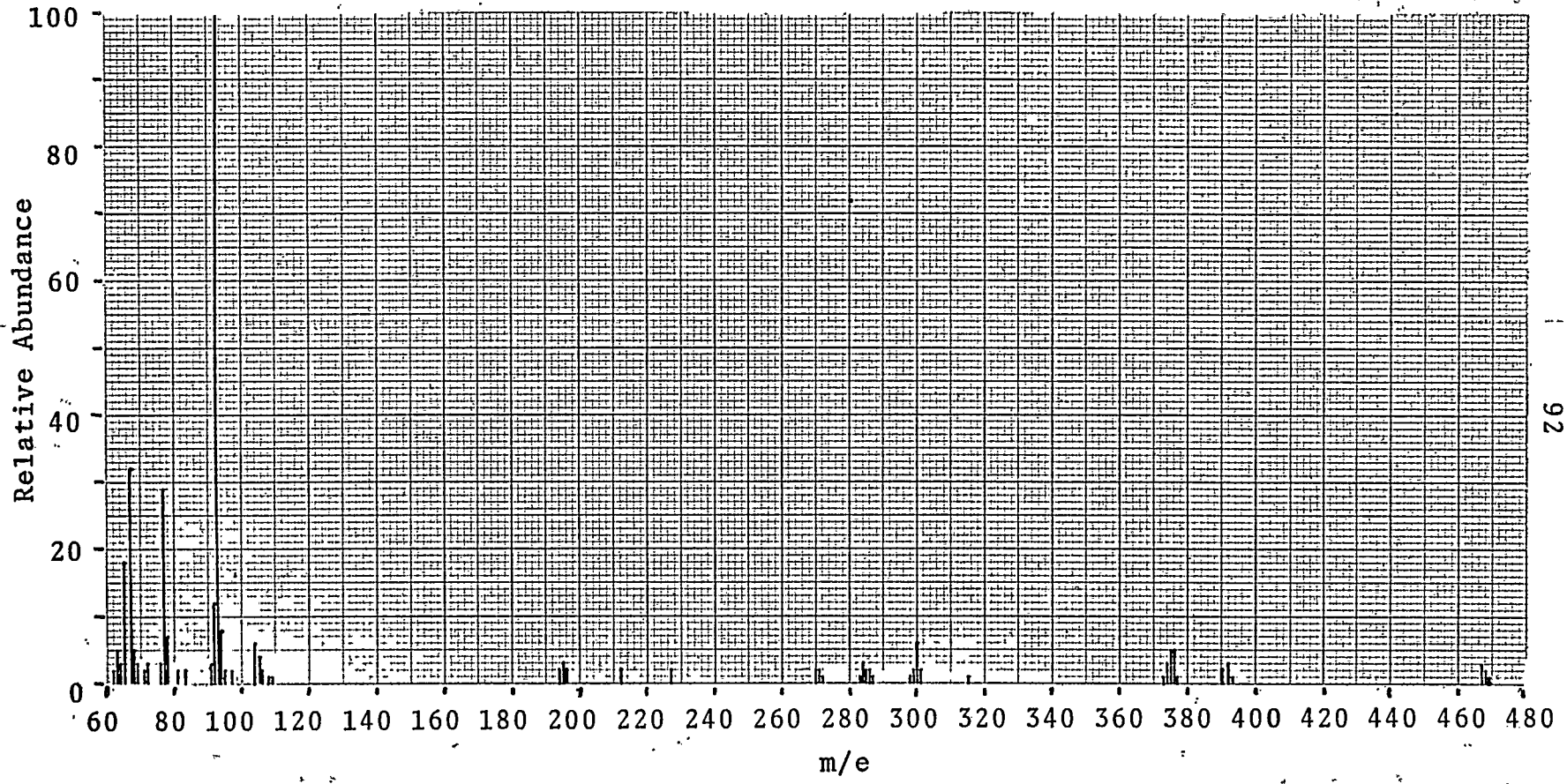
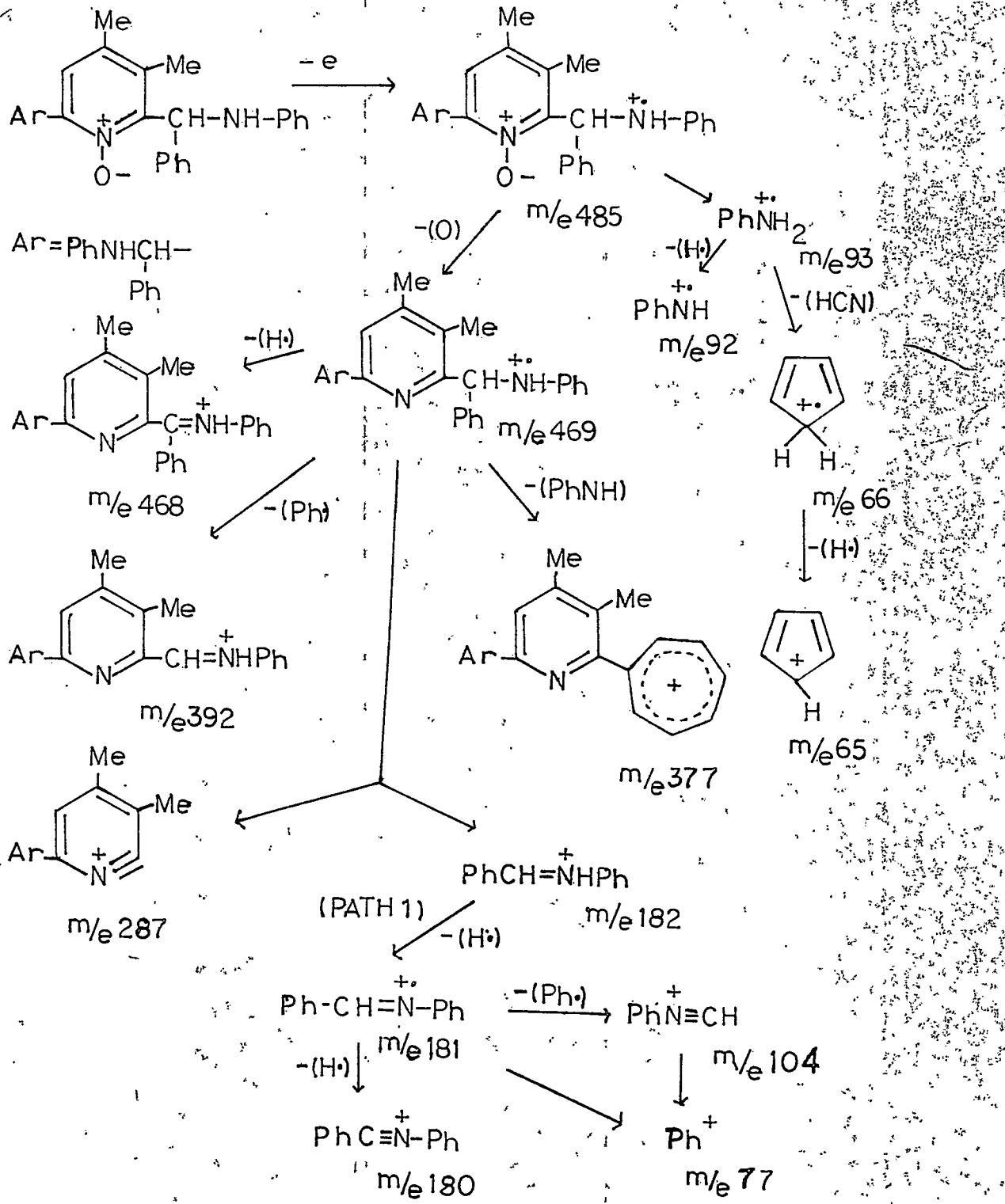


Figure 4.--Mass spectrum of 2,6-bis-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (70 eV)

SCHEME 4


Me
Me
Ar
CH-NH-Ph
Ph
O-
-e
CH-NH-Ph
m/e 485
PhNH2
m/e 93
-(O)
-(H•)
PhNH
m/e 92
-(HCN)
Ar=PhNHCH-
Ph
-(H•)
C=NH-Ph
m/e 468
m/e 469
-(Ph•)
-(PhNH)
CH=NHPh
m/e 392
m/e 66
-(H•)
m/e 377
m/e 65
m/e 287
PhCH=NHPh
(PATH 1)
-(H•)
m/e 182
Ph-CH=N-Ph
m/e 181
-(Ph•)
PhN≡CH
m/e 104
-(H•)
PhC≡N-Ph
m/e 180
Ph+
m/e 77

expected ion for LXXIV (R_1=R_2=CH_3) at m/e 182 due to PhCH=$\overset{+}{N}$H-Ph was present (Scheme 4).

The infrared spectrum of 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (LXXV, R_1=R_2=CH_3) exhibited an NH group (3330 cm^{-1}) and an $\overset{+}{N}$-O^- group (1260 cm^{-1}) (81). The n.m.r. spectrum exhibited a 1 H singlet at τ2.02 due to C_6-H, a complex 8 H multiplet at τ2.5-3.0 due to C_3-H, and 7 aromatic protons, a complex 3 H multiplet at τ3.20-3.55 due to 3 aromatic protons, a 1 H doublet ($\underline{J}$ = 3 Hz) at τ3.85 due to -C$\underline{H}$-, a 1 H doublet ($\underline{J}$ = 3 Hz) at τ5.22 due to -N$\underline{H}$- (disappears on addition of D_2O) and two 3 H singlets at τ7.84 and 7.90, respectively, due to the aromatic methyl groups.

The mass spectrum did not exhibit a molecular ion at m/e 304 ($C_{20}H_{20}N_2O^+$) but did show an ion at m/e 288 ($C_{20}H_{20}N_2^+$) due to loss of an oxygen atom (97, 104) and an ion at m/e 287 ($C_{20}H_{19}N_2^+$) due to the loss of an oxygen and hydrogen atom (97, 104). The remainder of the spectrum could be accounted for as shown under Scheme 5. The fragment ion at m/e 288 ($C_{20}H_{20}N_2^+$) could give an ion at m/e 196 ($C_{14}H_{14}N^+$) due to the loss of C_6H_5NH. Alternatively, it could give rise to fragment ions at m/e 106 ($C_7H_8N^+$) and m/e 182 ($C_{13}H_{12}N^+$). The ion at m/e 182 ($C_{13}H_{12}N^+$) can then give an ion at m/e 167

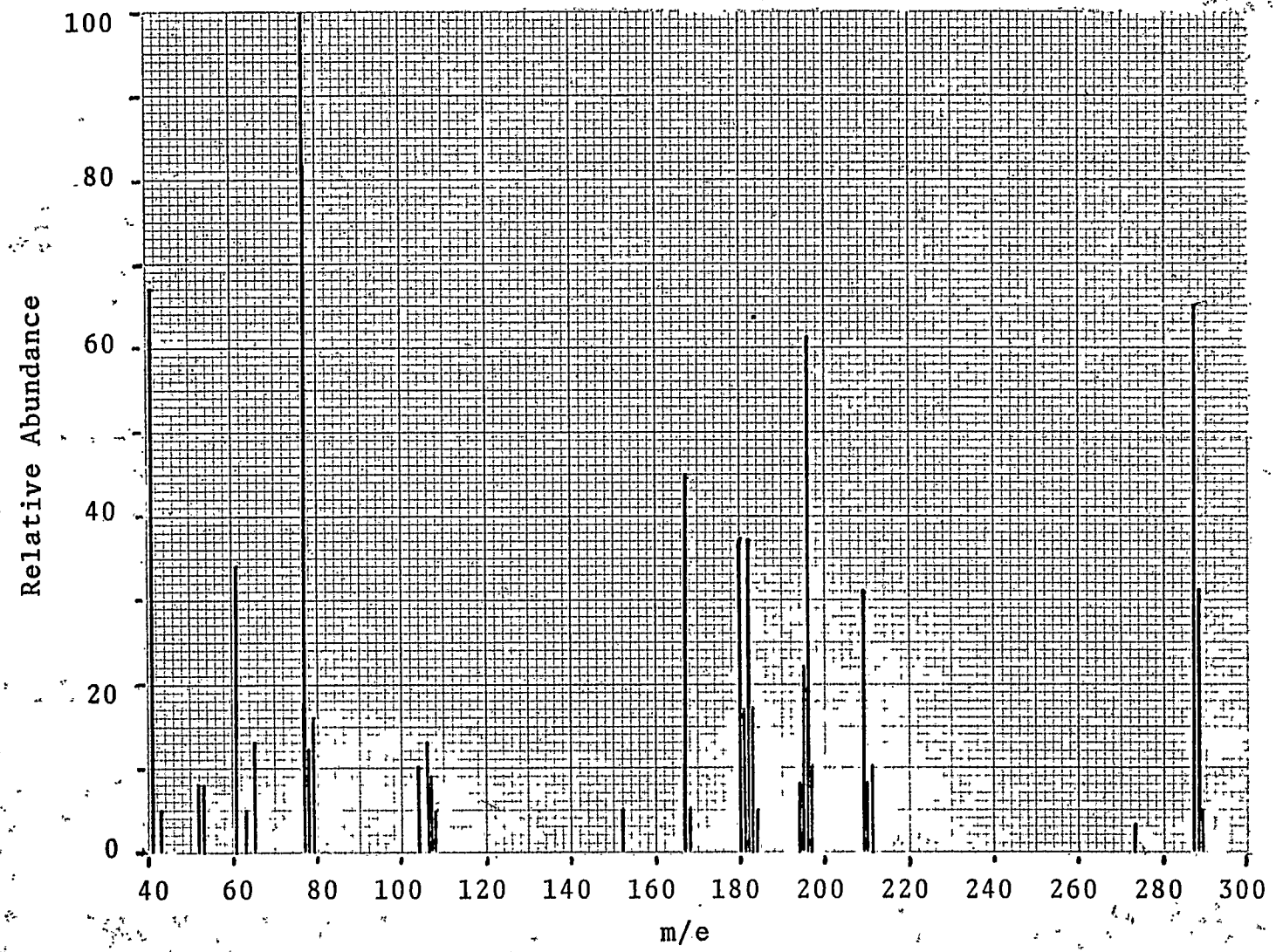
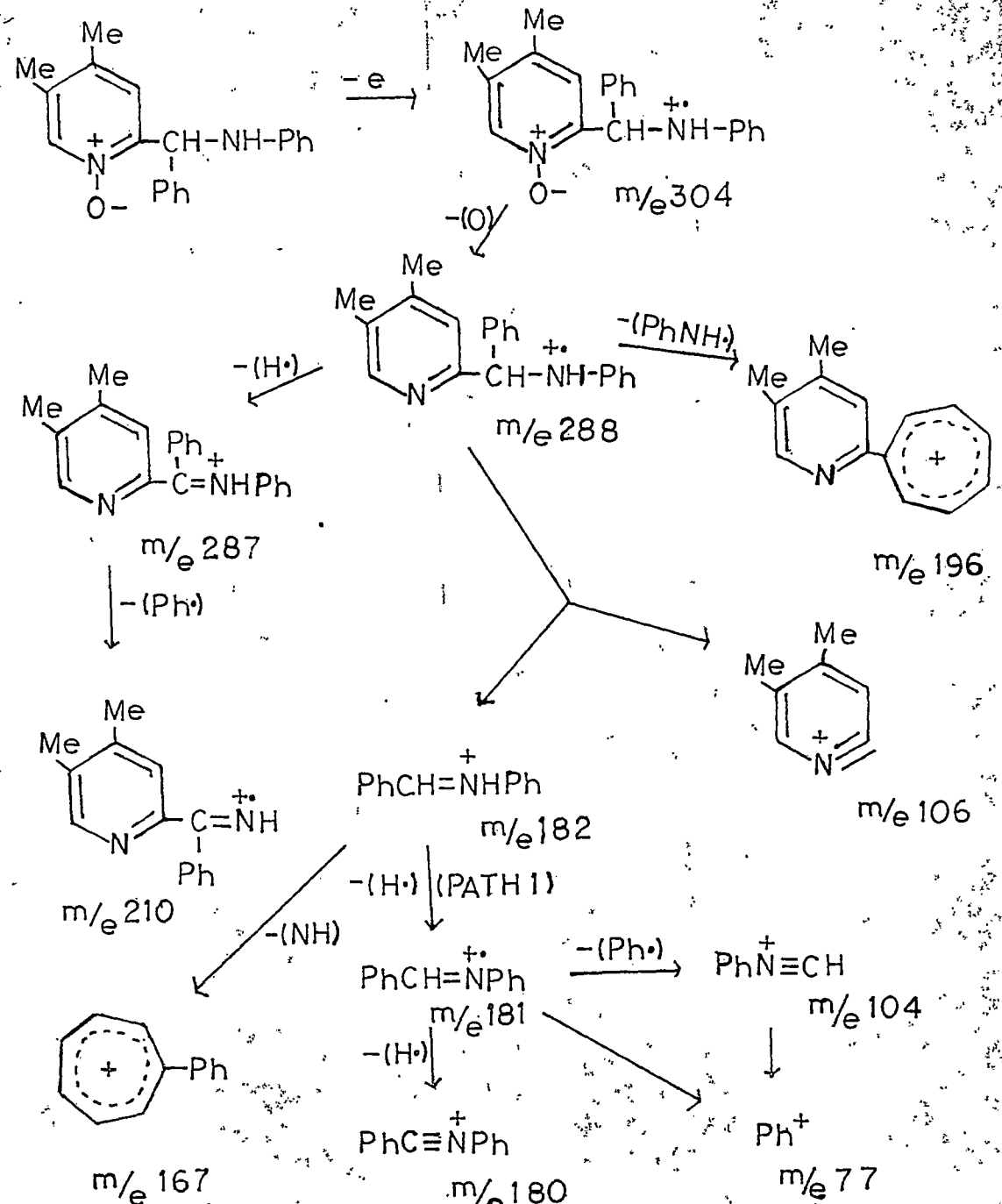


Figure 5.--Mass spectrum of 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (70 eV)

SCHEME 5


Me
Me
CH-NH-Ph
Ph
N
O-
-e
Ph
CH-NH-Ph
m/e 304
-(O)
m/e 288
-(H•)
-(PhNH•)
m/e 287
-(Ph•)
m/e 196
m/e 106
PhCH=NHPh
m/e 182
m/e 210
-(H•) (PATH 1)
-(NH)
PhCH=NPh
m/e 181
-(Ph•)
PhN≡CH
m/e 104
-(H•)
PhC≡NPh
m/e 180
Ph+
m/e 77
m/e 167

($C_{13}H_{11}^+$) due to the loss of NH or it can undergo further fragmentation as shown by Path 1.

The presence of a fragment ion at m/e 182 due to $PhCH=\overset{+}{N}HPh$ is further evidence in support of structure LXXIV ($R_1=R_2=CH_3$) discussed previously. The fragmentation patterns of LXXIV ($R_1=R_2=CH_3$) and LXXV ($R_1=R_2=CH_3$) are somewhat similar, but it appears that the primary ionization or ionizations may be different. The mass spectrum of 2,6-bis-(α-anilinobenzyl)-3,4-dimethylpyridine-1-oxide did not show the presence of the phenyltropylium cation ($C_{13}H_{11}^+$) and the base peak was the anilinium ion ($C_6H_5NH_2^+$). In contrast, 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide showed the presence of a phenyltropylium ion at m/e 167, and the base peak was the phenyl cation at m/e 77. These results suggest that expulsion of the anilinium ion from LXXIV ($R_1=R_2=CH_3$) is the major fragmentation but, with LXXV ($R_1=R_2=CH_3$), loss of oxygen and then consecutive fragmentation of the fragment ion at m/e 288 (Scheme 5) is the major pathway.

When the same reaction was repeated at 25° using ether as the solvent (5.2.9.2.0.b), 2,6-bis-(α-anilinobenzyl)-3,4-dimethylpyridine-1-oxide (31%) and 2-(α-anilinobenzyl)-4,5-dimethylpyridine-1-oxide (17.5%) were obtained (Table 4).

TABLE 4

Reaction of lithiopyridine-1-oxides with N-benzylideneaniline

N-oxide of	Solvent	% Products LXXIV	LXXV
3,4-Dimethyl-pyridine	THF (-65°)	61.8	12.1
	Et_2O (25°)	31.0	17.5
Pyridine	THF (-65°)	41.0	- -

Reaction of lithiopyridine-1-oxide with N-benzylideneaniline (5.2.6.1.0.a) gave 2,6-bis-(α-anilinobenzyl)pyridine-1-oxide (LXXIV, R_1=R_2=H, 41%) (Table 4). Its infrared spectrum showed the presence of an NH group (3400 cm^{-1}) and an $\overset{+}{N}$-O^- group (1230 cm^{-1}) (81). The n.m.r. spectrum exhibited a complex 17 H multiplet at τ2.40-3.15 due to C_3-H, C_4-H, C_5-H, and 14 aromatic protons, a complex 8 H multiplet at τ3.20-3.85 due to -CH-, and 6 aromatic protons, and a 2 H singlet at τ5.56 due to -NH- (disappears on addition of D_2O). The mass spectrum did not exhibit an $(M-16)^+$ ion at m/e 441 due to the loss of oxygen, but an ion at m/e 440 ($C_{31}H_{26}N_3^+$) due to the loss of an oxygen and hydrogen atom was present. The remainder of the fragmentation pattern (Scheme 6) is similar to that observed for LXXIV (R_1=R_2=CH_3), except that it appears that oxygen is being

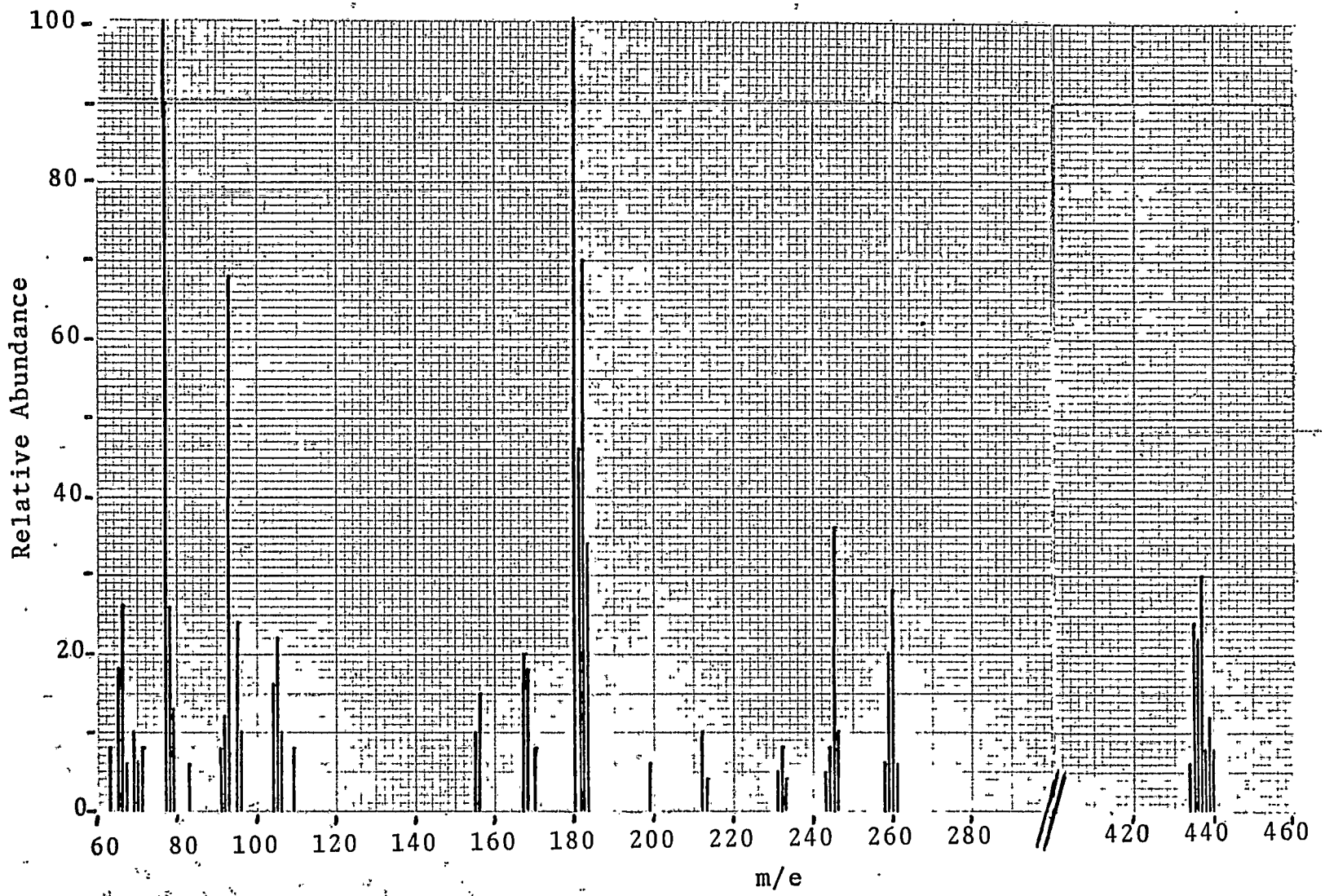
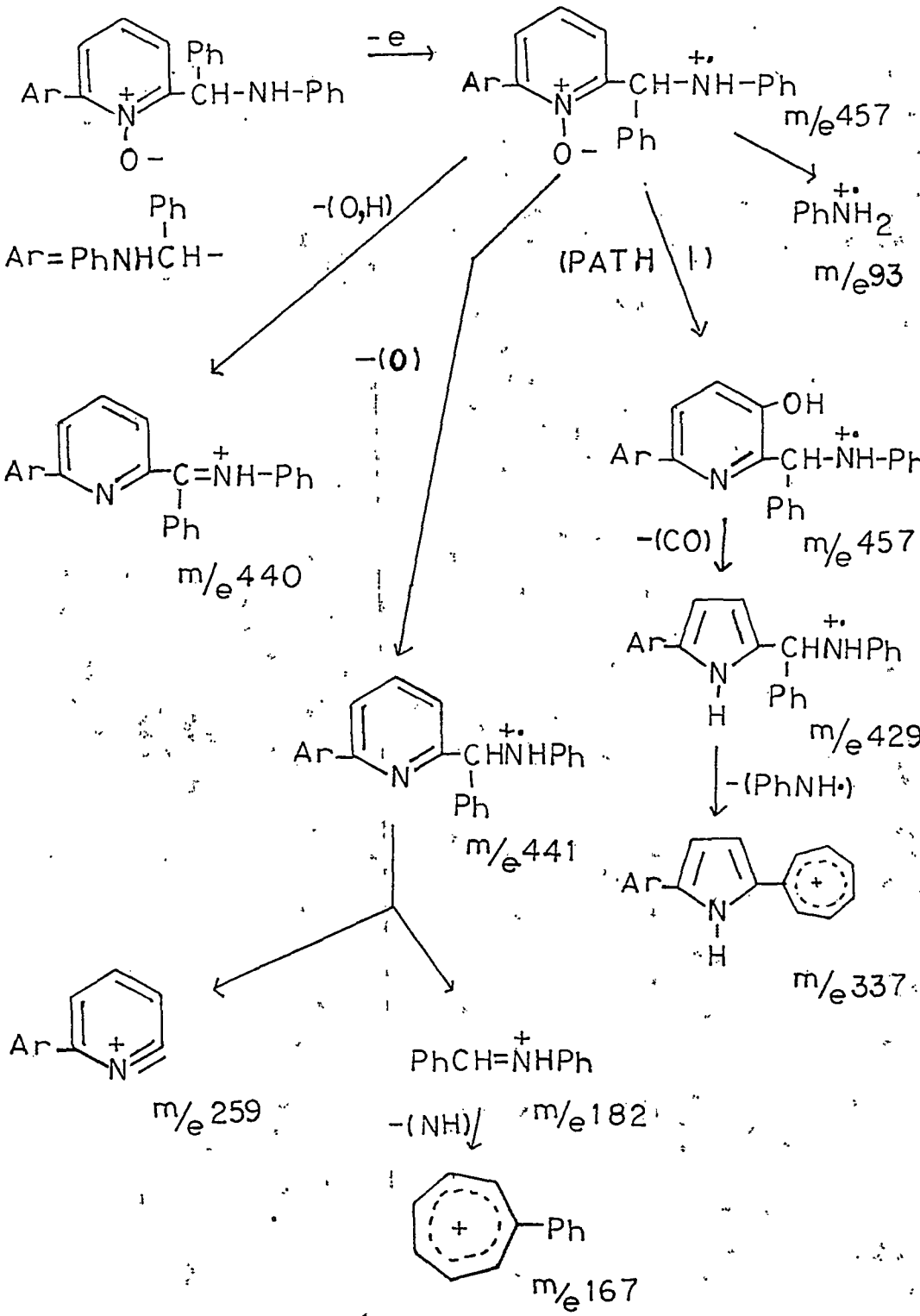


Figure 6.--Mass spectrum of 2,6-bis-(α-anilinobenzyl)pyridine-1-oxide (70 eV)

SCHEME 6


-e
Ar
Ph
CH-NH-Ph
O-
m/e457
PhNH2
m/e93
(PATH I)
Ar=PhNHCH-
-(O,H)
-(O)
OH
-(CO)
m/e457
CHNHPh
m/e429
-(PhNH·)
m/e441
m/e337
m/e259
PhCH=NHPh
m/e182
-(NH)
m/e167

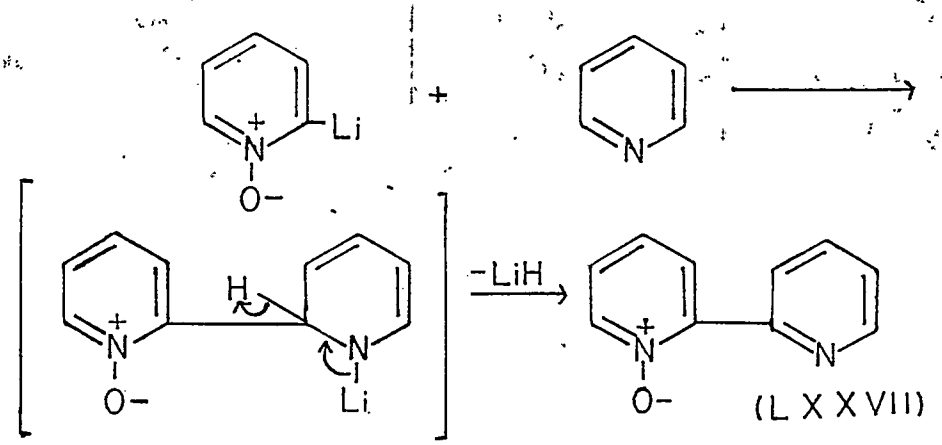
eliminated by some alternate pathway. This observation can be explained by loss of CO and then C_6H_6N from the molecular ion at m/e 457 ($C_{31}H_{27}N_3O^+$) to give an ion at m/e 337 ($C_{24}H_{21}N_2^+$) as shown under Scheme 6, Path 1. There is precedent for this pathway since photolysis of 2,6-disubstituted pyridine-1-oxides has been shown to give 2,6-disubstituted-3-hydroxypyridines (107) and 3-hydroxypyridine is known to lose CO (97) on electron bombardment.

The n.m.r. spectrum does not support the alternate structure LXXVI (R_1=R_2=R_3=H) since there were no resonances downfield of τ2.40, as discussed previously. Similarly the mass spectrum did not exhibit fragment ions at m/e 363 and m/e 273, which would have been expected for PhCH=$\overset{+}{N}$(Ph)CH(Ph)NHPh and Ph$\overset{+\cdot}{N}$=CH(Ph)NHPh, respectively. The expected ion at m/e 182 due to PhCH=$\overset{+}{N}$H-Ph was present.

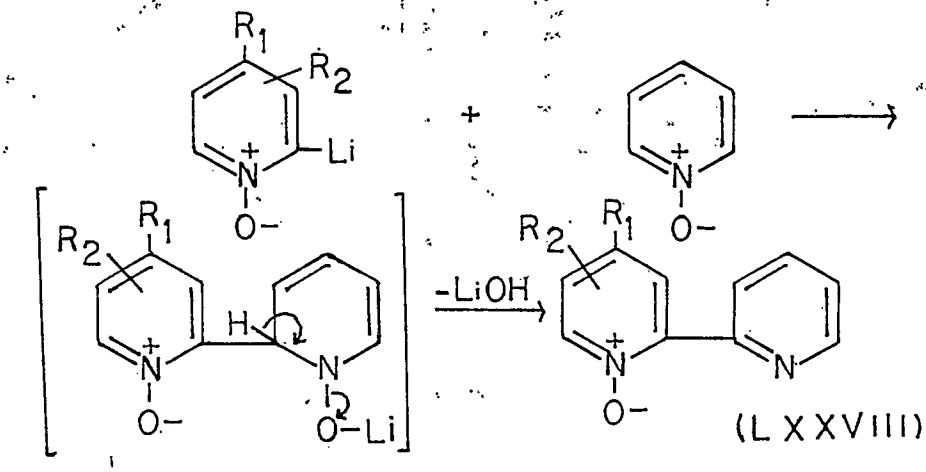
The reaction of organolithium reagents with pyridine or substituted pyridines (52, 83) usually proceeds readily to give high yields of the substituted products. It was hoped that the reaction of lithiopyridine-1-oxides with pyridine would yield 2-(2'-pyridyl)pyridine-1-oxides (LXXVII).

Treatment of the pyridine-1-oxide carbanion with pyridine gave rise to intractable tar and an oil probably

consisting of polydihydropyridine moieties. No 2-(2'-pyridyl)pyridine-1-oxide was detected.



It has been reported that reaction of phenylmagnesium bromide (49-51) or phenyllithium (99) with pyridine-1-oxide gives 2-phenylpyridine in low yield. Consequently, it was hoped that reaction of lithio-3,4-lutidine-1-oxide and pyridine-1-oxide would yield 2-(2'-pyridyl)-3,4-dimethylpyridine-1-oxides (LXXVIII) as illustrated below.



The reaction did not proceed as anticipated and starting material was recovered. None of the desired

product (LXXVIII) was detected. This reaction should clearly be examined further using different conditions.

3.2.0.0.0 Some other base-catalyzed reactions of pyridine-1-oxides

A variety of bases, other than n-butyllithium, were examined for their ability to generate the pyridyl-1-oxide carbanions (Table 5). A choice of suitable bases would be advantageous since it would increase the scope and versatility of the reaction.

The reaction of 4-methylpyridine-1-oxide with sodium amide and sulfur in liquid ammonia did not proceed. Similarly, the reaction of pyridine-1-oxide with lithium amide or lithium methoxide and sulfur did not occur. Reactions of substituted pyridine-1-oxides with lithium hydride and sulfur were more successful, however, and low yields of the corresponding cyclic thiohydroxamic acids were obtained as shown in Table 5. The best results were obtained when a mixture of dimethoxyethane (LXXIX) and 2-methoxyethanol (LXXX) or of dimethoxyethane (LXXIX) and diethyleneglycol monomethyl ether (LXXXI) (50:4 v/v) was used as the solvent (Table 5).

$CH_3OCH_2CH_2OCH_3$ (LXXIX)

$CH_3OCH_2CH_2OH$ (LXXX)

$CH_3OCH_2CH_2OCH_2CH_2OH$ (LXXXI)

Sodium bis-trimethylsilylamide (LXXXII) was also investigated as a possible substitute for n-butyllithium. It was chosen because it can be synthesized in nearly quantitative yield from readily available starting materials (80), is surprisingly stable to moisture and air, and can be used in a variety of solvents under a wide range of reaction conditions.

$$[(CH_3)_3\text{-}Si]_2NH + NaNH_2 \rightarrow [(CH_3)_3\text{-}Si]_2N\text{-}Na + NH_3$$

(LXXXII)

Reaction of the appropriate pyridine-1-oxide (XXVI) in benzene or tetrahydrofuran with sodium bis-trimethylsilylamide (LXXXII) and cyclohexanone gave a low yield of the corresponding 2-(1-hydroxycyclohexyl)pyridine-1-oxide (LXXIII) (Table 5).

The reaction of 3,4-dimethylpyridine-1-oxide with lithium bis-trimethylsilylamide (LXXXIII) and cyclohexanone in ether gave 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (LXXIII) and a new product, which was shown to be 3-methyl-4-(1-hydroxycyclohexylmethyl)pyridine-1-oxide (LXXXIV) (Table 5).

The structure assigned to LXXXIV is consistent with its infrared, n.m.r., and mass spectra, and elemental analyses.

TABLE 5

The use of bases other than butyllithium to generate the pyridyl-1-oxide carbanions

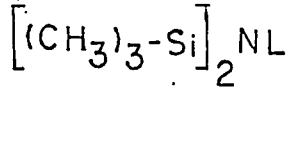
Pyridine-1-oxide (XXVI)						% Products	
R_1	R_2	Base	Solvent	Electrophile	Time (temp.)	XLII	XLIV
Me	H	$NaNH_2$	liq. NH_3	S_8	1 hr. (-33°)	- -	- -
H	H	$LiNH_2$	DME[a]	S_8	17 hr. (80°)	- -	- -
H	H	$LiOCH_3$	DME[a]	S_8	6 hr. (80°)	- -	- -
H	H	$LiOCH_3$	DME[a]-ME[b] (10:1 v/v)	S_8	20 hr. (80°)	- -	- -
Me	Me	LiH	DME[a]	S_8	20 hr. (80°)	- -	0.9
Me	Me	LiH	DME[a]-ME[b] (50:4 v/v)	S_8	14 hr. (80°)	5.5	5.2
H	H	LiH	DME[a]	S_8	18 hr. (80°)	12.0	- -
H	H	LiH	DME[a]-DME[c] (50:4 v/v)	S_8	18 hr. (80°)	19.5	- -
H	H	LiH	DME[a]-ME[b] (50:4 v/v)	S_8	18 hr. (80°)	21.5	- -
Me	H	LiH	DME[a]-ME[b] (50:4 v/v)	S_8	24 hr. (80°)	5.2	- -
H	H	LiH	DME[a]-ME[b] (53:1 v/v)	C_2H_4S	5 hr. (80°)	- -	- -

[a]Dimethoxyethane, [b]2-methoxyethanol, [c]diethyleneglycol monomethyl ether

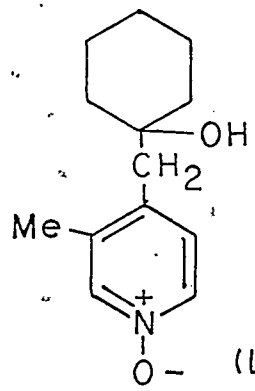
TABLE 5 (Continued)

Pyridine-1-oxide (XXVI) R_1	R_2	Base	Solvent	Electrophile	Time (temp.)	% Products LXXIII	LXXXIV
H	H	LiOEt	EtOH	cyclohexanone	19 hr. (78°)	- -	- -
H	H	STSA[d]	C_6H_6	cyclohexanone	1 hr. (80°)	0.85	- -
Me	Me	STSA[d]	C_6H_6	cyclohexanone	3 hr. (25°)	1.7	- -
Me	Me	STSA[d]	THF	cyclohexanone	20 hr. (25°)	1.4	- -
Me	Me	STSA[d]	THF	cyclohexanone	20 hr. (66°)	1.4	- -
Me	Me	LTSA[e]	Ether	cyclohexanone	1 hr. (25°)	4.0	2.6
Me	Me	LTSA[e]	Ether	cyclohexanone	20 hr. (25°)	4.5	3.3
H	H	TIOEt	Ether	cyclohexanone	17 hr. (25°)	- -	- -
H	H	TIOEt	EtOH	cyclohexanone	2 hr. (78°)	- -	- -
Me	Me	PDBP[f]	THF	cyclohexanone	20 hr. (25°)	- -	- -

[d]sodium bis-trimethylsilylamide, [e]lithium bis-trimethylsilylamide, [f]potassium 2,6-di-t-butylphenoxide



(LXXXIII)



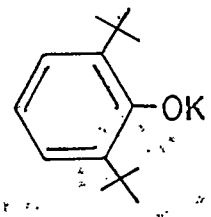
(LXXXIV)

The infrared spectrum showed the presence of a hydrogen-bonded OH group (3240 cm^{-1}) and an $\overset{+}{N}$-O^{-} group (1275 cm^{-1}) (81). The n.m.r. spectrum in trifluoroacetic acid exhibited an unsymmetrical 2 H doublet ($J_{5,6}$ = 6 Hz) at τ1.48 due to C_2-H, C_6-H, a 1 H doublet ($J_{5,6}$ = 6 Hz) at τ2.08 due to C_5-H, a 2 H singlet at τ6.89 due to C_4-CH_2-, a 3 H singlet at τ7.38 due to C_3-CH_3, and a 10 H singlet at τ8.28 due to the cyclohexyl ring protons. Failure to observe the OH proton may be due to rapid hydrogen exchange which would result in a very broad resonance which would not be detected. The n.m.r. spectrum of 3,4-lutidine-1-oxide in trifluoroacetic acid exhibited an unsymmetrical 2 H doublet ($J_{5,6}$ = 6 Hz) at τ1.48 due to C_2-H and C_6-H, a 1 H doublet ($J_{5,6}$ = 6 Hz) at τ2.24 due to C_5-H, and two 3 H singlets at τ7.41 and 7.49 due to the aromatic methyl protons. The n.m.r. spectrum of 3-methylpyridine-1-oxide (72) in 18N-D_2SO_4 exhibits resonances at τ1.28 due to C_2-H, and C_6-H, at

τ1.65 due to C_4-H, at τ1.97 due to C_5-H, and at τ7.38 due to C_3-CH_3. The mass spectrum exhibited a parent ion peak at m/e 221 and an $(M-18)^+$ ion at m/e 203 due to the loss of water (97). The most important fragmentation is expulsion of the 3,4-dimethylpyridine-1-oxide ion to give a fragment ion at m/e 123 (base peak) ($C_7H_9NO^+$) which can lose an oxygen atom to give an ion at m/e 107 ($C_7H_9N^+$) (97). There was no $(M-16)^+$ ion peak at m/e 205 due to the loss of an oxygen atom from the molecular ion.

The isolation of LXXXIV now provides the first example of base-catalyzed hydrogen abstraction of a C_4-methyl proton in this study.

The reactions of pyridine-1-oxide with lithium ethoxide or thallous ethoxide and cyclohexanone were unsuccessful. Similarly, the reaction of 3,4-lutidine-1-oxide with potassium 2,6-di-t-butylphenoxide (LXXXV) and cyclohexanone was unsuccessful and the starting materials were recovered (Table 5).



(LXXXV)

3.3.0.0.0 Dehydration and polymerization of some 2-substituted pyridine-1-oxide alcohols

Some of the 2-pyridyl alkanol-1-oxides prepared were dehydrated to give 2-vinylpyridine-1-oxide (LXIV) which, on polymerization, gave poly-2-vinylpyridine-1-oxides (LXV).

Using the method of Boekelheide and Scharrer (82), distillation of a mixture of 2-(2'-pyridyl)ethanol-N-oxide, potassium bisulfate, and methylene blue gave 2-vinylpyridine-1-oxide. The infrared spectrum showed the presence of olefinic unsaturation (1650 cm^{-1}) and an $\overset{+}{N}\text{-}O^{-}$ group (1225 cm^{-1}) (81). The n.m.r. spectrum exhibited a 1 H multiplet at τ1.82 due to C_6-H, a complex 4 H multiplet at τ2.34-3.00 due to C_3-H, C_4-H, C_5-H, and one vinyl proton (-C<u>H</u>=CH_2), a 1 H doublet ($J_{\underline{trans}}$ = 18 Hz) at τ3.93 due to one vinyl proton ($^{H}\!>\!C\!=\!C\!<^{H}_{\underline{H}}$), and a 1 H doublet ($J_{\underline{cis}}$ = 11 Hz) at τ4.44 due to the other vinyl proton ($^{H}\!>\!C\!=\!C\!<^{H}_{\underline{H}}$).

Polymerization of 2-vinylpyridine-1-oxide in the presence of <u>n</u>-butyllithium (5.4.4.0.0.a) or on standing at room temperature in chloroform (5.4.4.0.0.b) gave poly-(2-vinylpyridine-1-oxide). The n.m.r. spectrum in deuterium oxide exhibited a broad 1 H singlet at τ1.0-1.84 due to C_6-H, a broad 3 H singlet at τ1.84-3.00 due

to C_3-H, C_4-H, C_5-H, and a broad 3 H multiplet at τ5.2-8.7 due to -CH-CH_2-.

When 2-(2'-pyridyl)ethanol-N-oxide in sulfuric acid was heated at 80-85° for 1 hr., a mixture of 2-vinylpyridine-1-oxide and 2-(2'-pyridyl)ethanol-N-oxide was obtained (5.4.1.0.0.b). However when the above dehydration procedure was carried out at 140-145° for 4 hr., poly-(2-vinylpyridine-1-oxide) (98.5%) was obtained. The n.m.r. spectrum in deuterochloroform exhibited a broad 1 H singlet at τ1.0-1.64 due to C_6-H, a broad 3 H singlet at τ1.64-2.76 due to C_3-H, C_4-H, C_5-H, and a broad 3H multiplet at τ4.6-7.0 due to -CH-CH_2-.

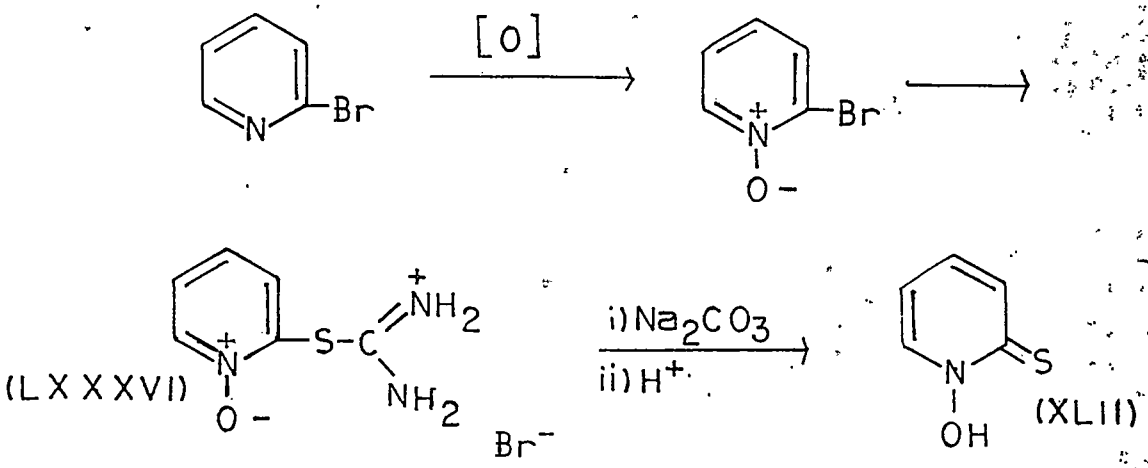
Similarly, treatment of 2-(1-hydroxyethyl)pyridine-1-oxide with sulfuric acid at room temperature for 16 hr. gave poly-(2-vinylpyridine-1-oxide).

3.4.0.0.0 Preparation of precursors and authentic samples

3.4.1.0.0 1-Hydroxy-2-pyridinethione

1-Hydroxy-2-pyridinethione was prepared by a series of reactions starting from 2-bromopyridine. Using the method of Shaw and his co-workers (18), oxidation of 2-bromopyridine with perbenzoic acid gave 2-bromopyridine-1-oxide which, on treatment with thiourea, gave 2-pyridyl-1-oxide isothiouronium bromide (LXXXVI).

Treatment of the above salt (LXXXVI) with aqueous sodium carbonate, and then acidification, gave 1-hydroxy-2-pyridinethione (XLII, $R_1=R_2=H$), identical (I.R. and n.m.r.) with the material described under 5.2.2.1.0.a.



3.4.2.0.0 1-Hydroxy-2-pyridone

Following the procedure of Shaw and his colleagues (18), treatment of 2-bromopyridine-1-oxide hydrochloride with aqueous sodium hydroxide and then acidification gave 1-hydroxy-2-pyridone identical with that obtained as under 5.5.4.0.0.

3.4.3.0.0 2-(2'-Pyridyl)ethanol-N-oxide

Oxidation of 2-(2-pyridyl)ethanol with 30% hydrogen peroxide in glacial acetic acid, according to the procedure of Boekelheide and Feely (79), gave 2-(2'-pyridyl)-ethanol-N-oxide as described under 5.5.5.0.0.

4.0.0.0.0 SOME *in vitro* PHARMACOLOGICAL TESTING RESULTS

Some of the cyclic thiohydroxamic acids prepared by thiation of lithiopyridine-1-oxides, as described above, were evaluated for their antibacterial and antifungal activity (Table 6-14) by the Warner-Lambert Research Institute.

The first *in vitro* antibacterial and antifungal screening was carried out in the absence of serum using the tube dilution method. The minimal concentration of thiohydroxamic acid required to prevent the growth of bacterial test organisms, *S. aur.*, *E. coli*, and *P. vulg.*, varied from 4 to 1000 ug./ml. as shown under Tables 6-9. The minimum concentration needed to inhibit the growth of fungal test organisms, *C. alb.* and *T. ment.*, varied from 4 to 16 ug./ml. (Tables 10-13). The marked activity shown by these thiohydroxamic acids warranted further their testing in the presence of serum.

A second *in vitro* antibacterial and antifungal screening was performed using a broad spectrum of bacterial and fungal test organisms in the presence of serum. The minimum concentration required to prevent the growth of bacterial test organisms, *S. aur.*, *D. pneu.*, *E. coli.*, *K. pneu.*, *Ps. aer.*, and *P. vulg.*, varied from

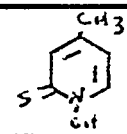
4 to 500 ug./ml. as shown under Tables 6-9. The minimal concentration needed to inhibit the growth of the fungal test organisms, C. alb., T. ment., A. nigr., S. schn., M. cani., and C. neof., varied from 8 to 125 ug./ml. (Tables 10-13).

It is particularly significant that the activity of these thiohydroxamic acids remains remarkably high in the presence of serum. The antifungal test results appear to be very promising since there does not appear to be a completely effective agent available for the control of S. schn., M. cani., or C. neof. The in vivo testing of these thiohydroxamic acids is now in progress.

2,2'-(1,1'-Dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)disulfide (or its isomer) was inactive as an antibacterial or antifungal agent (Table 14). This inactivity may be due to its low solubility.

TABLE 6

Antibacterial test results on 1-hydroxy-4-methyl-2-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIBACTERIAL SCREENING
IN VITRO

W NUMBER: X 72 1 1 | LOT NUMBER: | TEST NO.: 5 0 0

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
→ S. AUR		4	G A V I M I C		A 4		S
→ S. AUR		4	G A V I M I C		A 1		S
E. COLI		12.5	G A V I M I C		L 5		S
P. VULG		1000	G A V I M I C		Ø 1		S
			G A V I M I C				S
			G A V I M I C				S

23

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.

W14351A — CODE: R
4 — CODE: R
4 — CODE: R
6.3 — CODE: R
G 100 — CODE: R

40 - 42 | CODE | Activity: M K / M K / M K / S L | Set | CARD (TIS)

BIOLOGIST: J F M | MO.: 9 | YEAR: 6 9 | CHEMIST: D - K

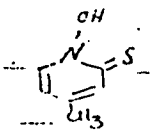
CC: F. J. TURNER

TESTED BY MICRO: Q. M. Allice | APPROVED: J. F. Martin | DATE: 9/15/69

REF. CPD. (R):
N.B. REF.: 8173

WARNER-LAMBERT RESEARCH INSTITUTE

500A-W FORM 1
67019



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIBACTERIAL SCREENING
BROAD SPECTRUM – *IN VITRO*

W NUMBER: X 72 1 1 | LOT NUMBER: | TEST NO.: 5 0 0

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
S. AUR		4	G A V I M I C		A 4		S
D. PNEU			G A V I M I C		B 1		S
E. COLI		6.3	G A V I M I C		L 5	6.3	S
K. PNEU		2	G A V I M I C		M 2	2	S
PS. AER		500	G A V I M I C		N 1	500	S
P. VULG		500	G A V I M I C		Ø 1	500	S

23

COMMENTS:
Compound exhibits marked activity in the presence of serum and is recommended for in vivo testing.

W14351A — CODE: R
4 — CODE: R
12.5 — CODE: R
3.1 — CODE: R
G- 100 — CODE: R
G+ 100 — CODE: R

40 - 42 | CODE | Activity: M K / M K / M K / M K / M K | Set | CARD (TIS)

BIOLOGIST: J F M | MO.: 9 | YEAR: 6 9 | CHEMIST: D - K

CC: F. J. TURNER

TESTED BY MICRO: Q. M. Allice | APPROVED: J. F. Martin | DATE: 9/29/69

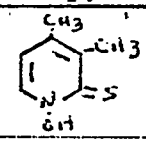
REF. CPD. (R):
N.B. REF.: 8244

WARNER-LAMBERT RESEARCH INSTITUTE

500 FORM 3
68008

TABLE 7

Antibacterial test results on 1-hydroxy-3,4-dimethyl-2-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIBACTERIAL SCREENING
IN VITRO

W NUMBER: X 7215 | LOT NUMBER: | TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	*In Vitro*	Strain	Static MIC γ/ML w/Serum	CODE
→ S. AUR		4	G A V I	M I C	A 4		S
→ S. AUR		4	G A V I	M I C	A 2		S
E. COLI		16	G A V I	M I C	L 5		S
P. VULG		125	G A V I	M I C	G 1		S
			G A V I	M I C			S
			G A V I	M I C			S

23

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.

W1435A	CODE		CODE	Activity	Set	CARD (TIS)
L	4 R			M K		δ
L	4 R			M K		δ
	63 R			M K		δ
G 1000	R			M K		δ
						δ
						δ

40 - 42

BIOLOGIST	MO.	YEAR	CHEMIST
JF	M	69	D - K

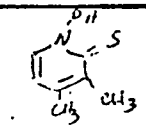
CC: F. J. TURNER

TESTED BY: MICRO A. M. Allen APPROVED: J. F. Martin DATE: 9/15/69

REF. CPD. (R):
N.B. REF.: 8173

WARNER-LAMBERT RESEARCH INSTITUTE

500A-W FORM 1
67019



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIBACTERIAL SCREENING
BROAD SPECTRUM – *IN VITRO*

W NUMBER: X 7215 | LOT NUMBER: | TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	*In Vitro*	Strain	Static MIC γ/ML w/Serum	CODE
S. AUR		63	G A V I	M I C	A 4	500	S
D. PNEU		16	G A V I	M I C	B 1		S
E. COLI		16	G A V I	M I C	L 5	16	S
K. PNEU		16	G A V I	M I C	M 2	16	S
PS. AER		63	G A V I	M I C	N 1	250	S
P. VULG		2	G A V I	M I C	G 1	500	S

23

COMMENTS:
Compound exhibits marked activity in the presence of serum and is recommended for in vivo testing.

W1435A	CODE		CODE	Activity	Set	CARD (TIS)
L	4			SL		δ
	16					δ
	31					δ
G 1000						δ
G 1000						δ

40 - 42

BIOLOGIST	MO.	YEAR	CHEMIST
JF	M	69	D - K

CC: F. J. TURNER

TESTED BY: MICRO A. M. Allen APPROVED: J. F. Martin DATE: 9/24/69

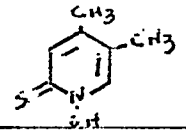
REF. CPD. (R):
N.B. REF.: 8244

WARNER-LAMBERT RESEARCH INSTITUTE

500 FORM 3
68008

TABLE 8

Antibacterial test results on 1-hydroxy-3,4-dimethyl-6-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIBACTERIAL SCREENING
IN VITRO

W NUMBER: X 7214 — LOT NUMBER: — — TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
→ S. AUREUS		4	GAVI MIC		A 4		S
→ S. AUREUS		4	GAVI MIC		A 1		S
E. COLI		31	GAVI MIC		L 5		S
P. VULG		250	GAVI MIC		Ø 1		S
			GAVI MIC				S
			GAVI MIC				S

23

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.

W14354H	CODE		CODE	Activity	Set	CARD (TIS)
L	R			M K		0
L	R			M K		0
G 1000	R			M Ø		0
						0
						0

40 - 42

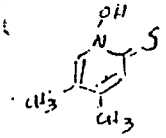
cc: E. J. TURNER

BIOLOGIST	MO.	YEAR	CHEMIST
JF	9	69	D-K

TESTED BY: MICRO — APPROVED: J. F. Martin — DATE: 9/15/69
REF. CPD. (R): N.B. REF.: 8123

WARNER-LAMBERT RESEARCH INSTITUTE

600A-W FORM 1 67015



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIBACTERIAL SCREENING
BROAD SPECTRUM – *IN VITRO*

W NUMBER: X 7214 — LOT NUMBER: — — TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
S. AUREUS		4	GAVI MIC		A 4		S
D. PNEUMO			GAVI MIC		B 1		S
E. COLI		31	GAVI MIC		L 5	63	S
K. PNEUMO		16	GAVI MIC		M 2	16	S
PS. AERUG		250	GAVI MIC		N 1	500	S
P. VULG		125	GAVI MIC		Ø 1	250	S

23

COMMENTS:
Compound exhibits marked activity in the presence of serum and is recommended for in vivo testing.
cc: F. J. TURNER

W14354H	CODE		CODE	Activity	Set	CARD (TIS)
L	R			M K		0
						0
	R			M K		0
	R			M K		0
G 1000	R			M G		0
G 1000	R			M K		0

40 - 42

BIOLOGIST	MO.	YEAR	CHEMIST
JF	9	69	D-K

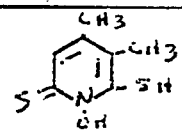
TESTED BY: MICRO — APPROVED: J. F. Martin — DATE: 9/24/69
REF. CPD. (R): N.B. REF.: 8244

WARNER-LAMBERT RESEARCH INSTITUTE

500 FORM 3 68006

TABLE 9

Antibacterial test results on 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIBACTERIAL SCREENING
IN VITRO

W NUMBER: X 7212 | LOT NUMBER: | TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
→ S. AUR		125	GAVI	MIC	A4		S
→ S. AUR		125	GAVI	MIC	A3		S
→ E. COLI		31	GAVI	MIC	L5		S
→ P. VULG		31	GAVI	MIC	Ø1		S
			GAVI	MIC			S
			GAVI	MIC			S

23

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.

W1435H	CODE
L	14 R
L	7 R
G	63 R
G	100 R

40 - 42 | CODE

Activity	Set	CARD (TIS)
M Ø		Ō
M Ø		Ō
M K		Ō
M K		Ō
		Ō
		Ō

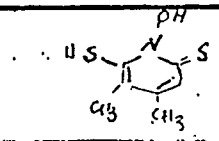
BIOLOGIST: JFM | MO. YEAR: 9 69 | CHEMIST: D-K

CC: F. J. TURNER

TESTED BY: MICRO A. M. Alice | APPROVED: J. F. Martin | DATE: 9/15/69

REF. CPD. (R): 8123
N.B. REF.:

WARNER-LAMBERT RESEARCH INSTITUTE
800A-W FORM 1
67019



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIBACTERIAL SCREENING
BROAD SPECTRUM – *IN VITRO*

W NUMBER: X 7212 | LOT NUMBER: | TEST NO.: 500

ORGANISM	#	Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain	Static MIC γ/ML w/Serum	CODE
S. AUR		125	GAVI	MIC	A4	250	S
D. PNEU			GAVI	MIC	B1		S
E. COLI		63	GAVI	MIC	L5	63	S
K. PNEU		63	GAVI	MIC	M2	63	S
PS. AER		125	GAVI	MIC	N1	50	S
P. VULG		63	GAVI	MIC	Ø1	50	S

23

COMMENTS:
Compound exhibits marked activity in the presence of serum and is recommended for in vivo testing.
CC: F. J. TURNER

W1435H	CODE
L	14 R
	7 R
	31 R
G	100 R
G	100 R

40 - 42 | CODE

Activity	Set	CARD (TIS)
S L		Ō
		Ō
M K		Ō
M K		Ō
M Ø		Ō
M Ø		Ō

BIOLOGIST: JFM | MO. YEAR: 9 69 | CHEMIST: D-K

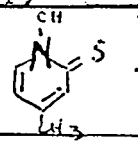
TESTED BY: MICRO A. M. Alice | APPROVED: J. F. Martin | DATE: 9/24/69

REF. CPD. (R): 8244
N.B. REF.:

WARNER-LAMBERT RESEARCH INSTITUTE
800 FORM 8
69008

TABLE 10

Antifungal test results on 1-hydroxy-4-methyl-2-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 2 1 1 . | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM	#
→ C . A L B	
→ T . M E N T	

Static MIC γ/ML w/o Ser.	UNITS	In Vitro						Strain	Static MIC γ/ML w/Serum	CODE
< 1/4	G A	V	I	M	I	C	A	I		S
< 4	G A	V	I	M	I	C	B	I		S
	G A	V	I	M	I	C				S
	G A	V	I	M	I	C				S
	G A	V	I	M	I	C				S
	G A	V	I	M	I	C				S

W1435 A	CODE		CODE	Activity	Set	CARD (TIS)
1 6	R			M K		0
< 4	R			M K		0
						0
						0
						0
						0

COMMENTS: Compound shows marked activity and will be tested in the presence of serum.

CC: E. L. TURNER

TESTED BY: MICRO — A. M. Glue — APPROVED: J. F. Martin — DATE: 9/15/69

BIOLOGIST: J E M — MO.: 9 — YEAR: 6 9 — CHEMIST: - K

REF. CPD. (R): — N.B. REF.: 8173

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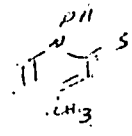
802 A-W FORM 1
67021



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 2 1 1 . | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM	#
C . A L B	
T . M E N T	
A . N I G R	
S . S C H N	
M . C A N I	
C . N E G F	

Static MIC γ/ML w/o Ser.	UNITS	In Vitro						Strain	Static MIC γ/ML w/Serum	CODE
< 1/4	G A	V	I	M	I	C	A	1		S
< 4	G A	V	I	M	I	C	B	1		S
1 6	G A	V	I	M	I	C	C	2		S
< 4	G A	V	I	M	I	C	E	1		S
< 4	G A	V	I	M	I	C	F	1		S
< 4	G A	V	I	M	I	C	G	1		S

W1435 A	CODE		CODE	Activity	Set	CARD (TIS)
1 6	R			M K		0
< 4	R			M K		0
3 1 6	R			M K		0
< 4	R			M K		0
< 4	R			M K		0
< 4	R			M K		0

COMMENTS: Compound exhibits MARKED activity in the PRESENCE OF SERUM and is RECOMMENDED FOR IN VIVO TESTING.

CC: E. L. TURNER

TESTED BY: MICRO — A. M. Glue — APPROVED: J. F. Martin — DATE: 9/29/69

BIOLOGIST: J E M — MO.: 9 — YEAR: 6 9 — CHEMIST: - K

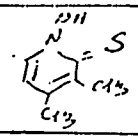
REF. CPD. (R): — N.B. REF.: 8244

WARNER-LAMBERT RESEARCH INSTITUTE

802 A-W FORM 8
68010

TABLE 11

Antifungal test results on 1-hydroxy-3,4-dimethyl-2-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7315 | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM: CALB / TMENT | #: 23

Static MIC γ/ML w/o Ser.: 4 / 4 | UNITS: G A V I M I C | In Vitro | Strain: A 1 / B 1

Static MIC γ/ML w/Serum: | CODE: S / S / S / S / S / S.

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.
CC: F. J. TURNER

W1435A: 16 R / 4 R | CODE

CODE | Activity: M K / M K | Set | CARD (TIS): 0 0 0 0 0 0

BIOLOGIST: J F M | MO. YEAR: 9 6 9 | CHEMIST: D — K

TESTED BY: MICRO Q.M.Q. APPROVED: J.F.M. DATE: 9/15/69

REF. CPD. (R):
N.B. REF.: 8173

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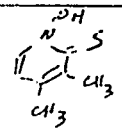
802 A-W FORM 1
67021



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7315 | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM: CALB / TMENT / ANIGK / SCHN / MCANI / CNEOF | #: 23

Static MIC γ/ML w/o Ser.: 4 / 4 / 4 / 4 / 4 / 4 | UNITS: G A V I M I C | In Vitro | Strain: A 1 / B 1 / C 2 / E 1 / F 1 / G 1

Static MIC γ/ML w/Serum: 16 / 8 / 8 / 8 / 4 / 4 | CODE: S / S / S / S / S / S

COMMENTS:
Compound shows marked activity in the presence of serum and will be recommended for EN vivo testing.
CC: F. J. TURNER

W1435A: 16 R / 4 R / 8 R / 8 R / 4 R / 16 R | CODE

CODE | Activity: M K / M K / M K / M K / M K / M K | Set | CARD (TIS): 0 0 0 0 0 0

BIOLOGIST: J F M | MO. YEAR: 9 6 9 | CHEMIST: D — K

TESTED BY: MICRO Q.M.Q. APPROVED: J.F.M. DATE: 9/29/69

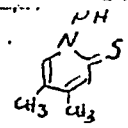
REF. CPD. (R):
N.B. REF.: 8244

WARNER-LAMBERT RESEARCH INSTITUTE

802 A-W FORM 5
68010

TABLE 12

Antifungal test results on 1-hydroxy-3,4-dimethyl-6-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 2 1 4 | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM	#
CANDIDA ALBICANS	
TRICHOPHYTON MENTAGROPHYTES	

Static MIC γ/ML w/o Ser. | UNITS: *In Vitro* | Strain

Static MIC γ/ML w/o Ser.	UNITS	Strain
1.6	GAVIMIC	A 1
< 4	GAVIMIC	B 1

Static MIC γ/ML w/Serum | CODE

Static MIC γ/ML w/Serum	CODE
	S
	S
	S
	S
	S
	S

40 - 42 (TIS)

W1435A	CODE
1.6	R
< 4	R

CODE

Activity	Set	CARD
M K		O
M K		O
		O
		O
		O
		O

COMMENTS:
Compound showed marked activity and will be tested in the presence of serum

CC: E. J. TURNER

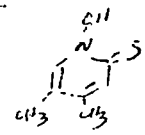
BIOLOGIST	MO.	YEAR	CHEMIST
J F M	9	6 9	D - K

TESTED BY: MICRO A. M. Alves APPROVED: J. F. Martin DATE: 9/15/69

REF. CPD. (R): 9173
N.B. REF.:

WARNER-LAMBERT RESEARCH INSTITUTE

502 A-W FORM 1
67021



MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 2 1 4 | LOT NUMBER: | TEST NO.: 5 0 2

ORGANISM	#
CANDIDA ALBICANS	
TRICHOPHYTON MENTAGROPHYTES	
ANISOSPORA GRISEA	
SCHIZOSACCHAROMYCES POMBE	
MICROSPORUM CANIS	
CRYPTOCOCCUS NEOFORMANS	

Static MIC γ/ML w/o Ser. | UNITS: *In Vitro* | Strain

Static MIC γ/ML w/o Ser.	UNITS	Strain
1.6	GAVIMIC	A 1
< 1.6	GAVIMIC	B 1
< 1.6	GAVIMIC	C 2
< 1.6	GAVIMIC	E 1
< 1.6	GAVIMIC	F 1
< 1.6	GAVIMIC	G 1

Static MIC γ/ML w/Serum | CODE

Static MIC γ/ML w/Serum	CODE
1.6	S
1.6	S
3.2	S
3.2	S
3.2	S
3.2	S

40 - 42 (TIS)

WF2574	CODE
1.6	R
< 1.6	R
1.6	R
3.2	R
3.2	R
< 1.6	R

CODE

Activity	Set	CARD
M K		O
M K		O
M K		O
M K		O
M K		O
M K		O

COMMENTS:
Compound shows marked activity and therefore will be recommended for IN VIVO testing.

CC: E. J. TURNER

BIOLOGIST	MO.	YEAR	CHEMIST
J F M	9	6 9	D - K

TESTED BY: MICRO A. M. Alves APPROVED: J. F. Martin DATE: 9/29/69

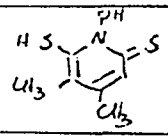
REF. CPD. (R): 8244
N.B. REF.:

WARNER-LAMBERT RESEARCH INSTITUTE

502 A-W FORM 8
68010

TABLE 13

Antifungal test results on 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione



MICROBIOLOGY TUBE DILUTION TESTS
1ST ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 3 1 3 — LOT NUMBER — TEST NO.: 5 0 2

ORGANISM	#
CANDIDA	
TRICHOPHYTON MENTAGROPHYTES	
ASPERGILLUS NIGER	
SACCHAROMYCES CEREVISIAE	
MICROSPORUM CANIS	
CANDIDA ALBICANS	

Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain
32	GAVI MIC		A 1
8	GAVI MIC		B 1
	GAVI MIC		
	GAVI MIC		
	GAVI MIC		
	GAVI MIC		

Static MIC γ/ML w/Serum	CODE
	S
	S
	S
	S
	S
	S

23

COMMENTS:
Compound shows marked activity and will be tested in the presence of serum.
cc: E. J. TURNER

W 1435 A	CODE
16	R
4	R

CODE	Activity
	M K
	M K

40 - 42

Set	CARD (TIS)
0	
0	
0	
0	
0	
0	

BIOLOGIST	MO.	YEAR	CHEMIST
J F M	9	6 9	D - K

TESTED BY: MICRO — A. M. Alves — APPROVED: J. F. Martin — DATE: 9/15/69
REF. CPD. (R): N.B. REF.: 8173
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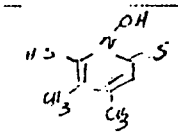


MICROBIOLOGY TUBE DILUTION TESTS
2ND ANTIFUNGAL SCREENING
IN VITRO

W NUMBER: X 7 3 1 3 — LOT NUMBER — TEST NO.: 5 0 2

ORGANISM	#
CANDIDA	
TRICHOPHYTON MENTAGROPHYTES	
ANIGER	
SCHIZOSACCHAROMYCES POMBE	
MICROSPORUM CANIS	
CANDIDA ALBICANS	

Static MIC γ/ML w/o Ser.	UNITS	In Vitro	Strain
16	GAVI MIC		A 1
8	GAVI MIC		B 1
16	GAVI MIC		C 2
16	GAVI MIC		E 1
16	GAVI MIC		F 1
16	GAVI MIC		G 1

Static MIC γ/ML w/Serum	CODE
16	S
16	S
32	S
32	S
32	S
16	S

23

COMMENTS:
Compound Exhibits MARKED ACTIVITY IN THE PRESENCE OF SERUM and will be Recommended FOR IN VIVO TESTING.
cc: E. J. TURNER

W-1435-M	CODE
16	R
16	R
32	R
16	R
16	R
16	R

CODE	Activity
	M K
	M K
	M K
	M K
	M K
	M K

40 - 42

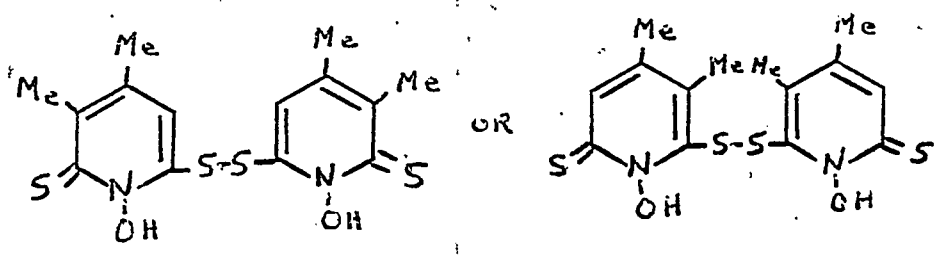
Set	CARD (TIS)
0	
0	
0	
0	
0	
0	

BIOLOGIST	MO.	YEAR	CHEMIST
J F M	9	6 9	D - K

TESTED BY: MICRO — A. M. Alves — APPROVED: J. F. Martin — DATE: 9/29/69
REF. CPD. (R): N.B. REF.: 8244
WARNER-LAMBERT RESEARCH INSTITUTE
502 A-W FORM B 68010

TABLE 14

Antibacterial and antifungal test results on 2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)-disulfide (or its isomer)



W NUMBER							L/- NUMBER				
X		1	2	4	3						
1	2	3	4	5	6	7	8	9	10	11	12

ANTIBACTERIAL - ANTIFUNGAL SCREENING *IN VITRO*

TEST NO.			
5	0	0	Y
5	0	2	Y
13	14	15	16

TEST NAME								
A	-	B	A	C	T	R		
A	-	F	U	N	G	L		
17	18	19	20	21	22	23	24 - 32	

In Vitro			
V	I		
V	I		
33	34	35 - 37	

ACTIVITY								
I	N	A	C	T				
I	N	A	C	T				
38	39	40	41	42	43 - 66			

Jdgmnt			
I	N		
I	N		
67	68		

Biologist			Mo.	Year		Chemist			TIS		
T	F	M	8	6	9	D	-	K	1	0	1
69	70	71	72	73	74	75	76	77	78	79	80

NB REF: 8123

COMMENTS:

TESTED BY: Q. M. Qhai APPROVED: J. F. Martin DATE: 9/15/69

MICRO
500Y, 502Y
67034

WARNER-LAMBERT RESEARCH INSTITUTE

5.0.0.0.0 EXPERIMENTAL

Melting points were determined on a Fisher-Johns or Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded using a Unicam SP 200 G, a Beckman IR 8, or a Perkin-Elmer 337 spectrophotometer as potassium bromide discs. N.m.r. spectra were determined using tetramethylsilane (TMS) as an internal standard for carbon tetrachloride and deuteriochloroform solutions or tetramethylsilane as an external standard in a sealed internal capillary for deuterium oxide solutions on a Varian A 60 or H A 100 Mc spectrometer. The mass spectra were recorded with an MS-12 or a CEC 21-104 mass spectrometer, and molecular weight determinations were performed with a Hitachi Perkin-Elmer Model 115 molecular weight apparatus. Fractions (150 ml) from column chromatography were collected, evaporated under reduced pressure, and analyzed by infrared spectroscopy for a preliminary determination of their composition. Dry oxygen-free nitrogen was obtained by passing it through a solution of sodium pyrogallate, concentrated sulfuric acid and anhydrous calcium sulfate. All non-aqueous reactions were protected by a drying tube of anhydrous calcium chloride or calcium sulfate.

5.1.0.0.0 Reagents and solvents

Commercial pyridine-1-oxide, 2-methylpyridine-1-oxide, and 3-methylpyridine-1-oxide (Reilly Tar and Chemical Corp.) were distilled *in vacuo* using a nitrogen bleed and the fractions, b.p. 80-82°/0.15 mm., 83-84°/0.15 mm, and 90-92°/0.15 mm., respectively, were collected and stored in a desiccator over anhydrous calcium sulfate.

n-Butyllithium (16-18% in *n*-hexane solution) was obtained from Alfa Inorganics and was assayed prior to use.

Anhydrous ether was boiled under reflux over lithium aluminum hydride for 2-4 hr., distilled in a closed system, and then stored in a desiccator over calcium sulfate.

Anhydrous tetrahydrofuran was boiled under reflux for 10 hr. over lithium aluminum hydride, distilled in a closed system, and then stored in a desiccator over calcium sulfate.

All solvents for chromatographic separations were distilled prior to use.

Silica gel powder (Baker 3405; 60-200 mesh) was used for column chromatography.

5.2.0.0.0 The generation of pyridyl-1-oxide carbanions and their subsequent condensation with electrophilic reagents

General Procedure: In a dry nitrogen atmosphere n-butyllithium (1.28 g., 0.02 mole, in hexane solution) was added slowly to a stirred solution (or suspension) of the pyridine-1-oxide (0.01 mole) in anhydrous tetrahydrofuran (or ether) (40-70 ml.) at -65° (Dry-ice acetone bath). After stirring the resulting dark red or brown solution for 1 hr., a solution of the appropriate electrophile (0.02 mole) in anhydrous tetrahydrofuran (or ether) (10 ml.) was added dropwise. The reaction mixture was stirred for the desired length of time at -65°, and then allowed to warm up to room temperature. Water (30 ml.) was added and the reaction products were isolated as described in individual cases.

5.2.1.0.0 Reactions with halogens to give halopyridine-1-oxides

5.2.1.1.0 Reaction of pyridine-1-oxide carbanion with bromine

(a) In tetrahydrofuran-ether (1:1 v/v). Pyridine-1-oxide (0.95 g., 0.01 mole) in anhydrous tetrahydrofuran (20 ml.) and ether (20 ml.) was cooled to -65° in a

Dry-ice acetone bath. The flask was flushed with dry oxygen-free nitrogen and n-butyllithium (1.28 g., 0.02 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred (1 hr.), after which bromine (1.6 g., 0.02 mole) in anhydrous ether (10 ml.) was added. The reaction was allowed to proceed 15 min., and then phenol (0.6 g., 0.0062 mole) was added. After 5 min. the reaction mixture was allowed to warm up to room temperature and the solvent was removed in vacuo to yield a brown oil. This was dissolved in water (30 ml.) and made strongly alkaline with aqueous sodium hydroxide. Extraction with chloroform (3 x 50 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a sand colored oil which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), petroleum ether-benzene (4:1 v/v), and petroleum ether-benzene (1:1 v/v) gave a brown oil (70 mg.) which appeared to be aliphatic and was not investigated. Further elution with benzene yielded a sand colored solid (0.102 g., 4.0%). Recrystallization from acetone gave 2,6-dibromopyridine-1-oxide as a white solid, m.p. 187-188° (decomp.) [reported (70), m.p. 186.5-188.5° (decomp.)]. ν_{max} (KBr): 3120 (w), 3090 (w), 1525 (w), 1435 (s), 1355 (s), 1255 (s), 1155 (w), 1130 (w),

1105 (m), 1070 (w), 840 (m), 765 (s), 745 (s), 700 (w), and 635 cm^{-1} (w). N.m.r. (deuterochloroform) τ: 2.36 [2 H doublet ($J_{3,4}$ = 8 Hz), C_3-H, C_5-H]; 3.08 [1 H triplet ($J_{3,4}$ = 8 Hz), C_4-H]. Mass spectrum m/e: 255 (57), 253 (100) (M^+), 251 (60), 239 (5), 237 (8), 235 (5), 223 (3), 158 (22), 156 (23), 146 (42), 144 (42), 119 (11), 117 (11), 95 (11), 94 (10), 93 (98), 81 (3), 79 (3), 77 (10), 76 (27), 75 (7), 65 (16), 64 (20), 63 (32), 62 (16), 61 (7), 51 (10), 50 (21), 44 (7), 39 (19), 38 (16), 37 (8), 30 (4), 28 (7), 26 (5), 18 (36), and 17 (8). Elution with benzene-ether (3:1 v/v) and ether yielded a brown non-crystallizable oil (0.152 g.) containing halogen which appears to be a bromophenol. Further elution with ether-ethanol (5:1 v/v) yielded a brown semi-solid which, on crystallization from acetone, gave 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (0.071 g., 4.1%), m.p. 232-234° (decomp.). (Anal. Found: C, 35.16; H, 1.79. $C_{10}H_6Br_2N_2O_2$ requires: C, 34.71; H, 1.75). ν_{max} (KBr): 3110 (w), 3050 (w), 1415 (m), 1390 (w), 1355 (s), 1265 (s), 1250 (s), 1220 (w), 1170 (w), 1130 (w), 1070 (m), 960 (w), 840 (m), 765 (s), 730 (w), 720 (w), and 680 cm^{-1} (w). N.m.r. (deuteroacetic acid) τ: 2.3-2.55 (2 H multiplet, C_5-H, C_5'-H); 2.6-2.85 (4 H multiplet, C_3-H, C_4-H, C_3'-H, C_4'-H). Mass spectrum m/e: 348 (50), 346 (100) (M^+), 344 (54), 331 (18), 329 (34),

327 (18), 303 (20), 301 (38), 299 (20), 251 (11), 250 (61), 249 (23), 248 (63), 247 (14), 240 (20), 238 (23), 222 (48), 220 (48), 211 (12), 209 (32), 208 (12), 207 (16), 206 (11), 186 (16), 185 (14), 183 (14), 170 (23), 169 (16), 159 (13), 158 (64), 157 (16), 156 (64), 153 (16), 146 (11), 142 (30), 141 (25), 140 (11), 129 (16), 128 (48), 127 (13), 126 (25), 119 (20), 117 (20), 115 (20), 114 (27), 103 (27), 102 (27), 101 (18), 100 (12), 99 (11), 90 (11), 89 (7), 88 (16), 87 (16), 86 (9), 79 (16), 78 (18), 77 (46), 76 (73), 75 (21), 74 (20), 65 (12), 64 (25), 63 (41), 62 (27), 61 (9), 55 (11), 52 (14), 51 (56), 50 (50), 39 (63), 38 (27) and 28 (11).

(b) In tetrahydrofuran-ether (1:1 v/v) (In the absence of phenol). Pyridine-1-oxide (0.95 g., 0.01 mole) in anhydrous tetrahydrofuran (20 ml.) and ether (20 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry oxygen-free nitrogen and n-butyllithium (1.28 g., 0.01 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred (1 hr.), after which bromine (1.6 g., 0.02 mole) in anhydrous ether (10 ml.) was added. The reaction was allowed to proceed for 15 min. and the mixture was then warmed up to room temperature. The reaction mixture was then poured into water (50 ml.). Extraction with chloroform (5 x 30 ml.), drying (K_2CO_3),

and evaporation of the chloroform under reduced pressure gave a brownish-black viscous oil which was chromatographed on a 2.5 x 10 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v) gave a yellow aliphatic oil (20 mg.) containing halogens, which was not investigated. Further elution with benzene gave a white solid which, on recrystallization from acetone (10 ml.), gave 6,6'-dibromo-2,2'-dipyridyl-1-oxide (0.102 g., 6.2%) as white flakes, m.p. 209-211° (decomp.). (Anal. Found: C, 36.40; H, 1.83. $C_{10}H_6Br_2N_2O$ requires: C, 36.84; H, 1.82). ν_{max} (KBr): 3110 (w), 3060 (w), 1570 (w), 1550 (m), 1530 (w), 1425 (s), 1400 (m), 1360 (s), 1265 (s), 1160 (m), 1070 (s), 980 (w), 855 (w), 800 (w), 775 (s), 740 (w), 725 (w), and 695 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 0.98 [1 H quartet ($J_{4',5'}$ = 8 Hz, $J_{3',5'}$ = 1 Hz), C_5'-H]; 1.73 [1 H quartet ($J_{4,5}$ = 8 Hz, $J_{3,5}$ = 2 Hz), C_5-H]; 2.25 [1 H quartet ($J_{3,4}$ = 8 Hz, $J_{3,5}$ = 2 Hz), C_3-H]; 2.35 [1 H doublet (J = 8 Hz), C_4'-H]; 2.48 [1 H quartet ($J_{3',4'}$ = 8 Hz, $J_{3',5'}$ = 1 Hz), C_3'-H]; 2.85 [1 H triplet (J = 8 Hz), C_4-H]. Mass spectrum: 332 (33), 330 (68) (M^+), 328 (37), 316 (2), 314 (4), 312 (2), 304 (15), 302 (15), 300 (17), 251 (22), 249 (23), 235 (13), 233 (13), 223 (20), 222 (17), 221 (18), 220 (7), 197 (5), 196 (5), 194 (5), 185 (7), 183 (5), 171 (13), 170 (100), 169 (10), 158 (18), 156 (18),

154 (8), 153 (25), 148 (15), 146 (15), 143 (7), 142 (65), 141 (13), 140 (7), 127 (7), 126 (20), 119 (8), 117 (8), 116 (7), 115 (18), 114 (17), 113 (8), 103 (13), 102 (7), 100 (10), 99 (8), 90 (8), 88 (10), 87 (8), 77 (18), 76 (38), 75 (15), 74 (8), 65 (7), 64 (12), 63 (21), 62 (12), 52 (7), 51 (17), 50 (27), 39 (28), and 28 (8). Continued elution with benzene gave 2,6-dibromopyridine-1-oxide (0.078 g., 3.1%) as a white solid, m.p. 187-188° (decomp.), identical (I.R.) with the same sample obtained previously (5.2.1.1.0.a). Elution with chloroform gave a black semi-solid which, on trituration with acetone, gave 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (0.023 g., 1.3%) as a white solid, m.p. 230° (decomp.), identical (I.R.) with the sample obtained above (5.2.1.1.0.a). The aqueous fraction was made alkaline with potassium carbonate. Extraction with chloroform (5 x 30 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a yellow semi-solid which, on trituration with acetone, gave more 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide (0.12 g., 6.9%; overall yield 8.2%) as a white solid, identical (m.p. and I.R.) with that isolated above.

(c) In ether-hexamethylphosphoramide. Pyridine-1-oxide (0.95 g., 0.01 mole) in anhydrous ether (40 ml.) and hexamethylphosphoramide (3 ml.) was treated with

n-butyllithium (1.28 g., 0.02 mole), and then with bromine (1.6 g., 0.02 mole) for 15 minutes as outlined in 5.2.1.1.0.b. The reaction product was made alkaline with potassium carbonate. Extraction with chloroform (6 x 50 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a brown oil which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (2:1 v/v) gave a yellow non-crystallizable oil (0.5 g.) which was not further investigated. Further elution with benzene yielded a yellow oil which, on crystallization from acetone, gave 2,6-dibromopyridine-1-oxide (0.020 g., 0.8%) as white needles, m.p. 186° (decomp.), identical (I.R.) to that obtained in the previous section (5.2.1.1.0.a). Elution with ether-ethanol (5:1 v/v) gave an oil which, on trituration with acetone, yielded 6,6'-dibromo-2,2'-dipyridyl-1,1'-dioxide as needles (0.077 g., 1.15%), m.p. 229-232° (decomp.), whose infrared spectrum was identical to the sample obtained in the previous section (5.2.1.1.0.a).

5.2.1.2.0 Reaction of 4-methylpyridine-1-oxide carbanion and bromine

4-Methylpyridine-1-oxide (1.09 g., 0.01 mole) in anhydrous tetrahydrofuran (40 ml.) was treated with

n-butyllithium (1.28 g., 0.02 mole), and then with bromine (1.6 g., 0.02 mole) for 15 min. as described under 5.2.1.1.0.b. Extraction with chloroform (5 x 30 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a brown semi-solid which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether-benzene (2:1 v/v), and then benzene gave a brown oil (35 mg.) which was not examined. Further elution with benzene-ether (3:1 v/v) gave 6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1-oxide (0.321 g., 18.1%) as a white solid, m.p. 166-167°, after recrystallization from acetone. (Anal. Found: C, 40.54; H, 2.76; N, 7.78. $C_{12}H_{10}Br_2N_2O$ requires: C, 40.25; H, 2.81; N, 7.82). ν_{max} (KBr): 3110 (w), 3060 (w), 1570 (s), 1540 (s), 1420 (m), 1390 (s), 1375 (m), 1355 (s), 1290 (w), 1255 (s), 1205 (s), 1150 (s), 1065 (s), 1030 (m), 875 (m), 850 (m), 805 (s), 705 (w), 685 (s), and 620 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 1.18 (1 H singlet, C_5'-H); 2.04 [1 H doublet ($J_{3,5}$ = 3 Hz), C_5-H]; 2.52 [1 H doublet ($J_{3,5}$ = 3 Hz), C_3-H]; 2.68 (1 H singlet, C_3'-H); 7.6 (6 H singlet, Ar-CH_3). Mass spectrum: 360 (52), 358 (100) (M^+), 356 (54), 344 (2), 342 (4), 340 (2), 331 (7), 329 (13), 327 (6), 318 (3), 316 (6), 314 (3), 279 (19), 278 (5), 277 (19), 263 (9), 261 (9), 252 (2), 251 (15), 250 (7), 249 (18), 248 (6), 247 (3),

239 (2), 237 (3), 236 (3), 234 (3), 199 (7), 198 (20), 197 (8), 181 (3), 170 (11), 169 (16), 162 (8), 160 (8), 154 (3), and 77 (3). Elution with ether gave 2,6-dibromo-4-methylpyridine-1-oxide (0.122 g., 4.6%) as a white solid, m.p. 154-155°, after recrystallization from benzene. (Anal. Found: C, 27.25; H, 1.96. $C_6H_5Br_2NO$ requires: C, 27.0; H, 1.89). ν_{max} (KBr): 3055 (w), 1590 (w), 1505 (w), 1430 (w), 1405 (m), 1390 (s), 1245 (s), 1220 (m), 1150 (m), 1080 (w), 845 (m), 800 (s), 760 (s), and 690 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.50 (2 H singlet, C_3-H, C_5-H); 7.70 (3 H singlet, Ar-CH_3). Mass spectrum: 269 (48), 267 (100) (M^+), 265 (50), 253 (2), 251 (4), 249 (2), 172 (7), 170 (7), 160 (12), 158 (12), 133 (10), 131 (12), 108 (5), 107 (78), 91 (7), 90 (9), 79 (7), 78 (29), 77 (2), 76 (7), 75 (7), 74 (4), 64 (9), 63 (9), 62 (4), 53 (17), 52 (28), 51 (38), 50 (14), 39 (14), 38 (5), 37 (4), 30 (4), and 27 (7). Further elution with ether-ethanol (5:1 v/v), ether-ethanol (1:1 v/v), and ethanol gave a brown solid which, on crystallization from glacial acetic acid, gave 6,6'-dibromo-4,4'-dimethyl-2,2'-dipyridyl-1,1'-dioxide (0.237 g., 12.7%) as a white solid, m.p. 219-222° (decomp.). (Anal. Found: C, 38.73; H, 2.86. $C_{12}H_{10}Br_2N_2O_2$ requires: C, 38.53; H, 2.69). ν_{max} (KBr): 3050 (w), 1520 (w), 1395 (s), 1300 (w), 1240 (s), 1220 (m), 1070 (w), 865 (w), 805 (s),

685 (w), and 610 cm^{-1} (w). N.m.r. (CD_3CO_2D) τ: 2.5 [2 H doublet ($J_{3,5} = J_{3',5'} = 3$ Hz), C_5-H, C_5'-H]; 2.86 [2 H doublet ($J_{3,5} = J_{3',5'} = 3$ Hz), C_3-H, C_3'-H]; 7.92 (6 H singlet, Ar-CH_3). Mass spectrum m/e: 376 (51), 374 (100) (M^+), 372 (57), 359 (21), 357 (40), 355 (21), 344 (10), 342 (14), 340 (6), 331 (24), 329 (49), 327 (25), 279 (10), 278 (48), 277 (23), 276 (47), 275 (13), 264 (9), 263 (20), 262 (8), 261 (15), 253 (18), 251 (33), 250 (78), 249 (40), 248 (78), 247 (21), 237 (14), 236 (15), 235 (14), 234 (14), 224 (21), 223 (10), 222 (18), 221 (8), 220 (9), 214 (10), 211 (9), 209 (7), 199 (24), 198 (21), 197 (29), 173 (10), 172 (44), 171 (14), 170 (60), 169 (70), 168 (17), 162 (13), 160 (15), 156 (41), 155 (17), 154 (21), 153 (10), 152 (8), 143 (14), 142 (17), 141 (21), 140 (30), 139 (10), 133 (22), 131 (24), 130 (10), 129 (10), 128 (20), 127 (24), 126 (9), 125 (10), 117 (38), 116 (26), 115 (26), 114 (10), 113 (10), 107 (10), 104 (41), 103 (41), 102 (20), 101 (10), 93 (14), 92 (25), 91 (78), 90 (78), 89 (30), 88 (10), 87 (10), 78 (30), 77 (59), 76 (29), 75 (28), 74 (15), 69 (16), 66 (22), 65 (44), 64 (57), 63 (78), 62 (21), 53 (80), 52 (65), 51 (79), 50 (39), 43 (21), 42 (51), 40 (40), 38 (78), and 27 (52).

5.2.1.3.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion and bromine

(a) In tetrahydrofuran (3 hr.). 3,4-Lutidine-1-oxide (0.86 g., 0.007 mole) in anhydrous tetrahydrofuran (40 ml.) was treated with n-butyllithium (0.90 g., 0.014 mole), and then with bromine (1.12 g., 0.014 mole) for 3 hr. at -65° as described in 5.2.1.1.0.b. The reaction mixture was poured into water (40 ml.) containing an excess of sodium thiosulfate. Extraction with chloroform (5 x 40 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a brown semi-solid. Trituration of this semi-solid with acetone (3 x 10 ml.) gave a white crystalline solid (45 mg., 3.2%) which, on recrystallization from chloroform-acetone or glacial acetic acid, gave 6,6'-dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide as a white solid, m.p. 200-202° (decomp.). (Anal. Found: C, 42.03; H, 3.74; N, 6.71. $C_{14}H_{14}Br_2N_2O_2$ requires: C, 41.71; H, 3.51; N, 6.97). ν_{max} (KBr): 3050 (w), 1470 (w), 1435 (m), 1415 (m), 1380 (s), 1355 (s), 1285 (m), 1260 (s), 1235 (m), 1215 (m), 1170 (s), 1155 (m), 1025 (m), 880 (w), 815 (m), 755 (m), 685 (w), and 630 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.50 (1 H singlet, C_5'-H); 2.88 (1 H singlet, C_3-H); 7.58 (3 H singlet, Ar-CH_3); 7.74 (3 H singlet, Ar-CH_3); 7.82 (3 H singlet, Ar-CH_3); 8.04

(3 H singlet, Ar-CH_3). Mass spectrum m/e: 404 (3), 402 (7) (M^+), 400 (3), 387 (47), 385 (80), 383 (40), 381 (69), 379 (100), 377 (49), 357 (19), 355 (29), 353 (13), 307 (21), 306 (16), 305 (22), 292 (23), 291 (51), 290 (37), 289 (47), 288 (19), 287 (16), 277 (27), 275 (31), 265 (11), 264 (10), 263 (17), 262 (13), 261 (11), 226 (12), 211 (16), 209 (17), 207 (11), 201 (11), 197 (16), 195 (16), 193 (13), 188 (25), 186 (39), 184 (17), 131 (16), 123 (12), 115 (15), 107 (19), 106 (39), 105 (29), 104 (31), 103 (16), 97 (11), 94 (11), 92 (15), 91 (20), 90 (16), 89 (13), 85 (51), 83 (73), 82 (26), 78 (39), 77 (73), 67 (39), 66 (21), 65 (39), 64 (17), 63 (27), 53 (31), 52 (26), 51 (60), 47 (19), 44 (100), 43 (59), and 39 (74). The acetone soluble portion from above was chromatographed on a 2.5 x 25 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v), petroleum ether-benzene (1:2 v/v), and then benzene gave a trace amount of oil. Further elution with benzene-ether (2:1 v/v) gave 2,6-dibromo-3,4-dimethylpyridine-1-oxide (0.25 g., 12.8%) as a white solid, m.p. 144°, after recrystallization from acetone. (Anal. Found: C, 30.22; H, 2.52; N, 4.80. $C_7H_7Br_2NO$ requires: C, 29.92; H, 2.51; N, 4.98). ν_{max} (KBr): 3050 (w), 1575 (w), 1440 (m), 1410 (m), 1375 (m), 1345 (s), 1260 (s), 1225 (w), 1170 (s), 1155 (m), 1035 (m),

895 (w), 830 (w), 780 (s), 690 (w), and 660 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 2.62 (1 H singlet, C_5-H); 7.62 (3 H singlet, C_3-CH_3); 7.68 (3 H singlet, C_4-CH_3). Mass spectrum m/e: 283 (33), 281 (72) (M^+), 279 (39), 267 (7), 265 (16), 263 (8), 186 (16), 184 (18), 174 (17), 172 (18), 159 (4), 157 (5), 148 (7), 146 (10), 143 (2), 141 (5), 139 (3), 133 (3), 131 (5), 122 (4), 121 (42), 120 (5), 106 (5), 105 (12), 104 (18), 95 (9), 93 (30), 92 (47), 91 (20), 90 (10), 89 (11), 78 (22), 77 (29), 76 (10), 75 (9), 68 (13), 67 (55), 66 (60), 65 (100), 64 (13), 63 (26), 62 (7), 53 (15), 52 (26), 51 (57), 50 (23), 43 (15), 41 (40), 39 (80), and 28 (40). Further elution with ether-ethanol (1:1 v/v) gave a black semi-solid which was subjected to preparative thin-layer chromatography on silica gel plates (0.5 mm.) using benzene-ether-ethanol (3:9:1 v/v) as the developing solvent. Removal and extraction of the silica gel fraction (R_f 0.07) with chloroform gave a yellow oil. Trituration of this oil with acetone (10 ml.) gave 6,6'-dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide (15 mg., 1.1%), identical (I.R. and m.p.) to the material isolated previously. Extraction of the remaining silica gel with chloroform gave only a trace amount of oil.

(b) <u>In tetrahydrofuran (15 min.)</u>. 3,4-Lutidine-1-oxide (0.86 g., 0.007 mole) in anhydrous tetrahydrofuran

(40 ml.) was treated with n-butyllithium (0.90 g., 0.014 mole) and then with bromine (1.12 g., 0.014 mole) for 15 min. as outlined previously (5.2.1.1.0.a). Phenol (0.45 g., 0.0048 mole) in anhydrous tetrahydrofuran (2 ml.) was then added and the reaction was allowed to proceed for 3 min., after which the mixture was allowed to warm up slowly to room temperature. Water (25 ml.) was added. Extraction with chloroform (4 x 50 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a pale brown semi-solid which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), and then petroleum ether-benzene (1:1 v/v) gave a yellow semi-solid which did not contain nitrogen and was not further investigated. Further elution with benzene gave phenol (43 mg.). Elution with benzene-ether (3:1 v/v) gave 2,6-dibromo-3,4-dimethylpyridine-1-oxide (0.457 g., 23.3%), identical (I.R. and m.p.) with the same sample isolated above (5.2.1.3.0.a). Further elution with benzene-ether (1:1 v/v), and then with ether gave a small amount of a yellow semi-solid which was not examined further. Elution with ether-ethanol (5:1 v/v) gave a brown oil which, on trituration with acetone (8 ml.), gave 6,6'dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide (22 mg., 1.6%), identical (I.R. and m.p.) with

that isolated as described in 5.2.1.3.0.a. The acetone-soluble oil did not contain halogen and was not examined further.

(c) In tetrahydrofuran (15 min., excess bromine removed with phenol and nitrogen gas). 3,4-Lutidine-1-oxide (0.86 g., 0.007 mole) in anhydrous tetrahydrofuran (40 ml.) was treated with n-butyllithium (0.90 g., 0.014 mole), and then with bromine (1.12 g., 0.014 mole) for 15 min. as described previously (5.2.1.1.0.a). Phenol (0.45 g., 0.048 mole) in anhydrous tetrahydrofuran (2 ml.) was added, and the reaction was allowed to proceed for 5 min. Dry, oxygen-free nitrogen gas was then bubbled through the reaction mixture for 15 min. at -65° and for an additional 25 min. while warming to room temperature. Water (20 ml.) was then added. Extraction with chloroform (4 x 50 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a yellow oil which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave 2,6-dibromo-3,4-dimethylpyridine-1-oxide (0.175 g., 8.9%), identical (I.R. and m.p.) with the sample isolated under 5.2.1.3.0.a. Similarly, elution with ether-ethanol (5:1 v/v), and then trituration of the oil with acetone gave 6,6'-dibromo-3',4,4',5-tetramethyl-2,2'-dipyridyl-1,1'-dioxide (30 mg., 2.4%), identical (I.R. and m.p.) with

the sample obtained previously (5.2.1.3.0.a).

5.2.1.4.0 Reaction of 3,4-dimethylpyridine-1-oxide and bromine in the absence of n-butyllithium

3,4-Lutidine-1-oxide (0.86 g., 0.007 mole) in anhydrous tetrahydrofuran (40 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry, oxygen-free nitrogen, and then bromine (1.12 g., 0.014 mole) in anhydrous ether (10 ml.) was added slowly. The mixture was stirred for 15 min., and then phenol (0.45 g., 0.048 mole) in anhydrous tetrahydrofuran (2 ml.) was added. After 5 min. the mixture was allowed to come to room temperature. Removal of the tetrahydrofuran under reduced pressure gave a yellow semi-solid which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), petroleum ether-benzene (2:1 v/v), benzene, benzene-ether (3:1 v/v), and then ether gave a pale yellow semi-solid (0.212 g.) which did not contain nitrogen and was not investigated. Further elution with ether-ethanol (2:1 v/v), and then ethanol gave a pale brown crystalline solid (0.876 g.) which was identical (I.R.) with 3,4-lutidine-1-oxide hydrobromide. Treatment with aqueous sodium hydroxide gave 3,4-lutidine-1-oxide, m.p. 135°.

5.2.1.5.0 Reaction of pyridine-1-oxide carbanion with chlorine

Pyridine-1-oxide (0.95 g., 0.01 mole) in anhydrous tetrahydrofuran (20 ml.) and ether (20 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry, oxygen-free nitrogen and n-butyllithium (1.28 g., 0.02 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred (1 hr.), after which chlorine gas was bubbled slowly (30 ml./min.) for a period of 15 min. into the reaction mixture. The reaction mixture was stirred at -65° for an additional 15 minutes, and was then allowed to warm up slowly to room temperature. Water (30 ml.) was added, and the acidic reaction mixture was made basic with potassium carbonate. Extraction with chloroform (5 x 30 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a brown viscous oil which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (2:1 v/v), and then benzene gave a yellow aliphatic oil (80 mg.) which appeared to be n-butyl chloride. Further elution with benzene-ether (3:1 v/v) gave a pale brown solid. Recrystallization from acetone yielded 2,6-dichloropyridine-1-oxide (74 mg., 4.5%) as a white solid, m.p. 139-140° [reported (71), m.p. 139.5-140.5°].

ν_{max} (KBr): 3110 (w), 3090 (w), 1530 (w), 1445 (s), 1360 (s), 1265 (s), 1155 (m), 1145 (s), 845 (m), 820 (s), 765 (s), and 705 cm^{-1} (w). N.m.r. ($CDCL_3$) τ: 2.56 [2 H doublet ($J_{3,4}$ = 8 Hz), C_3-H, C_5-H]; 2.92 [1 H triplet ($J_{3,4}$ = 8 Hz), C_4-H]. Mass spectrum: 167 (18), 165 (22), 163 (46) (M^+), 151 (3), 149 (12), 147 (21), 134 (10), 133 (10), 128 (7), 114 (18), 112 (61), 110 (21), 109 (7), 108 (31), 107 (7), 104 (7), 102 (97), 100 (43), 99 (11), 97 (25), 93 (86), 87 (10), 86 (8), 85 (25), 84 (7), 83 (10), 76 (87), 75 (71), 74 (44), 73 (99), 72 (25), 65 (17), 64 (26), 63 (100), 62 (74), 61 (43), 60 (14), 52 (7), 51 (65), 50 (77), 49 (98), 48 (11), 47 (24), 43 (35), 39 (100), 38 (57), 37 (49), 36 (15), 35 (18), 30 (35), and 28 (22). Further elution with ether and ether-ethanol (5:1 v/v) gave a black semi-solid. Attempted purification and separation of this fraction did not give rise to any characterizable product.

5.2.1.6.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with chlorine

3,4-Lutidine-1-oxide (0.86 g., 0.01 mole) in anhydrous tetrahydrofuran (40 ml.) was treated with n-butyllithium (1.28 g., 0.02 mole), and then with chlorine gas as described previously (5.2.1.5.0). Phenol (0.5 g., 0.0053 mole) was added, and the reaction mixture was

allowed to warm up to room temperature. The reaction mixture was poured into water (25 ml.), and the resulting acidic solution was made alkaline with potassium carbonate. Extraction with chloroform (5 x 30 ml.), drying (K_2CO_3), and evaporation of the chloroform under reduced pressure gave a black semi-solid which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), petroleum ether-benzene (1:1 v/v), and benzene gave a brown aliphatic semi-solid (0.364 g.) which did not contain nitrogen. This material was not investigated further. Elution with benzene-ether (3:1 v/v) yielded a brown semi-solid (0.136 g.). Recrystallization from acetone gave 2,6-dichloro-3,4-dimethylpyridine-1-oxide (0.117 g., 8.8%) as a white solid, m.p. 165-166°. (Anal. Found: C, 44.21; H, 3.74. $C_7H_7Cl_2NO$ requires: C, 43.78; H, 3.67). ν_{max} (KBr): 3120 (w), 1455 (m), 1420 (m), 1385 (m), 1365 (s), 1275 (s), 1195 (s), 1170 (m), 1050 (m), 905 (w), 860 (w), 830 (s), and 700 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 2.75 (1 H singlet, C_5-H); 7.62 (3 H singlet, C_3-CH_3); 7.68 (3 H singlet, C_4-CH_3). Mass spectrum: 195 (10), 193 (66), 191 (100) (M^+), 177 (6), 175 (7), 140 (7), 130 (16), 129 (5), 128 (21), 103 (7), 101 (6), 100 (12), 93 (6), 92 (17), 91 (6), 89 (7), 87 (11), 77 (10), 75 (7), 73 (6), 67 (31), 66 (7), 65 (34),

63 (10), 51 (19), 50 (8), 43 (10), 41 (11), 39 (19), 28 (5), and 27 (7). Further elution with ether, and ether-ethanol (5:1 v/v) gave a brown semi-solid (0.323 g.). Attempted separation and purification of this fraction did not yield any characterizable product.

5.2.2.0.0 Reactions with sulfur to give 1-hydroxy-2-pyridinethiones

5.2.2.1.0 Reaction of pyridine-1-oxide carbanion with sulfur

(a) In tetrahydrofuran (-65°). Pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry oxygen-free nitrogen and n-butyl-lithium (2.56 g., 0.04 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred (1 hr.), after which sulfur (1.28 g., 0.04 g. atom) was added. The reaction was allowed to proceed for 30 minutes and then the mixture allowed to come to room temperature. It was then poured into water (40 ml.), and acidified to pH 2 with 18% hydrochloric acid. Extraction with chloroform (8 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a black semi-solid which was extracted with hot 95% ethanol (60 ml.). A brown plastic-like solid (1.9 g.) was

insoluble and was filtered. Attempted separation and identification of this solid did not give any characterizable products. Evaporation of the ethanol solution yielded a brown solid which was chromatographed on a 2.5 x 60 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), and then petroleum ether-benzene (2:1 v/v) gave a yellow oil (36 mg.) which was not examined. Further elution with petroleum ether-benzene (1:1 v/v) gave 1-hydroxy-2-pyridinethione (0.20 g., 7.9%). Recrystallization from ethanol yielded a white solid, m.p. 68° [reported (18), m.p. 68-70°]. ν_{max} (KBr): 3120 (m), 2650 (w), 1610 (m), 1580 (s), 1500 (s), 1460 (s), 1375 (s), 1265 (s), 1140 (s), 1115 (m), 1085 (m), 1030 (w), 1015 (w), 810 (s), 750 (s), 710 (s), 690 (s), 580 (m), 565 (w), 530 (s), 510 (m), and 415 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 1.93 [1 H doublet ($J_{5,6}$ = 7 Hz) of doublets ($J_{4,6}$ = 1.50 Hz) of doublets ($J_{3,6}$ = 0.75 Hz), C_6-H]; 2.37 [1 H doublet ($J_{3,4}$ = 8.5 Hz) of doublets ($J_{3,5}$ = 1.75 Hz) of doublets ($J_{3,6}$ = 0.75 Hz), C_3-H]; 2.74 [1 H doublet ($J_{3,4}$ = 8.5 Hz) of doublets ($J_{4,5}$ = 7 Hz) of doublets ($J_{4,6}$ = 1.50 Hz), C_4-H]; 3.23 [1 H doublet ($J_{5,6}$ = 7 Hz) of doublets ($J_{4,5}$ = 7 Hz) of doublets ($J_{3,5}$ = 1.75 Hz), C_5-H]; -1.6 (1 H broad singlet, hydroxyl, disappears on addition of D_2O). Further elution with benzene, benzene-ether (1:1 v/v),

and then ether gave a black tar (0.345 g.) which could not be characterized.

(b) In ether (room temperature). Pyridine-1-oxide (1.9 g., 0.02 mole) suspended in anhydrous ether (75 ml.) was cooled to -65° in a Dry-ice acetone bath, and the flask was flushed with dry oxygen-free nitrogen. n-Butyllithium (2.56 g., 0.04 mole) was added slowly and the resulting mixture was stirred for 20 minutes, after which it was allowed to warm up to room temperature during 30 minutes. Sulfur (1.28 g., 0.04 g. atom) was added and the reaction was allowed to proceed for 30 minutes. Water (30 ml.) was then added and the sulfur which precipitated (0.40 g.) m.p. 118°, was filtered. The reaction mixture was acidified to pH 2 with 18% hydrochloric acid. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown oil which was extracted with hot ethanol (60 ml.). A brown plastic-like solid (0.205 g.), similar to that obtained in 5.2.2.1.0.a, was insoluble and was filtered. Evaporation of the ethanol gave a brown semi-solid which was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°) gave a yellow aliphatic oil (0.40 g.) which did not contain nitrogen. This fraction was not examined. Further elution with

benzene gave a brown oil. Extraction of this oil with 20% aqueous sodium hydroxide (10 ml.), acidification of the aqueous alkaline fraction, and then extraction with chloroform (3 x 30 ml.) gave a dull green solid. Sublimation (50°/0.1 mm.) gave 1-hydroxy-2-pyridinethione (0.256 g., 10.1%) as a white solid, m.p. 68°, identical (I.R.) to the sample obtained in 5.2.2.1.0.a. Further elution with ether, and then methanol gave intractable tar (1.24 g.). The aqueous acidic reaction product was made alkaline with sodium hydroxide. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave unreacted pyridine-1-oxide (0.20 g.).

5.2.2.1.1 Attempted reaction of 1-hydroxy-2-pyridinethione with 2,4-dinitrochlorobenzene

Sodium hydroxide in water (1 ml. of a 10% solution) was added slowly with stirring to a solution of 1-hydroxy-2-pyridinethione (0.27 g., 0.002126 mole) in 95% ethanol (5 ml.). 2,4-Dinitrochlorobenzene (0.429 g., 0.002126 mole) in ethanol (5 ml.) was then added with stirring and the mixture boiled under reflux for 40 minutes. After cooling, the solvent was removed in vacuo to give a brown semi-solid which was chromatographed on a neutral

2.5 x 20 cm. alumina column. Elution with 95% ethanol, and then recrystallization from the same solvent gave the sodium salt of 2,4-dinitrophenol (0.39 g.) as yellow crystals, m.p. > 295°. The infrared spectrum was identical to that of an authentic sample.

5.2.2.2.0 Reaction of 4-methylpyridine-1-oxide carbanion with sulfur

Using the procedure outlined under 5.2.2.1.0.a, 4-methylpyridine-1-oxide (2.18 g., 0.02 mole), n-butyllithium (2.56 g., 0.04 mole), and sulfur (1.28 g., 0.04 g. atom) gave a black semi-solid which was extracted with hot ethanol (60 ml.). A brown plastic-like solid (1.22 g.) was insoluble and was filtered. Attempted purification and identification of this solid did not yield any characterizable product. Evaporation of the ethanol gave an orange semi-solid which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v), and benzene yielded a sandy solid (1.092 g., 38.7%). Recrystallization from ethanol gave 1-hydroxy-4-methyl-2-pyridinethione as a white solid, m.p. 59° [reported (18), m.p. 59-61°]. N.m.r. ($CDCl_3$) τ: 2.1 [1 H doublet, ($J_{5,6}$ = 7 Hz), C_6-H]; 2.54 [1 H doublet ($J_{3,5}$ = 2 Hz), C_3-H]; 3.46 [1 H quartet ($J_{5,6}$ = 7 Hz),

($J_{3,5}$ = 2 Hz), C_5-H]; 7.76 (3 H singlet, Ar-CH_3); -1.8 (1 H broad singlet, hydroxyl, exchanges readily with deuterium oxide). ν_{max} (KBr): 3110 (w), 3060 (w), 3030 (m), 2850 (w), 1610 (m), 1550 (s), 1460 (s), 1430 (m), 1380 (m), 1285 (m), 1245 (w), 1205 (w), 1190 (s), 1145 (m), 1080 (m), 1040 (w), 895 (m), 855 (m), 785 (s), 710 (m), 580 (m), 540 (s), and 425 cm^{-1} (m). Mass spectrum m/e: 142 (14), 141 (100) (M^+), 125 (13), 124 (15), 123 (3), 97 (25), 96 (6), 95 (3), 93 (40), 92 (16), 83 (6), 81 (8), 80 (22), 78 (4), 71 (3), 70 (3), 69 (7), 66 (14), 65 (18), 58 (5), 57 (6), 54 (3), 53 (26), 52 (5), 51 (10), 50 (6), 45 (18), 44 (3), 41 (4), 40 (4), 39 (40), 38 (6), 37 (3), and 28 (9). Further elution with benzene-ether (3:1 v/v) gave a black tar (0.6 g.) which was not investigated further.

5.2.2.3.0 Reaction of 4-chloro-3-methylpyridine-1-oxide carbanion with sulfur

Following the procedure described in 5.2.2.1.0.a, 4-chloro-3-picoline-1-oxide (2.86 g., 0.02 mole), n-butyllithium (2.56 g., 0.04 mole), and sulfur (1.28 g., 0.04 g. atom) yielded a brown semi-solid which was extracted with hot ethanol (80 ml.). A brown plastic-like solid (1.006 g.) was insoluble and was filtered. Attempted purification and characterization of this

solid did not give any identifiable products. The ethanol soluble portion was concentrated *in vacuo* to give a semi-solid which was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°) gave sulfur (115 mg.), m.p. 117°. Further elution with petroleum ether-benzene (1:1 v/v) gave a brown semi-solid which, on recrystallization from 95% ethanol, gave 1-hydroxy-4-chloro-3-methyl-6-pyridinethione (0.395 g., 11.45%) as a yellow solid, m.p. 99-101°. ν_{max} (KBr): 3100 (m), 2750 (w), 1600 (m), 1550 (s), 1480 (m), 1440 (s), 1420 (s), 1360 (s), 1240 (s), 1180 (w), 1165 (s), 1130 (m), 1035 (s), 955 (s), 815 (s), 795 (s), 705 (m), 580 (m), 555 (s), 500 (w), and 445 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.1 (1 H singlet, C_2-H); 2.36 (1 H singlet, C_5-H); 7.74 (3 H singlet, Ar-CH_3); 0.1 (1 H broad singlet, hydroxyl, exchanges readily with D_2O). Mass spectrum m/e: 177 (37), 176 (9), 175 (100) (M^+), 161 (4), 160 (6), 159 (11), 158 (13), 133 (4), 131 (13), 129 (7), 127 (19), 126 (4), 123 (8), 122 (4), 115 (4), 96 (4), 95 (6), 69 (4), 51 (4), and 44 (6). Further elution with benzene, benzene-ether (3:1 v/v), ether, ether-ethanol (4:1 v/v), and then ethanol gave intractable products (1.83 g.).

A solution of 1-hydroxy-4-chloro-3-methyl-6-pyridinethione (87.5 mg., 0.0005 mole) in 0.5 N sodium

hydroxide (1 ml., 0.0005 mole), and a solution of zinc chloride (34 mg., 0.00025 mole) in water (3 ml.) were mixed. The white solid which precipitated immediately was filtered and washed with water (5 ml.), ethanol (5 ml.), and ether (5 ml.). Recrystallization from dioxan (25 ml.) gave the zinc salt of 1-hydroxy-4-chloro-3-methyl-6-pyridinethione (89 mg., 86%) as fine white crystals, m.p. 292-294° (decomp.). (Anal. Found: C, 34.99; H, 2.69. $C_{12}H_{10}Cl_2N_2O_2S_2Zn$ requires: C, 34.77; H, 2.43). ν_{max} (KBr): 3080 (m), 1580 (m), 1525 (m), 1420 (m), 1370 (s), 1250 (s), 1240 (s), 1230 (m), 1190 (m), 1160 (w), 1130 (s), 1030 (m), 960 (w), 810 (s), 715 (s), 705 (s), 615 (w), 590 (w), and 460 cm^{-1} (w). Mass spectrum m/e: 418 (15), 416 (34), 414 (46) (M^+), 401 (21), 400 (51), 399 (38), 398 (70), 397 (40), 396 (51), 395 (25), 384 (17), 382 (23), 380 (19), 242 (34), 240 (53), 238 (53), 226 (23), 225 (19), 224 (34), 223 (21), 222 (36), 221 (21), 174 (21), 173 (17), 172 (13), 161 (27), 160 (40), 159 (100), 158 (93), 157 (76), 126 (49), 124 (21), 123 (23), 122 (95), 114 (23), 113 (23), 112 (36), 99 (27), 96 (31), 95 (37), 91 (23), 90 (36), 78 (30), 65 (34), 64 (30), 63 (59), 51 (32), 45 (42), 44 (53), 39 (63), and 28 (67).

5.2.2.4.1 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with sulfur

(a) In tetrahydrofuran at -65°. Using the general procedure outlined under 5.2.2.1.0.a, 3,4-lutidine-1-oxide (2.46 g., 0.02 mole), n-butyllithium (2.56 g., 0.04 mole), and sulfur (1.28 g., 0.04 g. atom) gave a yellow solid which was extracted with warm ethanol (60 ml.). 2,2'-(1,1'-Dihydroxy-4,4',5,5'-tetramethyl-dipyridyl-6,6'-dithione)disulfide (1.39 g., 37.4%) was insoluble and was filtered. Recrystallization from chloroform gave yellow crystals, m.p. 186-187°. (Anal. Found: C, 45.25; H, 4.24. $C_{14}H_{16}N_2O_2S_4$ requires: C, 45.14; H, 4.33). ν_{max} (KBr): 3050 (w), 2945 (w), 2910 (w), 2325 (w), 1570 (m), 1550 (m), 1490 (s), 1440 (s), 1410 (s), 1380 (s), 1355 (s), 1245 (s), 1220 (w), 1200 (m), 1155 (m), 1020 (m), 985 (w), 860 (m), 840 (w), 805 (m), 670 (m), 605 (w), 580 (w), 550 (w), 530 (w), and 485 cm^{-1} (w). N.m.r. (pyridine-d_5) τ: 2.94 (2 H singlet, C_3-H, C_3'-H); 7.50 (6 H singlet, Ar-CH_3); 8.1 (6 H Ar-CH_3). M (osmometer), 370. Calcd. for $C_{14}H_{16}N_2O_2S_4$, 372.

Evaporation of the alcohol from the alcoholic extract above gave a yellow solid which was chromatographed on a 2.5 x 60 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), and then petroleum

ether-benzene (1:1 v/v) gave sulfur (50 mg.) m.p. 118°. Further elution with petroleum ether-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.388 g., 12.5%). Recrystallization from benzene and then sublimation (125°/1.75 mm.) gave a white solid, m.p. 128-129°. (Anal. Found: C, 54.18; H, 5.96. C_7H_9NOS requires: C, 54.18; H, 5.84). ν_{max} (KBr): 3100 (m), 3090 (m), 2980 (m), 2925 (m), 2700 (m), 1610 (m), 1560 (s), 1480 (s), 1440 (s), 1375 (s), 1260 (m), 1235 (s), 1180 (s), 1105 (m), 1045 (s), 1020 (m), 950 (m), 845 (s), 790 (s), 750 (w), 615 (s), 550 (s), 500 (w), and 435 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 2.12 [1 H doublet ($J_{5,6}$ = 6 Hz), C_6-H]; 3.44 [1 H doublet ($J_{5,6}$ = 6 Hz), C_5-H]; 7.58 (3 H singlet, Ar-CH_3); 7.74 (3 H singlet, Ar-CH_3); -2.35 (1 H broad singlet, hydroxyl, exchanges with deuterium oxide). Mass spectrum m/e: 157 (4), 156 (9), 155 (100) (M^+), 140 (6), 139 (29), 138 (84), 137 (9), 136 (10), 111 (3), 107 (6), 106 (14), 104 (10), 103 (3), 95 (5), 94 (18), 93 (9), 92 (35), 80 (6), 79 (12), 78 (9), 77 (18), 69 (6), 67 (5), 65 (11), 53 (11), 52 (6), 51 (11), 50 (4), 45 (10), 41 (4), 39 (15), 36 (7), and 28 (6). Continued elution with petroleum ether-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.748 g., 24.1%). Recrystallization from benzene and then sublimation (125°/1.75 mm.) gave a white solid,

m.p. 121-122°. (Anal. Found: C, 53.85; H, 5.86. C_7H_9NOS requires: C, 54.18; H, 5.84). ν_{max} (KBr): 3110 (w), 3040 (m), 2840 (m), 1620 (m), 1540 (s), 1460 (s), 1440 (s), 1390 (m), 1350 (s), 1260 (m), 1210 (m), 1180 (m), 1150 (s), 1030 (s), 1000 (s), 845 (m), 795 (m), 730 (w), 645 (s), 595 (m), 560 (m), 545 (m), 470 (w), and 420 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.22 (1 H singlet, C_2-H); 2.64 (1 H singlet, C_5-H); 7.84 (3 H singlet, Ar-CH_3); 7.87 (3 H singlet, Ar-CH_3); -0.47 (1 H broad singlet, hydroxyl, exchanges readily with D_2O). Mass spectrum m/e: 157 (5), 156 (18), 155 (100) (M^+), 141 (10), 139 (11), 138 (20), 125 (13), 123 (9), 111 (18), 110 (6), 107 (29), 106 (12), 97 (6), 95 (4), 94 (12), 93 (6), 92 (7), 83 (4), 81 (6), 80 (11), 79 (11), 78 (5), 77 (11), 71 (4), 70 (4), 69 (6), 68 (3), 67 (17), 66 (5), 65 (14), 63 (4), 58 (4), 53 (14), 52 (4), 51 (11), 50 (4), 45 (14), 44 (5), 43 (4), 41 (11), 39 (32), 31 (6), and 28 (14).

Using the procedure outlined in 5.2.2.3.0, 1-hydroxy-3,4-dimethyl-2-pyridinethione (77.5 mg., 0.0005 mole), sodium hydroxide (1 ml., 0.0005 mole), and zinc chloride (34 mg., 0.00025 mole) yielded the zinc salt of 1-hydroxy-3,4-dimethyl-2-pyridinethione (93 mg., 98.4%) as fine yellow crystals, m.p. 283-285° (decomp.), after recrystallization from dioxan (25 ml.). (Anal. Found:

C, 44.54; H, 4.28. $C_{14}H_{16}N_2O_2S_2Zn$ requires: C, 44.99; H, 4.31). ν_{max} (KBr): 3090 (m), 3070 (m), 2980 (w), 2915 (w), 1610 (w), 1550 (m), 1460 (s), 1400 (s), 1245 (s), 1220 (s), 1180 (s), 1165 (w), 1045 (s), 1020 (m), 960 (w), 835 (w), 810 (s), 760 (m), 615 (s), and 480 cm^{-1} (m). Mass spectrum m/e: 376 (38), 374 (35), 372 (52) (M^+), 360 (52), 359 (35), 358 (60), 357 (42), 356 (86), 355 (44), 344 (15), 342 (22), 340 (30), 229 (8), 222 (19), 221 (15), 220 (28), 219 (16), 218 (42), 206 (13), 205 (12), 204 (22), 203 (13), 202 (30), 201 (15), 155 (7), 154 (21), 153 (15), 152 (16), 140 (19), 139 (100), 138 (100), 137 (100), 136 (41), 125 (10), 123 (15), 107 (32), 106 (86), 104 (23), 95 (12), 94 (26), 93 (28), 92 (46), 91 (12), 80 (16), 79 (45), 78 (29), 77 (61), 67 (13), 66 (13), 65 (41), 64 (10), 53 (22), 52 (19), 51 (28), 45 (16), 44 (45), 41 (16), 39 (38), and 28 (64).

Following the procedure described in 5.2.2.3.0, 1-hydroxy-3,4-dimethyl-6-pyridinethione (77.5 mg., 0.0005 mole), sodium hydroxide (1 ml., 0.0005 mole), and zinc chloride (34 mg., 0.00025 mole) gave the zinc salt of 1-hydroxy-3,4-dimethyl-6-pyridinethione (93 mg., 98.4%) as fine white crystals, m.p. > 300°, after recrystallization from dioxan. (Anal. Found: C, 44.57; H, 4.56. $C_{14}H_{16}N_2O_2S_2Zn$ requires: C, 44.99; H, 4.31). ν_{max} (KBr): 3030 (w), 2960 (w), 2919 (w), 1600 (m),

1505 (m), 1460 (s), 1430 (m), 1365 (w), 1340 (m), 1275 (w), 1262 (m), 1220 (w), 1195 (w), 1160 (s), 1035 (m), 1000 (w), 865 (m), 800 (m), 735 (w), 650 (m), 607 (w), and 510 cm^{-1} (m). Mass spectrum m/e: 376 (29), 374 (41), 372 (66) (M^+), 360 (24), 358 (38), 356 (55), 344 (5), 342 (7), 340 (10), 244 (14), 243 (67), 222 (13), 220 (21), 218 (33), 206 (45), 204 (36), 202 (55), 154 (19), 139 (45), 138 (28), 111 (9), 107 (17), 106 (100), 95 (13), 94 (21), 79 (41), 77 (29), 67 (16), 65 (10), 53 (14), 51 (10), 44 (14), 41 (13), 39 (24), and 28 (13). Further elution with benzene-ether (3:1 v/v) gave a trace of product which was not investigated.

(b) In ether at room temperature. Using the procedure described previously (5.2.2.1.0.b), 3,4-lutidine-1-oxide (1.23 g., 0.01 mole), n-butyllithium (1.28 g., 0.02 mole), and sulfur (0.64 g., 0.02 g. atom) gave a yellow solid which was extracted with warm ethanol (25 ml.). The yellow insoluble solid was filtered and recrystallized from chloroform to give 2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)-disulfide (0.392 g., 21.1%), as yellow crystals, m.p. 186-187°, identical (I.R.) with the product isolated above (5.2.2.4.1.a). Evaporation of the ethanol gave a yellow solid which was chromatographed on a 2.5 x 58 cm. silica gel column. Elution with petroleum ether

(b.p. 30-60°) gave sulfur (30 mg.). Further elution with petroleum ether-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.123 g., 7.9%) as yellow needles, m.p. 126-127°, identical (I.R. and n.m.r.) with the product isolated in 5.2.2.4.1.a. Elution with benzene gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.113 g., 7.3%) as yellow needles, m.p. 120-121°, identical (I.R. and n.m.r.) with the product obtained previously (5.2.2.4.1.a). Further elution with ether gave a black tar (0.452 g.) which could not be purified or characterized. Elution with methanol gave 3,4-lutidine-1-oxide (0.205 g.). The acidic solution was basified with sodium hydroxide. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave unreacted 3,4-lutidine-1-oxide (0.202 g.).

5.2.2.4.2 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with sulfur monochloride

Following the procedure outlined in 5.2.2.1.0.a, 3,4-lutidine-1-oxide (1.23 g., 0.01 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.28 g., 0.02 mole), and then with sulfur monochloride (0.844 g., 0.00625 mole) in anhydrous tetrahydrofuran (10 ml.) for 30 minutes. The reaction mixture was

allowed to warm up to room temperature, and water (60 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a black oil (0.96 g.) which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°), and then petroleum ether-benzene (1:2 v/v) gave a yellow oil (0.096 g.) which did not contain nitrogen, and was not examined further. Further elution with benzene and benzene-ether (3:1 v/v) gave a black oil (90 mg.) which was not investigated. Elution with methanol gave a black solid which, on crystallization from acetone, gave 3,4-lutidine-1-oxide (0.104 g.), identical (I.R.) with an authentic sample. Extraction of the silica gel in a Soxhlet extractor with methanol for 6 hr. gave a negligible amount of a black tar. The aqueous alkaline reaction product was made acidic with 18% hydrochloric acid. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown oil which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:2 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.072 g., 4.6%) as yellow needles, m.p. 126-127°, identical (I.R.) with the sample obtained under

5.2.2.4.1.a. Continued elution with petroleum ether-benzene (1:2 v/v), and then benzene gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.116 g., 7.5%) as a yellow solid, m.p. 120-121°, identical (I.R.) with the material isolated in 5.2.2.4.1.a. Elution with ether gave a black tar (0.098 g.) which was not characterized.

5.2.2.4.3 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with ethylene sulfide

3,4-Lutidine-1-oxide (2.46 g., 0.02 mole) suspended in anhydrous ether (70 ml.) was treated with n-butyl-lithium (2.56 g., 0.04 mole), and then with ethylene sulfide (2.4 g., 0.04 mole) in anhydrous ether (25 ml.) for 2 hr. as described in 5.2.2.1.0.b. Water (100 ml.) was added and the reaction product was acidified to pH 2 with 18% hydrochloric acid. The white ethylene sulfide polymer (2.01 g.) which precipitated out of solution was filtered. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown oil which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:2 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.24 g., 7.7%) as yellow needles, m.p. 126-127°, identical (I.R.) with the same material isolated in

5.2.2.4.1.a. Continued elution with petroleum ether-benzene (1:2 v/v), and then benzene gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.343 g., 11%) as a yellow solid, m.p. 127-128°, after recrystallization from benzene. Elution with ether and then ethanol gave a black tar (0.43 g.) which was not investigated further.

5.2.2.4.4 Attempted acetylation of 1-hydroxy-3,4-dimethyl-6-pyridinethione

1-Hydroxy-3,4-dimethyl-6-pyridinethione (0.41 g., 0.00264 mole) in acetic anhydride (3.6 g., 0.03528 mole), and concentrated sulfuric acid (2 drops) were boiled gently under reflux (1 hr.). Water (20 ml.) was added to the cooled mixture which was then made alkaline with 20% aqueous sodium hydroxide. Extraction of the black oily reaction product with ether (4 x 50 ml.), drying (Na_2SO_4), and evaporation of the ethereal extract under reduced pressure gave a black semi-solid (0.218 g.). A black ether-insoluble solid (0.25 g.) was filtered from the aqueous reaction mixture. These combined products were chromatographed on a 2.5 x 22 cm. alumina column. Elution with benzene and then benzene-ether (3:1 v/v) gave a brown oil (0.225 g.) consisting of six components which were not investigated. Further elution with ether-ethanol (5:1 v/v) gave a brown oil (0.125 g.)

consisting of 7 components as shown by gas chromatography. These products were not examined.

5.2.2.4.5 Attempted reaction of 1-hydroxy-3,4-dimethyl-6-pyridinethione with o-nitrochlorobenzene

1-Hydroxy-3,4-dimethyl-6-pyridinethione (0.1 g., 0.0006452 mole) was added with stirring to a solution of sodium ethoxide (14.8 mg. sodium in 2 ml. ethanol, 0.0006452 mole). o-Nitrochlorobenzene (0.102 g., 0.0006452 mole) in absolute ethanol (3 ml.) was added and the resulting cloudy solution was stirred (18 hr.) at room temperature. Water (75 ml.) was then added. Extraction with chloroform (5 x 30 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave o-nitrochlorobenzene (0.1 g.). The aqueous alkaline reaction mixture was acidified with 18% hydrochloric acid. Extraction with chloroform (4 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave unreacted 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.098 g.), identical (I.R.) with the starting material.

5.2.2.4.6 Reduction of 2,2'-(1,1'-dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)disulfide

2,2'-(1,1'-Dihydroxy-4,4',5,5'-tetramethyldipyridyl-6,6'-dithione)disulfide (1.0 g.) was added slowly over a period of 10 min. to a stirred suspension of lithium aluminum hydride (0.076 g., 0.002 mole) in dry tetrahydrofuran (25 ml.). Hydrogen was rapidly evolved. The reaction mixture was stirred (1 hr.) at room temperature and then boiled under reflux for 30 minutes. It was cooled to 0°, and water (20 ml.) was added cautiously. The resulting green suspension was acidified to pH 2 with 18% hydrochloric acid and diluted to a volume of 150 ml. with water. Extraction with chloroform (3 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione (0.99 g., 98.5%) as yellow needles, m.p. 120-122°, after recrystallization from carbon tetrachloride. (Anal. Found: C, 45.29; H, 5.02. $C_7H_9NOS_2$ requires: C, 44.89; H, 4.84). ν_{max} (KBr): 3030 (w), 2950 (w), 2900 (w), 2350 (m), 1530 (s), 1450 (m), 1400 (s), 1350 (m), 1330 (s), 1260 (s), 1230 (m), 1210 (m), 1160 (w), 1055 (m), 1025 (m), 1000 (w), 855 (s), 835 (s), 810 (m), 695 (w), 670 (s), 640 (s), 590 (w), and 450 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 3.32 (1 H singlet, C_5-H); 7.75 (3 H singlet, Ar-CH_3); 7.81 (3 H

singlet, Ar-CH_3); 1.32 (2 H broad singlet, sulfhydro and hydroxyl, exchanges readily with deuterium oxide). Mass spectrum m/e: 189 (4), 188 (3), 187 (46) (M^+), 171 (76), 170 (55), 155 (7), 152 (5), 143 (11), 139 (21), 138 (21), 137 (8), 136 (27), 127 (20), 126 (11), 122 (7), 121 (11), 119 (31), 117 (31), 112 (5), 111 (4), 109 (7), 106 (7), 104 (8), 97 (8), 95 (14), 94 (15), 92 (8), 91 (7), 82 (9), 80 (20), 79 (7), 78 (7), 77 (15), 69 (11), 67 (17), 66 (7), 65 (14), 60 (9), 59 (8), 58 (7), 55 (11), 53 (16), 51 (15), 47 (8), 45 (29), 44 (16), 43 (15), 41 (24), 39 (35), 36 (30), 35 (8), 34 (20), 33 (9), 32 (20), and 28 (100).

Following the procedure described in 5.2.2.3.0, 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione (93.5 mg., 0.0005 mole), sodium hydroxide (1 ml., 0.0005 mole), and zinc chloride (34 mg., 0.00025 mole) gave a zinc salt of 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione as a dull yellow solid (80 mg., 72.7%), m.p. > 300°, after washing with hot dioxan. (Anal. Found: C, 38.45; H, 3.09. $C_{14}H_{16}N_2O_2S_4Zn$ requires: C, 38.40; H, 3.68). ν_{max} (KBr): 2920 (w), 2850 (w), 1580 (s), 1525 (s), 1450 (s), 1410 (s), 1385 (m), 1350 (s), 1255 (m), 1200 (s), 1130 (w), 1050 (m), 1025 (m), 845 (m), 820 (s), 705 (s), 615 (w), 515 (w), and 490 $cm.^{-1}$ (m).

5.2.2.4.7 Reaction of 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione with 2,4-dinitrochlorobenzene

A solution of sodium ethoxide in ethanol (3 ml., 0.002 mole) containing 1-hydroxy-2-sulfhydro-3,4-dimethyl-6-pyridinethione (0.187 g., 0.001 mole), and a solution of 2,4-dinitrochlorobenzene (0.404 g., 0.002 mole) in absolute ethanol (3 ml.) were stirred at room temperature (4.5 hr.). The reaction mixture was poured into water (50 ml.), and the pH adjusted to 10 with aqueous sodium hydroxide. Extraction with chloroform (3 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave 2,4-dinitroethoxybenzene (0.265 g.), m.p. 86° [reported (73), m.p. 85°]. The aqueous alkaline layer was then adjusted to pH 2 with aqueous hydrochloric acid. Extraction with chloroform (3 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave 1-hydroxy-2-(2',4'-dinitrophenylthio)-4,5-dimethyl-6-pyridinethione (0.209 g., 59.2%) as yellow crystals, m.p. 175-177°, after recrystallization from chloroform-carbon tetrachloride (4:1 v/v). (Anal. Found: C, 44.19; H, 3.20. $C_{13}H_{11}N_3O_5S_2$ requires: C, 44.18; H, 3.12). ν_{max} (KBr): 3090 (w), 2920 (w), 1580 (s), 1505 (s), 1460 (m), 1430 (m), 1370 (m), 1330 (s), 1250 (m), 1225 (w), 1200 (m),

1160 (w), 1145 (w), 1100 (w), 1055 (s), 920 (m), 905 (m), 855 (w), 830 (s), 740 (m), and 725 cm^{-1} (s). Mass spectrum m/e: 353 (3), 354 (4), 353 (24) (M^+), 338 (4), 337 (15), 336 (9), 291 (7), 290 (4), 289 (6), 274 (8), 259 (8), 245 (8), 244 (6), 243 (8), 200 (10), 187 (31), 184 (88), 183 (18), 171 (25), 170 (36), 155 (12), 154 (24), 136 (20), 119 (18), 117 (18), 107 (25), 92 (25), 91 (38), 85 (15), 83 (46), 79 (25), 69 (17), 67 (22), 64 (35), 63 (50), 62 (25), 53 (42), 51 (28), 48 (22), 45 (21), 39 (33), 38 (20), 30 (100), and 28 (46).

5.2.3.0.0 Reactions with oxygen to give 1-hydroxy-2-pyridones

5.2.3.1.0 Reaction of pyridine-1-oxide carbanion with oxygen

Pyridine-1-oxide (1.33 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry, oxygen-free nitrogen, and n-butyllithium (1.8 g., 0.028 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred (1 hr.), after which dry oxygen gas was bubbled into the reaction mixture (30 ml./min.) for a period of 15 minutes. The brown reaction mixture was allowed to warm up to room temperature and water (40 ml.) was added. The mixture

was then acidified to pH 2 with 18% hydrochloric acid. Extraction with chloroform (8 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown viscous oil (0.948 g.) which was chromatographed on a 2.5 x 50 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a yellow aliphatic oil (0.136 g.) which was not investigated further. Elution with ether gave an orange semi-solid (0.067 g.) which could not be crystallized, did not sublime, and did not give a ferric chelate. Further elution with ether-methanol (5:1 v/v), and then methanol gave a brown solid (0.60 g.) which did not ignite, sublime, yield a ferric chelate, contain halogen and could not be recrystallized. This material was not characterized.

5.2.3.2.0 Reaction of 4-methylpyridine-1-oxide carbanion with oxygen

Using the procedure outlined in 5.2.3.1.0, 4-picoline-1-oxide (1.53 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole), and oxygen gave a greenish brown tarry semi-solid which was chromatographed on a 2.5 x 50 cm. silica gel column. Elution with benzene-ether (3:1 v/v), and then ether yielded 1-hydroxy-4-methyl-2-pyridone (0.223 g., 12.7%). Recrystallization from

acetone and then sublimation (115°/0.4 mm.) gave white crystals, m.p. 131-132° [reported (74), m.p. 129-130°]. N.m.r. ($CDCl_3$) τ: 2.42 [1 H doublet ($J_{5,6}$ = 7 Hz), C_6-H]; 3.56 [1 H doublet ($J_{3,5}$ = 2 Hz), C_3-H]; 3.90 [1 H quartet ($J_{5,6}$ = 7 Hz; $J_{3,5}$ = 2 Hz), C_5-H]; 7.82 (3 H singlet, Ar-CH_3); -2.08 (1 H singlet, hydroxyl, exchanges readily with deuterium oxide). ν_{max} (KBr): 3100 (w), 2940 (w), 2550 (m), 1650 (s), 1550 (s), 1460 (m), 1340 (m), 1240 (w), 1185 (s), 1120 (w), 1035 (w), 1025 (w), 955 (w), 850 (m), 790 (m), 770 (s), 750 (w), 720 (w), 640 (w), 610 (m), 600 (w), 545 (w), 445 (w), and 425 cm^{-1} (w). Mass spectrum m/e: 126 (5), 125 (71) (M^+), 110 (5), 109 (71), 97 (15), 96 (22), 82 (4), 81 (18), 80 (100), 79 (5), 78 (5), 70 (4), 69 (13), 68 (7), 67 (5), 66 (7), 65 (7), 64 (4), 63 (4), 55 (7), 54 (13), 53 (65), 52 (27), 51 (24), 50 (16), 49 (4), 44 (7), 43 (9), 42 (11), 41 (22), 40 (13), 39 (45), 38 (18), 37 (9), 32 (18), 28 (51), and 27 (40). The acidic aqueous layer was adjusted to pH 12 with aqueous sodium hydroxide. Extraction with chloroform (8 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure yielded 4-picoline-1-oxide (0.325 g.).

5.2.3.3.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with oxygen

Using the procedure described in 5.2.3.1.0, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyl-lithium (1.8 g., 0.028 mole), and oxygen gave a brown solid which was chromatographed on a 2.5 x 52 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridone (0.194 g., 10%) as a white solid, m.p. 169-170°, after recrystallization from acetone and then sublimation (100°/0.125 mm.). (Anal. Found: C, 60.36; H, 6.61. $C_7H_9NO_2$ requires: C, 60.42; H, 6.52). ν_{max} (KBr): 3115 (m), 2920 (m), 2500 (m), 1620 (s), 1500 (s), 1370 (m), 1330 (m), 1280 (m), 1235 (s), 1210 (s), 1165 (w), 1105 (s), 1025 (m), 975 (m), 910 (m), 785 (s), 765 (s), 750 (s), 710 (m), 690 (m), 605 (m), 585 (w), 555 (m), 515 (s), 490 (m), and 460 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.50 [1 H doublet ($J_{5,6}$ = 7 Hz), C_6-H]; 3.90 [1 H doublet ($J_{5,6}$ = 7 Hz), C_5-H]; 7.84 (3 H singlet, Ar-CH_3); 7.90 (3 H singlet, Ar-CH_3); -1.26 (1 H singlet, hydroxyl, exchanges readily with D_2O). Mass spectrum m/e: 140 (8), 139 (100) (M^+), 123 (91), 111 (19), 110 (21), 96 (8), 95 (25), 94 (76), 93 (13), 92 (6), 80 (25), 79 (10), 78 (6), 77 (10), 68 (11), 67 (41), 66 (16), 65 (19), 55 (10), 53 (19), 52 (13), 51 (16), 50 (8), 44 (19), 41 (41),

40 (13), 39 (54), 38 (8), 36 (25), and 28 (29). Continued elution with benzene-ether (3:1 v/v) yielded 1-hydroxy-3,4-dimethyl-6-pyridone (0.27 g., 13.9%). Recrystallization from acetone and then sublimation (125°/0.175 mm.) gave a white solid, m.p. 195°. (Anal. Found: C, 60.51; H, 6.68. $C_7H_9NO_2$ requires: C, 60.42; H, 6.52). ν_{max} (KBr): 3100 (m), 2995 (m), 2940 (m), 2700 (m), 1660 (s), 1580 (s), 1490 (s), 1440 (m), 1390 (w), 1330 (s), 1270 (w), 1250 (w), 1200 (w), 1175 (s), 1105 (w), 1030 (w), 1015 (m), 855 (s), 845 (s), 840 (m), 750 (s), 715 (m), 590 (w), 510 (m), and 445 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 2.54 (1 H singlet, C_2-H; 3.54 (1 H singlet, C_5-H); 7.88 (3 H singlet, Ar-CH_3); 7.98 (3 H singlet, Ar-CH_3); -1.18 (1 H singlet, hydroxyl, exchanges readily with deuterium oxide). Mass spectrum m/e: 140 (8), 139 (100) (M^+), 123 (54), 111 (21), 110 (23), 96 (9), 95 (17), 94 (7), 93 (9), 80 (15), 69 (7), 68 (10), 67 (35), 66 (17), 65 (18), 63 (6), 56 (4), 55 (10), 54 (4), 53 (15), 52 (13), 51 (15), 50 (6), 44 (5), 43 (10), 42 (10), 41 (38), 40 (13), 39 (50), 38 (8), and 28 (13). Further elution with ethanol gave a brownish-black semi-solid which was dissolved in 95% ethanol (20 ml.). Addition of water precipitated a pink solid which was heated on a steam bath (2 hr.) with 18% hydrochloric acid. Extraction with chloroform

(5 x 30 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a reddish-brown solid which, on sublimation (140°/0.125 mm.), gave 1-hydroxy-3,4-dimethyl-6-pyridone (19 mg., 1%) (overall yield, 14.9%), m.p. 195°, identical (I.R.) with the product isolated above.

5.2.4.0.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with benzyl bromide

(a) (2 Equiv. n-BuLi, 2 equiv. $PhCH_2Br$, 30 min.). 3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry oxygen-free nitrogen and n-butyllithium (1.8 g., 0.028 mole) was added slowly to the stirred solution. The dark brown solution was stirred for 1 hr., after which benzyl bromide (4.78 g., 0.028 mole) in anhydrous tetrahydrofuran (10 ml.) was slowly added. The reaction was allowed to proceed for 30 min. and the mixture was then warmed to room temperature. Water (40 ml.) was added and the mixture extracted with chloroform (6 x 75 ml.), the solvent dried (Na_2SO_4), and evaporated under reduced pressure to give a dark brown oil, distillation of which gave a pale yellow liquid (1.2 g.) which came over at 140°/0.1 mm. (bath temperature), a white solid (35 mg.)

at 260°/0.1 mm. (bath temp.), m.p. 122° (whose infrared spectrum was identical with that of trans-stilbene), and 3,4-lutidine-1-oxide (20 mg.) at 280°/0.1 mm. (bath temp.), m.p. 135°. Gas liquid chromatography of the yellow liquid using a 5 ft. x ¼ in. column packed with 20% SE-30 on Chromosorb W (60-80 mesh) at 142° and a helium flow rate of 60 ml./min. gave three components in the ratio of 2 : 3.6 : 6.05 (as calculated from the relative areas under the curves, not molar ratios) which were collected directly onto potassium bromide powder. The infrared spectra and retention times were identical with those of authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide, respectively.

(b) (2 Equiv. n-BuLi, 1 equiv. $PhCH_2Br$, 30 min.). Using the procedure outlined in 5.2.4.0.0. a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole), and benzyl bromide (2.39 g., 0.014 mole) gave a brown oil (4.3 g.). Distillation of this oil (2.15 g.) yielded a pale yellow liquid (0.7 g.), b.p. 140°/0.1 mm. (bath temp.), and a white solid (0.2 g.), m.p. 122°, b.p. 260°/0.1 mm. (bath temp.); the infrared spectrum of the latter was identical with that of an authentic sample of trans-stilbene. The remainder of the oil (2.15 g.) was chromatographed on a 2.5 x 30 cm. silica gel column. Elution with ether-methanol

(3:1 v/v) gave a brown semi-solid. Recrystallization from petroleum ether (b.p. 60-100°)-benzene (1:4 v/v) gave 3,4-lutidine-1-oxide (0.20 g.) as needles, m.p. 135°. Concentration and then cooling of the mother liquor gave trans-stilbene (0.18 g.), m.p. 122°. Further elution with methanol gave 3,4-lutidine-1-oxide (0.242 g.). Gas liquid chromatography of the pale yellow liquid on a 6.5 ft. x ¼ in. column packed with 10% SE-52 on Chromosorb W (60-80 mesh) at 125° and a helium flow rate of 60 ml./min. resolved two components which were collected directly onto potassium bromide powder. The infrared spectra and retention times were identical with those of authentic samples of benzaldehyde and 3,4-lutidine, respectively. The uncorrected relative ratios (not molar) of these two compounds as calculated from the areas under the curves were 5.7 : 6.4, respectively.

(c) (1 Equiv. n-BuLi, 1 equiv. $PhCH_2Br$, 30 min.). Using the procedure described in 5.2.4.0.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (0.9 g., 0.014 mole), and benzyl bromide (2.39 g., 0.014 mole) gave a dark green semi-solid which was distilled at 140°/0.1 mm. (bath temp.) to yield a colorless liquid (1.37 g.). Gas liquid chromatography of this liquid, using the column and conditions outlined in

5.2.4.0.0.b, gave three components in the ratio of 2.4 : 1.12 : 9.45 (as calculated from the relative areas under the curves) which were collected directly onto potassium bromide powder. The infrared spectra and retention times were identical with those of authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide, respectively.

(d) (2 Equiv. n-BuLi, 1 equiv. $PhCH_2Br$, 4 min.). Using the procedure outlined in 5.2.4.0.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole), and then benzyl bromide (2.39 g., 0.014 mole) in anhydrous tetrahydrofuran (10 ml.) was added slowly during 3 min. The reaction was allowed to proceed for 1 min. and then 18% hydrochloric acid (30 ml.) was added to the reaction mixture. It was warmed slowly to room temperature, extracted with chloroform (6 x 75 ml.), the solvent dried (Na_2SO_4), and evaporated under reduced pressure to give a yellow oil which, on trituration with acetone, yielded 1-benzyloxy-3,4-dimethylpyridinium bromide (1.1 g., 26.7%) as white crystals, m.p. 125-126°, after recrystallization from 95% ethanol. (Anal. Found: C, 56.89; H, 6.03. $C_{14}H_{16}BrNO \cdot \frac{1}{2}C_2H_5OH$ requires: C, 56.79; H, 6.04). ν_{max} (KBr): 3640 (m), 3540 (m), 3425 (m), 3060 (m), 3005 (s), 2975 (s),

2910 (m), 1500 (s), 1470 (s), 1405 (m), 1390 (s), 1315 (w), 1300 (w), 1175 (w), 1155 (w), 1035 (m), 970 (m), 950 (w), 910 (s), 855 (s), 835 (s), 775 (s), 765 (s), 745 (s), 705 (s), 695 (w), 620 (w), 560 (m), and 505 cm^{-1} (w). N.m.r. (D_2O) τ (after thorough drying): 0.86 [1 H doublet ($J_{2,6}$ = 2 Hz), C_2-H]; 0.96 [1 H quartet ($J_{5,6}$ = 7 Hz, $J_{2,6}$ = 2 Hz), C_6-H]; 1.96 [1 H doublet ($J_{5,6}$ = 7 Hz), C_5-H]; 2.32 (5 H multiplet, phenyl group); 4.17 (2 H singlet, -CH_2-), 7.22 (3 H singlet, Ar-CH_3); 7.32 (3 H singlet, Ar-CH_3). Distillation of the oil obtained from the mother liquor gave a pale yellow liquid (0.64 g.) at 140°/0.1 mm. (bath temp.), and 3,4-lutidine-1-oxide (0.374 g.) at 280°/0.1 mm. (bath temp.). Gas liquid chromatography of the yellow oil was achieved using the column and conditions described in 5.2.4.0.0.b. The sample was resolved into three components in the ratio (not molar) of 1.54 : 1.1 : 14.5 (as calculated from the relative areas under the peaks) which were collected directly onto potassium bromide. The infrared spectra and retention times were identical with those of authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide, respectively.

5.2.4.1.0 1-Benzyloxy-3,4-dimethylpyridinium bromide

3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry, oxygen-free nitrogen and benzyl bromide (4.78 g., 0.028 mole) in anhydrous tetrahydrofuran (10 ml.) was added slowly. The reaction was allowed to proceed for 30 min. and the mixture was then warmed to room temperature. Water (40 ml.) was added and the pH adjusted to 10 using aqueous sodium hydroxide. Extraction with chloroform (6 x 75 ml.), drying the extract (Na_2SO_4), and removal of the chloroform under reduced pressure gave a yellow viscous oil which crystallized on standing. Recrystallization from 95% ethanol gave 1-benzyloxy-3,4-dimethyl-pyridinium bromide (3.1 g., 75.4%) as white crystals, m.p. 125-126°, identical (I.R. and n.m.r.) with the sample obtained previously (5.2.4.0.0.d). Removal of the ethanol from the mother liquor yielded a yellow oil (1.0 g.) which was examined by gas liquid chromatography using the column and conditions described in 5.2.4.0.0.a. The oil was resolved into three components in the ratio (not molar) of 2 : 10 : 8.8 (as calculated from the relative areas under the peaks) which were collected directly onto potassium bromide. The infrared spectra and retention times were identical with

those of authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide, respectively.

5.2.4.2.0 Decomposition of 1-benzyloxy-3,4-dimethyl-pyridinium bromide

(a) On distillation. 1-Benzyloxy-3,4-dimethyl-pyridinium bromide (1.272 g.) was distilled at 160-310°/ 0.1 mm. (bath temp.) to yield a pale yellow oil (0.8 g.), another oil which collected and then solidified in the condenser (0.10 g.) [identical (I.R.) with an authentic sample of 1-benzyloxy-3,4-dimethylpyridinium bromide] after washing with acetone, and a white solid (0.12 g.) which solidified in the distilling head, and was identical (I.R. and m.p.) with an authentic sample of 3,4-lutidine-1-oxide. Gas liquid chromatography of the yellow oil using the column and conditions described in 5.2.4.0.0.b gave three components in the ratio (not molar) of 14.6 : 10.7 : 46.2 (as calculated from the areas under the curves). These were collected directly onto potassium bromide powder. The infrared spectra and retention times were identical with those of authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide, respectively.

(b) On boiling under reflux in tetrahydrofuran. A mixture of 3,4-lutidine-1-oxide (2.46 g., 0.02 mole) and

benzyl bromide (3.42 g., 0.02 mole) in anhydrous tetrahydrofuran (80 ml.) was boiled under reflux for 2 hr. A small aliquot (1 ml.) was removed and the tetrahydrofuran was evaporated under reduced pressure to give 1-benzyloxy-3,4-dimethylpyridinium bromide (50 mg.), as a white crystalline solid, identical (I.R. and n.m.r) with that obtained in 5.2.4.0.0.d. The salt was then boiled under reflux for an additional 238 hr. The warm tetrahydrofuran solution "A" was decanted leaving a brown insoluble oily semi-solid "B." "B" was then washed well with warm tetrahydrofuran (2 x 30 ml.) and this extract was combined with "A." Evaporation of the tetrahydrofuran from "A" under reduced pressure gave a moist, yellow, needle-shaped solid (3.87 g.). Recrystallization from absolute ethanol (15 ml.) gave 1-benzyloxy-3,4-dimethylpyridinium bromide (0.815 g.) as white crystals, m.p. 125-126°, identical (I.R. and n.m.r.) with that obtained in 5.2.4.0.0.d. The mother liquor was concentrated down to 10 ml. On cooling a second crop of crystals (0.64 g.), m.p. 80°, was obtained which was shown to be a 1:1 mixture of 3,4-lutidine-1-oxide hydrobromide and N-benzyloxy-3,4-dimethylpyridinium bromide by comparison with the infrared and n.m.r. spectra of authentic samples. The ratio of the two compounds was calculated from the n.m.r. integral of the

alpha protons in the mixture. The solvent was removed from the mother liquor under reduced pressure at room temperature to give a yellow solid which, on trituration with acetone (10 ml.), gave 3,4-lutidine-1-oxide hydrobromide (0.432 g.) m.p. 169-170°. ν_{max} (KBr): 3120 (w), 3090 (s), 3010 (s), 2900 (m), 2450 (s), 1615 (m), 1490 (s), 1440 (s), 1400 (s), 1330 (m), 1275 (m), 1225 (w), 1215 (m), 1170 (s), 1155 (s), 1040 (s), 1020 (s), 965 (w), 920 (m), 860 (s), 760 (w), 735 (s), 695 (s), 690 (s), 550 (s), 500 (s), 460 (w), and 445 cm^{-1} (m). N.m.r. (D_2O) τ: 1.01 [2 H doublet ($J_{5,6}$ = 7 Hz), C_2-H, C_6-H]; 1.75 [1 H doublet ($J_{5,6}$ = 7 Hz), C_5-H]; 7.02 (3 H singlet, Ar-CH_3); 7.10 (3 H singlet, Ar-CH_3). Basification of a portion of the 3,4-lutidine-1-oxide hydrobromide above gave 3,4-lutidine-1-oxide. The solvent was removed from the acetone solution above to yield a brown oil which was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a yellow liquid (1.30 g.) which does not contain nitrogen. Gas liquid chromatography of this liquid using a 6 ft. x 3/10 in. column packed with 20% SE-30 on Gas Chrom Q (60-100 mesh) with a helium flow rate of 60 ml./min. and temperature programing from 100-260° at 4°/min. gave at least 5 components which were not further investigated. Further elution with

ether-methanol (2:1 v/v) gave a brown tarry semi-solid (0.47 g.) which was not characterized. Fraction "B" was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with ether-methanol (2:1 v/v), and then methanol gave a brown viscous oil which, on trituration with acetone, gave 1-benzyl-3,4-dimethylpyridinium bromide (0.628 g.) as white crystals, m.p. 206-207°, after recrystallization from absolute methanol. (Anal. Found: C, 60.54: H, 5.91. $C_{14}H_{16}BrN$ requires: C, 60.45; H, 5.80). ν_{max} (KBr): 3075 (w), 3030 (s), 3000 (s), 2940 (s), 1630 (s), 1505 (m), 1490 (s), 1475 (s), 1450 (s), 1430 (m), 1380 (m), 1295 (w), 1250 (m), 1228 (s), 1210 (s), 1155 (m), 1145 (s), 1080 (w), 1032 (s), 970 (m), 935 (m), 900 (s), 870 (w), 840 (s), 820 (m), 810 (s), 780 (m), 755 (w), 730 (s), 700 (s), 620 (s), 565 (w), 525 (m), 505 (m), 455 (w), and 430 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 0.3 (1 H singlet, C_2-H); 0.56 [1 H doublet ($J_{5,6}$ = 7 Hz), C_6-H]; 2.16 (3 H multiplet, C_5-H, C_2'-H, C_6'-H); 2.66 (3 H multiplet, C_3'-H, C_4'-H, C_5'-H); 3.79 (2 H singlet, -CH_2-); 7.48 (3 H singlet, Ar-CH_3); 7.51 (3 H singlet, Ar-CH_3). Attempted separation and purification of the acetone soluble portion from above did not yield any characterizable products.

(c) Thermal decomposition in the injector port. A sample of 1-benzyloxy-3,4-dimethylpyridinium bromide

was subjected to gas liquid chromatography using a 6 ft. x 3/16 in. column packed with 20% SE-30 on Gas Chrom Q (60-100 mesh) at 100° with a helium flow-rate of 60 ml./min. and an injector temperature of 215°. After decomposition in the injector port the sample was resolved into three components in the area ratio of 1 : 1.13 : 6.56 with retention times of 10.7 to 10.8, 14.2, and 24.7 min., respectively. Authentic samples of benzaldehyde, 3,4-lutidine, and benzyl bromide exhibited retention times of 10.8-10.9, 14.3, and 24.7 min., respectively.

5.2.5.0.0 Reaction of 4-methylpyridine-1-oxide with methyl p-toluenesulfonate

4-Methylpyridine-1-oxide (1.53 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65° in a Dry-ice acetone bath and the flask was flushed with dry nitrogen. Methyl p-toluenesulfonate (2.6 g., 0.014 mole) in anhydrous tetrahydrofuran (10 ml.) was added slowly during three minutes. The reaction was allowed to proceed for 30 min. and the mixture was then allowed to warm up to room temperature. Water (40 ml.) was added and the pH adjusted to 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under

reduced pressure gave 1-methoxy-4-methylpyridinium toluene p-sulfonate (3.6 g., 87%) as needles, m.p. 154-155° [reported (75) m.p. 154.5-155.5°], after recrystallization from ethanol. ν_{max} (KBr): 3100 (m), 3065 (w), 3040 (m), 2980 (w), 1625 (m), 1595 (w), 1500 (s), 1490 (m), 1460 (m), 1280 (m), 1200 (s), 1170 (s), 1120 (s), 1105 (m), 1030 (s), 1010 (s), 970 (s), 960 (m), 860 (w), 835 (s), 820 (s), 805 (w), 730 (w), 720 (m), 685 (s), and 665 cm^{-1} (m).

5.2.6.0.0 Reactions with epoxides to give polymers

5.2.6.1.0 Reaction of pyridine-1-oxide carbanion with ethylene oxide

(a) In tetrahydrofuran (3 hr., -15°). Pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous tetrahydrofuran (70 ml.) was cooled to -65°, the flask was flushed with dry, oxygen-free nitrogen and n-butyllithium (2.56 g., 0.04 mole) was added slowly to the stirred solution. The dark brown solution which resulted was stirred for 1 hr. and then ethylene oxide (4.4 g., 0.1 mole) in anhydrous tetrahydrofuran (10 ml.) was added slowly during 5 minutes. The reaction was allowed to proceed for 3 hr. at -15° and the mixture was warmed to room temperature. Water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation

of the chloroform under reduced pressure gave a black semi-solid which was chromatographed on a 2.5 x 40 cm. alumina column. Elution with benzene-ether (3:1 v/v), and then with ether gave a yellow oil (0.256 g., 9.5%), the infrared spectrum of which was identical with that of an authentic sample of 2-n-butylpyridine. M (mass spectrum), 135. N.m.r. ($CDCl_3$) τ: 1.50 [1 H quartet ($J_{5,6}$ = 6 Hz; $J_{4,6}$ = 2 Hz), C_6-H]; 2.46 [1 H sextet ($J_{4,5} = J_{3,4}$ = 7 Hz; $J_{4,6}$ = 2 Hz), C_4-H]; 2.96 (2 H multiplet, C_3-H, C_5-H); 7.22 [2 H triplet (J = 7 Hz), $-CH_2-$]; 8.16-8.46 (2 H complex multiplet, $-CH_2-$); 8.49-8.82 (2 H complex multiplet, $-CH_2-$); 9.06 [3 H triplet (J = 7 Hz), $-CH_3$]. Further elution with ether-methanol (10:1 v/v), ether-methanol (2:1 v/v), and then methanol gave a brown semi-solid (1.28 g.) which appears to be a mixture of pyridine-1-oxide and a higher molecular weight product. N.m.r. ($CDCl_3$) τ: 1.74 (2 H multiplet, C_2-H, C_6-H of pyridine-1-oxide); 2.66 (3 H multiplet, C_3-H, C_4-H, C_5-H of pyridine-1-oxide); 4.76 (1 H broad singlet, may be hydroxyl); 6.3 (2 H broad singlet, $-CH-$); 7.14 (2 H broad singlet, $-CH_2-$). Mass spectrum: m/e 95 (100) (M^+) and m/e 79 (44) are the two most abundant peaks in the spectrum and are due to pyridine-1-oxide. Other less abundant peaks due to the higher molecular weight product occurred at m/e 106 (18),

109 (15), 122 (11), 155 (15), 156 (37), and 170 (8). The infrared spectrum of this material exhibited all those absorptions present in pyridine-1-oxide itself as well as bands at 2960 (s), 2930 (s), and 2875 cm^{-1} (s).

(b) In ether (3 hr., -15°). Pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous ether (70 ml.) was treated with n-butyllithium (2.56 g., 0.04 mole) and then with ethylene oxide (4.4 g., 0.1 mole) as described in 5.2.6.1.0.a. The brown oil obtained was chromatographed on a 2.5 x 20 cm. alumina column. Elution with benzene-ether (3:1 v/v) gave 2-butylpyridine (0.436 g., 16.5%), identical (I.R.) with that obtained in 5.2.6.1.0.a. Further elution with ether and ether-methanol (1:1 v/v) gave a brown viscous oil (0.896 g.) similar to that obtained in 5.2.6.1.0.a on elution with ether-methanol and methanol.

(c) In ether (2 hr., room temperature). Pyridine-1-oxide (1.9 g., 0.02 mole) suspended in anhydrous ether (70 ml.) was treated with n-butyllithium (2.56 g., 0.04 mole) and then with ethylene oxide (2.46 g., 0.056 mole) for 2 hr. at room temperature as outlined in 5.2.6.1.0.a. The brown semi-solid obtained was chromatographed on a 2.5 x 30 cm. alumina column. Elution with benzene, benzene-ether (3:1 v/v), and then ether gave an orange oil (0.525 g.) which appears to consist of a

mixture of 2-butylpyridine and a higher molecular weight product similar to that described in 5.2.6.1.0.a. Further elution with ether-methanol (3:1 v/v) and then methanol gave a brown viscous oil (0.817 g.) similar to that eluted with ether-methanol and methanol described in 5.2.6.1.0.a.

5.2.6.2.0 Reaction of 4-methylpyridine-1-oxide carbanion with ethylene oxide

(a) In ether (20 hr.). 4-Picoline-1-oxide (1.53 g., 0.014 mole) suspended in anhydrous ether (75 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) and then ethylene oxide (2.46 g., 0.056 mole) for 20 hr. at room temperature as described in 5.2.6.1.0.a. The black sticky semi-solid obtained was chromatographed on a 2.5 x 35 cm. alumina column. Elution with benzene-ether (3:1 v/v) gave a light brown oil (0.19 g.). ν_{max} (Film): 3100 (w), 3040 (w), 2960 (s), 2930 (s), 2860 (m), 1600 (w), 1470 (w), 1270 (m), 1100 (m), 1025 (m), 810 (m), 760 (m), and 680 cm^{-1} (s). This material was not investigated further. Elution with ether-methanol (10:1 v/v), and then ether-methanol (2:1 v/v) gave a brown oil (1.872 g.). ν_{max} (Film): 3300 (s), 3020 (m), 2950 (s), 2870 (s), 1600 (s), 1570 (m), 1460 (s), 1380 (s), 1220 (s), 1120 (m), 1140 (s), 820 (w), 750 (s), and

665 cm^{-1} (s). Distillation of this oil at 140°/0.075 mm. gave a pale yellow liquid. N.m.r. ($CDCl_3$) τ: 1.4-2.2 (2 H complex multiplet, C_6-H); 2.6-3.3 (2 H complex multiplet, C_3-H, C_5-H); 5.46 (1 H broad singlet, hydroxyl); 6.1-6.7 (2 H multiplet, -CH-); 7.0-7.5 (2 H complex multiplet, $-CH_2-$); 7.66 (3 H singlet, $Ar-CH_3$); 8.0-9.2 (? H complex multiplet, $-CH_2-$).

(b) In ether (10 hr.). 4-Picoline-1-oxide (1.53 g., 0.014 mole) suspended in anhydrous ether (75 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) and then with ethylene oxide (2.46 g., 0.056 mole) for 10 hr. at room temperature as outlined in 5.2.6.1.0.a. The dark brown product (2.46 g.) obtained was dried in vacuo at room temperature and a molecular weight determination ($CHCl_3$) was carried out using an osmometer. A value corresponding to a molecular weight of 1866 was obtained for this compound. A sample of the polymer was purified by dissolution in acetone and then reprecipitation with ether. This process was repeated several times to give a brown stretchy hygroscopic solid. The n.m.r. spectrum of this product was not well resolved and the integral could not be measured accurately. N.m.r. ($CDCl_3$) τ: 1.4-2.2 (2 H complex multiplet, C_6-H); 2.5-3.5 (2 H complex multiplet, C_3-H, C_5-H); 5.5-6.6 (4 H complex

multiplet, -CH-, -CH_2-); 7.0-9.3 (? H complex multiplets, -CH_2-, -CH_3).

(c) In ether (2 hr.). 4-Picoline-1-oxide (1.53 g., 0.014 mole) suspended in anhydrous ether (75 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) and then with ethylene oxide (2.46 g., 0.056 mole) for 2 hr. at room temperature as outlined in 5.2.6.1.0.a. The brown stretchy semi-solid [1.8 g., 95%, calculated as poly-(4-methyl-2-vinylpyridine-1-oxide)] obtained was dried in vacuo at room temperature and a molecular weight determination ($CHCl_3$) was carried out using an osmometer. A value corresponding to a molecular weight of 812 was obtained.

5.2.6.3.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with ethylene oxide

(a) In tetrahydrofuran (-65°, 30 min.). Using the procedure outlined in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) was treated with n-butyllithium (1.8 g., 0.028 mole) to give the 3,4-dimethylpyridine-1-oxide carbanion which was then allowed to react with ethylene oxide (1.23 g., 0.028 mole) for 30 min. at -65°. The yellow solid obtained was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with ether-methanol (5:1 v/v), ether-methanol (2:1 v/v), and then methanol

gave unreacted 3,4-lutidine-1-oxide in almost quantitative yield, identical (I.R.) with an authentic sample.

(b) In tetrahydrofuran (3 hr., -15°). Using the procedure outlined in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole) and ethylene oxide (3.69 g., 0.084 mole) gave an orange viscous oil which was chromatographed on a 2.5 x 40 cm. alumina column. Elution with ether-methanol (20:1 v/v) and then with ether-methanol (5:1 v/v) gave a yellow oil (0.722 g.) which appears to be a mixture of 3,4-lutidine-1-oxide and a higher molecular weight product in a ratio of 2:1 as calculated from the n.m.r. integral. N.m.r. ($CDCl_3$) (3,4-lutidine-1-oxide portion) τ: 2.08 [2 H doublet ($J_{5,6}$ = 7 Hz), C_2-H, C_6-H]; 2.99 [1 H doublet ($J_{5,6}$ = 7 Hz), C_5-H]; 7.81 (3 H singlet, Ar-CH_3); 7.85 (3 H singlet, Ar-CH_3): (higher molecular weight portion) τ: 2.27 (1 H singlet, C_6-H); 2.78 (1 H singlet, C_3-H); 5.04 (1 H broad singlet, hydroxyl); 6.14 [2 H triplet (J = 6 Hz), -CH_2-]; 6.70 (3 H singlet, -CH-); 6.96 [2 H triplet (J = 6 Hz), -CH_2-]; 7.78 (3 H singlet, Ar-CH_3); 7.90 (3 H singlet, Ar-CH_3). Mass spectrum m/e: 149 (0.3) (M^+), 148 (0.2), 133 (1), 132 (1.3), 123 (7), 107 (21), 106 (10), 92 (4), 87 (10), 83 (100), 79 (8), 49 (8), 48 (11), 47 (24), 32 (13), 31 (22), and 28 (2). The infrared spectrum (liquid film)

exhibits all those absorptions present in 3,4-lutidine-1-oxide as well as peaks at 3300 (s), 2960 (s), 2940 (s), 2875 (s), 1200 (m), 1100 (m), 1060 (s), 870 (m), and 825 cm^{-1} (m). Further elution with ether-methanol (2:1 v/v) gave a viscous yellow oil (0.225 g.), b.p. 140°/0.075 mm. (Anal. Found: C, 63.00; H, 7.98). ν_{max} (liquid film): 3325 (s), 2960 (s), 2940 (s), 2875 (s), 1460 (s), 1200 (s), 1225 (w), 1200 (m), 1130 (w), 1100 (s), 1060 (s), 1030 (m), 880 (w), 820 (w), 755 (s), and 670 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 1.86-2.12 (2 H multiplet, C_6-H); 2.84-3.12 (2 H multiplet, C_3-H, C_5-H); 5.20 (2 H singlet, hydroxyl, exchanges readily with D_2O); 6.10 [2 H triplet (J = 6 Hz), -CH_2]; 6.40 [2 H singlet, -CH-]; 6.70 [2 H triplet (J = 6 Hz); -CH_2-]; 6.80 [2 H triplet (J = 6 Hz), -CH_2-]; 7.74 (3 H singlet, Ar-CH_3); 7.76 (3 H singlet, Ar-CH_3); 7.79 (3 H singlet, Ar-CH_3); 8.06 (3 H singlet, Ar-CH_3). M (mass spectrum): 167 (5) (M^+), 165 (11), 164 (9), 163 (6), 162 (5), 151 (21), 150 (38), 149 (14), 148 (16), 147 (8), 146 (11), 137 (17), 135 (26), 134 (61), 133 (20), 132 (29), 133 (54), 121 (100), 120 (64), 117 (12), 108 (10), 107 (65), 106 (51), 105 (11), 95 (10), 94 (15), 93 (18), 92 (19), 91 (30), 81 (8), 80 (18), 79 (49), 78 (18), 77 (64), 67 (27), 66 (12), 65 (32), 63 (16), 62 (5), 54 (12), 53 (90), 52 (21), 51 (39), 50 (17),

45 (30), 43 (18), 41 (36), 39 (65), and 28 (90). Further elution with methanol gave a brown stretchy solid (0.160 g.). ν_{max} (KBr): 3350 (s), 2960 (s), 2940 (s), 2875 (s), 1450 (s), 1380 (s), 1265 (s), 1180 (m), 1135 (w), 1100 (s), 1060 (s), 875 (w), 800 (w), and 600 cm^{-1} (w). ν_{max} ($CHCl_3$): 2980 (s), 2950 (s), 2930 (s), 2860 (s), 1440 (s), 1250 (s), 1210 (m), 1135 (m), 1090 (s), 1040 (m), 940 (w), 860 (w), and 655 cm^{-1} (w). This polymer was purified by dissolution in 95% ethanol and reprecipitation by the addition of ether. This procedure was repeated three times to give a pale yellow elastic solid, m.p. 69° (slow decomp. begins). N.m.r. ($CDCl_3$) τ: 1.98 (1 H broad singlet, C_2-H); 2.94 (2 H broad singlet, C_3-H); 6.12 (?5 H broad singlet, -CH-); 6.34 (?12 H singlet, -CH-); 7.74 (?16 H multiplet, Ar-CH_3). (Anal. Found: C, 48.87; H, 8.33). $C_9H_{11}NO$ would require: C, 72.44; H, 7.43).

(c) In ether (16 hr., room temp.). 3,4-Lutidine-1-oxide (1.72 g., 0.014 mole), suspended in anhydrous ether (75 ml.), was treated with n-butyllithium (1.8 g., 0.028 mole) as described in 5.2.6.1.0.a, and then allowed to warm up to room temperature during 20 min. to give the 3,4-dimethylpyridine-1-oxide carbanion. Ethylene oxide (2.46 g., 0.056 mole) in anhydrous ether (10 ml.) was added and the reaction was allowed to

proceed for 16 hr. at room temperature, after which water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange viscous semi-solid which was chromatographed on a 2.5 x 37 cm. alumina column. Elution with ether-methanol (10:1 v/v), and then ether-methanol (2:1 v/v) gave a yellow oil (1.95 g.), identical (I.R. and n.m.r.) with the product eluted with ether-methanol (2:1 v/v) under 5.2.6.3.0.b. Further elution with methanol gave an elastic-like solid (0.574 g.), identical (I.R. and n.m.r.) with the product obtained on elution with methanol in 5.2.6.3.0.b.

A portion of the yellow oil (1.0 g.), eluted with ether-methanol above, in concentrated sulfuric acid (25 ml.) was stirred for 30 min. at room temperature and then the mixture was made alkaline with sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown stretchy solid, identical (I.R. and n.m.r.) with the polymer obtained on elution with methanol above.

(d) In ether (2 hr., room temp.). Using the procedure outlined in 5.2.6.3.0.c, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole), and ethylene oxide (2.46 g., 0.056 mole) were allowed to react for 2 hr. at room temperature. The

orange viscous sticky semi-solid (2.22 g.) obtained was purified by dissolving in acetone and then reprecipitating the polymer by the addition of ether. This procedure was repeated twice to give a yellow solid (0.5 g.), m.p. 80-140° (decomp.), identical (I.R. and n.m.r.) with the polymer obtained in 5.2.6.3.0.b on elution with methanol. A molecular weight determination ($CHCl_3$) on this polymer gave a value corresponding to a molecular weight of 2222. The acetone-ether mother liquor was concentrated and dried in vacuo to give a viscous oil with a molecular weight ($CHCl_3$) of 311.

(e) In ether (8 hr., room temp.). Using the procedure described in 5.2.6.3.0.c, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole), and ethylene oxide (2.46 g., 0.056 mole) were allowed to react for 8 hr. at room temperature. The pale brown stretchy semi-solid obtained was dried in vacuo. A molecular weight determination ($CHCl_3$) on this product gave a value corresponding to a molecular weight of 431.

(f) In ether (18 hr., room temp.). Using the procedure described in 5.2.6.3.0.c, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole), n-butyllithium (1.8 g., 0.028 mole), and ethylene oxide (4.92 g., 0.112 mole) were allowed to react for 18 hr. at room temperature. The

reaction product was purified by dissolving in acetone and then reprecipitating the polymeric material by the addition of ether. This procedure was repeated twice to give a brown stretchy solid (0.9 g.), identical (I.R.) with the polymer obtained in 5.2.6.3.0.b. A molecular weight determination ($CHCl_3$) on this polymer gave a value corresponding to a molecular weight of 1215. The acetone-ether mother liquor was concentrated and dried in vacuo to give a viscous oil (1.3 g.).

(g) In ether (inverse addition). 3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) suspended in anhydrous ether (40 ml.) was cooled to -65° and the flask was flushed with dry nitrogen. n-Butyllithium (1.8 g., 0.028 mole) was then added slowly. The yellow suspension was stirred for 30 min. at -65° and was then allowed to warm up to room temperature over a period of 30 min. The resulting reddish-brown solution of lithio-3,4-lutidine-1-oxide was added dropwise over a period of 20 min. to a solution of ethylene oxide (2.46 g., 0.056 mole) in anhydrous ether (30 ml.). The reaction was allowed to proceed for an additional 30 min. and then water (20 ml.) was added. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange viscous oil which was chromatographed on a 2.5 x 37 cm. alumina

column. Elution with ether gave an orange oil (65 mg.) which was not examined. Further elution with ether-methanol (10:1 v/v) gave an orange semi-solid (0.65 g.) which, on recrystallization from acetone, gave 3,4-lutidine-1-oxide, m.p. 135°, identical (I.R.) with an authentic sample. Elution with ether-methanol (2:1 v/v) gave a yellow oil (0.984 g.), identical (I.R. and n.m.r.) with the product obtained on elution with ether-methanol (2:1 v/v) as under 5.2.6.3.0.b.

5.2.6.4.0 Attempted reaction of 3,4-dimethylpyridine-1-oxide carbanion with cyclohexene oxide

(a) In tetrahydrofuran (-65°, 30 min.). Using the procedure outlined in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) was treated with n-butyllithium (1.8 g., 0.028 mole) to give the 3,4-lutidine-1-oxide carbanion which was then allowed to react with cyclohexene oxide (1.24 g., 0.0126 mole) for 30 min. at -65°. 18% Hydrochloric acid (30 ml.) was added and the mixture was allowed to warm up to room temperature. The acidic mixture was made alkaline with aqueous sodium hydroxide and the aqueous layer was saturated with sodium chloride. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a yellow solid which, on recrystallization from

acetone, gave 3,4-lutidine-1-oxide (0.54 g.), m.p. 135°. The above mother liquor was concentrated *in vacuo* to give a yellow semi-solid which was chromatographed on a 2.5 x 30 cm. silica gel column. Elution with benzene-ether (1:3 v/v) gave a light brown oil (1.008 g.) which did not contain nitrogen and was not further investigated. Elution with ether-methanol (5:1 v/v), ether-methanol (2:1 v/v), and then methanol gave unreacted 3,4-lutidine-1-oxide (1.10 g.).

(b) *In tetrahydrofuran-hexamethylphosphoramide (5:1 v/v) (2 hr., -15°).* Using the procedure described in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) and hexamethylphosphoramide (14 ml.) was treated with *n*-butyllithium (1.8 g., 0.028 mole) and then with cyclohexene oxide (2.48 g., 0.0252 mole) in anhydrous tetrahydrofuran (10 ml.) for 2 hr. at -15°. The brown crystalline solid obtained was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene-ether (3:1 v/v), and then with ether gave a brown semi-solid (40 mg.) which was not examined. Further elution with ether-methanol (2:1 v/v) gave 3,4-lutidine-1-oxide (1.625 g.), identical (I.R.) with an authentic sample.

(c) *In tetrahydrofuran (3 hr., -15°).* 3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous

tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) and the resulting carbanion was then allowed to react with cyclohexene oxide (2.48 g., 0.0252 mole) for 3 hr. at -15° as described in 5.2.6.1.0.a. The yellow solid obtained was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with ether-methanol (10:1 v/v), ether-methanol (2:1 v/v), and then methanol gave unchanged 3,4-lutidine-1-oxide (1.59 g.).

5.2.6.5.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with styrene oxide

(a) In ether (12 hr., room temp.). Using the procedure outlined in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) was suspended in anhydrous ether (70 ml.) and treated with n-butyllithium (1.8 g., 0.028 mole). The mixture was allowed to come to room temperature over a period of 20 min. Styrene oxide (3.36 g., 0.028 mole) in anhydrous ether (10 ml.) was added dropwise and the reaction was allowed to proceed for 12 hr. at room temperature. Water (40 ml.) was then added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange oil which was triturated with petroleum ether (b.p. 30-60°) to remove unreacted styrene oxide.

The orange oil was dried *in vacuo* to give a flaky yellow solid (3.19 g.), m.p. 80-110°. A molecular weight determination ($CHCl_3$) on this product gave a value corresponding to a molecular weight of 653. The reaction product was purified by dissolution in benzene and then reprecipitation by the addition of petroleum ether (b.p. 30-60°). (Anal. Found: C, 76.26; H, 7.02. $(C_{13}H_{16}NO)_n$ would require: C, 77.21; H, 7.98). ν_{max} (KBr): 3070 (w), 3130 (w), 2960 (w), 2930 (w), 2870 (w), 1490 (w), 1440 (s), 1260 (m), 1195 (m), 1095 (m), 1060 (s), 1030 (m), 915 (w), 880 (w), 750 (s), 705 (s), and 535 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.12 (1 H broad singlet, C_2-H); 2.86 (6 H complex multiplet, C_3-H, C_6H_5-); 6.6 (3 H complex multiplet, -CH-, -CH_2-); 7.86 (6 H multiplet, Ar-CH_3). There was no change in the spectrum on addition of deuterium oxide. Mass spectrum m/e: 316 (2), 241 (3), 240 (2), 239 (2), 227 (7), 226 (17), 225 (6), 213 (5), 212 (8), 211 (11), 210 (6), 209 (4), 208 (10), 197 (9), 196 (10), 150 (6), 137 (20), 136 (9), 135 (5), 134 (8), 123 (28), 122 (13), 121 (100), 120 (44), 108 (14), 107 (53), 106 (56), 105 (76), 92 (10), 91 (21), 79 (35), 78 (8), 77 (91), 67 (9), 65 (10), 53 (13), 52 (10), 51 (33), 50 (14), 39 (21), and 28 (20). A portion of the reaction product (1.147 g.) was chromatographed on a 2.5 x 30 cm. alumina column. Elution with

ether gave an orange solid (51 mg.). Further elution with ether-methanol (3:1 v/v) yielded an orange solid (0.895 g.), while further elution with methanol gave an orange-brown solid (92 mg.). The infrared spectra (KBr) of the three fractions above were all identical.

(b) In ether (inverse addition). Using the method described in 5.2.6.3.0.g, 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) suspended in anhydrous ether (70 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) to give a solution of lithio-3,4-lutidine-1-oxide. This solution was then added dropwise during 30 min. to a solution of styrene oxide (3.36 g., 0.028 mole) in anhydrous ether (30 ml.). The reaction was allowed to proceed for 9 hr. at room temperature and then water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange, viscous oil which was triturated with petroleum ether (b.p. 30-60°) to remove unreacted styrene oxide. The orange pasty solid was then chromatographed on a 2.5 x 30 cm. alumina column. Elution with ether gave a yellow solid (0.118 g.). Further elution with ether-methanol (3:1 v/v) and then methanol gave an orange solid (2.018 g.). The infrared spectra (KBr) of these two fractions were identical with those obtained in 5.2.6.5.0.a.

5.2.7.0.0 Reaction of pyridine-1-oxide carbanion with acetaldehyde

Pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (2.56 g., 0.04 mole), and then with acetaldehyde (1.76 g., 0.04 mole) for 30 min. at -65° as described in 5.2.6.1.0.a. The orange viscous oil (2.6 g.) obtained was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a brown aliphatic oil (0.198 g.) which was not investigated. Further elution with benzene-ether (3:1 v/v) and then ether gave 2,6-di-(1-hydroxyethyl)pyridine-1-oxide (1.103 g., 30.1%) as a yellow oil after distillation at 127°/0.075 mm. The oil crystallized on standing to give a white solid, m.p. 70-72°. (Anal. Found: C, 58.45; H, 7.52. $C_9H_{13}NO_3$ requires: C, 58.99; H, 7.15). ν_{max} (liquid film): 3350 (s), 2975 (s), 2930 (s), 2875 (m), 1450 (m), 1390 (s), 1300 (w), 1240 (s), 1220 (s), 1170 (w), 1135 (s), 1075 (m), 1025 (w), 930 (w), 900 (w), 845 (m), 800 (m), 760 (s), and 670 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 2.56 (3 H singlet, C_3-H, C_4-H, C_5-H); 4.18 (2 H singlet, hydroxyls, exchange readily with deuterium oxide); 4.76 [2 H quartet (J = 6.5 Hz); -C<u>H</u>-CH_3]; 8.47 [6 H doublet (J = 6.5 Hz), -CH-C<u>H</u>$_3$]. M (mass spectrum): 166 (5), 165 (45), 164 (7), 151 (4), 150 (47), 148 (19),

147 (9), 132 (11), 123 (9), 122 (31), 121 (20), 120 (8), 119 (13), 108 (13), 106 (28), 105 (46), 104 (31), 93 (18), 80 (28), 79 (27), 78 (37), 77 (16), 67 (6), 66 (6), 65 (11), 64 (4), 63 (5), 53 (13), 52 (23), 51 (28), 50 (13), 45 (17), 43 (100), 41 (10), and 39 (19). The molecular ion at m/e 183 did not appear in the spectrum. Further elution with ether-methanol (4:1 v/v), and then methanol gave 2-(1-hydroxyethyl)pyridine-1-oxide (1.01 g., 36.3%) as a yellow oil after distillation at 110°/0.075 mm. The oil crystallized on standing to give a needle-shaped solid, m.p. 97-98° [reported (76), m.p. 97-99°]. ν_{max} (liquid film): 3350 (s), 2960 (s), 2920 (s), 2860 (m), 1440 (m), 1410 (s), 1225 (s), 1205 (m), 1175 (m), 1130 (m), 1090 (m), 1025 (w), 940 (w), 840 (s), 765 (m), and 665 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 1.85 [1 H quartet ($J_{5,6}$ = 6 Hz; $J_{4,6}$ = 2 Hz), C_6-H]; 2.46 [1 H quartet ($J_{3,4}$ = 8 Hz; $J_{3,5}$ = 3 Hz), C_3-H]; 2.60-2.94 (2 H complex multiplet, C_4-H, C_5-H); 4.02 (1 H singlet, hydroxyl, exchanges readily with D_2O); 4.76 [1 H quartet (J = 6.5 Hz), -C<u>H</u>-CH_3]; 8.47 [3 H doublet (J = 6.5 Hz), -CH-C<u>H</u>$_3$]. M (mass spectrum): 137 (5), 122 (9), 121 (45), 108 (11), 106 (11), 95 (32), 93 (25), 92 (7), 80 (14), 79 (100), 78 (80), 66 (5), 65 (6), 63 (5), 53 (10), 52 (49), 51 (43), 50 (19), 43 (40), 40 (8), 39 (35),

38 (9), and 28 (31). The molecular ion at m/e 139 did not appear in the spectrum.

5.2.8.0.0 Reactions with cyclohexanone at room temperature to give tertiary alcohols

5.2.8.1.0 Reaction of pyridine-1-oxide carbanion with cyclohexanone

Pyridine-1-oxide (0.95 g., 0.01 mole), suspended in anhydrous ether (70 ml.), was cooled to -65° in a Dry-ice acetone bath. The flask was flushed with dry, oxygen-free nitrogen and n-butyllithium (1.28 g., 0.02 mole) was added slowly to the stirred suspension. The brownish-yellow suspension which resulted was stirred for 1 hr. and then allowed to warm up to room temperature over a period of 20 min. Cyclohexanone (1.96 g., 0.02 mole) in anhydrous ether (10 ml.) was added and the reaction was allowed to proceed for 30 min. at room temperature. Water (40 ml.) was then added to the green solution. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange oil which slowly solidified. The reaction product was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene gave a yellow oil (0.198 g.) which did not contain nitrogen and was not investigated. Further elution with

benzene-ether (3:1 v/v) gave 2,6-di-(1'-hydroxycyclohexyl)pyridine-1-oxide (1.062 g., 36.5%) as white crystals, m.p. 159-161° [reported (66) m.p. 158°] after recrystallization from acetone. ν_{max} (KBr): 3275 (m), 3180 (m), 2920 (s), 2850 (s), 1460 (m), 1440 (m), 1375 (s), 1290 (w), 1275 (m), 1180 (s), 1140 (m), 1125 (m), 1055 (w), 1040 (m), 985 (s), 855 (m), 810 (s), 790 (s), 780 (s), 760 (s), 710 (s), 680 (s), 605 (s), 505 (m), and 435 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 2.5-2.9 (5 H multiplet, C_3-H, C_4-H, C_5-H, hydroxyls, the hydroxyls exchange with D_2O); 7.50-8.86 (20 H complex multiplet, cyclohexyl rings). Further elution with ether gave 2-(1'-hydroxycyclohexyl)pyridine-1-oxide (0.241 g., 12.5%) as a white solid, m.p. 89-91° [reported (67) m.p. 89-90°] after recrystallization from acetone. ν_{max} (KBr): 3150 (m), 3070 (m), 2960 (s), 2940 (s), 2860 (s), 1470 (m), 1430 (s), 1310 (m), 1290 (w), 1220 (w), 1235 (s), 1190 (s), 1180 (s), 1145 (m), 985 (m), 975 (w), 905 (w), 860 (w), 840 (w), 820 (m), 760 (s), 740 (m), 730 (s), 700 (s), 560 (w), 550 (w), 510 (w), and 490 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 1.84 [1 H doublet ($J_{5,6}$ = 6 Hz), C_6-H]; 2.41 (1 H singlet, hydroxyl, exchanges readily with D_2O); 2.54-3.04 (3 H complex multiplet, C_3-H, C_4-H, C_5-H); 7.32-8.92 (10 H complex multiplet, cyclohexyl

ring). Further elution with methanol yielded pyridine-1-oxide (0.252 g.).

5.2.8.2.0 Reaction of 4-methylpyridine-1-oxide carbanion with cyclohexanone

Using the procedure described in 5.2.8.1.0, 4-picoline-1-oxide (1.09 g., 0.01 mole), n-butyllithium (1.28 g., 0.02 mole) and cyclohexanone (1.96 g., 0.02 mole) gave a viscous yellow semi-solid which was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene gave a yellow oil (0.225 g.) which did not contain nitrogen and was not investigated. Elution with benzene-ether (3:1 v/v) gave 2,6-di-(1'-hydroxycyclohexyl)-4-picoline-1-oxide (0.76 g., 24.9%) as white crystals, m.p. 202-204° [reported (66) m.p. 198-199°], after recrystallization from acetone. ν_{max} (KBr): 3225 (s), 2930 (s), 2855 (s), 1600 (w), 1460 (s), 1440 (s), 1400 (s), 1345 (m), 1290 (w), 1270 (s), 1195 (s), 1185 (s), 1170 (s), 1155 (m), 1140 (s), 1035 (m), 985 (s), 862 (s), 790 (s), 710 (s), 700 (s), 670 (s), 605 (m), 520 (s), 510 (m), 500 (m), and 440 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 2.48 (2 H singlet, hydroxyls, exchange with D_2O); 2.89 (2 H singlet, C_3-H, C_5-H); 7.63 (3 H singlet, Ar-CH_3); 7.7-8.8 (20 H complex multiplet, cyclohexyl rings). Further elution with ether

yielded 2-(1'-hydroxycyclohexyl)-4-picoline-1-oxide (0.409 g., 19.8%) as a white solid, m.p. 113-115° [reported (66) m.p. 115°], after recrystallization from acetone. ν_{max} (KBr): 3160 (m), 3080 (w), 3040 (w), 2960 (s), 2930 (s), 2860 (s), 1480 (s), 1470 (s), 1440 (s), 1305 (w), 1275 (w), 1210 (s), 1185 (s), 1175 (s), 1140 (m), 1040 (w), 990 (m), 980 (s), 845 (s), 835 (s), 790 (s), 775 (m), 745 (s), 735 (s), 705 (w), 660 (w), and 565 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 1.97 [1 H doublet ($J_{5,6}$ = 6 cps), C_6-H]; 2.15 (1 H singlet, hydroxyl, exchanges readily with D_2O); 2.85 [1 H doublet ($J_{3,5}$ = 2 Hz), C_3-H]; 3.0 [1 H quartet ($J_{5,6}$ = 6 Hz; $J_{3,5}$ = 2 Hz), C_5-H]; 7.65 (3 H singlet, Ar-CH_3); 7.4-8.8 (10 H complex multiplet, cyclohexyl ring). Further elution with ether-methanol (2:1 v/v) gave 4-picoline-1-oxide (0.337 g.), identical (I.R.) with an authentic sample.

5.2.8.3.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with cyclohexanone

3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) suspended in anhydrous ether (70 ml.) was treated with n-butyl-lithium (1.8 g., 0.028 mole) and then with cyclohexanone (2.75 g., 0.028 mole) as described in 5.2.8.1.0. The yellow solid obtained was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene-ether

(3:1 v/v) gave 2,6-di-(1'-hydroxycyclohexyl)-3,4-dimethylpyridine-1-oxide (0.695 g., 15.6%) as white crystals, m.p. 193-195° [reported (67) m.p. 189-190°], after recrystallization from acetone. ν_{max} (KBr): 3250 (m), 3145 (m), 2940 (s), 2860 (s), 1440 (s), 1390 (s), 1270 (m), 1205 (s), 1190 (m), 1175 (m), 1140 (s), 1040 (m), 1020 (m), 985 (s), 880 (m), 840 (w), 815 (m), 775 (m), 765 (m), 750 (s), 710 (s), 670 (s), 660 (s), 595 (m), 515 (w), 485 (w), and 470 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 0.88 (1 H broad singlet, hydroxyl, exchanges with D_2O); 2.66 (1 H broad singlet, hydroxyl, exchanges readily with D_2O); 2.93 (1 H singlet, C_5-H); 7.59 (3 H singlet, Ar-CH_3); 7.70 (3 H singlet, Ar-CH_3); 7.74-8.90 (20 H complex multiplet, cyclohexyl rings). Elution with ether gave 2-(1'-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (1.245 g., 56.3%) as fine white needles, m.p. 152-154° [reported (67) m.p. 148-149°], after recrystallization from acetone. ν_{max} (KBr): 3140 (w), 3080 (w), 3040 (m), 2930 (s), 2850 (m), 1440 (s), 1380 (m), 1320 (w), 1265 (s), 1170 (s), 1160 (s), 1135 (s), 1100 (m), 1020 (s), 980 (s), 910 (w), 870 (m), 795 (m), 735 (s), 595 (s), 515 (w), 505 (w), and 485 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.05 (1 H singlet, C_6-H); 2.26 (1 H broad singlet, hydroxyl, exchanges readily with D_2O); 2.89 (1 H singlet, C_3-H); 7.71 (3 H singlet, Ar-CH_3); 7.80

(3 H singlet, Ar-CH_3); 7.85-8.92 (10 H complex multiplet, cyclohexyl ring). Mass spectrum: 222 (16), 221 (14) (M^+), 205 (17), 204 (100), 203 (15), 186 (11), 179 (9), 178 (68), 176 (10), 175 (9), 174 (19), 164 (19), 162 (20), 160 (7), 158 (10), 151 (8), 150 (18), 148 (10), 147 (25), 146 (14), 145 (7), 138 (22), 136 (7), 134 (29), 132 (9), 124 (10), 121 (17), 120 (11), 108 (11), 107 (66), 106 (81), 79 (30), 77 (26), 55 (10), 53 (11), 51 (8), 41 (19), 39 (18), and 28 (18). Further elution with methanol gave 3,4-lutidine-1-oxide (0.023 g.).

5.2.9.0.0 Reactions with Schiff bases to give secondary amines

5.2.9.1.0 Reaction of pyridine-1-oxide carbanion with N-benzylideneaniline

Using the procedure outlined in 5.2.6.1.0.a, pyridine-1-oxide (0.95 g., 0.01 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.28 g., 0.02 mole) and then with N-benzylideneaniline (3.62 g., 0.02 mole) for 1 hr. at -65°. Water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and removal of the chloroform under reduced pressure gave a viscous yellow oil which was chromatographed on a 2.5 x 42 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene

(1:1 v/v) gave a mixture of N-benzylideneaniline and benzaldehyde (1.86 g.) which was not examined further. Elution with benzene gave aniline (0.255 g.) as a yellow liquid, identical (I.R.) with an authentic sample. Further elution with benzene-ether (3:1 v/v) gave 2,6-bis-(α-N-phenylaminobenzyl)pyridine-1-oxide (1.87 g., 40.9%) as a dull yellow solid, m.p. 105°, after recrystallization from 75% ethanol. (Anal. Found: C, 81.31, H, 6.08. $C_{31}H_{27}NO$ requires: C, 81.36; H, 5.95). ν_{max} (KBr): 3400 (m), 3100 (m), 3080 (w), 3050 (m), 3020 (m), 2950 (w), 1590 (s), 1490 (s), 1430 (m), 1415 (m), 1315 (s), 1230 (s), 1180 (m), 1150 (w), 1125 (w), 1075 (w), 1025 (w), 990 (w), 865 (w), 835 (m), 770 (m), 745 (s), 690 (s), and 612 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 2.40-3.15 (17 H complex multiplets, C_3-H, C_4-H, C_5-H, 14 aromatic protons); 3.20-3.85 (8 H complex multiplets, -CH-, 6 aromatic protons); 5.56 (2 H singlet, -NH-, exchanges readily with D_2O). M (mass spectrum): 440 (8), 439 (12), 338 (8), 337 (30), 336 (22), 335 (24), 334 (6), 261 (6), 260 (28), 259 (20), 258 (6), 246 (10), 245 (36), 244 (8), 243 (5), 233 (4), 232 (8), 231 (5), 213 (4), 212 (10), 199 (6), 183 (34), 182 (80), 181 (46), 180 (100), 170 (8), 168 (18), 167 (20), 156 (15), 155 (10), 109 (8), 106 (10), 105 (22), 104 (16), 95 (24), 94 (10), 93 (78), 92 (12), 91 (8), 83 (6), 79 (13), 78 (26),

77 (100), 71 (8), 70 (6), 69 (10), 67 (6), 66 (26), 65 (18), 63 (8), 57 (16), 56 (12), 55 (12), 52 (16), 51 (38), 50 (10), 44 (16), 43 (18), 41 (20), and 29 (30). The molecular ion at m/e 457 did not appear in the spectrum.

5.2.9.2.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with N-benzylideneaniline

(a) In tetrahydrofuran (-65°, 60 min.). Using the procedure outlined in 5.2.6.1.0.a, 3,4-lutidine-1-oxide (1.23 g., 0.01 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.28 g., 0.02 mole) and then with N-benzylideneaniline (3.62 g., 0.02 mole) for 1 hr. at -65°. The yellow solid obtained was chromatographed on a 2.5 x 45 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v) gave a mixture of benzaldehyde and benzylideneaniline (0.575 g.). Elution with benzene gave aniline (0.187 g.) (identical I.R.). Elution with benzene-ether (3:1 v/v) gave 2,6-bis-(α-N-phenylaminobenzyl)-3,4-dimethylpyridine-1-oxide (3.0 g., 61.8%) as a dull yellow solid, m.p. 125°, after recrystallization from 95% ethanol. (Anal. Found: C, 81.95; H, 6.74. $C_{33}H_{31}N_3O$ requires: C, 81.64; H, 6.44). ν_{max} (KBr): 3350 (m), 3080 (w), 3040 (m), 3010 (m), 1580 (s), 1480 (s),

1430 (s), 1410 (m), 1310 (s), 1255 (s), 1215 (w), 1175 (m), 1150 (w), 1120 (w), 1065 (m), 1025 (m), 990 (w), 955 (w), 865 (w), 740 (s), and 685 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 2.55-3.15 (15 H complex multiplets, C_5-H, 14 aromatic protons); 3.25-3.70 (6 H complex multiplet, 6 aromatic protons); 3.89 (2 H broad singlet, -CH-); 5.49 (2 H singlet, -NH-, exchanges readily with D_2O); 7.77 (3 H singlet, Ar-CH_3); 7.89 (3 H singlet, Ar-CH_3). M (mass spectrum): 469 (1), 468 (2), 467 (3), 393 (1), 392 (3), 390 (2), 377 (1), 376 (5), 375 (5), 374 (3), 373 (1), 315 (1), 301 (2), 300 (6), 299 (2), 298 (1), 287 (1), 286 (2), 285 (2), 284 (3), 283 (1), 272 (1), 271 (2), 270 (2), 227 (2), 212 (2), 196 (2), 195 (3), 194 (2), 182 (20), 181 (26), 180 (34), 109 (1), 106 (2), 105 (4), 104 (6), 97 (2), 95 (2), 94 (8), 93 (100), 92 (12), 91 (3), 90 (2), 83 (2), 81 (2), 78 (7), 77 (29), 76 (3), 71 (2), 69 (3), 68 (5), 67 (32), 65 (18), 64 (3), 63 (5), 62 (2), 57 (3), 55 (4), 54 (4), 53 (2), 52 (5), 51 (12), 50 (4), 47 (8), 46 (3), 44 (7), 43 (3), 41 (7), 39 (13), and 38 (4). The molecular ion at m/e 485 did not appear in the spectrum. Elution with ether-methanol (10:1 v/v) gave an orange solid which, on recrystallization from acetone, gave 2-(α-N-phenylaminobenzyl)-4,5-dimethylpyridine-1-oxide as a white solid (0.368 g., 12.1%), m.p. 212-213°. (Anal. Found: C, 78.85; H, 6.77.

$C_{20}H_{20}N_2O$ requires: C, 78.91; H, 6.62). ν_{max} (KBr): 3330 (m), 3300 (m), 3100 (w), 3080 (w), 3055 (w), 3040 (w), 3020 (w), 1700 (m), 1590 (s), 1510 (m), 1490 (s), 1440 (s), 1390 (m), 1300 (s), 1275 (m), 1260 (s), 1185 (m), 1170 (m), 1125 (w), 1085 (w), 1030 (w), 1020 (w), 1005 (w), 990 (w), 920 (w), 865 (m), 830 (w), 750 (s), 720 (s), and 690 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 2.02 (1 H singlet, C_6-H); 2.5-3.0 (8 H complex multiplet, C_3-H, 7 aromatic protons); 3.2-3.55 (3 H complex multiplet, aromatic protons); 3.85 [1 H doublet ($\underline{J}$ = 3 Hz), -C$\underline{H}$-]; 5.22 (1 H singlet, -N$\underline{H}$-, exchanges readily with D_2O); 7.84 (3 H singlet, Ar-CH_3); 7.90 (3 H singlet, Ar-CH_3). M (mass spectrum): 289 (5), 288 (31), 287 (65), 273 (3), 211 (10), 210 (8), 209 (31), 197 (10), 196 (61), 195 (22), 194 (8), 184 (5), 183 (17), 182 (37), 181 (17), 180 (37), 168 (5), 167 (45), 152 (5), 108 (5), 107 (9), 106 (13), 104 (10), 79 (16), 78 (12), 77 (100), 65 (13), 63 (5), 53 (8), 52 (8), 51 (34), 43 (5), 41 (67), 39 (18), and 28 (18). The molecular ion at m/e 304 did not appear in the spectrum.

(b) <u>In ether (room temp.)</u>. 3,4-Lutidine-1-oxide (1.72 g., 0.014 mole) suspended in anhydrous ether (75 ml.) was treated with <u>n</u>-butyllithium (1.8 g., 0.028 mole) and then with <u>N</u>-benzylideneaniline (5.06 g., 0.028 mole) for 1 hr. at room temperature as described in 5.2.8.1.0.

The orange viscous oil obtained was chromatographed on a 2.5 x 45 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v) gave a mixture of benzaldehyde and N-benzylideneaniline (1.75 g.). Further elution with benzene gave aniline (99 mg.). Elution with benzene-ether (3:1 v/v) gave 2,6-bis-(α-N-phenylaminobenzyl)-3,4-dimethylpyridine-1-oxide (2.10 g., 31%), identical (I.R. and m.p.) with the material isolated as under 5.2.9.2.0.a. Further elution with ether-methanol (10:1 v/v) gave 2-(α-N-phenylaminobenzyl)-4,5-dimethylpyridine-1-oxide (0.742 g., 17.5%) as a white solid, identical (I.R. and m.p.) with that obtained as under 5.2.9.2.0.a. Elution with methanol gave 3,4-lutidine-1-oxide (0.71 g.).

5.2.9.3.0 Reaction of pyridine-1-oxide carbanion with pyridine

(a) In tetrahydrofuran (-65°, 1 hr.). Pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (2.56 g., 0.04 mole), and then with pyridine (3.16 g., 0.04 mole) for 1 hr. at -65° as described in 5.2.6.1.0.a. The reaction mixture was allowed to warm up to room temperature and then oxygen gas was bubbled into the mixture for 5 min. Water (30 ml.) was added. Extraction with chloroform

(6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown oil which was chromatographed on a 2.5 x 30 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a brown oil (0.332 g.) which was extracted with warm petroleum ether (b.p. 60-100°) (30 ml.) and decolorized by the addition of charcoal. Attempted crystallization of the yellow oil obtained (0.20 g.) from petroleum ether (b.p. 60-100°) failed. ν_{max} (liquid film): 3070 (w), 3010 (w), 2960 (s), 2930 (s), 2860 (s), 1580 (s), 1560 (s), 1260 (w), 1150 (w), 1085 (w), 1040 (w), 990 (w), 765 (s), 750 (s), 740 (s), and 610 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 1.2-3.2 (26 H complex multiplets, aromatic protons); 7.22 [12 H quartet ($\underline{J}$ = 8 Hz), -$C\underline{H}_2$-]; 8.0-9.2 (75 H complex multiplet, -$C\underline{H}_2$-). Gas liquid chromatography of this oil using the column and conditions described in 5.2.4.0.0.a, and programing from 100° to 250° at 4°/min. gave one component which was not collected or identified. M (mass spectrum) m/e 327 (M^+). Further elution with ether gave a brown oil. Extraction of this oil with warm petroleum ether (b.p. 60-100°) (30 ml.) and evaporation of the solvent gave a yellow oil (0.15 g.) which exhibited one peak when subjected to gas liquid chromatography using the column and conditions described above or to thin layer chromatography using benzene-ether

(3:1 v/v) as the developing solvent. ν_{max} (liquid film): 3060 (w), 2960 (s), 2930 (s), 2870 (s), 1580 (s), 1560 (s), 1460 (s), 1420 (s), 1380 (s), 1225 (m), 1130 (w), 1060 (m), 1035 (m), 990 (w), 840 (m), and 770 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 1.2-3.2 (5 H complex multiplets, aromatic protons); 8.1-9.4 (8 H complex multiplets, -$C\underline{H}_2$-). M (mass spectrum) m/e 170 (M^+). Elution with ether-methanol (5:1 v/v) and then with methanol gave a brown intractable solid (0.719 g.) which was not characterized.

(b) <u>In ether (1 hr., room temp.)</u>. Pyridine-1-oxide (0.95 g., 0.01 mole), suspended in anhydrous ether (70 ml.), was treated with <u>n</u>-butyllithium (1.28 g., 0.02 mole) and then with pyridine (1.58 g., 0.02 mole) for 1 hr. at room temperature as described in 5.2.8.1.0. The ethereal solvent was then distilled and simultaneously replaced with dry toluene (100 ml.). The toluene solution was boiled under reflux for 6 hr., cooled to room temperature, and treated carefully with water (30 ml.). Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a black semi-solid which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with benzene gave a yellow aliphatic oil (42 mg.) which was not examined further. Elution with

benzene-ether (3:1 v/v) and then ether gave a brown oil (0.291 g.). ν_{max} (liquid film): 3050 (w), 3000 (w), 2950 (s), 2915 (s), 2860 (s), 2840 (s), 1570 (s), 1550 (s), 1450 (s), 1410 (s), 1210 (w), 1140 (w), 1080 (w), 1030 (w), 980 (w), and 750 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 1.0-3.1 (poorly resolved multiplets, aromatic protons); 8.0-9.3 (complex multiplets, -$C\underline{H}_2$-). M (mass spectrum) m/e 328 (M^+). This material was not identified. Elution with ether-methanol (2:1 v/v) gave a black intractable tar (0.22 g.) which was not characterized.

5.2.9.4.0 Reaction of 3,4-dimethylpyridine-1-oxide carbanion with pyridine-1-oxide

Using the method described in 5.2.6.3.0.g, 3,4-lutidine-1-oxide (1.23 g., 0.01 mole), suspended in anhydrous ether (70 ml.), was treated with n-butyllithium (1.28 g., 0.02 mole) to give a solution of lithio-3,4-lutidine-1-oxide. This solution was then added slowly to a suspension of pyridine-1-oxide (1.9 g., 0.02 mole) in anhydrous ether (50 ml.) under an atmosphere of nitrogen and the resulting suspension was boiled under reflux for 1 hr. The reaction mixture was cooled to room temperature and oxygen gas was bubbled through the mixture. Water (30 ml.) was then added slowly. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and

evaporation of the chloroform under reduced pressure gave a yellow oil which was chromatographed on a 2.5 x 30 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a brown aliphatic oil (50 mg.) which was not investigated. Elution with ether-methanol (2:1 v/v), and then methanol gave 3,4-lutidine-1-oxide (0.88 g.), identical (I.R.) with an authentic sample. The solvent was removed from the aqueous reaction product to give a black intractable tar.

5.2.10.0.0 Attempted reaction of 4-methylpyridine-1-oxide carbanion with ethyl vinyl ether

4-Picoline-1-oxide (1.53 g., 0.014 mole) in anhydrous tetrahydrofuran (70 ml.) was treated with n-butyllithium (1.8 g., 0.028 mole) and then with ethyl vinyl ether (2.016 g., 0.028 mole) for 30 min. at -65° as described in 5.2.6.1.0.a. The brown oil obtained was chromatographed on a 2.5 x 38 cm. silica gel column. Elution with ether-methanol (3:1 v/v) and then methanol gave unreacted 4-picoline-1-oxide (0.85 g.), identical (I.R.) with an authentic sample.

5.3.0.0.0 Some other base-catalyzed reactions of pyridine-1-oxides

5.3.1.0.0 Attempted reaction of 4-methylpyridine-1-oxide with sodium amide and sulfur

4-Picoline-1-oxide (2.18 g., 0.02 mole) was added slowly to a stirred suspension of sodium amide (0.78 g., 0.02 mole) in liquid ammonia (140 ml.) and the grey suspension was stirred for 1 hr. Sulfur (1.28 g., 0.04 g. atom) was then added and the suspension was stirred for 1 hr., after which the reaction mixture was allowed to warm up to room temperature and the ammonia evaporated. Water (100 ml.) was added to the black semi-solid and the resulting yellow suspension was acidified to pH 2 with 18% hydrochloric acid. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a yellow solid which was chromatographed on a 2.5 x 25 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°) gave unreacted sulfur (0.85 g.), m.p. 115-117°. Further elution with ether-ethanol (3:1 v/v) gave 4-picoline-1-oxide (0.318 g.) as needles, m.p. 185-187°, after recrystallization from acetone. The aqueous acidic layer from above was adjusted to pH 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave 4-picoline-1-oxide (1.2 g.), identical (I.R.) with an authentic sample.

5.3.2.0.0 Attempted reaction of pyridine-1-oxide and lithium amide with sulfur

Under a nitrogen atmosphere pyridine-1-oxide (0.95 g., 0.01 mole) was added to a suspension of lithium amide (0.46 g., 0.02 mole) in anhydrous dimethoxyethane (50 ml.). The mixture was heated to 80° and sulfur (0.32 g., 0.01 g. atom) was added. The resulting brown suspension was boiled under reflux for an additional 17 hr. Water (20 ml.) was added to the cooled reaction mixture which was then acidified to pH 2 with 18% hydrochloric acid. The unreacted sulfur (0.225 g.) which precipitated was filtered. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave pyridine-1-oxide (54 mg.). The aqueous acidic layer was adjusted to pH 10 with aqueous sodium hydroxide. Extraction of the alkaline mixture with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave pyridine-1-oxide (0.495 g.).

5.3.3.0.0 Attempted reaction of pyridine-1-oxide and lithium methoxide with sulfur

(a) In dimethoxyethane (6 hr., 80°). Under an atmosphere of nitrogen, a mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium methoxide (0.53 g.,

0.014 mole) suspended in anhydrous dimethoxyethane (50 ml.) were heated at 80° for 1 hr., and then sulfur (0.384 g., 0.012 g. atom) was added. The suspension was boiled under reflux for 6 hr., then cooled to room temperature. Water (30 ml.) was added and the mixture was acidified to pH 2 with 18% hydrochloric acid. The unreacted sulfur which precipitated (0.332 g.), m.p. 120°, was filtered. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave pyridine-1-oxide (0.201 g.), identical (I.R.) with an authentic sample. The aqueous acidic layer was adjusted to pH 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave unreacted pyridine-1-oxide (0.436 g.).

(b) <u>In dimethoxyethane and 2-methoxyethanol (10:1 v/v).</u> A mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium methoxide (1.59 g., 0.042 mole) suspended in anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (5 ml.) were heated at 80° for 1 hr. Sulfur (0.384 g., 0.012 g. atom) was added and the mixture was boiled under reflux for an additional 20 hr. The reaction mixture was cooled and water (30 ml.) was added. The mixture was then acidified to pH 2 using 18% hydrochloric

acid and the sulfur which precipitated (0.28 g.), m.p. 118°, was filtered. The acidic aqueous solution, which does not give a purple color on addition of ferric chloride solution, was adjusted to pH 10 using aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave unreacted pyridine-1-oxide (0.782 g.), identical (I.R.) with an authentic sample.

5.3.4.0.0 Reaction of pyridine-1-oxide and lithium ethoxide with cyclohexanone

Under an atmosphere of nitrogen a mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium ethoxide (1.04 g., 0.02 mole) in absolute ethanol (50 ml.) were boiled under reflux for 1 hr. Cyclohexanone (0.98 g., 0.01 mole) was added and the mixture was boiled under reflux for an additional 19 hr. Water (30 ml.) was then added to the cooled solution. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a yellow oil which was chromatographed on a 2.5 x 40 cm. silica gel column. Elution with benzene, benzene-ether (3:1 v/v), and then ether gave a yellow aliphatic oil

(0.894 g.) which does not contain nitrogen and was not investigated further. Elution with methanol gave unreacted pyridine-1-oxide (0.724 g.).

5.3.5.1.0 Reaction of 3,4-dimethylpyridine-1-oxide and lithium hydride with sulfur

(a) In dimethoxyethane (20 hr.). Under a nitrogen atmosphere a mixture of 3,4-lutidine-1-oxide (1.23 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in anhydrous dimethoxyethane (50 ml.) was heated at 80° for 1 hr. Sulfur (0.48 g., 0.015 g. atom) was added and the resulting green suspension was boiled under reflux for 20 hr. The reaction mixture was cooled and water (30 ml.) was added very cautiously. The mixture was acidified to pH 2 with 18% hydrochloric acid and the sulfur which precipitated (0.252 g.) was filtered. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown solid which was chromatographed on a 2.5 x 47 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v) gave sulfur (20 mg.), m.p. 118°. Further elution with benzene gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.014 g., 0.9%), identical (I.R. and n.m.r.) with the product described under 5.2.2.4.1.a. Elution with benzene-ether (3:1 v/v) gave

a black tar (31 mg.) which was not investigated further. Elution with methanol yielded 3,4-lutidine-1-oxide (0.69 g.). The acidic aqueous layer from above was adjusted to pH 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform gave unreacted 3,4-lutidine-1-oxide (0.348 g.).

(b) <u>In dimethoxyethane and 2-methoxyethanol (50:4 v/v)</u>. A mixture of 3,4-lutidine-1-oxide (1.23 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (4 ml.) was allowed to react with sulfur (0.32 g., 0.01 g. atom) at 80° for 14 hr. as described in 5.3.5.1.0.a. The reaction mixture was acidified to pH 2 with 18% hydrochloric acid and the sulfur which precipitated (0.148 g.), m.p. 119°, was filtered. The acidic aqueous mixture was extracted and dried as outlined in 5.3.5.1.0.a, to give a brown solid which was chromatographed on a 2.5 x 45 cm. silica gel column. Elution with petroleum ether (b.p. 60-100°) gave sulfur (8 mg.), m.p. 118°. Further elution with petroleum ether (b.p. 60-100°)-benzene (1:1 v/v) gave 1-hydroxy-3,4-dimethyl-2-pyridinethione (0.081 g., 5.2%), identical (I.R. and n.m.r.) with the product isolated as under 5.2.2.4.1.a. Elution with benzene and then benzene-ether

(3:1 v/v) gave 1-hydroxy-3,4-dimethyl-6-pyridinethione (0.086 g., 5.5%), identical (I.R.) with the product obtained as under 5.2.2.4.1.a. Elution with methanol gave a black solid which, on sublimation at 80°/0.1 mm., gave 3,4-lutidine-1-oxide (60 mg.). The acidic aqueous layer from above was adjusted to pH 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave 3,4-lutidine-1-oxide.

5.3.5.2.0 Reaction of pyridine-1-oxide and lithium hydride with sulfur

(a) In dimethoxyethane (80°, 18 hr.). A mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in anhydrous dimethoxyethane (50 ml.) was heated with sulfur (0.489 g., 0.015 g. atom) for 18 hr. at 80° as described in 5.3.5.1.0.a. The mixture was acidified to pH 2 with 18% hydrochloric acid and the sulfur which precipitated (0.221 g.), m.p. 119°, was filtered. The acidic mixture was extracted and the extract dried as outlined in 5.3.5.1.0.a to give a brown liquid which was chromatographed on a 2.5 x 42 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°) gave sulfur (13 mg.), m.p. 118°. Elution with petroleum ether (b.p. 30-60°)-

benzene (1:2 v/v) and benzene gave 1-hydroxy-2-pyridinethione (0.152 g., 12%), identical (I.R. and n.m.r.) with that isolated in 5.2.2.1.0.a. Further work up only gave unreacted pyridine-1-oxide (0.433 g.).

(b) In dimethoxyethane and 2-(2-methoxyethoxy)-ethanol (50:4 v/v, 80°, 18 hr.). A mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in anhydrous dimethoxyethane (50 ml.) and 2-(2-methoxyethoxy)ethanol (4 ml.) was heated with sulfur (0.32 g., 0.01 g. atom) for 18 hr. at 80° as described in 5.3.5.1.0.a. Work up as under (a) above gave 1-hydroxy-2-pyridinethione (0.246 g., 19.45%).

(c) In dimethoxyethane and 2-methoxyethanol (50:4 v/v, 80°, 18 hr.). A mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (4 ml.) was allowed to react with sulfur (0.32 g., 0.01 g. atom) for 18 hr. at 80° as outlined in 5.3.5.1.0.a. Chromatography yielded 1-hydroxy-2-pyridinethione (0.273 g., 21.5%).

5.3.5.3.0 Reaction of 4-methylpyridine-1-oxide and lithium hydride with sulfur

A mixture of 4-picoline-1-oxide (1.09 g., 0.01 mole) and lithium hydride (0.795 g., 0.1 mole) suspended in

anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (4 ml.) was heated with sulfur (0.32 g., 0.01 g. atom) for 24 hr. at 80°. Work up gave a green oil which was chromatographed on a 2.5 x 42 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°) gave sulfur (5 mg.). Elution with benzene and then benzene-ether (3:1 v/v) gave 1-hydroxy-4-methyl-2-pyridinethione (0.081 g., 5.2%). 4-Picoline-1-oxide (0.40 g.) was recovered.

5.3.5.4.0 Reaction of pyridine-1-oxide and lithium hydride with ethylene sulfide

Under an atmosphere of nitrogen a mixture of pyridine-1-oxide (0.95 g., 0.01 mole) and lithium hydride (0.283 g., 0.03 mole) suspended in anhydrous dimethoxyethane (50 ml.) and 2-methoxyethanol (0.76 g., 0.01 mole) was heated to 80° and then ethylene sulfide (0.90 g., 0.015 mole) in monoglyme (10 ml.) was added. Heating at 80° was continued for 5 hr. Water (30 ml.) was added and the mixture acidified to pH 2 with 18% hydrochloric acid. The white, insoluble ethylene sulfide polymer (0.85 g.), m.p. 198-200° (decomp.), was filtered. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and removal of the chloroform under reduced pressure gave pyridine-1-oxide (0.1 g.). Pyridine-1-oxide (0.38 g.) was also

recovered from the aqueous acidic layer in the usual way (5.3.5.2.0.a).

5.3.6.0.0 Reaction of pyridine-1-oxide and sodium bis-trimethylsilylamide with cyclohexanone

Under a nitrogen atmosphere a mixture of 1,1,1,3,3,3-hexamethyldisilazane (4.5 g., 0.028 mole) and sodium amide (1.09 g., 0.028 mole) suspended in anhydrous benzene (30 ml.) was boiled under reflux until the sodium amide had dissolved and the evolution of ammonia had ceased. Pyridine-1-oxide (1.33 g., 0.014 mole) was added and the dark brown solution which resulted was boiled under reflux for 1 hr. 15 min. Cyclohexanone (2.74 g., 0.028 mole) was then added and heating under reflux continued for 1 hr. Water (40 ml.) was added to the cold reaction mixture. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown oil which was chromatographed on a 2.5 x 25 cm. silica gel column. Elution with petroleum ether (b.p. 30-60°)-benzene (1:1 v/v) gave a mixture of 1,1,1,3,3,3-hexamethyldisilazane and cyclohexanone (0.685 g.) which was not examined further. Elution with benzene-ether (3:1 v/v) gave a brown oil (0.134 g.) which exhibited strong carbonyl absorption and was not investigated. Elution

with ether yielded 2-(1'-hydroxycyclohexyl)pyridine-1-oxide (0.023 g., 0.85%), m.p. 89-91°, after recrystallization from acetone. The infrared spectrum of this product was identical with that product described in 5.2.8.1.0. Further elution with ether-methanol (3:1 v/v) and then methanol yielded unreacted pyridine-1-oxide (0.131 g.).

5.3.6.1.0 Reaction of 3,4-dimethylpyridine-1-oxide and sodium bis-trimethylsilylamide with cyclohexanone

(a) (3 hr. at room temp.). Under a nitrogen atmosphere a mixture of 1,1,1,3,3,3-hexamethyldisilazane (4.5 g., 0.028 mole) and sodium amide (1.09 g., 0.028 mole) suspended in anhydrous benzene (50 ml.) were boiled under reflux until the evolution of ammonia had ceased. The flask was flushed with nitrogen and 3,4-lutidine-1-oxide (1.72 g., 0.014 mole) in anhydrous benzene (25 ml.) was added. The resulting reddish-brown solution was stirred for 1 hr. at room temperature. Cyclohexanone (2.74 g., 0.028 mole) in anhydrous benzene (10 ml.) was added and stirring was continued for an additional 3 hr. at room temperature after which water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure

gave an orange liquid which was chromatographed on a 2.5 x 22 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a brown aliphatic oil (0.285 g.) which was not investigated further. Elution with ether gave 2-(1'-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (0.052 g., 1.68%) as a white solid, m.p. 148°, after recrystallization from acetone. Further elution with methanol gave 3,4-lutidine-1-oxide (1.01 g.).

(b) In tetrahydrofuran (20 hr., room temp.). Under an atmosphere of nitrogen a solution of sodium bis-trimethylsilylamide (1.76 g., 0.0096 mole) in anhydrous tetrahydrofuran (20 ml.) was added to a solution of 3,4-lutidine-1-oxide (0.59 g., 0.0048 mole) and cyclohexanone (0.94 g., 0.0096 mole) in anhydrous tetrahydrofuran (30 ml.). The dark brown solution which resulted was stirred at room temperature for 20 hr., and then water (40 ml.) was added. Extraction with chloroform (5 x 30 ml.), drying (Na_2SO_4), and removal of the chloroform under reduced pressure gave a yellow solid which was chromatographed on a 2.5 x 25 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a yellow aliphatic oil (0.086 g.) which was not investigated further. Elution with ether yielded a yellow semi-solid, which on recrystallization from acetone, gave 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (0.015 g.,

1.41%) as a white solid, m.p. 150°. Further elution with ether-methanol (3:1 v/v) and then methanol gave 3,4-lutidine-1-oxide (0.352 g.).

(c) In tetrahydrofuran (20 hr., 66°). A mixture of sodium bis-trimethylsilylamide (1.76 g., 0.0096 mole), 3,4-lutidine-1-oxide (0.59 g., 0.0048 mole) and cyclohexanone (0.94 g., 0.0096 mole) in anhydrous tetrahydrofuran (50 ml.) was boiled under reflux for 20 hr. as outlined in 5.3.6.1.0.a. The brown oil obtained was chromatographed on a 2.5 x 20 cm. silica gel column. Elution with benzene and then benzene-ether (3:1 v/v) yielded a brown aliphatic oil (0.123 g.) which was not examined. Elution with ether gave 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (0.015 g., 1.41%). Elution with ether-methanol (2:1 v/v) and then methanol gave 3,4-lutidine-1-oxide (0.252 g.).

5.3.7.0.0 Reaction of 3,4-dimethylpyridine-1-oxide and lithium bis-trimethylsilylamide with cyclohexanone

(a) In ether (1 hr., room temp.). A solution of 1,1,1,3,3,3-hexamethyldisilazane (2.25 g., 0.014 mole) in anhydrous ether (70 ml.) was cooled to -65° in a Dry-ice acetone bath and the flask was flushed with nitrogen. n-Butyllithium (0.896 g., 0.014 mole) was added slowly

and the mixture was allowed to warm up to room temperature over a period of 30 min. 3,4-Lutidine-1-oxide (0.861 g., 0.007 mole) was added and the mixture was stirred for an additional 30 min. at room temperature. Cyclohexanone (1.37 g., 0.014 mole) in anhydrous ether (10 ml.) was added and the reaction was allowed to proceed for 1 hr. at room temperature, after which water (40 ml.) was added. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange liquid which was chromatographed on a 2.5 x 35 cm. silica gel column. Elution with benzene-ether (3:1 v/v) gave a yellow aliphatic oil (57 mg.) which was not investigated further. Elution with ether yielded 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (0.061 g., 4%) as a white solid, m.p. 152-154°. Elution with ether-methanol (2:1 v/v) gave an orange semi-solid (0.751 g.) which was extracted with warm acetone (15 ml.). A white insoluble solid was filtered. Recrystallization from chloroform-acetone (1:4 v/v) gave 3-methyl-4-(1-hydroxycyclohexylmethyl)-pyridine-1-oxide (0.04 g., 2.6%) as white crystals, m.p. 217-219°. (Anal. Found: C, 70.35; H, 8.79. $C_{13}H_{19}NO_2$ requires: C, 70.55; H, 8.65). ν_{max} (KBr): 3240 (s), 2960 (m), 2940 (s), 2895 (m), 2855 (m), 1480 (s), 1455 (s), 1420 (m), 1410 (m), 1390 (m), 1370 (m), 1320 (w),

1305 (m), 1275 (s), 1250 (w), 1230 (w), 1205 (w), 1185 (s), 1175 (s), 1160 (s), 1125 (s), 1070 (m), 1050 (m), 1030 (m), 1000 (s), 990 (m), 925 (s), 845 (s), 800 (w), 755 (m), 715 (w), 700 (w), 630 (s), 575 (m), 540 (m), and 520 cm^{-1} (s). N.m.r. (CF_3CO_2H) τ: 1.48 [2 H doublet ($J_{5,6}$ = 6 Hz), C_2-H, C_6-H]; 2.08 [1 H doublet ($J_{5,6}$ = 6 Hz), C_5-H]; 6.89 (2 H singlet, C_4-CH_2-); 7.38 (3 H singlet, C_3-CH_3); 8.28 (10 H singlet, cyclohexyl ring). M (mass spectrum) m/e: 222 (1), 221 (3) (M^+), 203 (1), 124 (8), 123 (100), 122 (8), 108 (3), 107 (25), 106 (38), 99 (19), 81 (27), 79 (5), 77 (5), 69 (2), 67 (3), 65 (3), 57 (3), 55 (11), 53 (5), 51 (3), 43 (8), 42 (4), 41 (11), 39 (6), and 28 (6). The acetone mother liquor from above was concentrated *in vacuo* and the orange semi-solid obtained was sublimed at 140-220°/ 0.075 mm. to yield 3,4-lutidine-1-oxide (0.40 g.).

(b) *In ether (20 hr., room temp.)*. Under an atmosphere of nitrogen *n*-butyllithium (0.896 g., 0.014 mole) was added slowly to a solution of 1,1,1,3,3,3-hexamethyldisilazane (2.52 g., 0.014 mole) in anhydrous ether (70 ml.). The mixture was stirred for 30 min. at room temperature and then 3,4-lutidine-1-oxide (0.861 g., 0.007 mole) was added to give a reddish-brown solution which was stirred for 1 hr. Cyclohexanone (1.37 g., 0.014 mole) in anhydrous ether (10 ml.) was added and

the reaction was allowed to proceed for 20 hr. at room temperature, after which water (40 ml.) was added. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave an orange oil which was chromatographed on a 2.5 x 32 cm. silica gel column. Work up as above yielded 2-(1-hydroxycyclohexyl)-4,5-dimethylpyridine-1-oxide (0.07 g., 4.5%), and 3-methyl-4-(1-hydroxycyclohexyl-methyl)pyridine-1-oxide (0.051 g., 3.3%) as white crystals, m.p. 217-219°. 3,4-Lutidine-1-oxide (0.31 g.) was recovered.

5.3.8.0.0 Attempted reaction of pyridine-1-oxide and thallous ethoxide with cyclohexanone

(a) In ether (17 hr., room temp.). Under an atmosphere of nitrogen thallous ethoxide (2.49 g., 0.01 mole) was added to a suspension of pyridine-1-oxide (1.045 g., 0.011 mole) in anhydrous ether (60 ml.) and the resulting brown mixture was stirred for 2 hr. at room temperature. Cyclohexanone (0.98 g., 0.01 mole) was added and the reaction was allowed to proceed for an additional 17 hr., after which water (30 ml.) was added. Only unchanged starting materials were recovered.

(b) In absolute ethanol (2 hr., reflux temp.). Under an atmosphere of nitrogen a mixture of

pyridine-1-oxide (1.045 g., 0.011 mole) and thallous ethoxide (2.49 g., 0.01 mole) in absolute ethanol (50 ml.) were boiled under reflux for 3 hr. Cyclohexanone (0.98 g., 0.01 mole) was added and heating under reflux was continued for 2 hr. Water (30 ml.) was then added to the cool solution. The usual work up gave only unchanged pyridine-1-oxide (0.80 g.).

5.3.9.0.0 Attempted reaction of 3,4-lutidine-1-oxide and potassium 2,6-di-t-butylphenoxide with cyclohexanone

Potassium metal (0.782 g., 0.02 mole) was placed in a dry 3-necked 100 ml. flask equipped with a condenser, pressure-equalizing dropping funnel and magnetic stirrer. The flask was flushed with nitrogen and a solution of 2,6-di-t-butylphenol (4.94 g., 0.024 mole) in anhydrous tetrahydrofuran (50 ml.) was added slowly at room temperature. Following the initial vigorous reaction the mixture was boiled under reflux for 1 hr. and then cooled to room temperature. 3,4-Lutidine-1-oxide (1.23 g., 0.01 mole) and then cyclohexanone (1.96 g., 0.02 mole) in anhydrous tetrahydrofuran (10 ml.) were added and stirring at room temperature was continued for an additional 20 hr. after which water (25 ml.) was added.

Unchanged 3,4-dimethylpyridine-1-oxide (1.20 g.) was recovered.

5.4.0.0.0 Dehydration and polymerization of some 2-pyridylalkanol-1-oxides

5.4.1.0.0 Dehydration of 2-(2'-pyridyl)ethanol-N-oxide

(a) By distillation. A finely ground mixture of 2-(2'-pyridyl)ethanol-N-oxide (7.0 g.), freshly fused potassium bisulfate (1.0 g.) and methylene blue (0.2 g.) was distilled at 110°/0.075 mm. [reported (82) b.p. 150-200°/0.1 mm] to give 2-vinylpyridine-1-oxide (3.0 g., 49.2%) as a yellow oil. ν_{max} (liquid film): 3080 (m), 1650 (m), 1480 (s), 1425 (s), 1310 (w), 1225 (s), 1205 (s), 1165 (w), 1115 (w), 1060 (w), 1030 (w), 1000 (m), 945 (m), 850 (s), and 770 cm^{-1} (s). N.m.r. ($CDCl_3$) τ: 1.82 (1 H complex multiplet, C_6-H); 2.34-3.0 (4 H complex multiplets, C_3-H, C_4-H, C_5-H, vinyl proton); 3.93 [1 H doublet (J = 18 Hz), vinyl proton]; 4.44 [1 H doublet (J = 11 Hz), vinyl proton].

(b) Heating with sulfuric acid. 2-(2'-pyridyl)-ethanol-N-oxide (0.5 g.) in conc. sulfuric acid (2.5 ml.) was heated at 80-85° for 1 hr. Water (10 ml.) was added slowly to the acidic solution and the pH was then adjusted to 9 by the addition of sodium carbonate. The alkaline solution was extracted with chloroform (6 x 30 ml.)

and the extract dried (Na_2SO_4). Evaporation of the chloroform gave 2-(2'-pyridyl)ethanol-N-oxide (0.181 g.), identical (n.m.r.) with an authentic sample. The aqueous alkaline solution was concentrated in vacuo to give a dull yellow solid which was extracted with chloroform (2 x 75 ml.). Evaporation of the dried (Na_2SO_4) extract gave a mixture (0.275 g.) of 2-(2'-pyridyl)ethanol-N-oxide and 2-vinylpyridine-1-oxide in the ratio of 1:1 as calculated from the n.m.r. integral.

5.4.2.0.0 Dehydration and polymerization of 2-(2'-pyridyl)ethanol-N-oxide

2-(2'-Pyridyl)ethanol-N-oxide (1.12 g.) in concentrated sulfuric acid (5 ml.) was heated at 140-145° for 4 hr. Water (10 ml.) was added and the pH of the acidic solution was adjusted to 9 with aqueous sodium hydroxide. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform under reduced pressure gave a brown hygroscopic solid (0.578 g.). The aqueous alkaline solution was concentrated in vacuo to give a white solid which was extracted with chloroform (2 x 50 ml.), the extract dried (Na_2SO_4), and the chloroform evaporated under reduced pressure to give a brown hygroscopic solid (0.383 g.). The combined products (98.5% yield) were dissolved in chloroform and the polymer was

reprecipitated by the addition of acetone. This process was repeated several times to give poly-(2-vinylpyridine-1-oxide) as a yellow hygroscopic solid, m.p. 195° (decomp.) [reported (24) m.p. about 220° (decomp.)]. N.m.r. ($CDCl_3$) (internal TMS capillary) τ: 1.0-1.64 (1 H broad singlet, C_6-H); 1.64-2.76 (3 H broad singlet, C_3-H, C_4-H, C_5-H); 4.6-7.0 (3 H broad doublet, -$C\underline{H}_2$-$C\underline{H}$-).

5.4.3.0.0 Dehydration and polymerization of 2-(1-hydroxyethyl)pyridine-1-oxide

A solution of 2-(1-hydroxyethyl)pyridine-1-oxide (0.269 g.) in concentrated sulfuric acid (2 ml.) was stirred for 16 hr. at room temperature. Water (20 ml.) was added and the pH of the acidic solution was adjusted to 9 with solid sodium carbonate. The solvent was removed in vacuo to give a tan-colored solid which was extracted with chloroform (3 x 50 ml.). The extract was dried (Na_2SO_4) and the chloroform evaporated under reduced pressure to give poly-(2-vinylpyridine-1-oxide) as a hygroscopic solid (0.229 g., 98%). The polymer was purified by dissolving in chloroform and then reprecipitation by the addition of acetone. This process was repeated several times to give a tan colored solid, m.p.

about 190° (decomp.) [reported (24) m.p. about 220° (decomp.)].

5.4.4.0.0 Polymerization of 2-vinylpyridine-1-oxide

(a) In the presence of n-butyllithium. A solution of 2-vinylpyridine-1-oxide (2.5 g.) in dry toluene (50 ml.) was added dropwise over a period of 20 min. to a well stirred mixture of n-butyllithium (0.3 g. in n-hexane 1.5 ml.), paraffin wax (1 g.) and dry toluene (100 ml.) at 50° in an atmosphere of nitrogen. The mixture was stirred for an additional 3 hr. at 50° and then methanol (40 ml.) was added. The solvent was removed under reduced pressure and the flaky yellow solid which remained was extracted with warm petroleum ether (b.p. 30-60°) (3 x 50 ml.) and then ether (100 ml.) to remove the paraffin wax. The remaining yellow insoluble flaky solid (2.42 g.) was purified by dissolution in methanol and then reprecipitation by the addition of ether. This process was repeated several times to yield poly-(2-vinylpyridine-1-oxide) as a yellow solid, m.p. 220-240° (decomp.) [reported (24) m.p. about 220° (decomp.)]. N.m.r. (D_2O) (internal TMS capillary) τ: 1.0-1.84 (1 H broad singlet, C_6-H); 1.84-3.0 (3 H broad singlet, C_3-H, C_4-H, C_5-H); 5.2-8.7 (3 H -CH-CH_2-).

(b) On standing at room temperature. A solution of 2-vinylpyridine-1-oxide (0.24 g.) in chloroform (20 ml.) was allowed to stand at room temperature for 48 hr. The solvent was removed in vacuo to give poly-(2-vinylpyridine-1-oxide) as a white solid (0.20 g., 96%), m.p. 220-240° (decomp.). The polymer was washed with acetone and dried at 80°/0.075 mm. for 18 hr. N.m.r. (D_2O) (internal TMS capillary) τ centered at: 1.6 (1 H broad singlet, C_6-H); 2.4 (3 H broad singlet, C_3-H, C_4-H, C_5-H); 6.4 (1 H broad singlet, -CH-); 7.6 (2 H broad singlet, $-CH_2-$).

5.5.0.0.0 Preparation of precursors and authentic samples

5.5.1.0.0 3,4-Dimethylpyridine-1-oxide

[cf. Jones and Rao (77)]

A solution of 3,4-dimethylpyridine (40 g.) in glacial acetic acid (300 ml.) and 30% hydrogen peroxide (80 ml.) was boiled under reflux for 12 hr. A portion of the solvent was distilled (150 ml.) and the acidic mixture was adjusted to pH 10 with aqueous sodium hydroxide. Extraction with chloroform (6 x 175 ml.), drying (Na_2SO_4), and evaporation of the chloroform gave 3,4-dimethylpyridine-1-oxide (42 g., 91%) as white crystals, m.p. 135° [reported (77) m.p. 128-130°], after

recrystallization from acetone. ν_{max} (KBr): 3090 (m), 3070 (m), 2980 (w), 2925 (w), 1670 (m), 1480 (s), 1455 (s), 1380 (m), 1280 (m), 1305 (m), 1265 (s), 1250 (m), 1230 (m), 1175 (s), 1155 (s), 1140 (s), 1030 (s), 900 (m), 850 (s), 770 (s), 755 (s), 705 (m), 630 (w), and 580 cm^{-1} (w). N.m.r. ($CDCl_3$) τ: 1.97 (1 H singlet, C_2-H); 2.04 [1 H doublet ($J_{5,6}$ = 6 Hz), C_6-H]; 2.95 [1 H doublet ($J_{5,6}$ = 6 Hz), C_5-H]; 7.60 (3 H singlet, C_3-CH_3); 7.79 (3 H singlet, C_4-CH_3).

5.5.2.0.0 4-Chloro-3-methylpyridine-1-oxide

[cf. Taylor and Crovetti (78); Katrizky (75)]

3-Methylpyridine-1-oxide (10.0 g.) was added slowly to a cooled (0-5°) mixture of concentrated sulfuric acid (35 ml.) and concentrated nitric acid (28 ml.). The pale yellow solution was heated at 100-105° for 2 hr. After cooling, the reaction mixture was poured onto ice, and solid sodium carbonate was added until the pH was 2. A yellow insoluble solid was filtered, washed with water (50 ml.), chloroform (100 ml.), and then discarded. The aqueous solution was extracted with chloroform (6 x 150 ml.), dried (Na_2SO_4) and the solvent evaporated to give 4-nitro-3-picoline-1-oxide (10.1 g., 72.3%), m.p. 136° [reported (78), m.p. 137°], after recrystallization from acetone.

Acetyl chloride (40 ml.) was slowly added to 4-nitro-3-methylpyridine-1-oxide (8.0 g.), and the mixture was heated on a steam bath for 5 min. Crushed ice was added to the orange reaction mixture and the resulting solution was adjusted to pH 9 with aqueous sodium hydroxide. Extraction with chloroform (6 x 100 ml.), drying (Na_2SO_4), and evaporation of the chloroform gave 4-chloro-3-methylpyridine-1-oxide (6.7 g., 89.5%) as a white solid, m.p. 119-120° [reported (75) m.p. 122-123°], after recrystallization from acetone.

5.5.3.0.0 1-Hydroxy-2-pyridinethione

[cf. Shaw, Bernstein, Losee and Lott (18)]

2-Bromopyridine-1-oxide (7.0 g., 0.044 mole) was added to a chloroform solution of perbenzoic acid (prepared from benzoyl peroxide) containing a 20% excess of the oxidizing agent. After 4 days at room temperature, the chloroform solution was extracted with 20% hydrochloric acid (3 x 30 ml.). The acidic extracts were evaporated to dryness in vacuo and the residue was crystallized from absolute ethanol to give 2-bromopyridine-1-oxide hydrochloride (6.2 g., 66%), as white crystals, m.p. 135° [reported (18) m.p. 135-136°].

A solution of 2-bromopyridine-1-oxide hydrochloride (1.94 g., 0.01 mole) and thiourea (0.97 g., 0.01 mole) in absolute ethanol (30 ml.) was boiled under reflux for

1 hr. The precipitate of 2-pyridyl-1-oxide isothiourea hydrobromide (1.8 g., 72%), m.p. 160° (decomp.) [reported (18) m.p. 160-160.5° (decomp.)], was filtered. A solution of the above compound (1.25 g., 0.005 mole) and sodium carbonate (1 g.) in water (25 ml.) was kept for 4 hr. at room temperature. The solution was acidified to pH 2 with 18% hydrochloric acid. Extraction with chloroform (6 x 50 ml.), drying (Na_2SO_4), and evaporation of the chloroform gave 1-hydroxy-2-pyridinethione (0.5 g., 78%) as a white solid, m.p. 68° [reported (18) m.p. 68-70°].

5.5.4.0.0 1-Hydroxy-2-pyridone

[cf. Shaw, Bernstein, Losee and Lott (18)]

A solution of 2-bromopyridine-1-oxide hydrochloride (0.7 g., 0.0031 mole) and 10% aqueous sodium hydroxide (5 ml.) was heated on a steam-bath for 90 min. The mixture was acidified with 18% hydrochloric acid and evaporated to dryness *in vacuo* and the residue was extracted with chloroform in a Soxhlet extractor. Evaporation of the chloroform and then recrystallization from benzene gave 1-hydroxy-2-pyridone (0.2 g., 54%) as needles, m.p. 148° [reported (11) m.p. 149-150°]. N.m.r. ($CDCl_3$) τ: 0.42 (1 H singlet, hydroxyl, exchanges readily with D_2O); 2.24 [1 H quartet, ($J_{5,6}$ = 6.5 Hz; $J_{4,6}$ = 1.5 Hz), C_6-H]; 2.64 [1 H sextet

($J_{3,4}$ = $J_{4,5}$ = 9 Hz; $J_{4,6}$ = 2 Hz), C_4-H]; 3.60 [1 H quartet ($J_{3,4}$ = 9 Hz; $J_{3,5}$ = 1.5 Hz), C_3-H]; 3.68 [1 H quartet ($J_{5,6}$ = 6.5 Hz; $J_{3,5}$ = 1.5 Hz), C_5-H].

5.5.5.0.0 2-(2'-Pyridyl)ethanol-N-oxide

[cf. Boekelheide and Feely (79)]

A solution of 30% hydrogen peroxide (10 ml.) was added slowly to a solution of 2-(2-pyridyl)ethanol (24.6 g.) in glacial acetic acid (200 ml.) and the resulting mixture was heated at 80° for 2 hr. A second addition of 30% hydrogen peroxide (10 ml.) was made and heating at 80° was continued for 2 hr. After a final addition of 30% hydrogen peroxide (20 ml.) the mixture was heated at 80° for a further 9 hr. The mixture was concentrated under reduced pressure and the pH adjusted to 9 with aqueous sodium hydroxide. Extraction with chloroform (6 x 75 ml.), drying (Na_2SO_4), and evaporation of the chloroform gave 2-(2'-pyridyl)ethanol-N-oxide as a yellow oil (25 g., 90%). Crystallization from ethyl acetate gave white crystals, m.p. 92-94° [reported (79) m.p. 93-95°]. ν_{max} (KBr): 3250 (s), 3080 (m), 2970 (m), 2870 (m), 1480 (m), 1430 (s), 1250 (s), 1235 (s), 1170 (w), 1125 (w), 1065 (m), 1055 (s), 1030 (m), 870 (s), 775 (s), 750 (m), 730 (m), and 575 cm^{-1} (m). N.m.r. ($CDCl_3$) τ: 1.82 [1 H quartet ($J_{5,6}$ = 6 Hz; $J_{4,6}$ = 2 Hz), C_6-H]; 2.54-2.94 (3 H complex multiplets,

C_3-H, C_4-H, C_5-H); 4.64 (1 H singlet, hydroxyl, exchanges readily with D_2O); 6.08 [2 H triplet ($\underline{J}$ = 6 Hz), -$C\underline{H}_2$-]; 6.88 [2 H triplet ($\underline{J}$ = 6 Hz), -$C\underline{H}_2$-].

5.5.6.0.0 N-Benzyl-4,5-dimethylpyridinium bromide

A solution of 3,4-dimethylpyridine (1.06 g., 0.01 mole) and benzyl bromide (1.71 g., 0.01 mole) in absolute ethanol (50 ml.) was boiled under reflux for 10 hr. The solvent was removed in vacuo to give N-benzyl-4,5-dimethylpyridinium bromide (2.58 g., 93.5%) as white crystals, m.p. 206-207°, after recrystallization from absolute ethanol, identical (I.R. and n.m.r.) with the sample isolated as under 5.2.4.2.0.b.

5.5.7.0.0 Sodium bis-trimethylsilylamide

[cf. Wannagat and Niederprüm (80)]

Under a nitrogen atmosphere 1,1,1,3,3,3-hexamethyldisilazane (9.0 g., 0.056 mole) and sodium amide (2.18 g., 0.056 mole) suspended in anhydrous benzene (50 ml.) were boiled under reflux until the evolution of ammonia had ceased. The solution was filtered and then concentrated to a volume of 20 ml. On cooling, sodium bis-trimethylsilylamide (2.5 g., 24.5%) crystallized, m.p. 165-167° [reported (80) m.p. 165-167°]. The mother liquor was concentrated in vacuo to give a moist white solid which, on recrystallization from benzene gave more

sodium bis-trimethylsilylamide (2.6 g., 25.4%; overall yield 50%).

6.0.0.0.0 BIBLIOGRAPHY

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Synthesis of 1-Hydroxy-2-pyridinethiones, 1-Hydroxy-2-pyridones and Halopyridine 1-Oxides: Reactions of Lithiopyridine 1-Oxides

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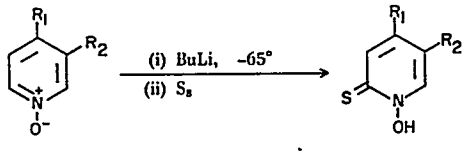
Sir:

Treatment of pyridine 1-oxides with *n*-butyllithium at −65° gives lithiopyridine 1-oxides which were shown to react with carbonyl compounds (1). Addition of sulfur in excess to the lithiopyridine 1-oxide solutions now provides a convenient route to the pharmacologically interesting 1-hydroxy-2-pyridinethiones, and interesting novel products are obtained by the addition of bromine.

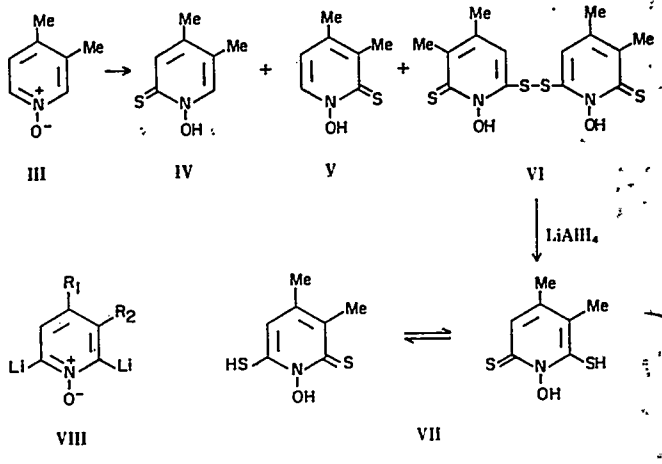
Pyridine 1-oxide (Ia) itself gave the parent 1-hydroxy-2-pyridinethione (IIa), m.p. 68°, [reported (2) m.p. 68-70°] in low (8%) yield, while 4-picoline 1-oxide (Ib) gave the 4-methyl derivative (IIb), m.p. 59°, in 39% yield (3). 4-Chloro-3-methylpyridine 1-oxide (Ic) gave the 6-thione (11.5%), m.p. 99-101°, a rather unstable compound which decomposes violently, together with at least one high molecular weight product. All of the 1-hydroxy-2-pyridinethiones (cyclic thiohydroxamic acids) gave zinc salts. 3,4-Lutidine 1-oxide (III) gave an interesting result:



I II

(a) $R_1 = R_2 = H$
(b) $R_1 = Me$, $R_2 = H$
(c) $R_1 = Cl$, $R_2 = Me$

both possible 1-hydroxy-2-pyridinethiones (IV) (24%), m.p. 121-122°, and (V) (12.5%), m.p. 128-129°, were obtained together with a dimeric product (VI) (37.4%), m.p. 186-187° (the orientation of the methyl groups is uncertain and two isomeric symmetrical structures are possible which could not be distinguished apart by mass or nmr spectroscopy or by its reactions. The unsymmetrical structure is eliminated since the nmr spectrum (in deuteriopyridine) exhibits only three peaks, one at τ 2.9, due to the two pyridine protons, and two at τ 7.46 and 7.97 due to the two types of methyl groups). Reduction of VI with lithium aluminum hydride gave the 1-hydroxythiol thione (VII), m.p. 120-122°, in quantitative yield. Compound VII yields a 2,4-dinitrophenylsulfenyl derivative, m.p. 175-177°, and a zinc salt, m.p. >300°. The formation of VI



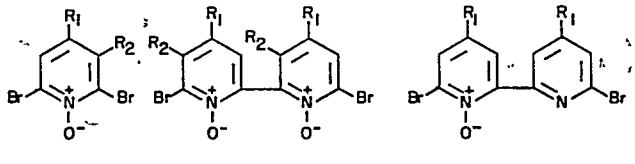
III IV V VI

VIII VII

suggests the possible intermediacy of the dilithio derivative (VIII; $R_1 = R_2 = Me$). No attempt has been made to optimize the yields in these or the other reactions described.

The reaction of the lithiopyridine 1-oxides with oxygen gave the corresponding hydroxamic acids, but in lower yields than the sulfur derivatives. No product could be obtained from Ia itself, but Ib gave 1-hydroxy-4-methyl-2-pyridone (14%), m.p. 129-130° (4). 3,4-Lutidine 1-oxide (III) gave a mixture of 1-hydroxy-4,5-dimethyl-2-pyridone (14%), m.p. 195°, and 1-hydroxy-3,4-dimethyl-2-pyridone (10%), m.p. 169-170°.

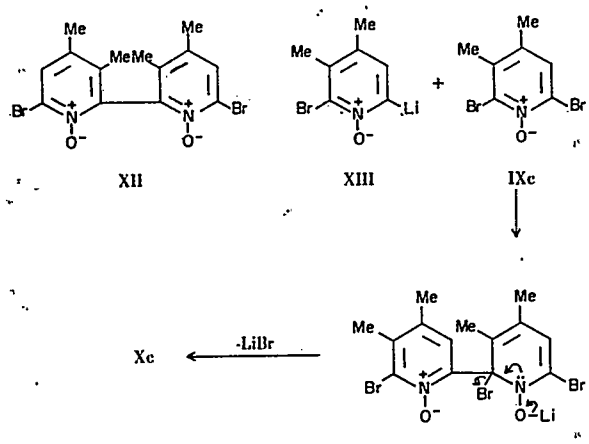
Addition of bromine to a cold (−65°) solution of the lithiopyridine 1-oxides in tetrahydrofuran gave a variety of dihalogenated products after short reaction periods whether or not the excess bromine was immediately removed by the addition of phenol. Three products were obtained from Ia and shown to be 2,6-dibromopyridine 1-oxide (IXa) (3%), m.p. 187-188° dec., [reported (5) m.p. 186.5-188.5°], 6,6'-dibromo-2,2'-dipyridyl 1,1'-di-



IX X XI

(a) $R_1 = R_2 = H$
(b) $R_1 = Me$, $R_2 = H$
(c) $R_1 = R_2 = Me$

oxide (Xa) (8.2%), m.p. 232-234° dec., and 6,6′-dibromo-2,2′-dipyridyl 1-oxide (XIa) (6.2%), m.p. 209-211° dec. Similarly, Ib gave IXb (5%), m.p. 154-155°, Xb (13%), m.p. 219-222° dec., and XIb (18%), m.p. 166-167°. On the other hand, III gave only 2,6-dibromo-3,4-dimethylpyridine 1-oxide (IXc) (13%), m.p. 144°, and Xc (4%), m.p. 200-202° dec. The structure of Xc was confirmed by its nmr spectrum. Had a symmetrical product, *e.g.* (XII), been the one formed one would have expected to see only one 2H peak due to the pyridine β-protons and two methyl peaks in the nmr. In actual practice, two 1H pyridine β-proton peaks were observed at τ 2.5 and 2.9 and four methyl singlet peaks were observed at τ 7.55, 7.7, 7.75 and 8, respectively, the ratio of the areas of the latter being 3:3:3:3. Xc undoubtedly arises from a nucleophilic addition of the monolithiated product (XIII) to IXc



and the observed orientation is consistent with the known effect of a 3-methyl group upon the addition of organolithium compounds to pyridines (6).

None of the bimolecular products were obtained in the reactions with chlorine gas. Pyridine 1-oxide gave a 4.5% yield of 2,6-dichloropyridine 1-oxide, m.p. 139-140° [reported (7) m.p. 139.5-140.5°], and III gave 2.6-dichloro-3,4-dimethylpyridine 1-oxide (8.8%), m.p. 165-166°.

In no case were any monobrominated or monochlorinated compounds obtained even when the amounts of halogen were decreased, and this implicates the intermediacy of the dianions VIII. No halogenated products were obtained in blank runs when the BuLi was omitted (8).

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