THE PREPARATION OF
3,4-DIAMINOPYRIDINE

BY

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ABSTRACT

The preparation of 3,4-diaminopyridine from pyridine was investigated, but found to be of little synthetic value because of the low yield obtained on the rearrangement of 4-nitraminopyridine to 3-nitro-4-aminopyridine. An attempt to nitrate nicotinamide-N-oxide resulted in the isolation of nicotinic acid-N-oxide. Attempts to nitrate nicotinic acid-N-oxide were unsuccessful. Attempts to oxidize 3-methylpyridine-N-oxide and 4-nitro-3-methylpyridine were unsuccessful. The nitration of 3-methylpyridine-N-oxide led to the isolation of 2-nitro-5-methylpyridine, which has not previously been reported as a by-product of that reaction.

STATEMENT OF PROBLEM

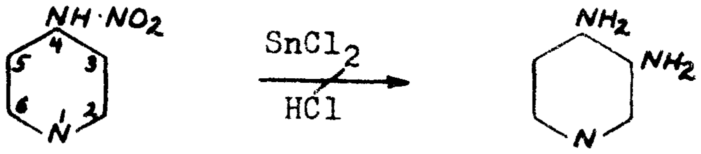
The purpose of this study was to investigate the preparation of 3,4-diaminopyridine.

INTRODUCTION

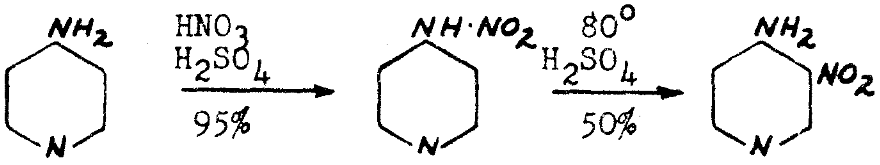
It was the purpose of this investigation to prepare 3,4-diaminopyridine by nitrating an appropriate pyridine-N-oxide to introduce a nitro group in the 4-position, which would then be reduced to an amino group. The amino group in the 3-position would be obtained by performing a Hofmann degradation on an amide group in that position. To this end nicotinamide-N-oxide and nicotinic acid-N-oxide were prepared; however, attempts to nitrate these compounds were unsuccessful. The attempts to oxidize 4-nitro-3-methylpyridine-N-oxide and 3-methylpyridine-N-oxide were also unsuccessful. Therefore, 4-nitropyridine-N-oxide was prepared from pyridine via pyridine-N-oxide. Reduction yielded 4-aminopyridine, which was converted to 4-nitraminopyridine. Rearrangement of this compound gave 3-nitro-4-aminopyridine, which was then reduced to the desired 3,4-diaminopyridine.

LITERATURE SEARCH

The preparation of 3,4-diaminopyridine (II) by the action of stannous chloride on 4-nitraminopyridine (I) was reported in 1924 by Koenigs, Kinne, and Weiss[1]; their procedure, however, "is stricken from the record"[2]. Koenigs, Mields, and Gurlt[3] described the preparation of 4-nitraminopyridine (I) from 4-aminopyridine (III) in 95 per cent yield, with subsequent rearrangement to 3-nitro-4-aminopyridine (IV) in 50 per cent yield by heating in sulfuric acid.

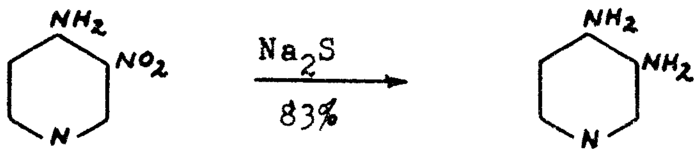


I II



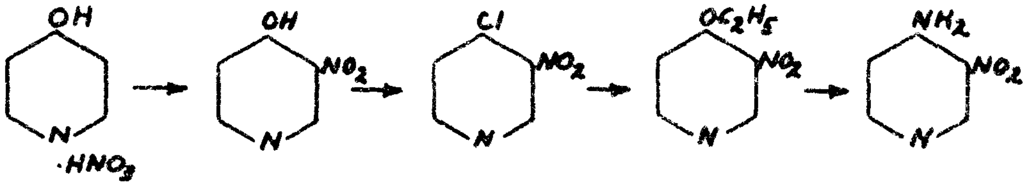
III I IV

Bremer[4] subsequently reported in 1935 the reduction of 3-nitro-4-aminopyridine by sodium hydrosulfite, and obtaining 3,4-diaminopyridine hydrochloride in 77 per cent yield. Koenigs, Bueren, and Jung[5] reported a similar reduction using sodium sulfide, obtaining 3,4-diaminopyridine in 83 per cent yield.



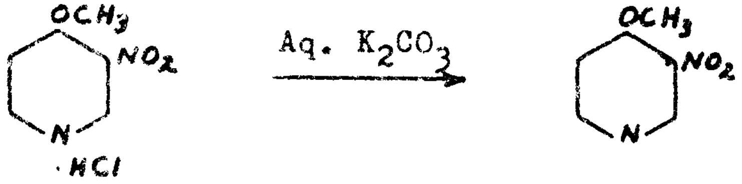
IV II

To obtain 3-nitro-4-aminopyridine, Koenigs and Freter[6] used the following sequence of reactions. Nitration of 4-hydroxypyridine nitrate (V) gave 3-nitro-4-hydroxypyridine (VI) in 56 to 68 per cent yield. This was chlorinated with a mixture of phosphorus pentachloride and phosphorus oxychloride, and the reaction mixture was treated with ethanol. The crystals thus isolated were believed by the authors to be 3-nitro-4-chloropyridine (VII); however, Bremer[7] later identified this compound as 3-nitro-4-ethoxypyridine hydrochloride (VIII). This was heated with ammonium hydroxide in a sealed tube at 120°C for 6 hours giving 3-nitro-4-aminopyridine. No yield data was given for the last two reactions mentioned. The 3-nitro-4-aminopyridine thus obtained was identical with that obtained by Koenigs et al[3] by the rearrangement of 4-nitraminopyridine.



V VI VII VIII IV

In a similar manner, Bremer[7] obtained a 70 per cent yield of 3-nitro-4-hydroxypyridine by the nitration of 4-hydroxypyridine nitrate. This was chlorinated by phosphorus pentachloride and phosphorus oxychloride to give 3-nitro-4-chloropyridine, which was then converted, by treating with methanol, to 3-nitro-4-methoxypyridine hydrochloride (IX). The overall yield from 3-nitro-4-hydroxypyridine was 85 per cent of theory. 3-Nitro-4-methoxypyridine (X) was obtained by neutralizing an aqueous solution of the hydrochloride salt with potassium carbonate and extracting with ethyl ether.



IX X

The 3-nitro-4-methoxypyridine has the advantage of not slowly polymerizing as the more reactive 3-nitro-4-chloropyridine does.

Weidenhagen and Weeden[8] employed the same sequence of reactions as Premer[7] to obtain 3-nitro-4-methoxypyridine which, by heating with ammonium hydroxide under pressure, was converted to 3-nitro-4-aminopyridine. This was reduced to 3,4-diaminopyridine in an undisclosed manner. Yields for these reactions were not reported. These authors also synthesized 2-substituted imidozolo derivatives by condensing 3,4-diaminopyridine with alkyl and aryl aldehydes. The aldehydes used include formaldehyde, acetaldehyde, propionaldehyde, benzaldehyde, anisaldehyde, and p-nitrobenzaldehyde.

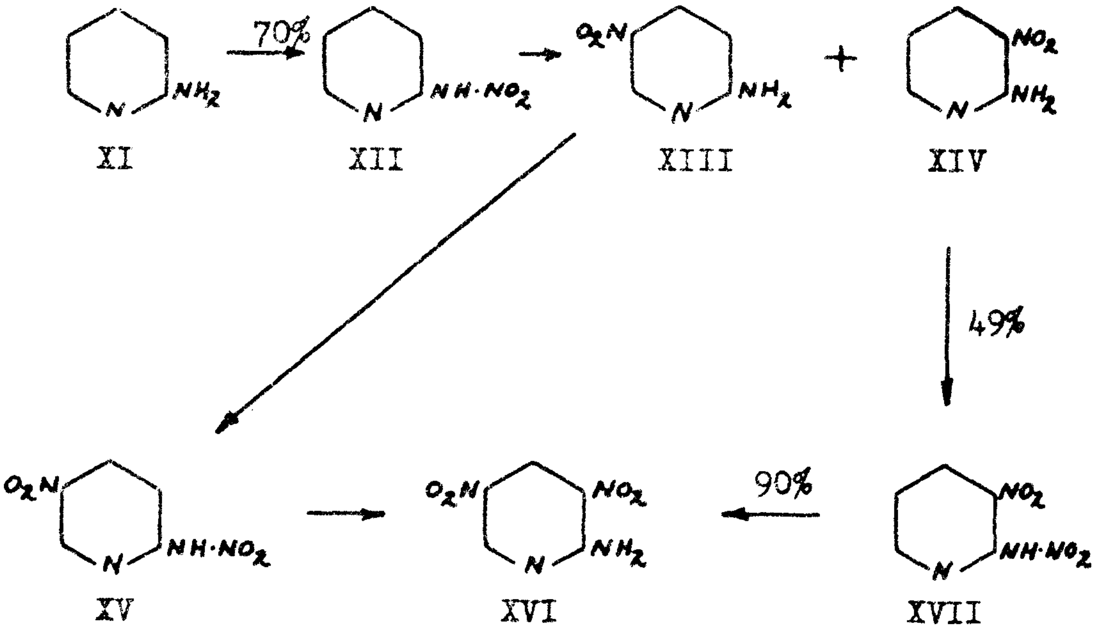
II

IMIDAZOLO-5',4'-
3,4-PYRIDINE

Kruger and Mann[9] also used a mixture of fuming nitric and sulfuric acids to nitrate 4-hydroxypyridine nitrate, and obtained 3-nitro-4-hydroxypyridine in 88 per cent yield. This compound was chlorinated in the usual manner to give an 82 per cent yield of 3-nitro-4-chloropyridine, which was isolated by distillation at reduced pressure.

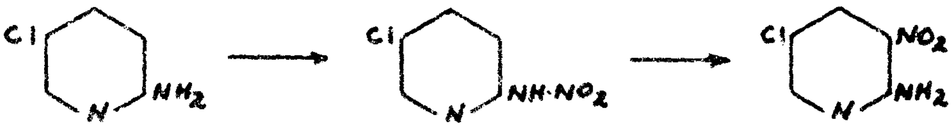
An alternate means of producing pyridyl nitro-amines involves the formation of pyridyl-nitramines and their rearrangement products, to which there are many references in the literature. Tschitschibabin[10,11] found that 2-aminopyridine (XI) formed 2-nitramino-pyridine (XII); Phillips[12] reported the nitration yield to be about 70 per cent. The 2-nitraminopyridine was rearranged to give two isomers, 5-nitro-2-aminopyridine

(XIII), and a lower proportion of 3-nitro-2-aminopyridine (XIV). Further action of nitric acid on 5-nitro-2-aminopyridine gives 5-nitro-2-nitraminopyridine (XV), and this underwent isomerization, although with more difficulty than the 2-nitraminopyridine, yielding 3,5-dinitro-2-aminopyridine (XVI).



In a similar manner, Tschitschibabin and Konowalowa[13] nitrated 2-amino-3-nitropyridine (XIV) giving 2-nitramino-3-nitropyridine (XVII) in 49 per cent yield; this was rearranged by Tschitschibatin and Kirssanow[14] to 3,5-dinitro-2-aminopyridine in 90 per cent yield by allowing a sulfuric acid solution of the compound to stand at room temperature for one day.

Tschitschibabin and Jegorow[15] nitrated 5-chloro-2-aminopyridine (XVIII) to form 5-chloro-2-nitraminopyridine (XIX), which was then rearranged to 5-chloro-3-nitro-2-aminopyridine (XX).

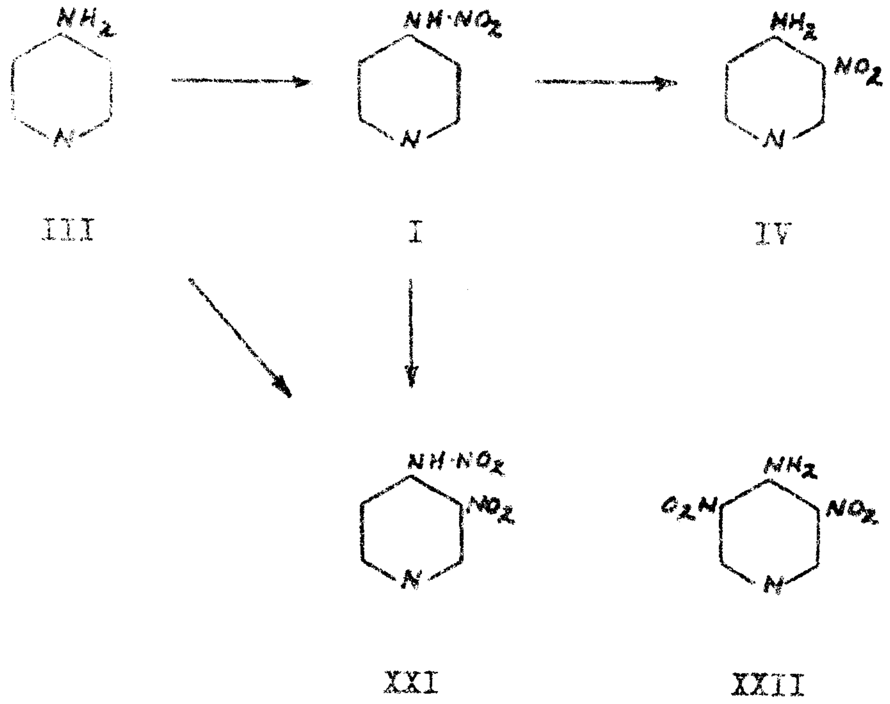


XVIII XIX XX

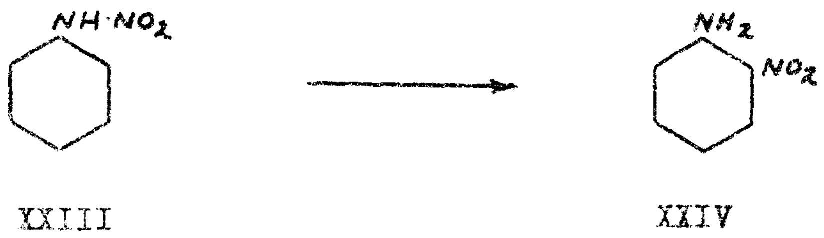
There is very little information in the literature concerning 3-nitraminopyridine. It was made by Tschitschibabin and Kirssanow[16], who note that the compound is decomposed when concentrated sulfuric acid is poured over it. No information has been found as to the rearrangement of 3-nitraminopyridine.

As mentioned previously, Koenigs, Mields, and Gurlt[3] nitrated 4-aminopyridine (III) in sulfuric acid to give 4-nitraminopyridine (I) in 95 per cent yield. Rearrangement of the 4-nitraminopyridine was effected by heating in concentrated sulfuric acid to 70-80°C, at which time a spontaneous reaction raised the temperature to 160°C. The 3-nitro-4-aminopyridine (IV) was isolated in 50 per cent yield by neutralizing an aqueous solution of the reaction mixture.

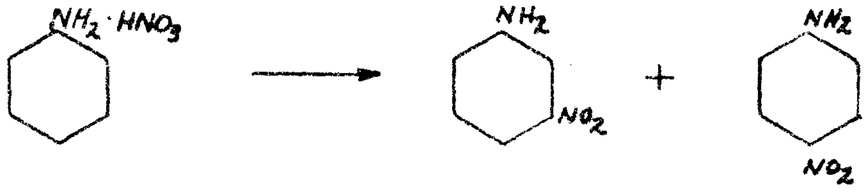
4-Aminopyridine was also nitrated to introduce two nitro groups, by heating the reaction mixture at 85-90°C. The 3-nitro-4-nitraminopyridine (XXI) was obtained in 68 to 85 per cent yield. By increasing the temperature of the reaction mixture to 170-175°C the rearrangement was carried out, giving 3,5-dinitro-4-aminopyridine (XXII). It is interesting to note that 3-nitro-4-nitraminopyridine can be prepared by the nitration of 4-nitraminopyridine, but not from 3-nitro-4-aminopyridine.



Little is known of the mechanism of the rearrangement of a nitramine. Hughes and Jones[17] made a study of the rearrangement of phenylnitramine (XXIII). It was confirmed that o-nitroaniline (XXIV) was the main product of the isomerization in 74 per cent aqueous sulfuric acid.



It was also found that m- and p-nitroanilines (XXVI and XXVII) are the main products formed by the addition of aniline nitrate (XXV) to concentrated sulfuric acid.



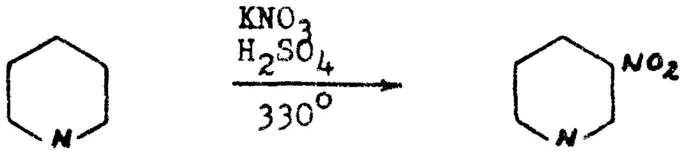
XXV XXVI XXVII

But the addition of phenylnitramine to the concentrated acid resulted in a violent reaction in which brown fumes were evolved and tarry products formed. It appears that the rearrangement proceeds more smoothly than the nitration in 74 per cent sulfuric acid, but that the nitration takes place more smoothly than the rearrangement in the anhydrous acid. This in itself indicated to the authors that there is no very close relationship between the two processes. Both reactions take place fairly smoothly with the formation of mononitroanilines in high yield, and only traces of tar, in sulfuric acid monohydrate (84-85 per cent) maintained just above its freezing point. For these conditions the proportions of the isomerides in the product of each reaction were determined by thermal analysis, with the following results:

	Per Cent Ortho	Per Cent Meta	Per Cent Para
Rearrangement of phenylnitramine	93	0	7
Nitration of aniline	6	34	59

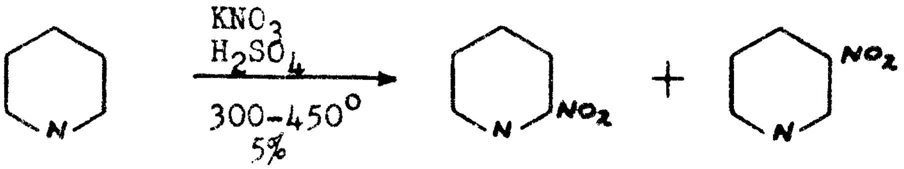
The authors conclude that two very different types of orientation are involved in these two reactions.

A recent development in pyridine chemistry has made possible the preparation of a large number of pyridine derivatives, especially those substituted in the 4-position. This development involves the formation of pyridine-N-oxides, and subsequently, their nitration. In order to understand the impact of this development one should understand that substitution reactions in the pyridine ring are much more difficult than they are in the benzene ring. For instance, Friedl[18] was able to make 3-nitropyridine (XXIX) only in low yield by adding potassium nitrate to a mixture of pyridine (XXVIII) and sulfuric acid at 330°C.



XXVIII XXIX

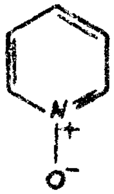
Likewise, den Hertog and Overhoff[19] were able to obtain mixtures of 2- and 3-nitropyridines (XXX and XXIX) in yields of about 5 per cent by adding a solution of pyridine in sulfuric acid to molten potassium nitrate at temperatures varying from 300°C to 450°C.



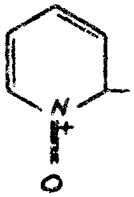
XXVIII XXX XXIX

The difficulty in substitution is attributed to the influence of the pyridine ring nitrogen. A result of the concentration of electrons toward the nitrogen atom is a deactivation of the 2- and 4-positions with respect to reagents that act by acquiring electrons, i.e., electrophilic reagents. This low electron density at the 2- and 4-positions makes these points susceptible to attack by reagents that act by donating electrons, or nucleophilic reagents.

If, however, pyridine is converted to pyridine-N-oxide, the over-all concentration of electrons is different from that existing in pyridine. This difference in electron concentration was first noted by Linton[20], who reported that the dipole moment of pyridine-N-oxide is 4.24 D, a value much lower than calculated from the group moment of the N-oxide function (4.38D) and the moment of pyridine. He concluded that the participation of structures B-D in the resonance system of pyridine-N-oxide was responsible.

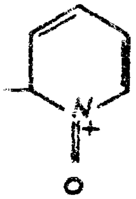


A

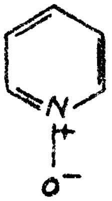


B

C



D

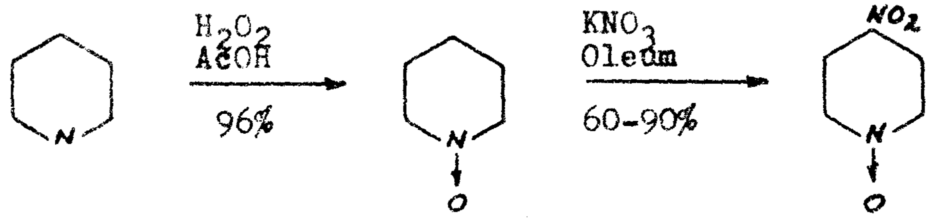


E

It was Ochiai[21] who realized the significance of this discovery. He conjectured that the increased concentration of electrons at the 2- and 4-positions would make pyridine-N-oxide more susceptible to substitution by electrophilic reagents than pyridine itself, and that the substitution would occur in the 2- and 4-positions. This prediction was confirmed by a nitration experiment in which 4-nitropyridine-N-oxide was produced in good yield, together with a small amount of 2-nitropyridine. It was further observed that the nitro group in the 4-position of pyridine-N-oxide was very reactive; it was easily reduced and displaced by nucleophilic reagents. Thus, Ochiai had developed a new method for the preparation of 4-substituted pyridine compounds.

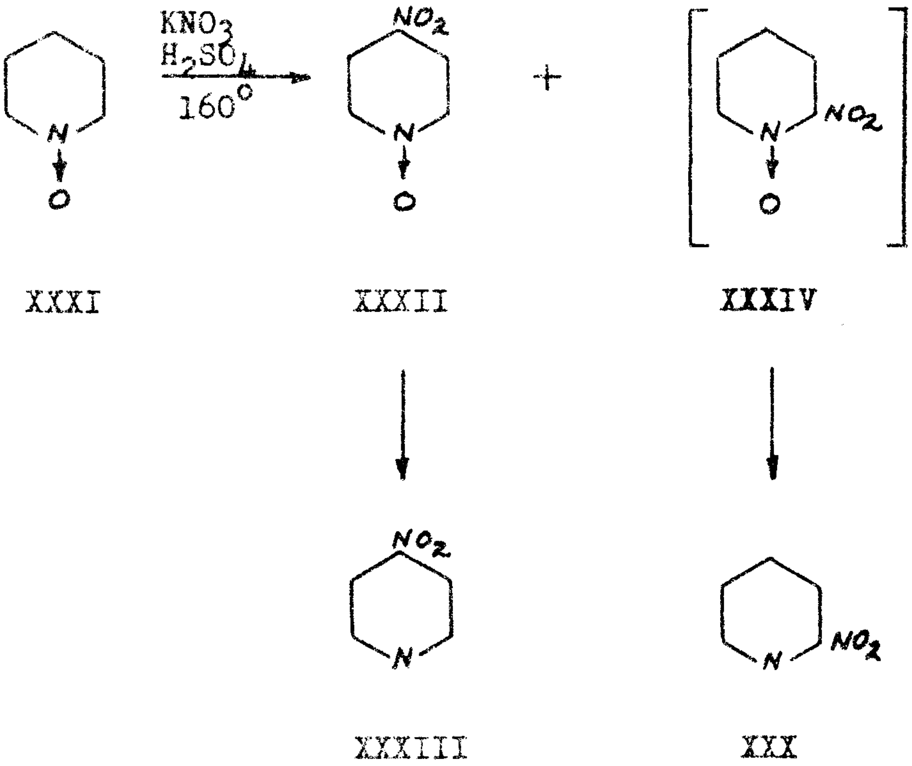
Ochiai[21] reported the preparation of pyridine-N-oxide (XXXI) from pyridine (XXVIII) by means of 30 per cent hydrogen peroxide in glacial acetic acid in 96 per cent yield. By heating the pyridine-N-oxide in a mixture of potassium nitrate and fuming sulfuric acid (17 per cent SO_3) on a water bath 4-nitropyridine-

N-oxide (XXXII) was obtained in 60-90 per cent yield.

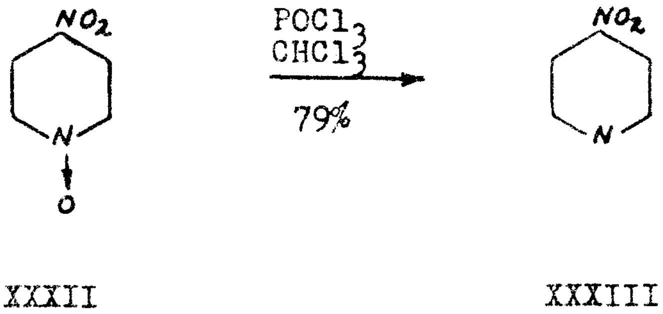


XXVIII XXXI XXXII

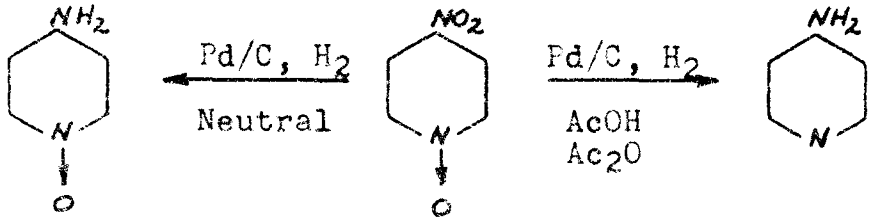
2-Nitropyridine (XXX) was isolated as a by-product of the nitration of pyridine-N-oxide in a mixture of concentrated nitric and sulfuric acids at 130°C, the yield under these conditions being 0.4 per cent of theory. By increasing the reaction temperature from 130°C to 160°C it was also possible to deoxidize a considerable portion of the 4-nitropyridine-N-oxide to 4-nitropyridine (XXXIII). Under these conditions the yield was 43 per cent 4-nitropyridine-N-oxide, 27 per cent 4-nitropyridine, and 7.6 per cent 2-nitropyridine. The originally formed 2-nitropyridine-N-oxide (XXXIV) was more easily deoxygenated than its 4-nitroisomer.



The N-oxide function of 4-nitropyridine-N-oxide can be reduced by heating with phosphorus oxychloride in chloroform to give 4-nitropyridine in 79 per cent yield.

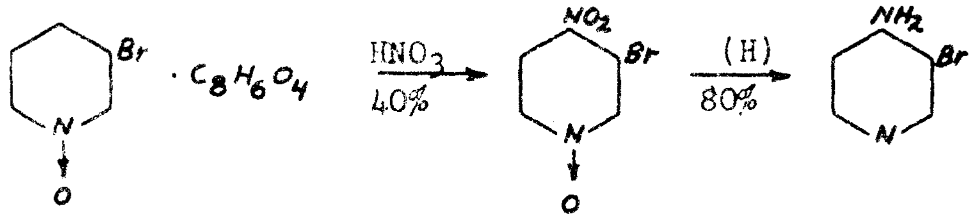


Upon hydrogenation in neutral medium using palladium-on-carbon as catalyst 4-nitropyridine-N-oxide was reduced to 4-aminopyridine-N-oxide (XXXV); however, if the reduction took place in acetic acid to which a small amount of acetic anhydride has been added, 4-aminopyridine (III) was formed. Reduction yields were not reported.

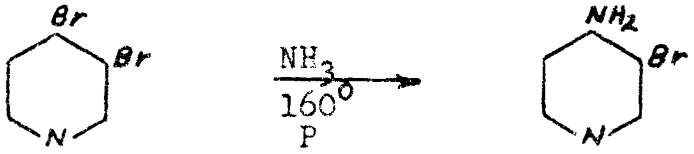


XXXV XXXII III

H. J. den Hertog has done extensive work with pyridine-N-oxide and its derivatives. Using essentially Ochiai's method, den Hertog and Combe[22] prepared 4-nitropyridine-N-oxide in 92 per cent yield based on pyridine. den Hertog and Overhoff[23] reduced 4-nitropyridine-N-oxide to 4-aminopyridine by means of iron powder in hot acetic acid, in practically quantitative yield. They also nitrated the phthalate of 3-bromopyridine-N-oxide (XXXVI) to form 3-bromo-4-nitropyridine-N-oxide (XXXVII) in 40 per cent yield, which was reduced in 80 per cent yield to give 3-bromo-4-aminopyridine (XXXVIII). den Hertog[24] has treated 3,4-dibromopyridine (XXXIX) with ammonia in a sealed tube at 160°C for 8 hours to obtain 3-bromo-4-aminopyridine (XXXVIII).

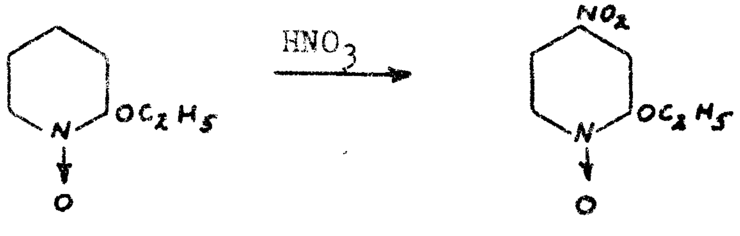


XXXVI XXXVII XXXVIII



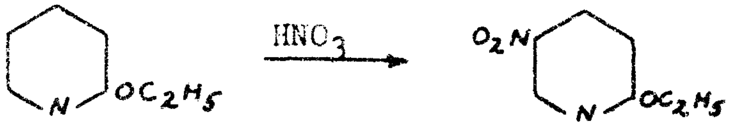
XXXIX XXXVIII

den Hertog, Kolder, and Combe[25] found that when some mono-substituted derivatives of pyridine-N-oxide containing a bromine atom, an ethoxy, methoxy, or a methyl group in positions 2 or 3 were heated with a mixture of fuming nitric and sulfuric acid, a nitro group was introduced in the 4-position. It was especially noted that 4-nitro-2-ethoxypyridine-N-oxide (XLI) was obtained from 2-ethoxypyridine-N-oxide (XL), the nitro group entering the meta-position with respect to the ortho-para directing ethoxy group.

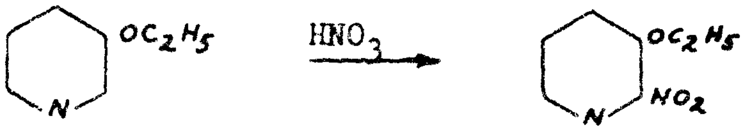


XL XLI

This was in contrast to the nitration of 2-ethoxypyridine (XLII), which substituted in the para-position giving 2-ethoxy-5-nitropyridine (XLIII), and of 3-ethoxypyridine (XLIV), which substituted in the ortho-position giving 2-nitro-3-ethoxypyridine (XLV).



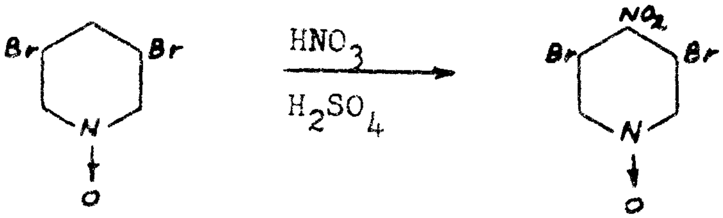
XLII XLIII



XLIV XLV

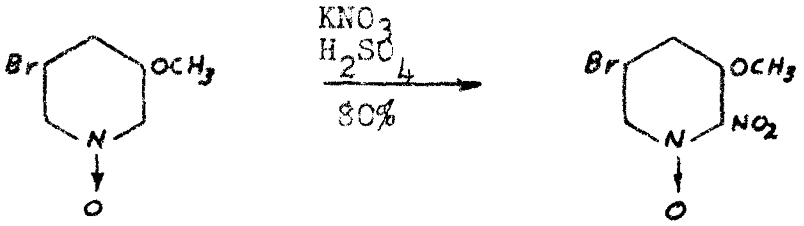
This difference in behavior was due to the effect of the N-oxide group.

The nitration of some di-substituted compounds has been investigated by den Hertog and his co-workers[26,27]. For example, heating 3,5-dibromopyridine-N-oxide (XLVI) in a mixture of fuming nitric acid and sulfuric acid yielded 4-nitro-3,5-dibromopyridine-N-oxide (XLVII) quantitatively.



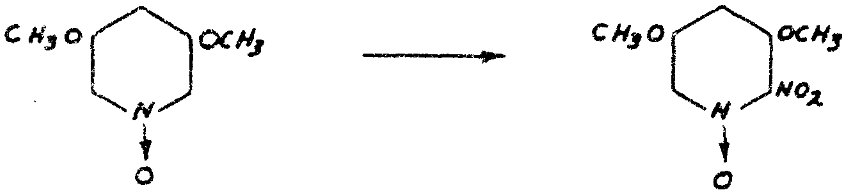
XLVI XLVII

Heating 3-methoxy-5-bromopyridine-N-oxide (XLVIII) in a mixture of potassium nitrate and sulfuric acid at 30-35°C for 24 hours gave 2-nitro-3-methoxy-5-bromopyridine-N-oxide (XLIX) in 80 per cent yield.



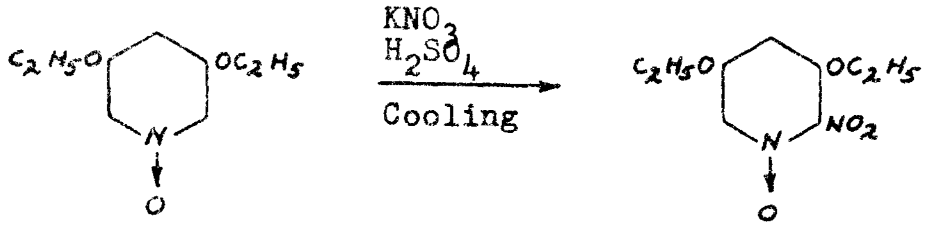
XLVIII XLIX

Likewise, nitration of 3,5-dimethoxypyridine-N-oxide (L) produced 2-nitro-3,5-dimethoxypyridine-N-oxide (LI).

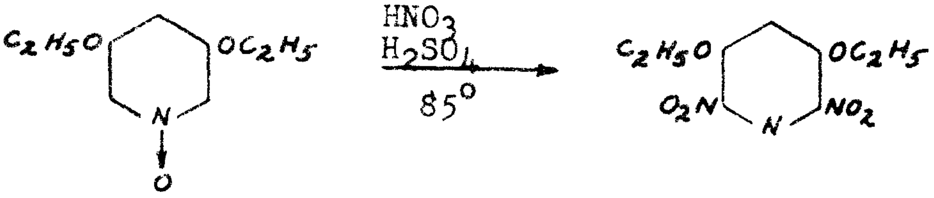


L LI

However, the products obtained from the nitration of 3,5-diethoxypyridine-N-oxide (LII) depended upon the conditions employed. With the use of potassium nitrate and sulfuric acid, with cooling, 2-nitro-3,5-diethoxypyridine-N-oxide (LIII) was obtained. But if the compound was heated at 85°C in a mixture of fuming nitric and sulfuric acids, dinitration and deoxidation occurred, and 2,6-dinitro-3,5-diethoxypyridine (LIV) was produced.



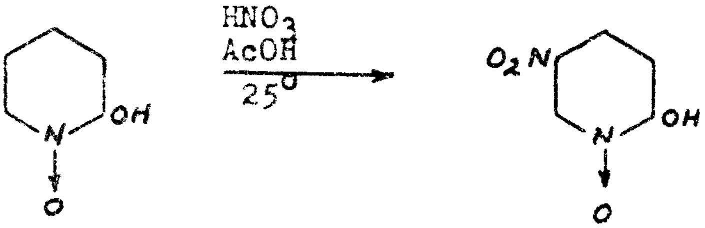
LII LIII



LII LIV

Thus it was seen that the ortho-para directing effect of two ethoxy or methoxy groups was greater than the effect of the N-oxide group.

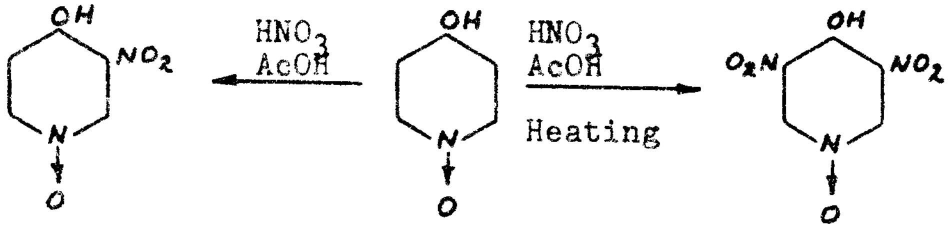
Lott and Shaw[28] nitrated 2-hydroxypyridine-N-oxide (LV) in acetic acid at room temperature, and obtained 2-hydroxy-5-nitropyridine-N-oxide (LVI) as the product.



LV LVI

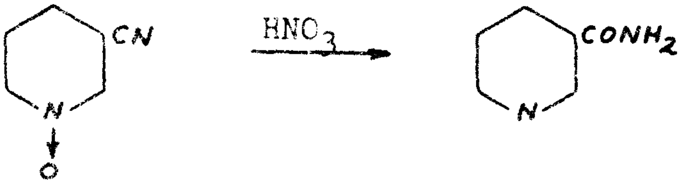
This work was confirmed by den Hertog and Van Ammers[29], who concluded that the effect of the hydroxy group was not surpassed by that of the N-oxide group.

Hayashi[30] nitrated 4-hydroxypyridine-N-oxide (LVII) in acetic acid solution. Depending on the temperature employed, either 3-nitro-4-hydroxypyridine-N-oxide (LVIII) or 3,5-dinitro-4-hydroxypyridine-N-oxide (LIX) was obtained.



LVIII LVII LIX

There is very little information concerning the nitration of pyridine-N-oxide derivatives containing a meta-directing substituent. Jujo[31] attempted to nitrate 3-cyanopyridine-N-oxide (LX); only deoxidation and hydrolysis occurred, and nicotinamide (LXI) was yielded. He concluded that the nitrile and carboxylic groups obstruct nitration in the pyridine nucleus just as they do in the benzene nucleus.

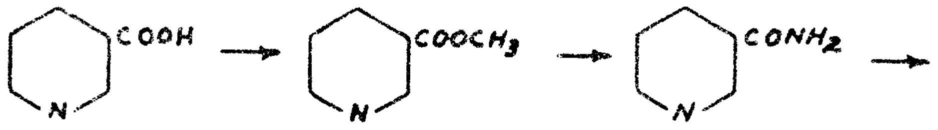


LX LXI

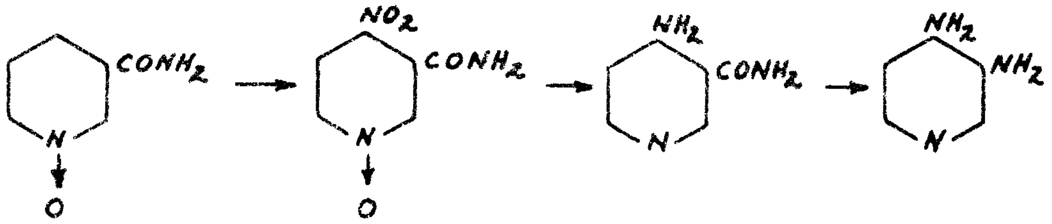
DISCUSSION

I. Attempt To Prepare 4-Nitro-Nicotinamide-N-Oxide and 4-Nitro-Nicotinic Acid-N-Oxide.

To produce 3,4-diaminopyridine by a method not previously investigated, it was decided to prepare 4-nitro-nicotinamide-N-oxide (LXV). This would be made by esterification of nicotinic acid (LXII) with methyl alcohol in the presence of sulfuric acid to give methyl nicotinate (LXIII), which would then be aminated by concentrated ammonium hydroxide to yield nicotinamide (LXI). Formation of nicotinamide-N-oxide (LXIV) by treatment with hydrogen peroxide in glacial acetic acid, it was believed, would permit nitration to follow with introduction of the nitro group in the 4-position. The 4-nitro-nicotinamide-N-oxide was then to be treated to simultaneously reduce the nitro group and the N-oxide function, thus producing 4-amino-nicotinamide (LXVI). Degrading the amide group by Hofmann's method would give the desired compound, 3,4-diaminopyridine (II).



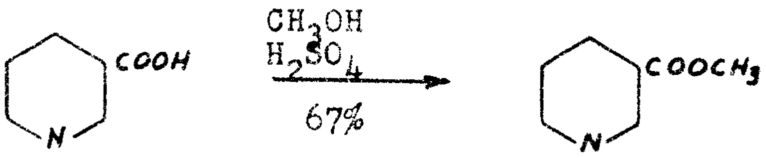
LXII LXIII LXI



LXIV LXV LXVI II

In the procedure described above, it was found that nitration of nicotinamide-N-oxide did not take place; instead, on one run, hydrolysis of the amide group occurred, and nicotinic acid-N-oxide (LXVIII) was obtained as the product. The procedures are discussed below.

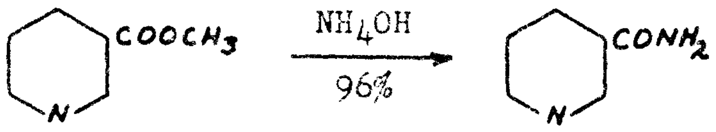
A. Methyl nicotinate.



LXII LXIII

Nicotinic acid (LXII) was esterified by methyl alcohol in the presence of sulfuric acid to give methyl nicotinate (LXIII) in 67 per cent yield. Distillation of the ester under reduced pressure afforded a fine, high-quality product, and this was the desired procedure although nicotinamide can also be made from the crude, non-distilled ester. After distillation the ester had a melting point of 40-41.5°C; the literature reports a melting point of 38°C.

B. Nicotinamide.



LXIII LXI

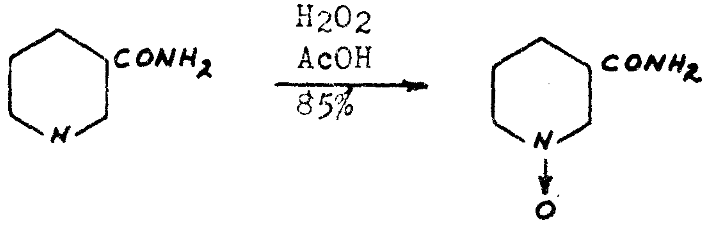
The amination of methyl nicotinate (LXIII) yielded nicotinamide (LXI). For the purpose of this work concentrated ammonium hydroxide (29 per cent) was used as the aminating agent. To increase the concentration, gaseous ammonia was passed into the mixture of methyl nicotinate and ammonium hydroxide at a temperature of 0-10°C.

Although most of the ester was converted to the amide in as short a time as 5.5 hours, allowing the mixture to stand at room temperature in a closed flask for 7 or 8 days permitted greater conversion, and gave a product having a higher melting point. The yield of nicotinamide having a melting point of 125.5-128°C was 9[illegible] per cent of theory. Ethyl acetate can be used as a recrystallization solvent.

La Forge[32] used this method to prepare nicotinamide from ethyl nicotinate in nearly quantitative yield. The melting point of the compound was not reported.

The literature gave 129-131°C as the melting point of nicotinamide.

C. Nicotinamide-N-oxide.

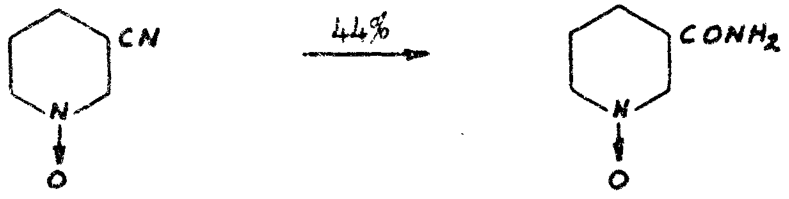


LXI LXIV

Nicotinamide-N-oxide (LXIV) was obtained in about

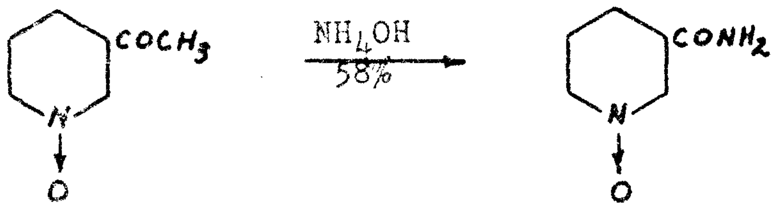
85 per cent yield by heating nicotinamide (LXI) with 1.5 equivalents of 30 per cent hydrogen peroxide in glacial acetic acid at 80°C for 8 hours. If the solution was cooled to room temperature to allow crystallization to take place about 35 per cent of the theoretical yield could be isolated directly by filtration. By concentrating the mother liquor under vacuum until crystallization took place and diluting the slurry with a solvent such as chloroform or methanol, an additional 50 per cent of the theoretical yield could be obtained. From this information, it is obvious that the best procedure is to concentrate the solution before allowing crystallization to take place. Concentration of the acetic acid solution at atmospheric pressure is to be avoided to minimize discoloration of the product. Nicotinamide-N-oxide is most conveniently recrystallized from hot water, giving white needles melting at 285.0-285.5°C dec.

Jujo[31] prepared nicotinamide-N-oxide (LXIV) from 3-cyanopyridine-N-oxide (LX) in 44 per cent yield. He reported the product to have a melting point of 275-276°C.



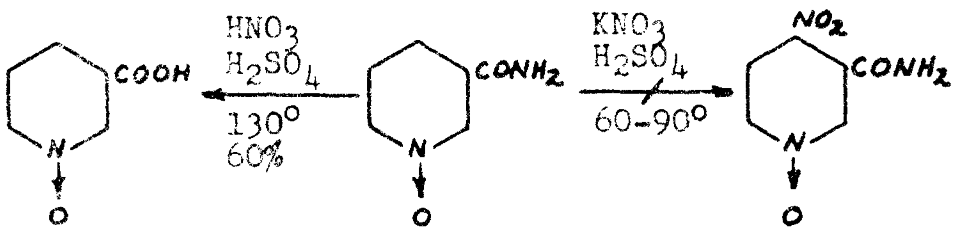
LX LXIV

Shimizu et al[33] prepared the compound in 58 per cent yield by amination of methyl nicotinate-N-oxide (LXVII). They reported a melting point of 282-284°C dec.



LXVII LXIV

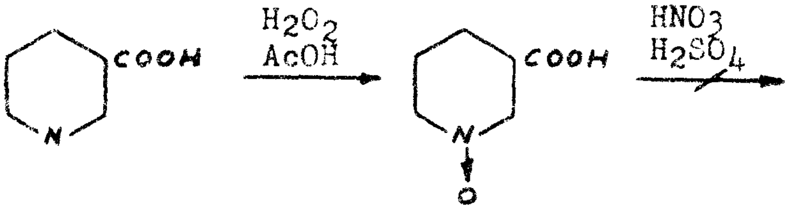
D. <u>Attempt to nitrate nicotinamide-N-oxide</u>.



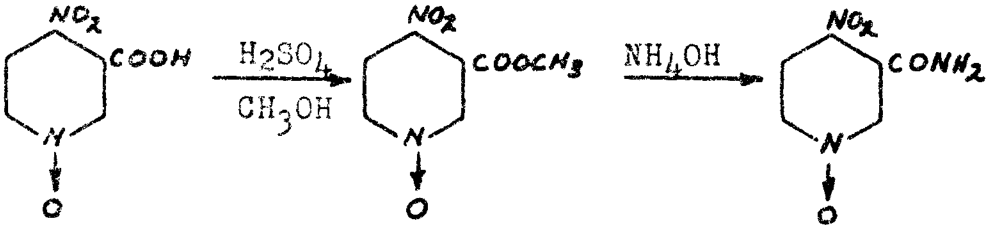
LXVIII LXIV LXV

In preliminary experiments, the attempts to nitrate nicotinamide-N-oxide (LXIV) were carried out under moderate conditions (heating in a mixture of potassium nitrate and sulfuric acid for several hours at 60-90°C). Neither product nor starting material was isolated by pouring the reaction mixture on ice and neutralizing with sodium carbonate. Under the most drastic conditions used (heating in a mixture of nitric and sulfuric acids at 123-130°C for 5 hours) hydrolysis of the amide group occurred, and nicotinic acid-N-oxide (LXVIII) was isolated in 60 per cent yield. This compound was identified by melting point, mixed melting point with an authentic sample of nicotinic acid-N-oxide, and by titration with a solution of sodium hydroxide.

In view of the fact that nicotinic acid-N-oxide was obtained by the attempted nitration of nicotinamide-N-oxide in a mixture of nitric and sulfuric acids, it was desirable to investigate an alternate route to 4-nitro-nicotinamide-N-oxide. Treatment of nicotinic acid (LXII) with hydrogen peroxide in glacial acetic acid would give nicotinic acid-N-oxide (LXVIII) which would be nitrated to give 4-nitro-nicotinic acid-N-oxide (LXIX). Esterification would give 4-nitro-methylnicotinate-N-oxide (LXX), which would be aminated to give 4-nitro-nicotinamide-N-oxide (LXV). This would then be treated as described previously.



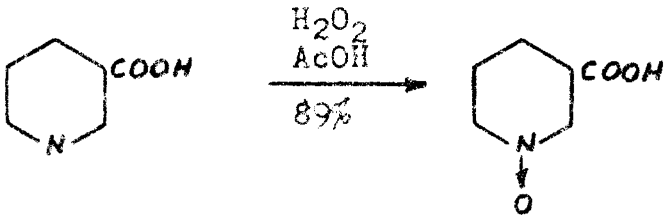
LXII LXVIII



LXIX LXX LXV

This procedure was found to be unworkable, however, since the nitration of nicotinic acid-N-oxide did not take place under the conditions employed. Following is a discussion of the procedures.

E. Nicotinic acid-N-oxide.

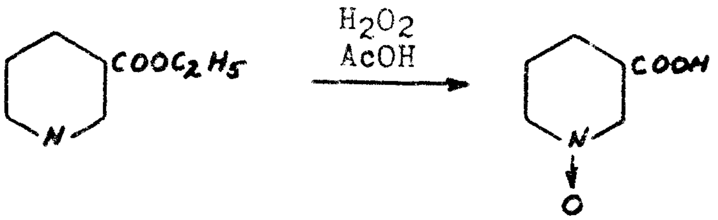


LXII LXVIII

Nicotinic acid-N-oxide (LXVIII) was made in 89 per cent yield by heating nicotinic acid (LXII) with 1.7 equivalents of 30 per cent hydrogen peroxide in glacial acetic acid at 70-80°C. In the two successful experiments heating times of 5 3/4 hours and 2¼ hours were employed, with similar results. The mixture was concentrated under vacuum to about one-half of the original volume, chilled, and filtered. Methyl alcohol served to wash the cake free of mother liquor. In each case the cake constituted an 81 per cent yield; an additional 8 per cent was obtained by concentrating the mother liquor under vacuum. After recrystallization from hot water the product had a melting point of 259-260°C dec.

In one experiment the reaction mixture turned to a dark brown color. After cooling to room temperature the suspension was filtered to give a 58 per cent yield of brown, impure product which, after recrystallization from hot water had a melting point of 254-256°C dec.

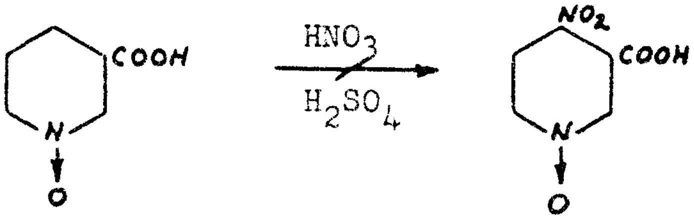
Shimizu et al[33] treated ethyl nicotinate (LXXI) with hydrogen peroxide and acetic acid for 7 hours at 90-95°C to obtain a product which they state to be nicotinic acid-N-oxide. The isolated material had a melting point of 160°C dec. (Perhaps this was a typographical error.)



LXXI LXVIII

Dal Monte Casoni[34], and Jerchel and Jacobs[35] reported nicotinic acid-N-oxide to have a melting point of 254°C.

F. Attempt to nitrate nicotinic acid-N-oxide.



LXVIII LXIX

The attempt to nitrate nicotinic acid-N-oxide (LXVIII) to give 4-nitro-nicotinic acid-N-oxide (LXIX) was not successful under the conditions employed. In each case the starting material was recovered by pouring the reaction mixture on ice and neutralizing the aqueous solution with sodium hydroxide. The precipitated nicotinic acid-N-oxide was then isolated by filtration. Under mild conditions (heating in a mixture of sulfuric acid and potassium nitrate or 70 per cent nitric acid at about 80°C for 3 to 5 hours) recovery amounted to about 90 per cent of the charge. When the reaction temperature was maintained at 125-130°C for 5.5 hours, a recovery of 58 per cent resulted. When the N-oxide was heated in a mixture of red fuming nitric and sulfuric acids at a temperature increasing from 80° to 114°C in a 3.5 hour period, the recovery was 58 per cent. The reduced recovery under the more stringent nitrating conditions suggests that a reaction may have taken place; no compound other than the starting material was isolated, however.

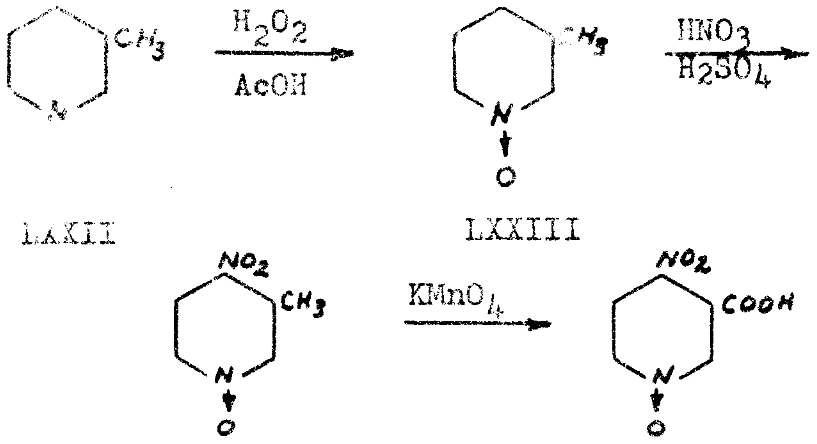
The difficulty in nitrating nicotinamide-N-oxide and nicotinic acid-N-oxide is attributed to two causes:

1) the effect of the N-oxide group is counteracted by the meta-directing effect of the carboxyl and amide group, and 2) the presence of the carboxyl or amide group deactivates the pyridine ring to such an extent that nitration becomes very difficult or impossible.

These beliefs are substantiated by the work of den Hertog[26,27], and Lott and Shaw[28], who showed that the effect of certain ortho-para directing groups is greater than that of the N-oxide group. Also, Jujo[31] attempted without success to nitrate a derivative containing a meta-directing group, i.e., 3-cyanopyridine-N-oxide. He concluded that the nitrile and carboxylic groups obstruct nitration in the pyridine nucleus.

II. Preparation of 4-Nitro-3-Methylpyridine-N-Oxide.

Since it was not possible to nitrate nicotinamide-N-oxide or nicotinic acid-N-oxide, another route was to be investigated. This would involve the formation of 3-methylpyridine-N-oxide (LXXIII) from 3-methylpyridine (LXXII). Nitration would give 4-nitro-3-methylpyridine-N-oxide (LXXIV), which would be oxidized to 4-nitro-nicotinic acid-N-oxide (LXIX). This compound would be treated as described previously.

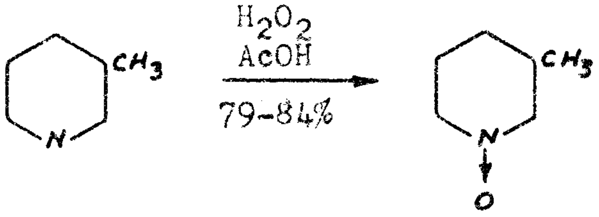


LXXII LXXIII

LXXIV LXIX

The first two reactions of this series were successful. However, the attempts to oxidize 4-nitro-3-methylpyridine-N-oxide under a limited number of conditions were unsuccessful.

A. 3-Methylpyridine-N-oxide.



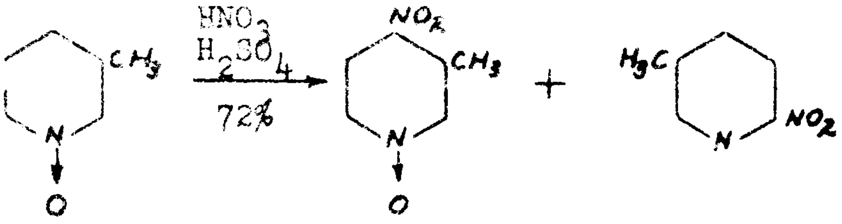
LXXII LXXIII

3-Methylpyridine-N-oxide (LXXIII) was obtained in 79 and 84 per cent yield by heating 3-methylpyridine (LXXII) with 1.7 equivalents of 30 per cent hydrogen peroxide in glacial acetic acid for about 8 hours at 80-90°C. After the reaction had taken place it was found necessary to remove the acetic acid by vacuum concentration as completely as possible in order to reduce the amount of potassium carbonate required to neutralize the residual acid. Use of a large amount of potassium carbonate is to be avoided since the salts, which are removed by filtration, tend to hold the product. The chloroform solution of the product is dried preferably with magnesium sulfate or sodium sulfate, to give a suspension which is easily filtered. The product was obtained by distillation at 153°C at 15 mm (136-138°C at 6 mm). When recrystallized from S.D. 3A ethanol the picrate of 3-methylpyridine-N-oxide had a melting point of 137-138.5°C.

This procedure follows that of Boekelheide and Linn[36] who obtained a yield of 77 per cent. They reported 3-methylpyridine-N-oxide to have a boiling point of 146-149°C at 15 mm, and the picrate to have a melting point of 138-139°C.

Jerchel and Jacobs[35] reported the product to have a boiling point of 156-158°C at 16 mm.

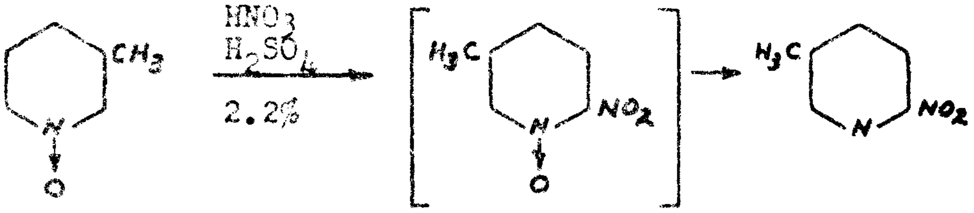
B. 4-Nitro-3-methylpyridine-N-oxide.



LXXIII LXXIV LXXV

3-Methylpyridine-N-oxide (LXXIII) was nitrated in mixed acid to give 4-nitro-3-methylpyridine-N-oxide (LXXIV) in yields varying from 37 to 72 per cent of theory, as well as a small amount of 2-nitro-5-methylpyridine (LXXV). Initially the reaction was exothermic; in the one run made using red fuming nitric acid, the temperature of the reaction mixture rose to 129°C after being heated on the steam bath to 90°C. A slow addition of the nitrating agent at steam bath temperature is recommended in order that the exothermic reaction can take place in an extended period of time. After the initial reaction, the mixture was heated at 90-95°C for 2 to 12.5 hours. The product was first isolated by extracting an aqueous solution of the reaction mixture with chloroform. A better method was to neutralize the aqueous solution with a solution of sodium hydroxide; the precipitated product was then isolated by filtration. Extraction of the aqueous mother liquor with chloroform yielded an additional amount of product. Continuous extraction of the mother liquor with ethyl ether was also employed. By recrystallizing from acetone or S.D. 3A ethanol glistening yellow crystals melting at 137-138°C were obtained. It was found that 4-nitro-3-methylpyridine-N-oxide could be sublimed in a cold-finger sublimation apparatus at 100-120°C at 2 mm.

In Run 24 the product obtained by neutralization of the aqueous solution of the reaction mixture was combined with that obtained by the continuous extraction of the aqueous mother liquor with ethyl ether. By recrystallizing from acetone two fractions of 4-nitro-3-methylpyridine-N-oxide were obtained, giving a yield of 53 per cent of theory. The mother liquor from the second fraction was evaporated on a steam bath to a mixture of oil and crystals having a pleasant odor. After prolonged heating on the steam bath it was noticed that material had collected on the side of the beaker. This was purified in a cold-finger sublimation apparatus, then recrystallized from hot water, yielding very pale yellow needles melting at 93-95°C. This was 2-nitro-5-methylpyridine (LXXV), which was a result of nitration in the 2-position to give 2-nitro-5-methylpyridine-N-oxide (LXXVI), coupled with deoxidation of the N-oxide function.



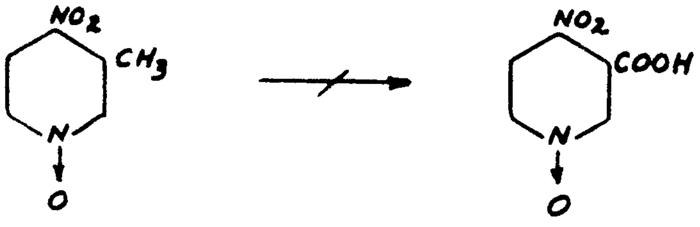
LXXIII LXXVI LXXV

The 2-nitro-5-methylpyridine, which was isolated in a yield of 2.2 per cent, had the characteristic pleasant odor mentioned above. Wiley and Hartman[37] reported 2-nitro-5-methylpyridine to have a melting point of 94-95°C.

In Run 35 the pleasant odor was again noted, but the fraction containing the 2-nitro-5-methylpyridine was not treated to isolate the compound.

In a review of literature concerning pyridine-N-oxide, Cislak[38] stated that Talikowa[39] had nitrated 3-methylpyridine-N-oxide. However, the available abstract did not describe the procedure, or give the yield or physical constants.

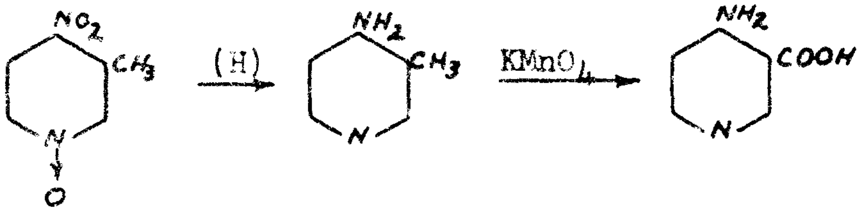
C. Attempt to oxidize 4-nitro-3-methylpyridine-N-oxide.



LXXIV LXIX

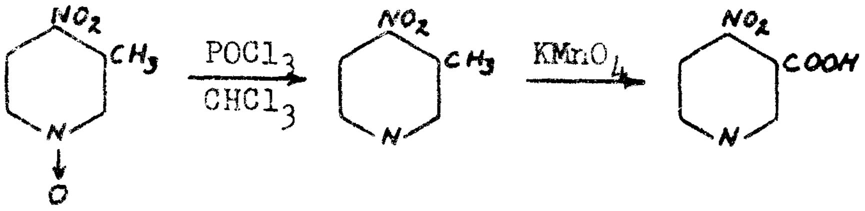
The attempts to oxidize 4-nitro-3-methylpyridine-N-oxide (LXXIV) to 4-nitro-nicotinic acid-N-oxide (LXIX) were unsuccessful under the conditions employed. Oxidants used included potassium permanganate, potassium permanganate in acid medium, and chromium trioxide in acid medium. In each case at least part of the starting material was recovered.

It is suggested that further oxidation attempts be made. Another variation would be to reduce the nitro group and the N-oxide function to give 3-methyl-4-aminopyridine (LXXVII); oxidation would then yield 4-aminonicotinic acid (LXXVIII).



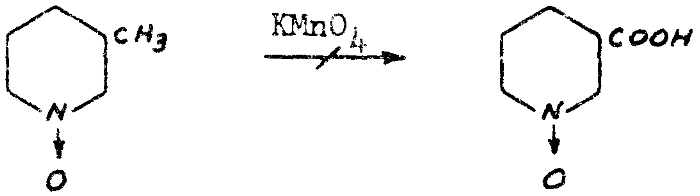
LXXIV LXXVII LXXVIII

Another route would involve the reduction of the N-oxide function using the method of Ochiai[21] to give 3-methyl-4-nitropyridine (LXXIX), which could then be subjected to oxidation to yield 4-nitro-nicotinic acid (LXXX).



LXXIV LXXIX LXXX

D. Attempt to oxidize 3-methylpyridine-N-oxide.

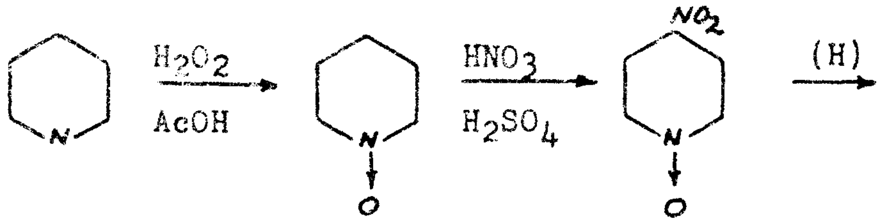


LXXIII LXVIII

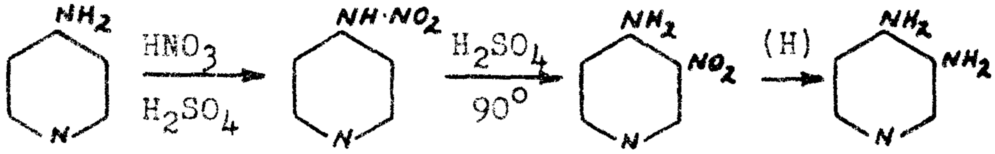
As a corollary experiment, an unsuccessful attempt was made to oxidize 3-methylpyridine-N-oxide (LXXIII) to nicotinic acid-N-oxide (LXVIII) by means of potassium permanganate. The starting material was recovered and was identified by its picrate, and by a mixed melting point with an authentic sample of 3-methylpyridine-N-oxide picrate.

III. Preparation of 3,4-Diaminopyridine.

Since the attempts to produce 4-nitro-nicotinamide-N-oxide had proved unsuccessful, another route to 3,4-diaminopyridine was investigated. This method began with the formation of pyridine-N-oxide (XXXI) from pyridine (XXVIII), and took advantage of the fact that pyridine-N-oxide can be nitrated to give 4-nitropyridine-N-oxide (XXXII). This compound was reduced to yield 4-aminopyridine (III), from which 4-nitraminopyridine (I) was produced. Rearrangement yielded 3-nitro-4-aminopyridine (IV), which was reduced to 3,4-diaminopyridine (II).

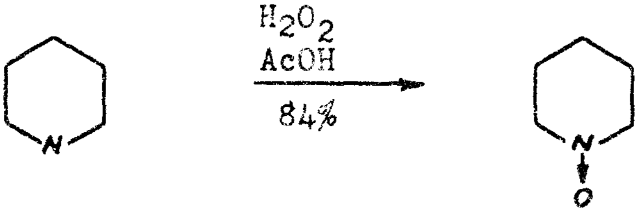


XXVIII XXXI XXXII



III I IV II

A. Pyridine-N-oxide.

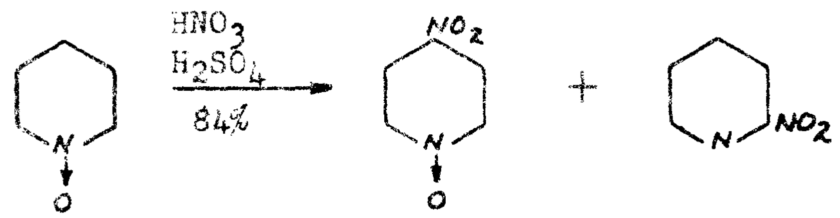


XXVIII XXXI

Pyridine-N-oxide (XXXI) was made in 84 per cent yield by heating pyridine (XXVIII) with 1.7 equivalents of 30 per cent hydrogen peroxide in glacial acetic acid.

It was found advantageous to remove the acetic acid by vacuum concentration as completely as possible before neutralizing the residual acid with potassium carbonate. It is necessary to allow sufficient time for the potassium acetate to crystallize, and to wash the cake with chloroform after the filtration. The product was distilled at 138-144°C at 15 mm.

B. 4-Nitropyridine-N-oxide.



XXXI XXXII XXX

Pyridine-N-oxide (XXXI) was nitrated to form 4-nitropyridine-N-oxide (XXXII) in yields varying from 60 to 84 per cent of theory. In one run, 2-nitropyridine (XXX) was isolated as a by-product in 0.5 per cent yield. Good yields were obtained by using 3 mols of red fuming nitric acid per mol of pyridine-N-oxide. The 4-nitropyridine-N-oxide was isolated by neutralizing an aqueous solution of the reaction mixture with sodium hydroxide solution, and filtering. An additional quantity of product was obtained by extracting the aqueous mother liquor with portions of chloroform, or in a continuous manner with ethyl ether. 4-Nitropyridine-N-oxide can be recrystallized from water, S.D. 3A ethanol, or acetone to give yellow crystals melting at 161.5-163°C.

The reation was at first carried out on a fairly small scale, with no difficulty, by combining the reactants and heating to steam bath temperature. On a larger scale a moderate exothermic reaction was noted when a temperature of about 90°C was reached. On a still larger scale, with the use of potassium nitrate and 20-23 per cent oleum, a violent exothermic reaction took place with loss of the greater portion of the mixture. After the initial reaction had subsided, the remainder of the mixture was heated at 95°C for 12 hours, and the product was isolated in the usual manner. The yield was estimated by noting the amount of sodium hydroxide solution required to neutralize the remainder of the reaction mixture.

Because of the violent reaction which took place, the nitration procedure was modified. To a solution of pyridine-N-oxide in sulfuric acid the nitrating agent (in this case, red fuming nitric acid) was slowly added at the reaction temperature at such a rate that only a moderate reaction took place. In this manner only a relatively small excess of nitrating agent was present at any time, and the reaction remained under control. This method gave the highest yield obtained for this reaction, i.e., 84 per cent of theory.

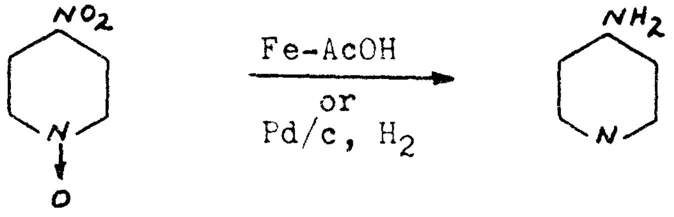
In Run 34 4-nitropyridine-N-oxide was isolated in the usual manner, by neutralizing an aqueous solution of the reaction mixture. The aqueous mother liquor was extracted continuously with ethyl ether, and the extract was evaporated to dryness. The resulting residue was recrystallized from S.D. 3A ethanol to yield an additional quantity of 4-nitropyridine-N-oxide. When the ethanol mother liquor was concentrated to a small volume and crystallization took place, the formation of two types of crystals was noted. This fraction was evaporated to dryness and subjected to steam distillation; the distillate was evaporated to dryness to give yellow crystals melting at 66-69°C. This is 2-nitropyridine (XXX) formed by the nitration of pyridine-N-oxide in the

2-position followed by deoxidation of the N-oxide function. This compound was isolated in 0.5 per cent yield, as compared with an 82 per cent yield of 4-nitropyridine-N-oxide.

Ochiai[21] had previously reported the isolation of 2-nitropyridine as a by-product of the nitration of pyridine-N-oxide in a mixture of concentrated nitric and sulfuric acids at 130°C, the yield under these conditions being 0.4 per cent of theory. The 2-nitropyridine was purified by chromatography from benzene, giving white plate-like crystals melting at 67-72°C.

den Hertog[23] obtained 4-nitropyridine-N-oxide in about 90 per cent yield by using six to ten mols of nitric acid per mol of pyridine-N-oxide.

C. 4-Aminopyridine



XXXII III

4-Nitropyridine-N-oxide (XXXII) was reduced to 4-aminopyridine (III) by two methods: 1) using iron powder and acetic acid, and 2) with hydrogen, using 5 per cent palladium-on-carbon as catalyst.

Yields of 75-80 per cent of theory were obtained using the iron-acetic acid method. On a scale comparable to that used by den Hertog[23] (4 g of starting material) no difficulty was encountered. On a larger scale however (50 g of starting material), the procedure proved to be cumbersome. In order that continuous extraction with ethyl ether could be employed, the ferric salts had to be removed from the aqueous, neutralized, reaction mixture. The removal of these salts by filtration was time-consuming. Also, it was necessary to extract the aqueous filtrate continuously with ethyl ether for an extended period of time (12 days) in order to isolate the product.

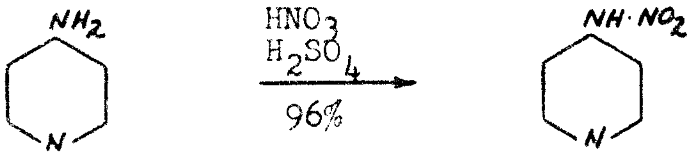
In view of these difficulties several catalytic reductions were carried out using 5 per cent palladium-on-carbon as the catalyst. The first reduction was carried out in glacial acetic acid containing 25 per cent of the theoretical amount of acetic anhydride required to take up the water of reaction, and at a hydrogen pressure of 50 lb./in.^{2}. After removing the catalyst and adding water, the solution was made strongly alkaline and extracted continuously with ethyl ether. Evaporating the ether to dryness and recrystallizing the residue from chloroform gave a 65 per cent yield of 4-aminopyridine melting at 157.5-160°C.

In Run 43, the reduction was carried out in glacial acetic acid containing 95 per cent of the theoretical amount required to take up the water of reaction at a hydrogen pressure of 1200 lb./in.^{2} and a temperature of 60°C. After removing the catalyst, water was added and the solution was concentrated to half volume under vacuum. Addition of sodium hydroxide solution to pH 8 caused a precipitate to form, which was filtered and washed with water. This had a melting point of 146.5-149°C, and was thought to be impure 4-aminopyridine. However, this was actually 4-acetaminopyridine (melting point 150°C). The aqueous filtrate was extracted continuously for 5 days with ethyl ether, giving off-white crystals melting at 148-157°C. This fraction was mostly 4-aminopyridine, but contained a small amount of 4-acetaminopyridine. Not realizing at the time the presence of two compounds, the two fractions were combined and recrystallized successively from chloroform and benzene, obtaining crystals melting at 116-138°C. The melting point indicated a mixture was present. The amount of acetic anhydride used was too great and caused acetylation of the 4-aminopyridine. Should 4-acetaminopyridine be desired as the product, this method appears to offer good possibilities.

In Run 51, the relatively same amount of acetic anhydride was used, and the reduction was carried out at a hydrogen pressure of 800 lb./in.^{2}. With external heating in addition to the heat of reaction a temperature of 120°C was reached. After removing the catalyst and concentrating the filtrate to an oil, the mixture was made strongly alkaline and allowed to stand overnight. This served to hydrolyze the acetylated product to the amine. The addition of more sodium hydroxide solution caused the amine to "salt out", making it possible to isolate most of the product by filtration. Continuous extraction of the filtrate gave an additional quantity of product. The two fractions were combined and recrystallized from benzene to give 4-aminopyridine melting at 158-160°C in 65 per cent yield.

Of the two methods investigated, iron-acetic acid and catalytic reduction, the latter offers more promise. Although more work should be done, it is felt that the information obtained in these experiments gives the basis of a good procedure.

D. <u>4-Nitraminopyridine</u>.

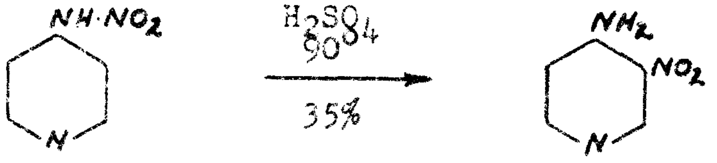


III I

4-Nitraminopyridine (I) was made in 85-96 per cent yields by the addition with cooling of fuming nitric acid (5 per cent excess) to a sulfuric acid suspension of 4-aminopyridine (III). After a complete solution was obtained by allowing the reaction mixture to come to room temperature, it was poured on 3 to 5 parts of ice per part of reaction mixture. The aqueous solution was then neutralized with 50 per cent sodium hydroxide solution to pH 6. The resulting precipitate was filtered, washed with water, and the cake was dried to give a yellow powder which decomposed at about 232°C. 4-Nitraminopyridine which was recrystallized from water decomposed at 236.5°C. The recrystallization from water was not well adapted to large scale use because of the low solubility of the compound (about 5 grams per liter at 80°C). 4-Nitraminopyridine is not appreciably soluble in the common organic solvents.

This procedure differs somewhat from that of Koenigs, Kinne, and Weiss[1], who isolated the product by pouring the reaction mixture into ice to obtain a nearly white precipitate in 95 per cent yield. After recrystallization from hot water slightly yellow needles melting at 243-244°C were obtained.

E. <u>3-Nitro-4-aminopyridine</u>.



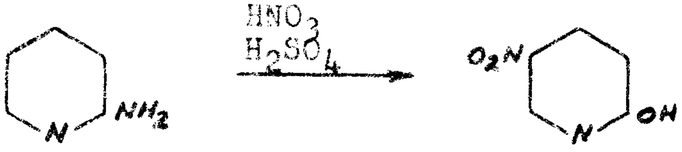
I IV

The rearrangement of 4-nitraminopyridine (I) to give 3-nitro-4-aminopyridine (IV) was investigated in order to increase the yield above the 50 per cent yield reported by Koenigs, Mields, and Gurlt[3]. It was found, however, that regardless of the conditions used the yield of crude 3-nitro-4-aminopyridine was about 40 per cent of theory. After recrystallization the yield of product generally amounted to 30-35 per cent. While Koenigs et al[3] used a ratio of 5 ml of concentrated sulfuric acid per gram of 4-nitraminopyridine, it was found that a ratio of 3 ml per gram was suitable. The spontaneous reaction usually took place when a temperature of 85-90°C had been reached, and could be moderated by heating slowly (in about 20 minutes) to that temperature. It appears that it is necessary for the exothermic reaction to take place in order that even the poor yield of 40 per cent of 3-nitro-4-aminopyridine can be obtained; Run 47, in which a definite temperature rise was not observed, gave a yield of 9 per cent 3-nitro-4-aminopyridine and 27 per cent 4-nitraminopyridine. Heating the reaction mixture after the initial reaction for as long as 12 hours at 94°C did not result in an increased yield of the desired product. Likewise, heating the mixture at 140-

160°C for 20 minutes did not result in an increase in yield. A solution of 4-nitraminopyridine in 85 per cent (rather than 96 per cent) sulfuric acid maintained at room temperature for three days yielded a 67 per cent recovery of 4-nitraminopyridine. Addition of 2.0 g of 4-nitraminopyridine to 20 ml of concentrated hydrochloric acid gave the white hydrochloride salt which remained undissolved after six days at room temperature, and heating at 90°C for 15 minutes. Neutralization of the mixture resulted in the recovery of 40 per cent of the starting material.

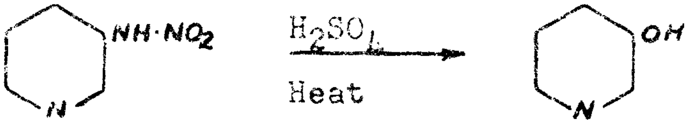
3-Nitro-4-aminopyridine can be purified by recrystallization from water. Another method was to precipitate the compound by the addition of benzene to a methanol solution which had been treated with decolorizing carbon. The compound was obtained as yellow crystals melting at 204.5-206°C. It was found that the product sublimed at 100-120°C at 1 mm. In a cold-finger sublimation apparatus, however, only a small amount of material could be sublimed at one time, and the operation was time-consuming. Therefore, this method of purification was not used extensively. Koenigs et al[3] reported 3-nitro-4-aminopyridine to have a melting point of 200°C.

It is possible that the 4-nitraminopyridine which is not rearranged to 3-nitro-4-aminopyridine is converted to 4-hydroxypyridine. This contention is based on references in the literature concerning the isolation of hydroxy compounds. Thus, Tschitschibabin[10] found that when the mixed products from the nitration of 2-aminopyridine (XI) were allowed to stand overnight, 2-hydroxy-5-nitropyridine (LXXXI) was obtained.



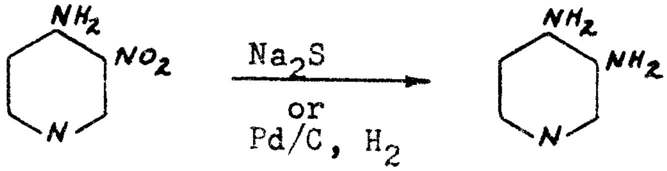
XI LXXXI

Likewise, Tschitschibabin and Kirssanow[16] found that heating 3-nitraminopyridine (LXXXII) in sulfuric acid formed chiefly 3-hydroxypyridine (LXXXIII).



LXXXII LXXXIII

F. 3,4-Diaminopyridine.



IV II

3-Nitro-4-aminopyridine (IV) was reduced to 3,4-diaminopyridine (II) by 1) the action of sodium sulfide, in 66 per cent yield, and 2) by hydrogenation using 5 per cent palladium-on-carbon as the catalyst, in 91 per cent yield.

The reduction with sodium sulfide was carried out in hot water; evaporating the reaction mixture to a relatively small volume and cooling caused the product to crystallize. By filtering the crystals a yield of 66 per cent of 3,4-diaminopyridine melting at 219-220°C dec was obtained. The disadvantage of this method stems from the fact that the product has appreciable solubility in cold water. By neutralizing the aqueous mother liquor, evaporating it to dryness, and extracting the salt cake with a solvent such a methanol an additional amount of product could be obtained.

Catalytic hydrogenation using 5 per cent palladium-on-carbon is the preferred method of reducing 3-nitro-4-aminopyridine. The solvent used was S.D. 3A ethanol, which could probably be substituted by methanol. A hydrogen pressure of 50 lb./in.^{2} was employed. After removal of the catalyst by filtration, the ethanol solution was evaporated to dryness to give crude product which was recrystallized from water, or by the addition of benzene to a methanol solution of the product. 3,4-Diaminopyridine was obtained in two fractions totaling 91 per cent of the theoretical yield, the main fraction having a melting point of 215.5-218.5°C dec.

Koenigs, Bueren, and Jung[5] reported 3,4-diaminopyridine to have a melting point of 218-219°C.

SUMMARY

1. Several pyridine-N-oxides have been prepared from pyridine compounds, including nicotinamide-N-oxide, nicotinic acid-N-oxide, and 3-methylpyridine-N-oxide.

2. Attempts to nitrate nicotinamide-N-oxide and nicotinic acid-N-oxide were unsuccessful.

3. The nitration of nicotinamide-N-oxide under certain conditions yielded nicotinic acid-N-oxide, an occurrence not previously reported.

4. Attempts to oxidize 4-nitro-3-methylpyridine-N-oxide and 3-methylpyridine-N-oxide were unsuccessful.

5. The nitration of 3-methylpyridine-N-oxide led to the isolation of 2-nitro-5-methylpyridine, which has not previously been reported as a by-product of that reaction.

6. The yields of the various intermediates obtained in the preparation of 3,4-diaminopyridine are shown as follows

	Yield per cent
Pyridine-N-oxide	84
4-Nitropyridine-N-oxide	84
4-Aminopyridine (by catalytic reduction)	65
4-Nitraminopyridine	96
3-Nitro-4-aminopyridine	38
3,4-Diaminopyridine (by catalytic reduction)	91
Overall yield	15.2

The overall yield of 15.2 per cent of theory is low primarily because of the costly rearrangement of 4-nitraminopyridine to 3-nitro-4-aminopyridine. Also, the yield of 65 per cent obtained on the reduction of 4-nitropyridine-N-oxide to 4-aminopyridine is low, and could probably be increased to 80 per cent by further investigation. If this were the case, and if the rearrangement could be accomplished in 50 per cent yield, an overall yield of 24.7 per cent would be attained. Even this yield is low, and it is concluded that this method of preparing 3,4-diaminopyridine has little synthetic value as compared with the method described in the literature using 4-hydroxypyridine as its starting material.

EXPERIMENTAL

Methyl Nicotinate

To 1170 ml of methyl alcohol in a 3 l. flask placed in an ice bath, 543 ml of 96 per cent sulfuric acid were added with agitation in a one-half hour period. To this solution 500 g of nicotinic acid were added, and the mixture was refluxed on a steam bath for 3 hours. The solution was cooled to room temperature, and with agitation poured into 1.5 kg of ice and 2 l. of water. After being neutralized with solid sodium carbonate to a pH of 6 to 7, the solution was extracted with five 1-l. portions of ethyl ether. The ether was evaporated on a steam bath, and the residue was distilled through a 3 cm by 55 cm column. The column contained .24" by .24" 316 stainless steel packing produced by Scientific Development Company, State College, Penna. The fraction boiling at 71-72°C at 2.5 mm was collected, and amounted to 374 g (67 per cent of theory). The distillate formed a white crystalline solid melting at 40-41.5°C. The literature gives a melting point of 38°C. (See Table 1.)

Nicotinamide

Forty grams of gaseous ammonia were passed into a mixture of 241 g of methyl nicotinate and 800 ml of 30 per cent ammonium hydroxide at 5-10°C. After standing in a closed flask for one day at room temperature, a small amount of nicotinamide crystallized in the form of needles. The suspension was cooled to 10°C and 30 g of gaseous ammonia were passed into the mixture. The suspension was allowed to stand at room temperature for seven days. It was then thoroughly chilled in an ice bath, filtered, and dried. This amounted to 144.5 g of white needles of nicotinamide melting at 125.5-129°C. The two fractions represent a yield of 96 per cent. The literature reports nicotinamide to have a melting point of 129-131°C. (See Table 2.)

Nicotinamide N-Oxide

A solution of 50 g of nicotinamide in 73 ml of 29 per cent hydrogen peroxide and 250 ml of glacial acetic acid was heated at 50-60°C with agitation for 1.5 hours, then allowed to stand overnight at room temperature. With agitation the solution was heated gradually to 80°C over a period of 8 hours and again allowed to stand overnight at room temperature. The resulting suspension was filtered, and the cake was washed with methanol on the filter and dried at 60°C, yielding 19.9 g (I) of white crystals melting at 283.5-284.5°C dec. The combined filtrate and washes were concentrated under vacuum until crystallization took place. The suspension was chilled to 5°C, filtered, and the cake was washes on the filter with methanol and dried at 60°C. This fraction amounted to 27.8 g (II) of off-white crystals melting at 279-280°C dec. An additional amount of impure product was isolated from the mother liquor by concentration and crystallization. The two fractions I and II represent a yield of 84 per cent.

Ten grams of I were dissolved in 150 ml of hot water and treated with a small amount of decolorizing carbon.[a] The suspension was filtered, and the filtrate was allowed to cool without disturbance. The resulting crystals were filtered, and washed with cold water, and dried at 60°C. The yield was 8.6 g of white needles melting at 285-285.5°C dec. (See Table 3.)

[a] Darco G-60 decolorizing carbon, manufactured by the Atlas Powder Company, was used throughout this thesis.

Jujo reported a melting point of 275-276°C dec. Shimizu et al[33] reported a melting point of 282-284°C dec.

Nicotinic Acid-N-Oxide

A solution of 100 g of nicotinic acid in 162 ml of 30.5 per cent hydrogen peroxide and 400 ml of glacial acetic acid was heated on a steam bath at 70-80°C for 2¼ hours, with agitation, at which time the nicotinic acid-N-oxide began to crystallize from solution. The suspension was allowed to stand at room temperature for one day, then concentrated on a steam bath under vacuum until a slurry was obtained. The slurry was chilled to 10°C, filtered, and washed with methyl alcohol, yielding 91.8 g (I) of white needles melting at 256.5-257°C dec. The mother liquor was evaporated to dryness at room temperature, and the residue was recrystallized from water to give 9.0 g (II) of off-white needles melting at 253-255°C dec. Fractions I and II represent a yield of 89 per cent of theory.

Fraction I (90.2 g) was dissolved in 1700 ml of water at 95°C, 300 ml of water were added, and the solution was treated with 5 g of decolorizing carbon for one-half hour. The suspension was filtered, and the filtrate was chilled to 10°C. The suspension was filtered, and the cake was washed with cold water and dried at 60°C to give 79.0 g (III) of white needles melting at 259-260°C dec.

A small portion of III was recrystallized from water to give white needles melting at 259-260°C dec.

Casoni[34] reported 254°C as the melting point of nicotinic acid-N-oxide; Shimizu et al[33] reported a melting point of 161°C dec. (Perhaps this was a typographical error.) (See Table 5.)

3-Methylpyridine-N-Oxide

A mixture of 405 g of 3-methylpyridine, 745 ml of 30.5 per cent hydrogen peroxide, and 1600 ml of glacial acetic acid was heated on a steam bath with agitation at 85-90°C for 30 minutes, then allowed to stand at room temperature overnight (15 hours). After the addition of 150 ml of 30.5 per cent hydrogen peroxide, the solution was heated at 84°C for 7.5 hours, then concentrated to an oil at 25" of vacuum.

After the addition of 500 ml of water the solution was again concentrated under vacuum. One liter of chloroform was added to the oil and the solution was shaken with an aqueous paste of potassium carbonate until no more carbon dioxide was evolved. The heavy paste was separated with difficulty by filtration and was washed with chloroform. The filtrate was dried over anhydrous magnesium sulfate, the suspension was filtered, and the solvent was removed under vacuum. After standing several days at room temperature, potassium acetate crystallized in the oil; 1 l. of chloroform was added, the suspension was dried with magnesium sulfate, and filtered. The chloroform was removed under vacuum, and the residual oil was distilled in a 3 cm by 55 cm packed column. The fraction boiling at 153°C at 15 mm (136-138°C at 6 mm) was collected as product, and amounted to 374 g (79 per cent of theory). On cooling the distillate formed large, yellow, oily crystals. When recrystallized from S.D. 3A ethanol the picrate of 3-methylpyridine-N-oxide formed yellow needles having a melting point of 136.5-138°C.

This procedure follows that of Boekelheide and Linn[36] who obtained a 77 per cent yield. They reported the product to have a boiling point of 146-149°C at 15 mm, and the picrate to have a melting point of 138-139°C. (See Table 7.)

4-Nitro-3-Methylpyridine-N-Oxide

Two hundred grams of 3-methylpyridine-N-oxide were slowly added as a liquid to 300 ml of 95 per cent sulfuric acid with agitation and cooling, at such a rate that the temperature did not rise above 40°C. With agitation and cooling 190 ml of red fuming nitric acid (d 1.60) were added to 300 ml of 96 per cent sulfuric acid in a 2 l. 3-neck flask, at such a rate that the temperature did not rise above 10°C. The sulfuric acid solution of 3-methylpyridine-N-oxide was then added to the nitrating mixture with agitation and cooling. With continued agitation, the solution was heated on a steam bath; when the temperature reached 90°C, the reaction became extremely exothermic, and the temperature rose quickly to 129°C, with copious evolution of brown fumes. When the reaction subsided, the solution was heated at 93°C for 12 hours. The mixture was cooled to room temperature, poured onto ice with agitation, and neutralized with 50 per cent sodium hydroxide solution to pH 3. The precipitated product was filtered, along with a quantity of sodium sulfate, washed with cold water, and dried at 60°C. The filtrate (including washes) (I) was reserved.

The cake was continuously extracted with acetone in a Soxhlet extractor. The red-colored acetone extract was concentrated on a steam bath. When crystallization took place, the suspension was chilled, filtered, and the cake was washed with cold acetone. This amounted to 193.5 g (II) of deep yellow crystals melting at 136-137.5°C. The mother liquor was treated in a similar manner to give 15.0 g (III) of deep yellow crystals melting at 135-137°C. The mother liquor of III was evaporated to dryness on a steam bath to give 30 g of a brown semi-crystalline mass which was not treated further.

The aqueous filtrate I was extracted with 7-500 ml portions of chloroform; the extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness on a steam bath. Recrystallization of the residue from S.D. 3A ethanol gave 4.9 g (IV) of yellow crystals melting at 132-135°C.

Fractions II, III, and IV totaling 208.2 g were dissolved in 1700 ml of acetone, an excess of acetone was added, and the solution was treated with 6 g of decolorizing carbon. After filtration, the solution was concentrated on a steam bath until crystallization took place. The suspension was chilled, filtered, and the cake was washed with cold acetone, yielding 189.2 g of yellow crystals melting at 136-138°C. The mother liquor was concentrated to obtain an additional 14.8 g of yellow crystals melting at 136-137°C. The yield of recrystallized product is 72 per cent of theory.

Talikowa has reported the preparation of 3-methyl-4-nitropyridine-N-oxide, but the available abstract of his paper does not give the preparative procedure, or the physical characteristics of the compound. (See Table 8.)

Attempts To Oxidize 4-Nitro-3-Methylpyridine-N-Oxide

A. *By potassium permanganate*. To a solution of

2.0 g of 4-nitro-3-methylpyridine-N-oxide in 65 ml of water, 6.2 g of potassium permanganate were added at 40°C in 10 minutes. The mixture was heated at 76-79°C for 45 minutes and filtered. The yellow filtrate was adjusted from pH 8 to pH 3 with dilute sulfuric acid, evaporated to a volume of 40 ml, and chilled. The resulting crystals were filtered and washed with cold water; after concentrating the filtrate a second crop was obtained. Each crop was recrystallized from S.D. 3A ethanol to give a total of 1.0 g of yellow crystals of 4-nitro-3-methylpyridine-N-oxide melting at 136-137.5°C.

B. <u>By potassium permanganate in acid medium</u>. At a temperature of 85-90°C 9.2 g of potassium permanganate were added in portions in 6.5 hours to a solution of 3.0 g 4-nitro-3-methylpyridine-N-oxide in 50 ml of water and 4.9 ml of 96 per cent sulfuric acid. The mixture was heated an additional 45 minutes at 85°C and filtered. The acidic filtrate (I) was extracted with 2-100 ml portions of chloroform which, when evaporated to dryness, gave 0.5 g of yellow crystals. This fraction was recrystallized from acetone to give yellow crystals melting at 136.5-137.5°C. The melting point was not depressed by addition of an authentic sample of 4-nitro-3-methylpyridine-N-oxide.

The aqueous filtrate (I) was extracted continuously with ethyl ether, which was evaporated to dryness to give 0.1 g of yellow residue.

C. By chromium trioxide in acid medium. To a solution of 3.0 g 4-nitro-3-methylpyridine-N-oxide in 20 ml of glacial acetic acid was added in portions in 1 hour a mixture containing 2.7 g of chromium trioxide in 7 ml of water, 15 ml of glacial acetic acid, and 1.6 ml of 96 per cent sulfuric acid. The addition was maintained at a temperature of 94-98°C, after which the mixture was heated at 92-94°C for 12.5 hours. After diluting the mixture with 100 ml of water it was extracted with 6-100 ml portions of chloroform. An unknown amount of chloroform solution was lost accidentally. The solution was evaporated to dryness to give 2.0 g of crystals which were recrystallized from acetone. The yellow crystals thus obtained had a melting point of 136.5-138°C. A mixture of this fraction with an authentic sample of 4-nitro-3-methylpyridine-N-oxide had a melting point of 135-137.5°C.

Attempt To Oxidize 3-Methylpyridine-N-Oxide.

In a 5 hour period 43.3 g of potassium permanganate were added in portions with agitation to a solution of 10.0 g of 3-methylpyridine-N-oxide in 150 ml of water. The temperature was maintained at 90°C during the addition, and the mixture was heated an additional 1.5 hours at 90°C. The suspension was filtered, and the yellow filtrate was adjusted from pH 9 to pH 2 by the addition of dilute sulfuric acid. The solution was evaporated to dryness on a steam bath, and the resulting residue was extracted several times with chloroform. After drying the solution over anhydrous sodium sulfate, and filtering, it was evaporated to an oil. The oil was subjected to vacuum to remove the solvent. The weight of oil was 7.8 g. The picrate of the oil melted at 137-138.5°C, and showed no depression in melting point when mixed with an authentic sample of 3-methylpyridine-N-oxide picrate.

Pyridine-N-Oxide

A mixture of 500 g reagent grade pyridine, 1250 ml of glacial acetic acid, and 700 ml of 30.5 per cent hydrogen peroxide was heated at 80-85°C with agitation for 1¼ hours. Then 520 ml of 30.5 per cent hydrogen peroxide were added, and the mixture was heated at 70-80°C for 12 hours. The yellow solution was concentrated under vacuum to an oil, 500 ml of water were added, and the solution again concentrated to an oil. The operation was repeated following the addition of another 250 ml of water. Anhydrous potassium carbonate was added to the yellow oil until no more carbon dioxide was evolved, and the oil was diluted with 2 l. of chloroform. After standing at room temperature for three days to allow potassium acetate to crystallize, the suspension was filtered and the cake was washed well with chloroform. The chloroform solution was dried with anhydrous magnesium sulfate, filtered, and concentrated on a steam bath. The resulting oil was distilled in a packed column (previously described), collecting the fraction boiling at 138-144°C at 15 mm. The distillate formed a slightly discolored (light tan) solid at room temperature. The yield was 507 g (84 per cent of theory). When recrystallized from S.D. 3A ethanol the picrate of pyridine-N-oxide forms yellow needles melting at 184-185°C.

Ochiai[21] reported a boiling point of 138-140°C at 15 mm.

4-Nitropyridine-N-Oxide

With agitation and cooling 200 g of solid pyridine-N-oxide were added to a flask containing 400 ml of 96 per cent sulfuric acid, at such a rate that the temperature did not rise above 35°C. The pyridine-N-oxide was washed in with an additional 200 ml of 96 per cent sulfuric acid. The solution was heated on a steam bath to 85°C, and the dropwise addition of 207 ml of red fuming nitric acid (d 1.60) was begun. When about one-half of the nitric acid had been added, the reaction became exothermic; the addition was discontinued and no heating was provided. In 20 minutes the temperature rose to 118°C, then subsided, after which the remainder of the nitric acid was added in a dropwise manner. The solution was heated on a steam bath at 95°C for 18 hours, poured on ice, and neutralized with 50 per cent sodium hydroxide solution to pH 4 with agitation and external cooling, a temperature of 40°C being maintained during most of the neutralization. The suspended product was filtered on a steam-heated Buchner funnel to prevent crystallization of the sodium sulfate. The cake was then washed with 3-300 ml portions of cold water. The dried cake amounted to 209.5 g (I) of yellow crystals melting at 160.5-163°C.

The mother liquor was extracted with 10-500 ml portions of chloroform. After being dried with anhydrous magnesium sulfate, the chloroform solution was concentrated on a steam bath until crystallization took place. The suspension was chilled and filtered, and the cake was washed with cold chloroform to yield 44.6 g (II) of deep yellow crystals melting at 161-163°C. The chloroform mother liquor was evaporated to dryness on a steam bath and the residue recrystallized from water to give 9.6 g of orange crystals melting at 100-149°C. This fraction was not treated further.

Fractions I and II (253 g) were dissolved in 2500 ml of hot water; the solution was treated with decolorizing carbon, filtered on a steam-heated Buchner funne, and concentrated on a steam bath to a volume of 1500 ml. After crystallization took place, the suspension was chilled to 5°C, filtered, and the cake was washed with cold water, giving 223 g of large yellow crystals melting at 161.5-163°C. The aqueous mother liquor was treated with decolorizing carbon, filtered, and concentrated until crystallizing took place. The suspension was chilled, filtered, and the cake was washed with cold water, giving an additional 23.8 g of yellow crystals melting at 161.4-162.8°C. The yield of recrystallized 4-nitropyridine-N-oxide was 84 per cent of theory.

Ochiai[21] reported the product to have a melting point of 159°C; den Hertog and Overhoff[23] reported a value of 159-160°C. (See Table 9.)

4-Aminopyridine.

A. By iron-acetic acid. With agitation and at a temperature of 70-80°C, 110 g of powdered iron (100 mesh) were added in one-half hour to a solution of 50.0 g of 4-nitropyridine-N-oxide in 625 ml of glacial acetic acid. The reaction was exothermic, and it was necessary to occasionally provide external cooling. The brown suspension was then heated on a steam bath at 93°C for 1 hour. After cooling the suspension to room temperature in an ice bath, 500 ml of water were added and the mixture was made strongly alkaline with 600 ml of 50 per cent sodium hydroxide solution. With the use of filter aid, the suspension was filtered and the cake was washed several times with cold water. The combined filtrate and washes were extracted in a liquid-liquid extractor with ethyl ether for a total of 12 days, and the ether was evaporated to dryness on a steam bath to give 26.5 g of crude 4-aminopyridine. This was dissolved in 800 ml of chloroform; the solution was treated with decolorizing carbon, filtered, and concentrated on a steam bath until crystallization took place. The suspension was chilled in an ice bath and filtered, and the cake was washed with ligroin, yielding 26.0 g (77 per cent of theory) of light tan crystals melting at 157.5-159.5°C.

By this method den Hertog and Overhoff[23] obtained 4-aminopyridine melting at 157-158°C. (See Table 10.)

B. <u>By catalytic reduction</u>. A mixture of 100 g of 4-nitropyridine-N-oxide in 300 ml of glacial acetic acid, 196 ml of acetic anhydride (95 per cent of the theoretical amount required to combine with the water of reaction), and 10 g of 5 per cent palladium on carbon was subjected to a hydrogen pressure of 800 lb./in.^{2} in a rocker bomb. The reaction took place quickly and within 5 minutes the temperature had risen from 24° to 120°C. Although most of the hydrogen was taken up in about 15 minutes, the mixture was maintained under hydrogen pressure for 3 hours. After releasing the hydrogen, the catalyst was removed by filtration. The filtrate was concentrated to an oil under vacuum, 100 ml of water was added, and the mixture again concentrated to an oil under vacuum. With cooling and agitation, 60 ml of 50 per cent sodium hydroxide solution were added to pH 8. After standing overnight 75 ml of 50 per cent sodium hydroxide solution were added and the resulting precipitate was filtered to give 49.7 g (I) of brown, granular material. The aqueous filtrate was extracted continuously for 4 days with ethyl ether, and the ether solution was evaporated to dryness to give 9 g (II) of an orange, slightly oily solid. Fractions I and II were combined and boiled with 6 l. of benzene (some insolubles were present). The suspension was treated with decolorizing carbon and filtered on a steam-heated Buchner funnel. After concentrating the filtrate to a volume of 1 l. on a steam bath and allowing crystallization to take place, the crystals were filtered and washed with benzene. The Yield of 4-aminopyridine was 43.6 g (65 per cent of theory) in the form of off-white crystals melting at 158-160°C. (See Table 11.)

4-Nitraminopyridine.

To 40 ml of 96 per cent sulfuric acid was added 18.0 g of 4-aminopyridine, with agitation and cooling, at such a rate that the temperature did not exceed 25°C. The 4-aminopyridine was washed in with 10 ml of 96 per cent sulfuric acid, and 9.5 ml of fuming nitric acid (d 1.48) were added in a 20 minute period, with cooling. At one point during the addition, the slurry thickened to a paste with a simultaneous rise in temperature from 10° to 30°C; in a few minutes, however, a thin slurry formed and the temperature dropped to 8°C. Agitation was continued for 2.5 hours, and the temperature was allowed to rise to 26°C. The deep yellow solution was poured on ice and the white precipitate was collected and washed with water, at which time the cake turned yellow. This portion amounted to 1.5 g (I) of yellow powder decomposing at 181°C; slurrying with water resulted in 1.1 g (II) of yellow powder decomposing at 234.5°C.

The filtrate from I was neutralized with 50 per cent sodium hydroxide solution to pH 6, and the precipitate was filtered and washed with water, giving 24.5 g of yellow powder decomposing at 232°C. The total yield of 4-nitraminopyridine was 25.6 g (96 per cent of theory).

Koenigs, Mields, and Gurlt[3] reported 4-nitraminopyridine to have a melting point of 243-244°C. (See Table 12.)

<u>3-Nitro-4-Aminopyridine</u>.

With agitation and cooling 25.0 g of 4-nitraminopyridine were added to 65 ml of 96 per cent sulfuric acid at such a rate that the temperature was maintained between 8°and 11°C. The starting material was washed in with 10 ml of 96 per cent sulfuric acid, and the suspension was allowed to come to room temperature. After heating on a steam bath to 40°C the mixture was an amber solution. With additional heating the solution began turning to a red color at about 70°C, and at 83°C the temperature began to rise rapidly due to a vigorous spontaneous reaction. Heating was discontinued and the temperature of the solution was maintained between 95° and 105°C by means of an ice bath. No brown fumes were visible at any time during the reaction. When the reaction had subsided and the temperature had fallen to 89°C the red solution was heated on a steam bath for 30 minutes. The temperature gradually rose to 99.5°C, then leveled at 93°C, indicating that even at this time a slightly exothermic reaction was taking place. When the heating period had been completed, the red-colored mixture was cooled to room temperature and poured onto 400 g of ice, and the flask was washed with 100 ml of water. The aqueous solution was then made strongly alkaline by the addition of 145 ml of 50 per cent sodium hydroxide solution, and the precipitate was filtered at 25°C (filtering on a steam-heated Buchner funnel would have prevented the crystallization of sodium sulfate). After drying at 60°C the cake (consisting of crude product and sodium sulfate) was boiled in 200 ml of S.D. 3A ethanol, the suspension was filtered and the cake washed with S.D. 3A ethanol. After treating the ethanol solution with decolorizing carbon, filtering, and concentrating to a volume of about 100 ml, 20 ml of hot water were added. After chilling in an ice bath, the suspension was filtered, and the cake was washed with cold water, to give 8.9 g (I) of a light brown powder melting at 204-205.5°C dec. By concentrating the mother liquor an additional 1.0 g (II) of brown powder melting at 187-194°C dec. was obtained. This fraction was upgraded by treating a methanol solution with decolorizing carbon and filtering. After concentrating the solution in a beaker to a volume of about 10 ml, 30 ml of benzene were added, and boiling was maintained until crystallization took place. The suspension was cooled and filtered, and the cake was washed with benzene, giving 0.8 g (III) of orange-yellow powder melting at 202.5-203°C dec. Fractions I and II were combined and recrystallized as above from methanol and benzene to give 7.9 g of yellow powder melting at 204.5-206°C. By concentrating the mother liquor an additional 1.6 g of orange-yellow powder melting at 202-204°C was obtained. Thus the yield of recrystallized 3-nitro-4-aminopyridine was 9.5 g, or 38 per cent of theory.

Koenigs et al[3] reported that when recrystallized from water, 3-nitro-4-aminopyridine formed yellow needles melting at 200°C. (See Table 13.)

3,4-Diaminopyridine.

A. Reduction using sodium sulfide. To a solution of 23.2 g of sodium sulfide nonohydrate in 50 ml of water 2.5 g of 3-nitro-4-aminopyridine were added in portions at 80-90°C in a 10 minute period. The solution quickly became strongly alkaline, and dark brown in color. After evaporating the solution to a volume of 35 ml crystallization began to take place. The mixture was allowed to cool to room temperature, chilled, and filtered, and the cake was washed with cold water. The cake consisted of 1.3 g (66 per cent of theory) of off-white glistening crystals melting at 219-220°C dec. The 3,4-diaminopyridine was recrystallized from water to give 0.65 g of white, glistening leaves melting at 218.5-220°C dec. By evaporating the mother liquor to a small volume an additional 0.5 g of off-white glistening leaves melting at 215-218.5°C dec. was obtained. The picrate was recrystallized from S.D. 3A ethanol giving red crystals melting at 235-236°C dec.

An analysis for nitrogen in 3,4-diaminopyridine (for $C_5H_7N_3$) gave the following results: theory, 38.51, found, 38.72.

By this method Koenigs, Bueren, and Jung[5] obtained 3,4-diaminopyridine melting at 218-219°C in 83.5 per cent yield. They obtained the picrate from ethanol as red needles melting at 235-237°C.

Bremer[4] isolated the product as the hydrochloride in 77 per cent yield. By treating the salt with dilute sodium hydroxide solution 3,4-diaminopyridine was obtained as colorless rhombes melting at 215-216°C.

Weidenhagen and Weeden[8] reduced 3-nitro-4-aminopyridine in an undisclosed manner to give 3,4-diaminopyridine melting at 215-216°C.

B. Catalytic reduction using palladium-on-carbon.

To a solution of 5.0 g of 3-nitro-4-aminopyridine in 200 ml of S.D. 3A ethanol at 50°C was added a suspension of 0.5 g of 5 per cent palladium-on-carbon in 10 ml of S.D. 3A ethanol. The suspension was washed into a Parr shaker bottle with 15 ml of S.D. 3A ethanol, in which the reduction took place at a hydrogen pressure of 50 lb./in.^{2}. After three hours had elapsed the pressure was released and the catalyst was removed by filtration. The yellow filtrate was treated with decolorizing carbon, the suspension was filtered, and the solution was evaporated on a steam bath to a small volume. The resulting suspension was evaporated to dryness in an oven to give 4.0 g of 3,4-diaminopyridine in the form of brown crystals. A solution of the crude product in 60 ml of methanol was treated with decolorizing carbon, the suspension was filtered, and the solution was concentrated to a volume of about 30 ml. To the solution was added 50 ml of benzene, and boiling was maintained until crystallization took place. The suspension was cooled and filtered, and the cake was washed with benzene, giving 2.8 g (71 per cent of theory) of tan crystals of 3,4-diaminopyridine melting at 215.5-218.5°C dec. A small amount of methanol was added to the mother liquor, which was then treated with decolorizing carbon, and filtered. Benzene was added to the filtrate, and the solution was concentrated on a steam bath until crystallization took place. The suspension was filtered to give 0.8 g of impure 3,4-diaminopyridine melting at 212-215°C dec. The two fractions represent a yield of 91 per cent.

TABLE 1

METHYL NICOTINATE

Run	1	2
Nicotinic Acid, g	150	500
Methanol, ml	350	1150
Sulfuric acid, 96%, ml	163	543
Reflux time, hrs.	2.5	3
Boiling Point		71-72°/2.5 mm
Yield, %	-	67
Notes	Extracted with benzene. Not distilled.	Extracted with ethyl ether. Distilled.

TABLE 2

NICOTINAMIDE

Run	2	4	9
Methyl nicotinate, g	59	129	241
Ammonium hydroxide, 29%, ml/g	3.4	3.3	3.3
Gaseous NH_3, g	50	50	70
Time	5.5 hrs. at 0-5°C.	5 hrs. at 0-5°C, 8 days at 25°C.	At 10°C, during NH_3 addition, 7 days at 25°C.
Yield, %	97	94.5	96
Melting point, °C	119.5 -121.5	123 -125.5	125.5 -128
Notes	From non-distilled methyl nicotinate		

TABLE 3

NICOTINAMIDE-N-OXIDE

Run		5	6	8
Nicotinamide		5.0	42.8	50
Acetic acid, ml/g		20	4.7	5
Hydrogen peroxide, 30%, mol/mol		1.5	1.5	1.5
Heating time		14 hrs. at 45-55°, 3 hrs. at 83°	1.5 hrs. at 85° 16 hrs. at 40° 3 hrs. at 60-90°	1.5 hrs. at 60° 16 hrs. at 25° to 80° in 8 hrs.
Yield, %		87	(I) 75 (II) 10	(I) 35 (II) 49
Melting point, °C		279-281 d.	(I) 275-280 d. (II) 260 d.	(I) 283.5-284.5 d. (II) 279-280 d.
Analyses For $C_6H_6O_2N_2$:				
	Theory			
C	52.17	52.14		52.19
H	4.38	4.27		4.15
N	20.28	20.14		20.05

TABLE 4

NITRATION OF NICOTINAMIDE-N-OXIDE

Run	7	10	20
Nicotinamide-N-oxide, g	20	18.4	5.0
Nitrating agent	KNO_3, 22 g	KNO_3, 20 g	70% HNO_3, 3.7 ml
Sulfuric acid, 96%, ml	40	36	10
Heating time	2.5 hrs. at 60-90°	3 hrs. at 83-90°C	5 hrs. at 123-130°C
Notes	Neither product nor starting material isolated	Neither product nor starting material isolated	3.0 g nicotinic acid-N-oxide obtained. Melting point: 259-260° d. Mixed melting point: 258.5-260° d.

TABLE 5

NICOTINIC ACID-N-OXIDE

Run		11	13	14
Nicotinic Acid, g		50	100	100
Acetic acid, ml/g		4	4	4
Hydrogen peroxide, 30%, mol/mol		1.7	1.8	1.8
Heating time		5.75 hrs. at 70-80°	1.25 hrs. at 90°	2.25 hrs. at 70-80°
Yield, %		81	58	(I) 81 (II) 8
Melting point, °C		259-260 d.	254-256 d.	(I) 256.5-257 d. (II) 253-255 d.
Analyses For $C_6H_5O_3N$:				
	Theory			
C	51.80			51.95
H	3.62			3.63
N	10.07			9.98
Note			Decomposed during reaction. Brown product.	

TABLE 6

NITRATION OF NICOTINIC ACID-N-OXIDE

Run	12	15	20	22
Nicotinic Acid-N-oxide	20	20	10	10
Nitrating agent	KNO_3 23 g	70% HNO_3, 14.6 ml	70% HNO_3, 7.3 ml	Red fuming HNO_3, 5 ml
Sulfuric acid, 96%, ml	40	40	20	20
Heating time	3 hrs. at 70-80°	5.25 hrs. at 85-90°	5.5 hrs. at 125-130°	3.5 hrs. at 80-114°
Recovery, %	93	90	58	58
Melting point, °C	256-259 d.	255-258 d.	255-257 d.	254-257 d.

TABLE 7

3-METHYLPYRIDINE-N-OXIDE

Run	16	25
3-Methylpyridine, g	100	405
Acetic acid, ml/g	4	4
Hydrogen peroxide, 30%, mol/mol	1.7	1.8
Heating time	1 hr. at 70-80° 16 hrs. at 25° 8 hrs. at 83-90°	0.5 hr. at 85° 16 hrs. at 25° 7.5 hrs. at 85°
Boiling point	137-147°/ 9 mm	153°/15 mm (136-138°/ 6 mm)
Yield, %	84	79
Picrate, melting point, °C		137-138.5

TABLE 8

4-NITRO-3-METHYLPYRIDINE-N-OXIDE

Run		17	18	24	35
3-Methylpyridine-N-oxide, g		20	20	55	200
Nitrating agent		70% HNO_3, 18.6 ml	70% HNO_3, 18.6 ml	70% HNO_3 51 ml	Red fuming HNO_3, 190 ml
Sulfuric acid, 96%, ml		51	50	138	600
Heating time		2 hrs. at 96°	4 hrs. at 97°	4.5 hrs. at 94°	12.5 hrs. at 93°
Yield, %		(37)	46	53	72
Melting point, °C		137-138	136-137	137-138	136-138
Analyses For $C_6H_6O_3N_2$:					
	Theory				
C	46.75				46.58
H	3.92				4.16
N	18.18				17.41
Note		Low yield due to physical loss.		2.2% 3-methyl-6-nitropyridine, melting point 93-95°, isolated as by-product.	

TABLE 9

4-NITROPYRIDINE-N-OXIDE

Run	28	31	34	39	40
Pyridine-N-oxide, g	20	40	92	200	200
Nitrating agent	KNO_3, 34 g	Red fuming HNO_3, 43 ml	Red fuming HNO_3, 100 ml	KNO_3, 340 g	Red fuming HNO_3, 207 ml
H_2SO_4, 96%, ml	70	120	275	(20% oleum, 600 ml)	600
Heating time	20 hrs. at 95°	1.5 hrs. at 93-95°	15 hrs. at 96°	12 hrs. at 95°	19 hrs. at 95°
Yield, %	61	63	82	(Est. 66)	84
Melting point, °C	162-163	161.5-163	161-162.5	161.5-162.5	161.5-163
Analyses For $C_5H_4O_3N_2$:					
	Theory				
C	42.82		42.81		42.79
H	3.60		3.35		3.41
N	20.00		20.30		19.81
Note			0.5% 2-nitropyridine, isolated as by-product.	Physical loss	

TABLE 10

4-AMINOPYRIDINE BY IRON-ACETIC ACID METHOD

Run	29	36	37
4-Nitropyridine-N-oxide, g	4.0	20	50
Acetic acid, ml	60	250	625
Iron powder, g	8.8	44	110
Heating time	1 hr. at 90°	1 hr. at 95°	1 hr. at 93°
Yield, %	75	80	77
Melting point, °C	158-160	153-156	157.5-159.5

TABLE 11

4-AMINOPYRIDINE BY CATALYTIC REDUCTION

Run	30	43	51
4-Nitropyridine-N-oxide, g	10	50	100
Acetic acid, ml	105	500	300
Acetic anhydride, ml	5	98	196
Palladium-on-carbon, 5%, g	0.5	4.8	10
Hydrogen pressure, lb/in^2	50	1200	800
Temperature, °C	40	60	To 120
Yield, %	65		65
Melting point, °C	157.5-160	116-138	159-160
Note		Mixture of 4-aminopyridine and 4-acetaminopyridine.	

TABLE 12

4-NITRAMINOPYRIDINE

Run	23	38	42	46	55
4-Amino-pyridine, g	1.5	2.0	10.5	18.0	22.0
Nitrating agent	Red fuming HNO_3, 1.1 ml	Fuming HNO_3, 1.0 ml	Fuming HNO_3, 5.5 ml	Fuming HNO_3, 9.5 ml	Fuming HNO_3, 11.6 ml
Sulfuric acid, 96%, ml	6	10	31	50	86
Yield, %	(54)	84.5	85	96	96
Melting point, °C	234 d.	231 d.	233 d.	232 d.	230 d.
Note	Low yield due to physical loss.				

TABLE 13

3-NITRO-4-AMINOPYRIDINE

Run	4-Nitramino-pyridine, g*	H_2SO_4, 96%, ml*	Heating time
41	1.8	7	1 hr. at 70-94°
44	8.0	26	Initially to 140°, 0.5 hr. 80-90°.
47	3.0 g 4-amino-pyridine	9	Form 4-nitramino-pyridine, heat 1 hr. 70-90°. No temperature rise noted.
48	3.0	9	Initially to 110°, 1 hr. at 80-90°.
49	3.0	9	Initially to 91°, 2 hrs. at 90-95°.
50	3.0	9	Initially to 90°, 12 hrs. at 94°.
52	2.0 g 4-amino-pyridine	6	100% excess fuming HNO_3 added at 90°; exothermic reaction. No precipitate on neutralization of reaction mixture.
53	3.0	9 ml 85% H_2SO_4	3 days at 25°
54	2.0	20 ml conc HCl	6 days at 25°, 15 min at 90°.
57	3.0	9	Initially to 150°, 20 min. at 140-160°.
58	25.0	75	Initially 95-105°, 30 min. at 93-99.5°.

* Unless otherwise noted.

TABLE 13 (continued)

3-NITRO-4-AMINOPYRIDINE

	Purification			Note
Run	System	Melting Point, °C	Yield %	
41	EtOH-H_2O	203-204	22	
44	EtOH-H_2O	205-206	33	Mercury in reaction mixture.
47	EtOH	I 196-198 II 230.5	9 27	3-Nitro-4-amino-pyridine
48	EtOH	204.5-205.5	30	Analysis for nitrogen: theory, 30.21 found, 29.93
49	Sublimed	200-203	27	
50		195-197	(37) Crude	
52				
53		232.5	67	4-nitramino-pyridine recovered
54		233	40	4-nitramino-pyridine recovered
57	EtOH-H_2O	204-205	33	
58	MeOH-Benzene	204.5-206	38	

TABLE 14

3,4-DIAMINOPYRIDINE BY CATALYTIC REDUCTION

Run	56	59
3-Nitro-4-amino-pyridine, g	0.35	5.0
S.D. 3A ethanol, ml	75	225
Palladium-on-carbon, 5%, g	0.1	0.5
Temperature, °C	27	50
Hydrogen pressure, lb/in^2	50	50
Yield, %	(I) 69 (II) 22	(I) 71 (II) 20
Melting point, °C	(I) 217-218.5 d. (II) 216-218 d.	(I) 215.5- (II) 212- 215 d.

Analysis
For $C_5H_7N_3$

	Theory	
N	38.51	38.57

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