HETEROCYCLES, Vol. 6, No. 5, 1977

Rearrangements of t-Amine Oxides

Shigeru Oae *
Department of Chemistry
University of Tsukuba
Ibaraki 300-31, Japan
and
Kenji Ogino
Department of Applied Chemistry
Osaka City University
Sumiyoshi-ku, Osaka 558, Japan

Heteroaromatic N-oxides and related tertiary amine oxides react with acylating agents and undergo various reactions depending upon the nature of the amine oxides, acylating agents,etc. These reactions are broadly divided into the following five basic types of reactions: 1) deoxygenative reduction, 2) rearrangement to ring carbon, 3) rearrangement to side chain carbon, 4) other hetero-aromatic rearrangements, 5) rearrangements of open-chain N-oxides.

Each of these five representative reactions are illustrated by numerous examples, including many of our mechanistic investigations, hoping eventually to serve as nice guides to new synthetic inventions and innovations. The contents of this review are the following:

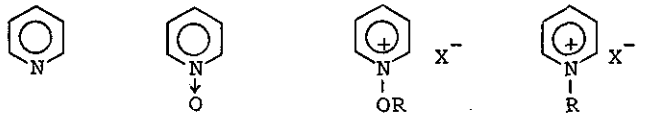
1. Introduction

A few books have already been published concerning physicochemical properties and chemical behaviors of substituted pyridine, quinoline, isoquinoline and other related heteroaromatic N-oxides.[1-3]

As compared to other fields of heterocyclic chemistry, the chemistry of heteroaromatic amine oxides has been extensively explored, not only because it has led to the syntheses of many biochemically and pharmaceutically important compounds, but due much to the pioneering works of late Professor Eiji Ochiai and his school in this Country.

Heteroaromatic amine oxides, such as pyridine and quinoline N-oxides, bearing a semipolar N-O linkage, i.e., $\geq N^{+}-O^{-}$, show different behaviors as compared to the corresponding un-oxidized mother heteroaromatics or related quaternary ammonium salts in the reactions with either electrophiles, nucleophiles or radicals and display interesting orientations and reactivities in substitution reactions, as was dramatically illustrated in the nitration of pyridine N-oxide by Ochiai et al. in their initial work.[1] Since the

N-oxide group is electron-withdrawing, it facilitates the nucleophilic substitution on the ring and activates methylene group at α- and γ-positions. The terminal oxygen being nucleophilic, protonation, alkylation and acylation take place on oxygen, often leading eventually to rearrangements or introduction of a new substituent into the ring.



R = H, alkyl, aryl, acyl

The N-oxides are also known to be mild oxidizing agents and oxidize sulfur compounds or even some acyl anhydrides.

Many examples of these reactions have been compiled in the literatures,[1-3] and known widely, however, their detailed mechanisms were not fully understood before around 1960, when we started our initial mechanistic investigation by the use of ^{18}O tracer technique. The first attempt was to see if the acyloxy migration from N atom to either ring carbon or methylene carbon is intra- or intermolecular in the reaction of pyridine and picoline N-oxides with acetic anhydride. Then the incipient formation of "anhydrobase" was examined, while the initial formation of acyloxy-pyridinium or -quinolinium acetate was well substantiated both by us and Traynelis' group. The first kinetic investigation on such rearrangement was carried out by Markgraf on the reaction of pyridine N-oxide and acetic anhydride, followed by our determinations of hydrogen-deuterium kinetic isotope effects which indicate rather precisely the rate-determining step of each of these reactions.[4]

In the initial stage of investigations, the mode of the N-O bond cleavage was suggested to be homolytic, but is now believed to be heterolytic, due mainly to the nice carbonium ion trapping experiments by Katritzky's group and Cohen's group.

Meanwhile, some acyl anhydrides, such as phenylacetic and ethoxyacetic anhydrides were found to reduce the N-oxides of pyridine bases back to original pyridine bases by deoxygenation. Both sulfonyl and sulfinyl chlorides also reduce the pyridine N-oxides.

Nitrones and azoxybenzenes are open-chain analogs of hetero-aromatic N-oxides. They also react with acylating agents similarly and give rearrangement products. The mechanisms of these rearrangements were also found to be similar upon somewhat detailed kinetic and isotopic tracer studies.

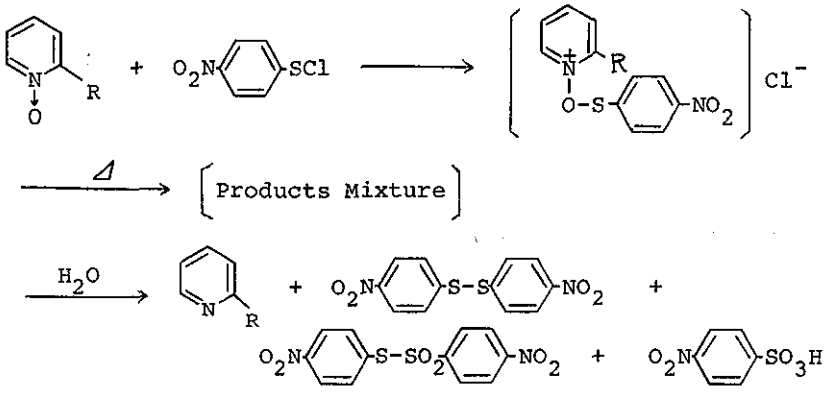
Since we initiated our investigation on the rearrangements of t-amine oxides, we have published more than fifty papers. However, a few remarks in some of our earlier papers contradict against the more recent ones and may lead readers to puzzle at what would be the real picture. Thus, we now have reassembled all our pertiment data and others of related investigations and would like to present the mechanistic pictures of these reactions in the light of newest available results.

This is not a review of all kinds of known reactions involving t-amine oxides but intending to show somewhat in detail the mechanisms of representative reactions of various types involving t-amine oxides and acylating agents. Once the mechanisms are well-understood, the synthetic utilizations of these and related reactions will automatically be developed in the next stage.

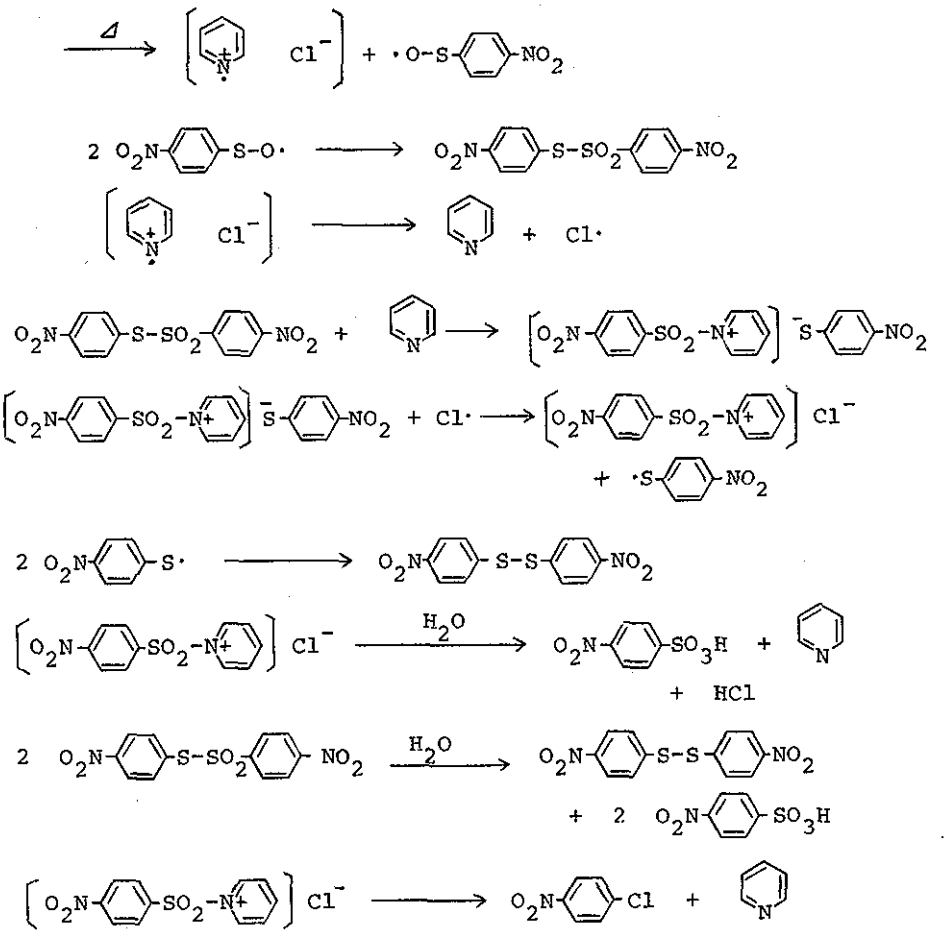
2. Deoxygenative Reductions of N-Oxides

Heteroaromatic amine oxides are readily reduced back to the original bases by oxygen-transfer reaction upon treatment with trivalent phosphorous compounds such as PCl_3, $(RO)_3P$, R_3P, sulfur compounds such as elemental sulfur, sulfur dioxides, sulfur dichloride, arenesulfenyl or -sulfinyl chloride and diaryl disulfide and also such a silane compound as $Cl_3SiSiCl_3$. Metal hydrides such as $LiAlH_4$, $NaBH_4$-$AlCl_3$ or R_3SnH are also good reducing agents to deoxyganate the N-oxides back to the amines.

Pyridine and picoline N-oxides react with p-nitrobenzenesulfenyl chloride and afford pyridine and picoline, besides dinitrodiphenyl disulfide, -thiosulfonate and the sulfonic acid together with a small amount of p-chloronitrobenzene as shown below.[5)]

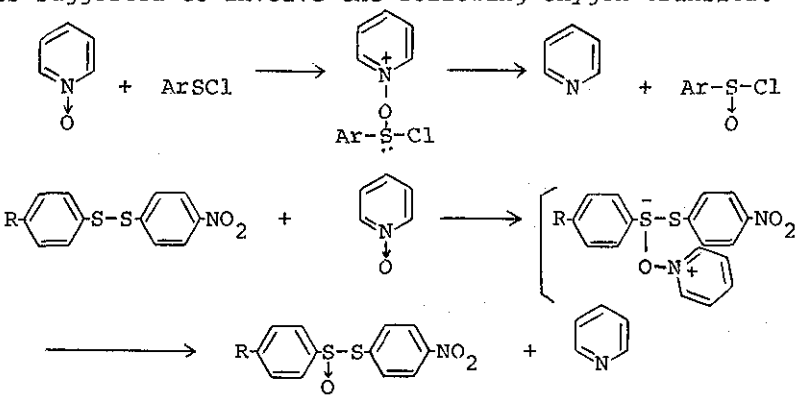


The appearance of clear-cut ESR signals during and shortly after the reaction was considered to support the mechanism involving homolytic N-O bond cleavage shown below:

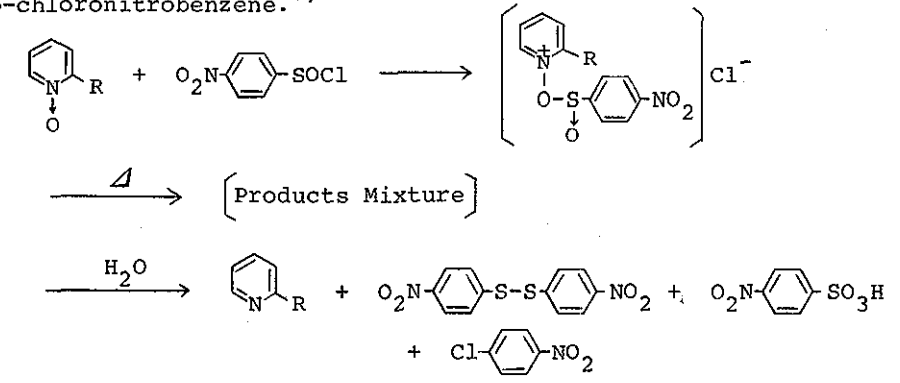


However, since the same ESR signals of the sulfenate radical could be observed in thermal disproportionation of di-p-nitrophenyl thiolsulfinate, which can be formed by the hydrolysis of the sulfinyl chloride, the direct oxygen-transfered product, the initial step of the main deoxygenative reduction could be a heterolytic oxygen transfer shown below, in view of a somewhat similar deoxyganative reduction of pyridine N-oxide by substituted diphenyl

disulfides in which the electron-donating substituent on diphenyl disulfide increases the rate (Hammett ρ =-0.7) while more basic γ-methoxypyridine (pKa=2.05 vs. 0.79 for unsubstituted pyridine), was found not to react at all with di-(p-nitrophenyl) disulfide under the same condition for pyridine N-oxide and the initial step is suggested to involve the following oxygen transfer.[6]



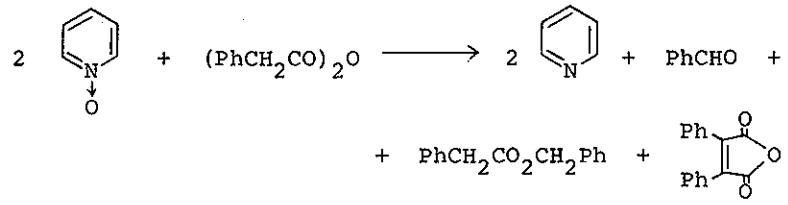
p-Nitrobenzenesulfinyl chloride also reacts with pyridine or picoline N-oxide forming N-arenesulfinoxy-pyridinium or picolinium salt, which upon further treatment eventually gives the reduced base, i.e., pyridine or picoline, besides the disulfide, the sulfonic acid and p-chloronitrobenzene.[7]

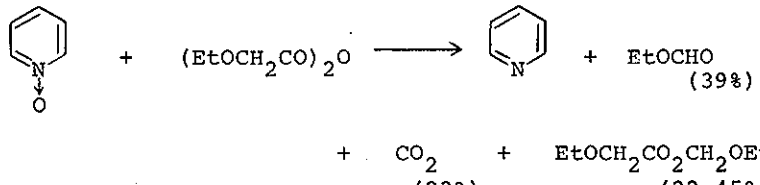


Although no detailed mechanistic investigation has been carried out,

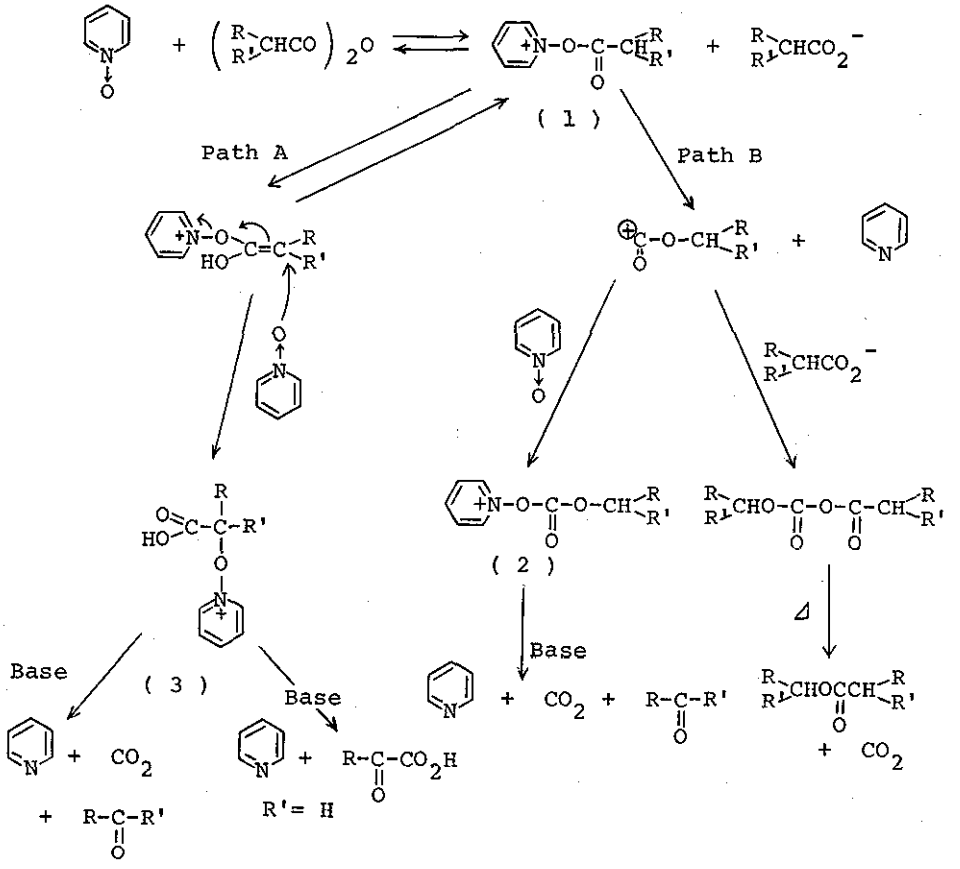
both reactions appear to follow similar mechanistic routes and resembles the deoxygenative reductions of sulfoxides. Many other examples of such deoxygenative reductions of N-oxides, sulfoxides and related compounds are reviewed in " Reduction Reactions " by us,[8] and hence not included.

While the reaction of pyridine or α- and γ-picoline N-oxides with acetic anhydride gives the corresponding rearrangement products, via acyloxy-migration, Rüchardt,[9] Cohen[10] and Koenig[11] observed that some α-substituted acetic anhydrides eventually reduce the N-oxides back to the original bases, evolving carbon dioxide from the anhydrides used. The first example is with phenylacetic anhydride shown below. Substituted phenylacetic, diphenylacetic anhydrides and anhydrides of α,β or β,γ-unsaturated carboxylic acids also react similarly.[12] Phenoxy- and ethoxy-acetic anhydrides also react with the N-oxides similarly as shown below.[12]





The general scheme of the reaction is shown below.



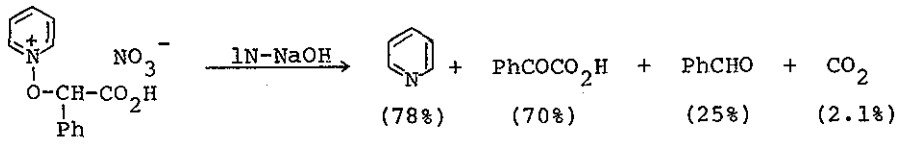
The initial step is undoubtedly the formation of O-acyloxypyridinium salt (1), however, there are three different mechanistic arguments as to the subsequent steps.

Koenig favored the carboxy-inversion mechanism, Path B, which involves the intermediate (2) on the basis of ^{18}O tracer experiments with ^{18}O-labeled phenylacetic acid and their observation of ester formation upon treatment of the intermediate, formed by

treating pyridine N-oxide with benzyl chloroformate.[13] However, scant formation of other such important products as benzaldehyde and bibenzyl ketone in their model experiment with benzyl chloroformate suggests that the carboxy-inversion mechanism is not the whole picture for the over-all reaction.

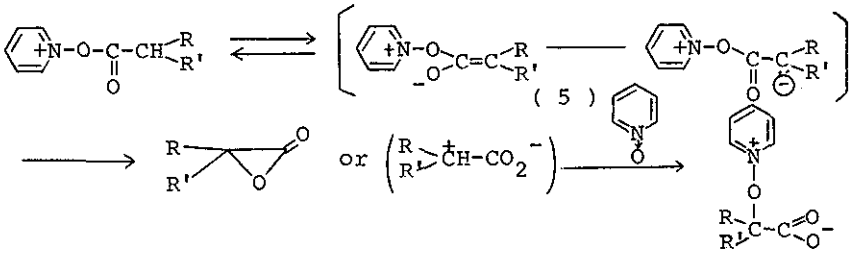
Cohen and Song examined the reaction of the N-oxide with diphenylketene or α-bromodiphenylacetic acid and suggested the reaction of pyridine N-oxide with diphenylacetic anhydride to proceed through Path A which involves the common intermediate.[14]

Recently, however, Sliwa and Tartar reexamined the reaction of pyridine N-oxide with α-halocarboxylic acid and isolated the intermediate (4) as its nitrate, which upon treatment with a base gave phenylglyoxylic acid and a small amount of decarboxylated product, i.e.,benzaldehyde.[15]

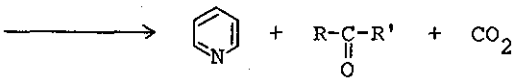


(4)

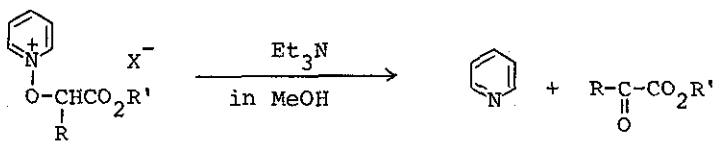
This experimental observation seems to suggest that the mechanism involving a betaine intermediate (5) and subsequent formation of α-lactone, postulated by Koenig,[2,11] is worthy for *reconsideration*.



(5)



The reaction of Sliwa and Tartar[15] can be applied to α-halocarboxylic esters which upon treatment with the N-oxide give α-ketoesters in high yields. Thus the reaction is a useful synthetic procedure of α-ketoesters by oxidizing α-halocarboxylic esters with the N-oxides, and is quite similar to the Kornblum reaction to prepare aldehydes or ketones by treating alkyl halides with DMSO.[16]

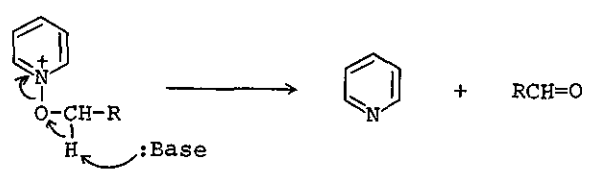


(89-97%)

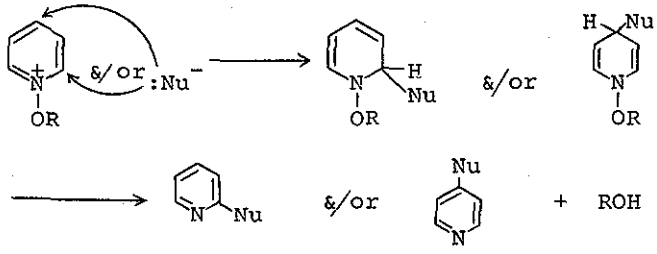
R, R' = H, Me, t-Bu, Ph
X = Br, NO_3, picrate

Unlike N-acyloxypyridinium salts which give various products, O-alkylpyridinium salts are better intermediates for the preparation of aldehydes and ketones, since O-alkylpyridinium salts give only aldehydes or ketones together with reduced pyridine upon treatment with bases, thus serving as an excellent synthetic procedure. O-Alkylpyridinium salts, however, give different products with other nucleophiles and Katritzky et al.[17] divided the reactions into the following four classes:

1) 1,2-Carbonyl-forming Elimination with Hard Bases

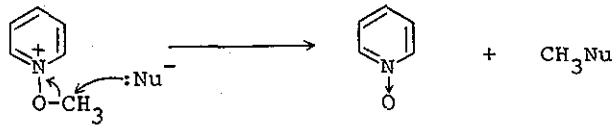


2) Nucleophilic Substitution with Soft Bases on Ring Carbon



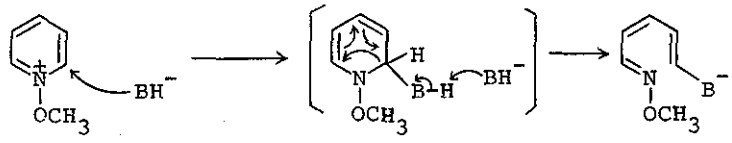
$Nu^- = CN^-, RS^-$, etc.

3) Nucleophilic Substitution on Alkyl Group with C-O Bond Cleavage by Soft Bases

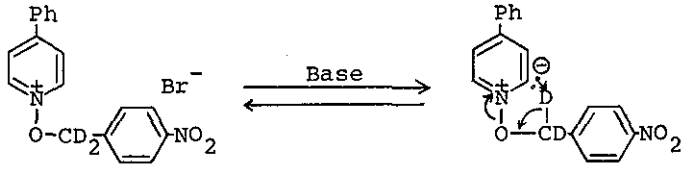


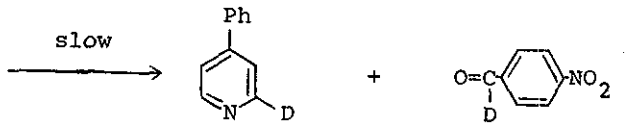
$Nu = NO_3^-, I^-, N_3^-, SCN^-, PhSO_2^-$, etc.

4) Ring Opening Cleavage with Hard Bases

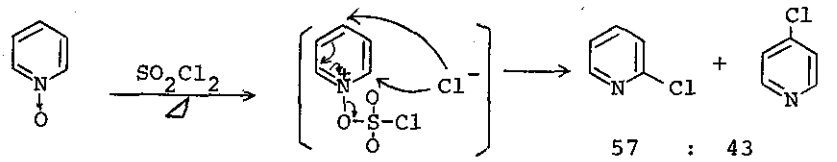


The reactions of class-1 type resembles the Kornblum reaction. Indeed, like the Kornblum reaction, an intramolecular Ei type elimination was observed with α-dideuterated p-nitrobenzyloxy-pyridinium salt as shown below.[18] Another similar reaction between lutidine N-oxide and styrene oxide is also known.[19]

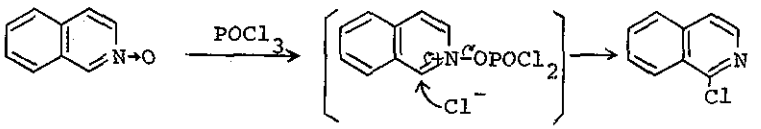




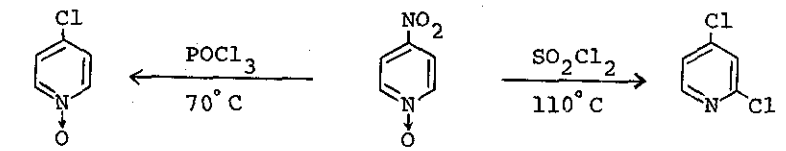
One of the earliest examples of deoxygenation is the deoxygenative chlorination of pyridine N-oxide with sulfuryl chloride, found by Bobranski and his co-workers in Poland.[20]

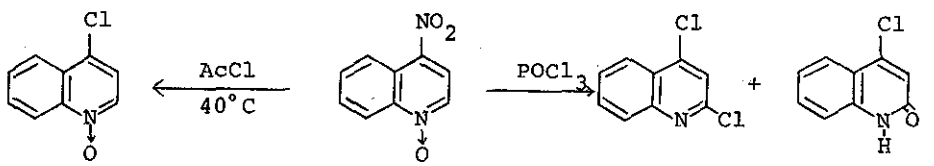


Other chlorinating agents such as phosphorous oxychloride also react similarly with γ-nitropyridine and isoquinoline N-oxides.[21]



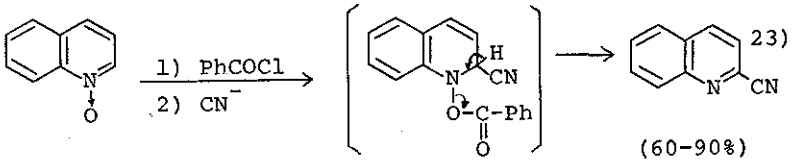
A few other reactions with these chlorinating reagents are shown below.[22]

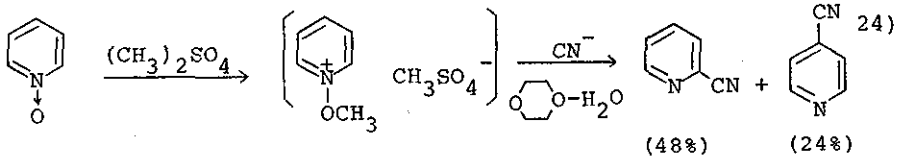




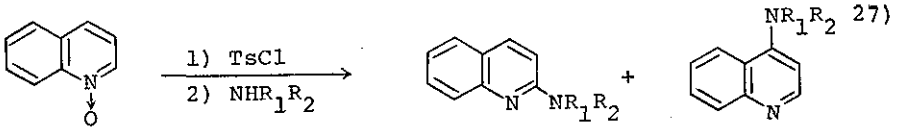
Since the acylation or even alkylation of the N-oxide function increases the electron-withdrawing nature to attract the nucleophilic substitution at α- and γ-positions, a combination of

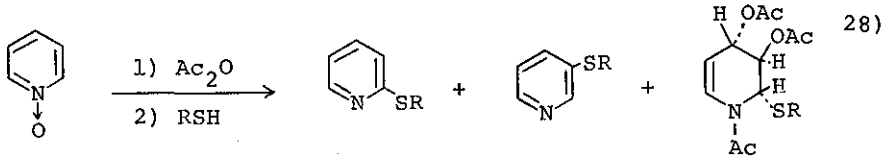
acylation or alkylation and subsequent treatment with nucleophiles has been used effectively for the introduction of nucleophilic substituents into the heteroaromatic rings by Henze's, Okamoto's and Hamana's groups and a few others as shown below.

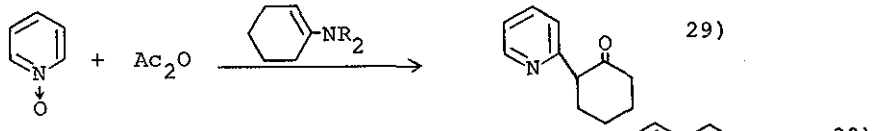


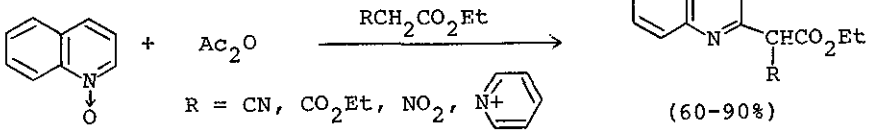


These reactions are modifications of the Reissert reaction.[25] Hamana compiled many reactions to introduce various nucleophilic substituents, including many of his group.[26] Some of the representative examples are shown below.



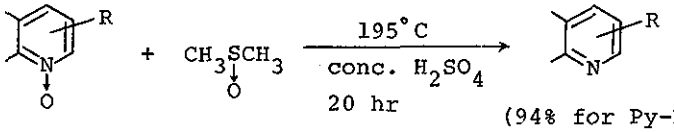






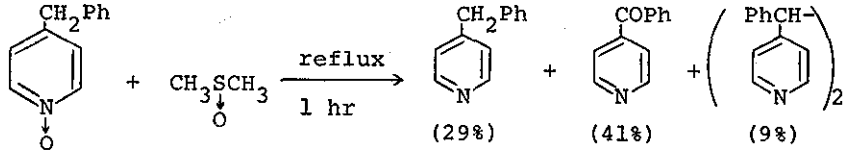
Abramovitch and his group developed procedures to introduce various substituents without cleaving N-O linkage of the N-oxides, such as alkylation,[31] acylation,[32] halogenation,[33] chloromercuration[34], thiolation,[35,36] aminoalkylation[37], etc., however, these reactions are beyond the scope of this review on deoxygenative reduction of the N-oxides.

Deoxygenations of substituted pyridine, quinoline and isoquinoline N-oxides were found to take place by heating with DMSO.[38]

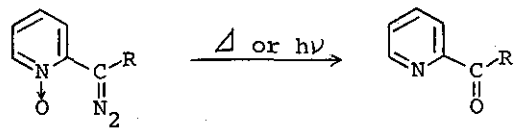


(94% for Py-N-oxide)

The formation of diphenyl sulfone in the deoxygenation of pyridine N-oxide with diphenyl sulfide suggests strongly that the reaction involves an oxygen-transfer. In the deoxygenation of 4-alkylpyridine N-oxides with DMSO, not only the reduced pyridine base but also other products, apparently formed from either 4-picolyl-cation or radical, were obtained.[39] An electron-transfer type mechanism may be operating in this reaction.

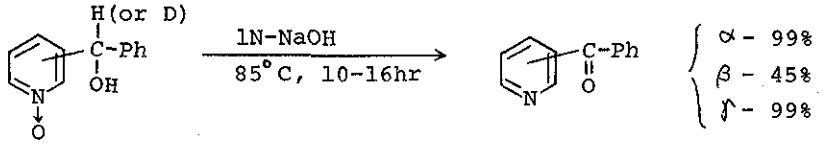


Deoxygenation of the N-oxides can be achieved by treating with dichlorocarbene from $PhHgCCl_3$,[40] or carbene from 9-diazofluorene.[41] Intramolecular deoxygenation, shown below, also takes place in high yields.[42]

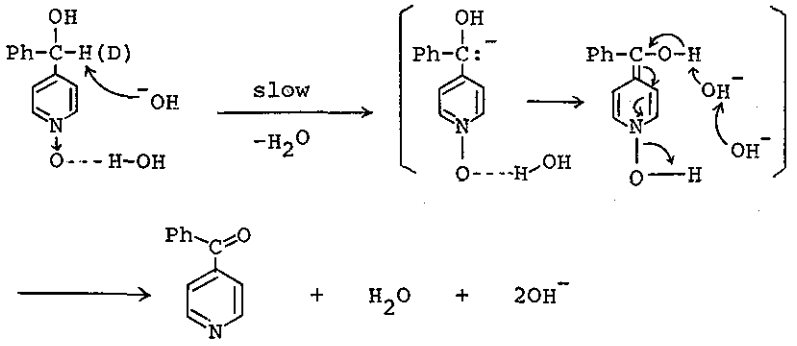


R = Me, t-Bu, Ph, and p-$O_2NC_6H_4$

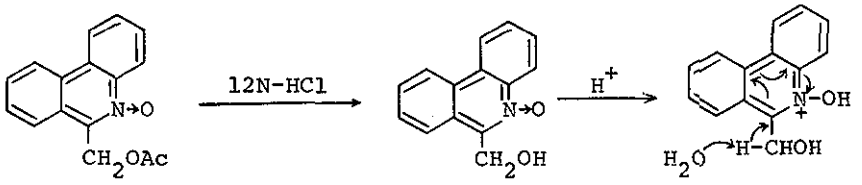
An interesting example is the following reaction, in which the hydrogen-deuterium kinetic isotope effect was found to be larger

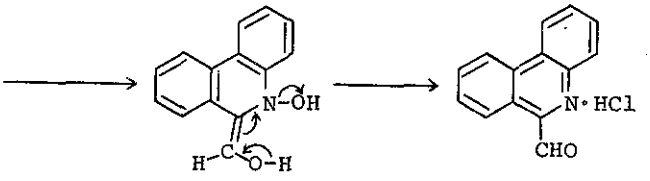


than 3 with (α-hydroxybenzyl)pyridine N-oxide,[43] suggesting that the rate-determining step to be the proton-removal as shown below.



A similar redox reaction was found in the acid-catalyzed intramolecular conversion of 6-acetoxymethyl phenanthridine N-oxide to the corresponding formyl derivative via " anhydrobase " as shown below.[44]



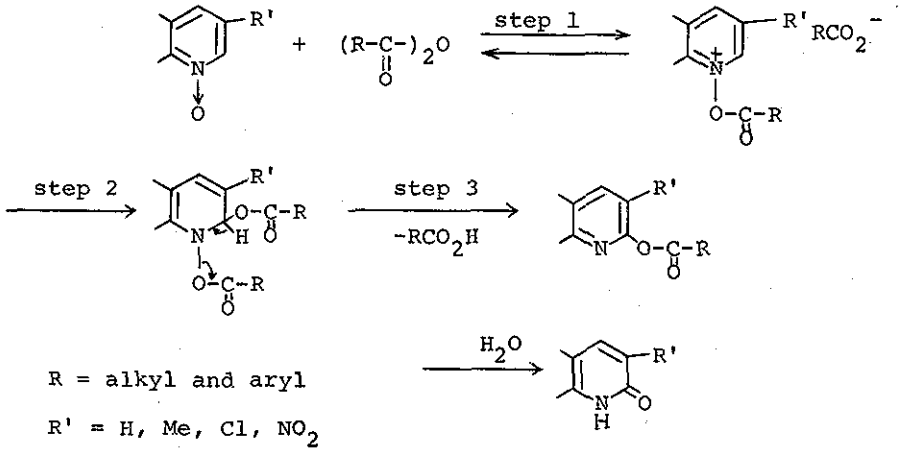


3. Reactions with Acylating Agents : Rearrangements to Heteroaromatic Ring

a). With Acyl Anhydride:

When pyridine or β-picoline N-oxide is treated with acetic anhydride, α- or γ-pyridone derivative is formed, via the initial formation of O-acetoxypyridinium acetate and subsequent acyloxy-migration from N to α- or γ-ring carbon. This reaction has been found general for most heteroaromatic N-oxides without alkyl substituent at either α- or γ-position and with many other acylating agents, and widely used for the syntheses of substituted pyridines, quinolines and isoquinolines.[1-3]

The general scheme of the reaction is as depicted below.

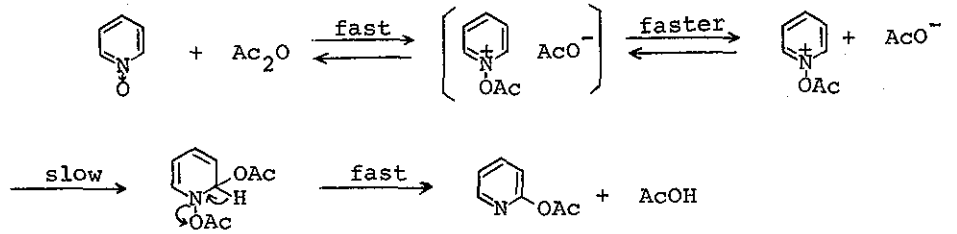


R = alkyl and aryl

R' = H, Me, Cl, NO_2

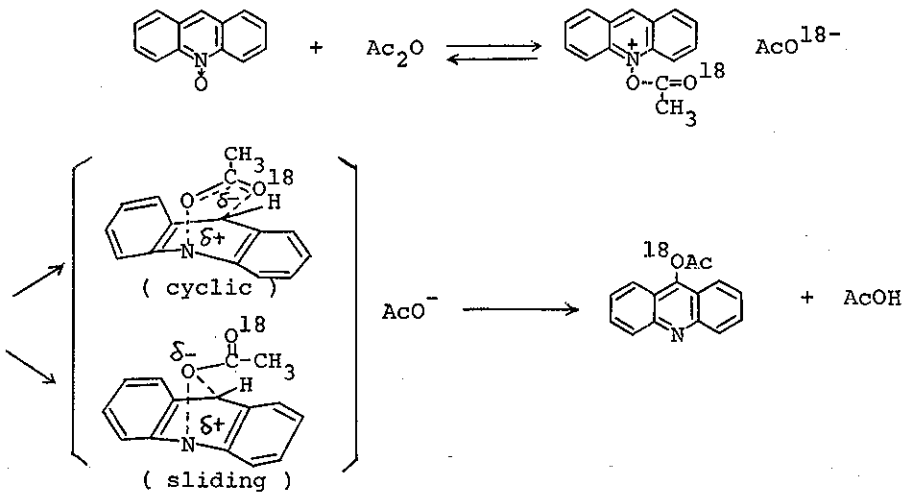
The formation of O-acyloxypyridinium acylate as an initial intermediate can be shown by trapping it as its perchlorate like in the case of quinaldine N-oxide with acetic anhydride,[45] thus showing that the rough mechanistic picture for the rearrangement of pyridine N-oxide with acetic anhydride,[46] postulated by Ochiai and Okamoto,[47] was found to be real.

Markgraf et al. undertook the first kinetic study of this reaction between pyridine N-oxide and acetic anhydride and suggested that the reaction involves the intermolecular nucleophilic attack of acetate anion on N-acetoxypyridinium ion on the basis of kinetic parameters ($\Delta H^{\ddagger}$= 29.2 kcal/mole, $\Delta S^{\ddagger}$= -5.5 e.u.) and others.[48] An ^{18}O-tracer experiment of the reaction of 3-picoline N-oxide with ^{18}O-labeled acetic anhydride, carried out by Oae and Kozuka[49] also confirmed the intermolecular nature of the rearrangement which demands all the oxygen atoms to be completely scrambled. Furthermore, the small but reverse kinetic isotope effect, i.e., k_H/k_D= 0.92, found with pyridine α-d_2 N-oxide, by Oae and Kozuka[50] revealed clearly that the rate-determining step of the reaction is the nucleophilic attack of acetate ion at α-ring carbon rather than the subsequent 1,2-elimination of acetic acid as shown below.

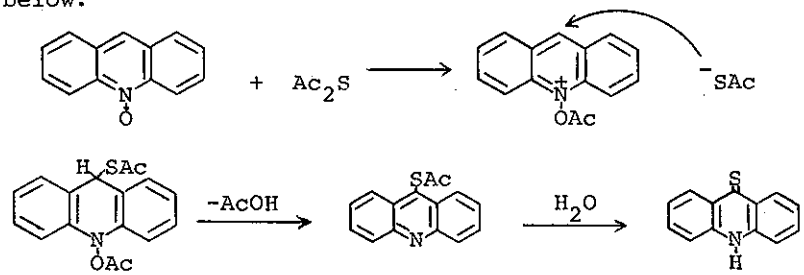


The reaction of acridine N-oxide with acetic anhydride was also kinetically investigated by Markgraf et al.[51,52] and suggested to

proceed via an intramolecular rearrangement involving the rate-determining N-O bond cleavage on the basis of activation parameters ($\Delta H^{\ddagger}$ = 12.2 kcal/mole, $\Delta S^{\ddagger}$= -32.2 e.u.) and no significant kinetic isotope effect k_H/k_D= 1.0 with 9-monodeuterated acridine N-oxide. Unlike the similar reaction of pyridine N-oxide, which proceeds via an intermolecular mechanism, that of acridine N-oxide is slow (the ratio of pseudo-unimolecular rate consts., $k_{py\rightarrow o}/k_{acr\rightarrow o}$= 4 x 10^6 at 25°C) and involves a transannular rearrangement. The results of ^{18}O-tracer experiments are also complicated [53] and the amount of ^{18}O-incorporation into the resulting acridone increased with the increase of solvent used. Apparently a large amount of solvent disfavors the sliding-type bridged ion-pair but favors the cyclic process, except in a polar medium, sulfolane, in which the sliding mechanism becomes more favored. The intramolecular process of this rearrangement may be depicted as shown below.[53]

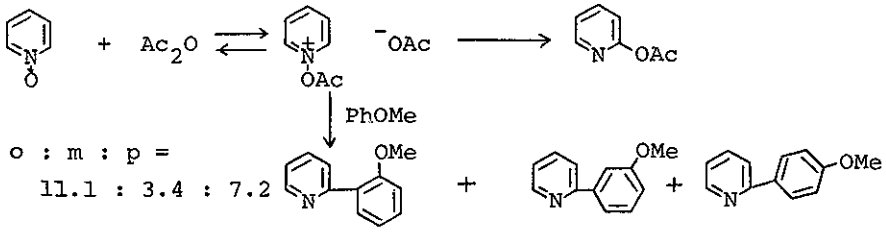


The reaction of acridine N-oxide with diacetyl sulfide was studied by Markgraf et al. and shown to give 9-thioacridone apparently via an intermolecular attack of acetylthiolate ion as shown below.[54]



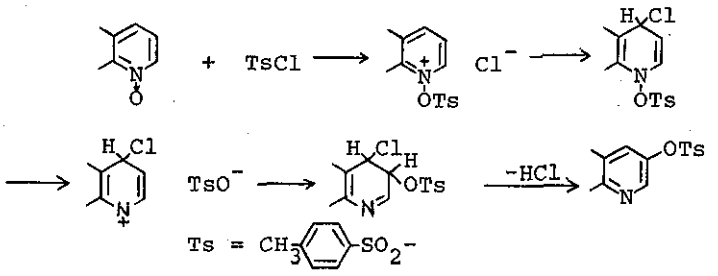
This appears to contradict the intramolecular nature of the rearrangement of acridine N-oxide with acetic anhydride. However, in view of the much larger nucleophilicity of acetylthiolate ion than that of acetate ion, the intermolecular nature of the rearrangement with the thio-analog of acetic anhydride is quite understandable.

When the reaction of pyridine N-oxide with acetic anhydride was conducted in anisole, a small amount of a mixture of 2-(o,m, and p-methoxyphenyl)pyridine was obtained besides the major normal product, pyridone.[55] This observation suggests again the mechanism to involve the nucleophilic attacks of both acetate ion and anisole on the most electron-defficient 2-position of N-acetoxypyridinium ion.

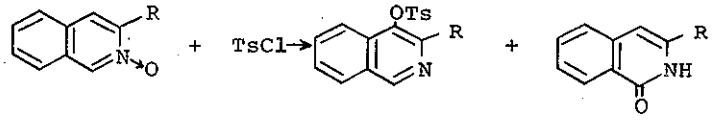


b). With Arenesulfonyl Halides

The reaction of pyridine or quinoline N-oxide with arenesulfonyl chloride, another acylating agent, is quite different from those with acetic anhydride and gives various products.[56,57] Among the products, β-tosyloxypyridine or -quinoline was isolated though in a low yield. This rather unusual rearrangement to β-position instead of normal α- or γ-position stimulated many further extensive investigations. A rough mechanistic route, suggested by previous workers,[57] shown below, was later found nearly in the right direction.

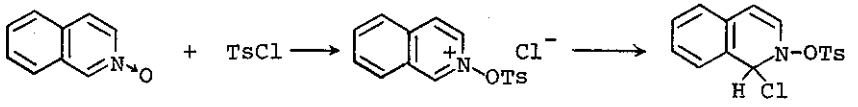


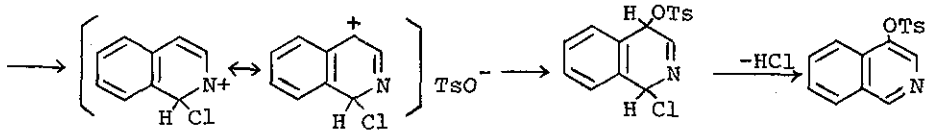
A similar reaction of isoquinoline- or 3-methylisoquinoline N-oxide is markedly mild and affords 4-tosyloxyisoquinoline and a small amount of isocarbostyril.[58]



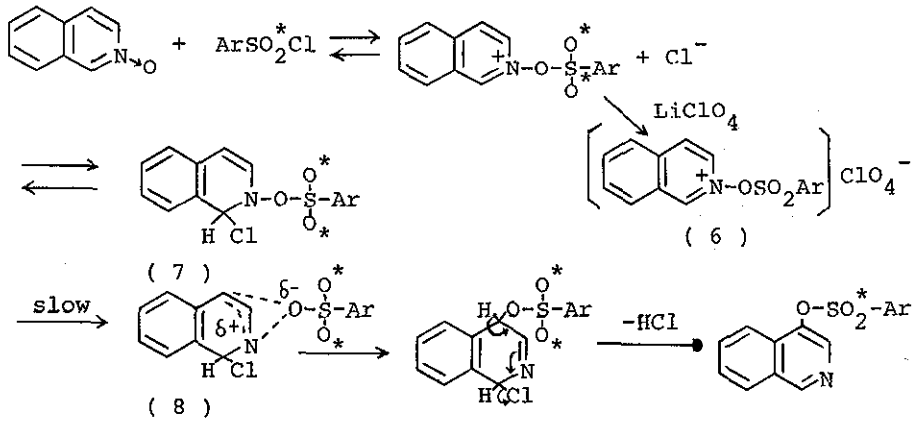
R = H, CH_3 (75%) (~10%)

A rough mechanistic picture, Ochiai and Ikehara intuitively suggested, was as imaginative as follows.





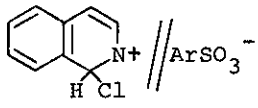
Their suggestion which pointed out the involvement of nucleophilic addition of chloride ion at 1-position is remarkable and was verified by the detailed analysis of the results of kinetic and isotopic tracer experiments of Oae, Kitao, Ogino, Kozuka, et al. who revealed the following scheme for the overall reaction.[59,60]



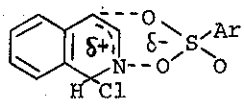
When isoquinoline N-oxide is treated with tosyl chloride in the presence of lithium perchlorate, one sees immediately the change of the U.V. spectrum. Furthermore, N-tosyloxyisoquinolinium perchlorate (6) can be isolated. This salt (6) does not give any rearrangement product upon heating. Meanwhile, the rate of the overall reaction is accelerated by the addition of chloride ion till it reaches a plateau, thus suggesting the incipient formation of 1-chloro-N-tosyloxy-1,2-dihydroisoquinoline (7), a kind of anhydrobase as the key intermediate of this reaction. The pseudo-

first-order rate constant increases markedly by the increase of the ionic strength of the reaction medium by salt effect, and also remarkably in polar media, while hydrogen-deuterium kinetic isotope effects, measured with 1-monodeuterated and 1,3,4-trideuterated isoquinoline N-oxides, were quite small ($^{k}H/k_{D}$= 1.16 and 1.22, resp.) which is the size of that expected from hyperconjugative β-hydrogen-deuterium isotope effect in solvolysis. A nice Hammett plot with σ-values of substituted benzenesulfonyl chlorides gave ρ-value of +2.0, suggesting strongly the cleavage of N-O linkage to be the rate-determining step of the over-all reaction.

The activation parameters of this reaction in dioxane were found to be ΔEa = 9.6 kcal/mole and $\Delta S^{\ddagger}$ = -40.2 e.u.. One characteristic feature of this reaction is the mode of arenesulfonoxy migration from N atom to 4-position of the ring. The resulting 4-tosyloxy-isoquinoline was found to retain practically the same ^{18}O-concentration of the original tosyl chloride in the sulfonyl group, depicting the rearrangement to proceed intramolecularly via a very tight ion-pair shown by (8). The negligible ^{18}O-scrambling in the resulting product by the addition of p-tosylate ion into the reaction system, also supports the intramolecular nature of the rearrangement and excludes the possibility of the solvent separated ion-pair (9) or cyclic ion-pair (10) as the intermediate.



(9)

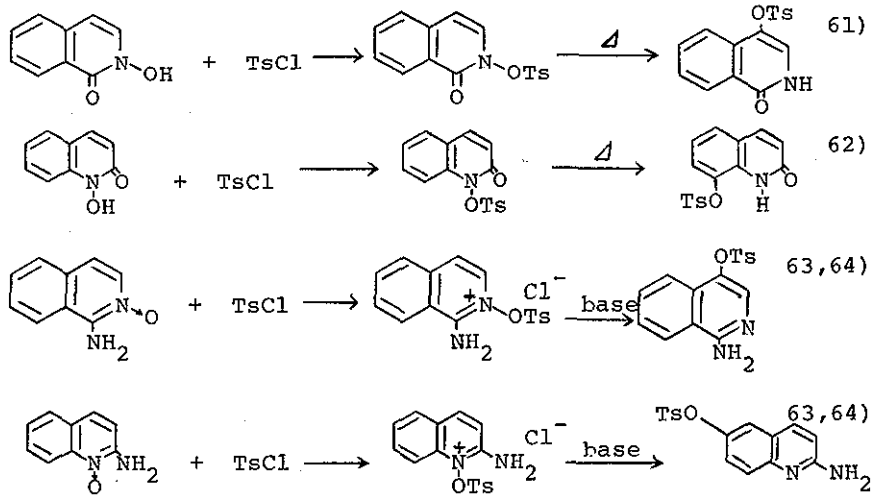


(10)

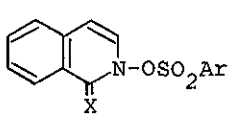
A similarly scant ^{18}O-scrambling was observed in the formation of β-tosyloxypyridine by the reaction of pyridine N-oxide with ^{18}O-

labeled p-tosyl chloride,[59] depicting the α,γ-tosyloxy migration to prceed via a similarly tight ion-pair as (8). The reaction of 3-methylisoquinoline N-oxide with p-tosyl chloride is considered to proceed in a similar fashion.

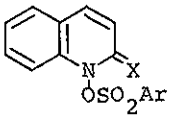
Similar rearrangements with tosyl chloride are known with N-hydroxyisocarbostyril, N-hydroxycarbostyril, 1-aminoisoquinoline N-oxide and 2-aminoquinoline N-oxide which give the corresponding rearrangement products in good yields as shown in the following equations.



Mechanisms of these rearrangements were studied through ^{18}O-tracer and kinetic experiments by Oae and Ogino.[65] Here again, the reaction proceeds via an intermediate (11) or (12), a kind of anhydrobase.

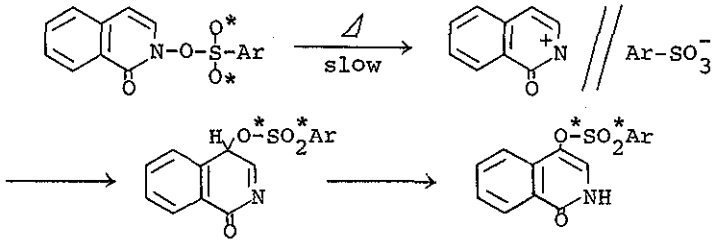


(11) X = O, NH



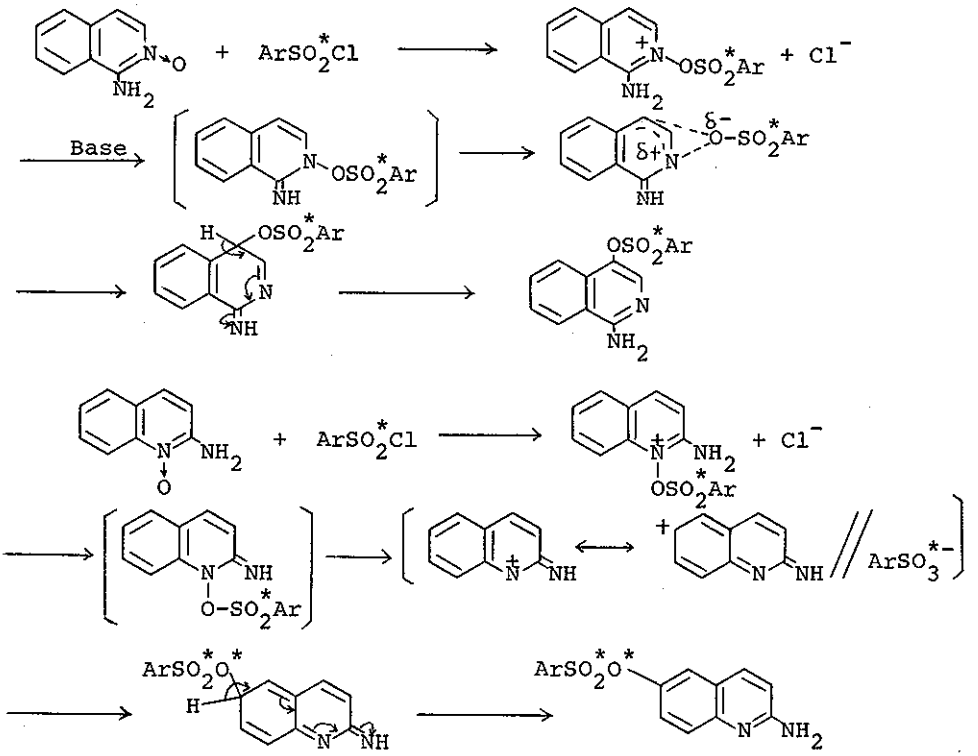
(12)

When X is oxygen, the N-arenesulfonoxy-intermediates can be isolated and upon heating in solvent, give the rearrangement products. The rearrangements of N-tosyloxyisocarbostyril and N-tosyloxycarbostyril with ^{18}O-labeled specifically on sulfonyl oxygens upon heating in either nitromethane or acetonitrile gave tosyloxy-migrated products in which all three oxygen atoms were found to be completely scrambled. Apparently the rearrangements proceed via " solvent-separated ion pairs ", unlike in the reaction of isoquinoline N-oxide with arenesulfonyl chloride. Activation parameters were found to be Ea = 28.0 kcal/mole, $\Delta S^{\ddagger}$ = +13.4 e.u. for N-tosyloxyisocarbostyril and Ea = 27.1 kcal/mole, $\Delta S^{\ddagger}$ = +9.5 e.u. for N-tosyloxycarbostyril. In the reaction of N-(substituted benzenesulfonoxy)isocarbostyrils, the Hammett plot with σ-values of the substituents gave a straight line with ρ = +1.6, while the rate was found to increase in polar media. Thus, the rate-determining step of the rearrangement is considered to be the S_N1 type N-O bond cleavage shown below.



In the reactions of α-aminoisoquinoline N-oxides with tosyl chlorides, O-tosylated salts are formed and can be isolated, however, upon treatment with bases, the subsequent rearrangements take place so quickly that the " anhydrobase " intermediates were neither isolated nor even detected in the U.V. spectra. The usual ^{18}O-tracer experiments with ^{18}O-labeled tosyl chloride were carried out

and 1-amino-4-tosyloxyisoquinoline was found to retain the original ^{18}O in the sulfonyl function, while all the three oxygen atoms of 2-amino-6-tosyloxyquinoline were found to be completely scrambled, revealing that the reaction of 1-aminoisoquinoline N-oxide with tosyl chloride proceeds via the intramolecular oxygen-bridged ion pair process like that of isoquinoline N-oxide, while that of 2-aminoquinoline N-oxide undergoes via the formation of the solvent separated ion pair intermediate as depicted in the following equations.

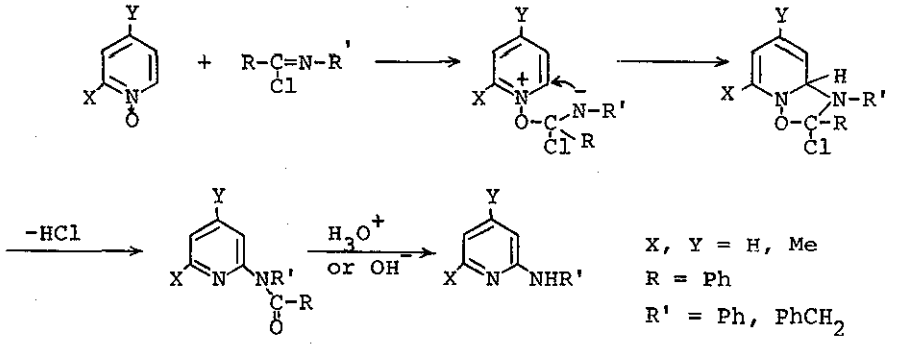


Obviously in the rearrangement of arenesulfonoxy to a distant position such as 6-position of 2-aminoquinoline N-oxide and also

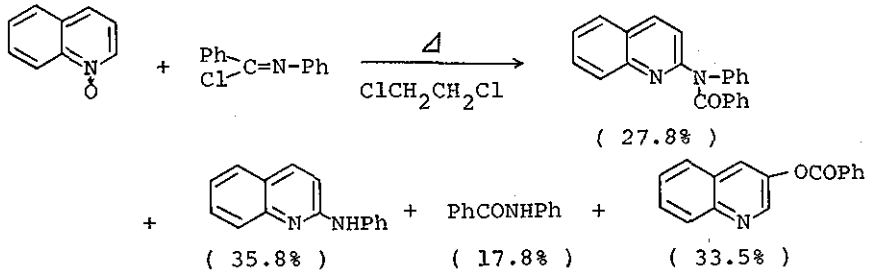
that to the benzene part as seen in the case of N-hydroxycarbostyril, the arenesulfonoxy group is completely broken from the N atom and all the three oxygen atoms are completely scrambled. The different behaviors shown in the similar α,β-arenesulfonoxy migrations in the thermolysis of N-arenesulfonoxycarbostyril and in the reaction of 1-aminoisoquinoline N-oxide with arenesulfonyl chloride may be due to the difference in stabilities of the intermediary anhydrobases.

c). 1,3-Dipolar Addition

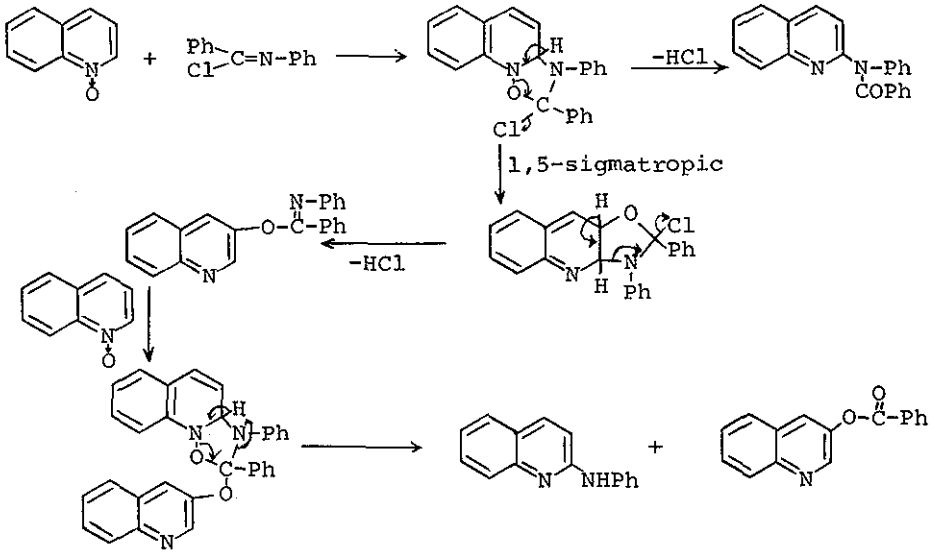
Heteroaromatic amine oxides are also 1,3-dipolar reagents.[66] Abramovitch and Shinkai[67] recently summarized a new type of rearrangement which appears to involve the initial concerted 1,3-dipolar addition and subsequent intramolecular rearrangement as shown below.



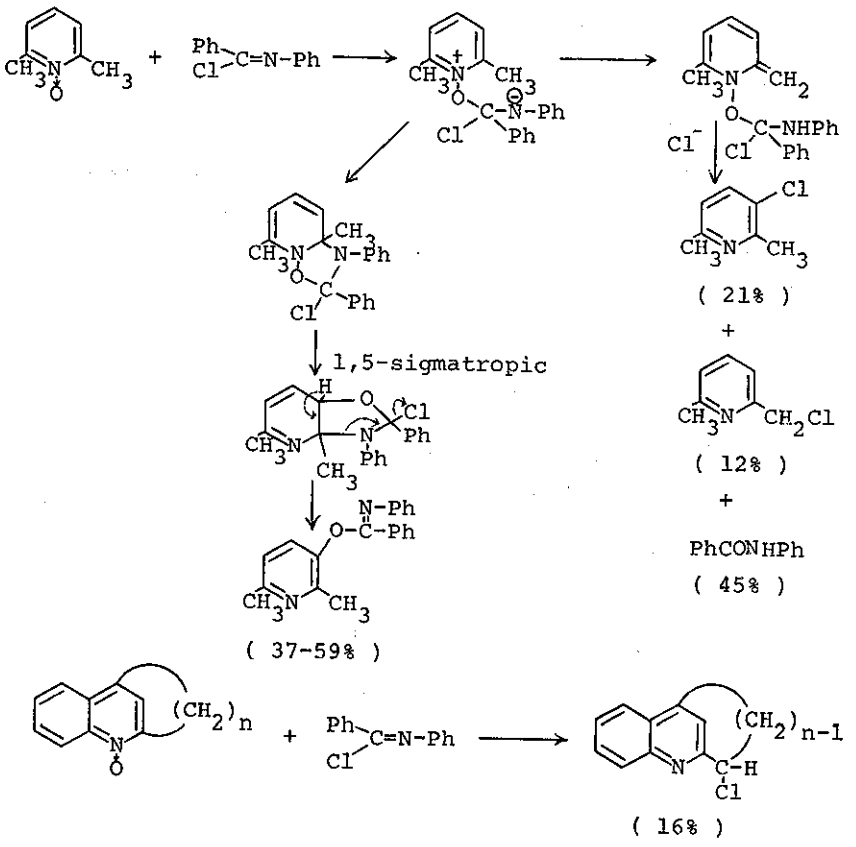
The reactions between heteroaromatic N-oxides and N-phenylbenzimidoyl chloride have been investigated in detail by Abramovitch's group[68] and Parham et al.[69] and shown to give not only 1,3-dipolar addition products but also 1,5-sigmatropic rearrangement products as shown below.



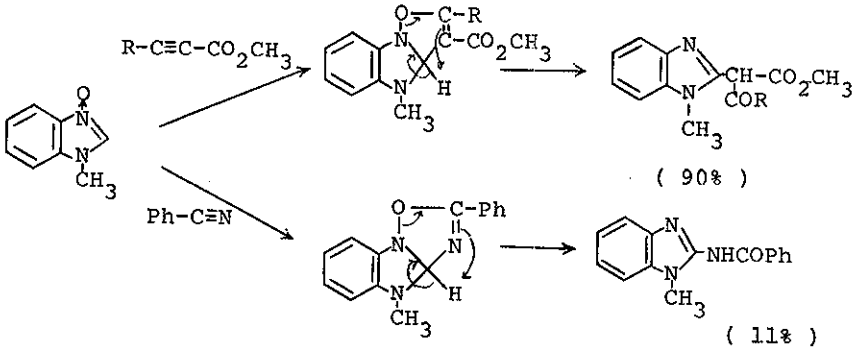
Following mechanism, involving the initial 1,3-dipolar addition, subsequent 1,5-sigmatropic shift, which is followed by another 1,3-dipolar addition to afford 2-anilinoquinoline and 3-benzoyloxyquinoline was presented. Formations of nearly equal amounts of the latter two products appear to support this mechanism.



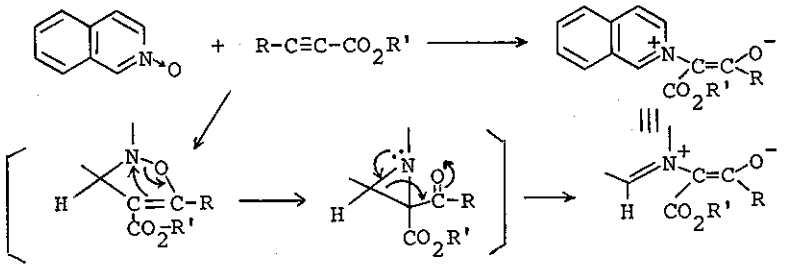
The reactions of α-alkylpyridine and quinoline N-oxides give β-acyloxy-derivatives, 1,5-sigmatropic shift products, undoubtedly formed via anhydrobases which also give side-chain chlorinated and β-chlorinated products as mechanistically depicted below.



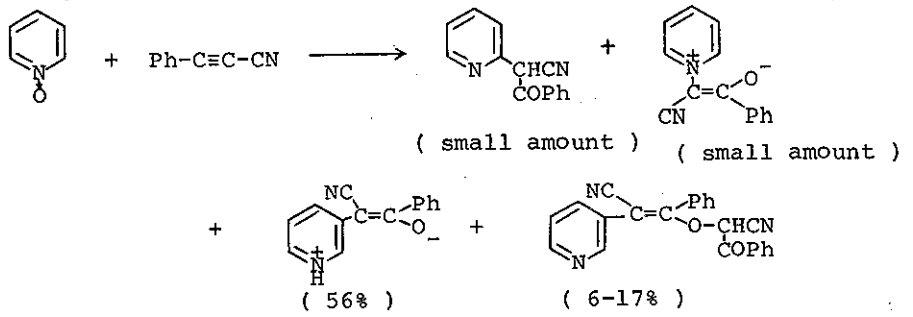
Activated acetylenes or nitriles are also known to act as dipolarophiles and add to the following N-oxide.[70]



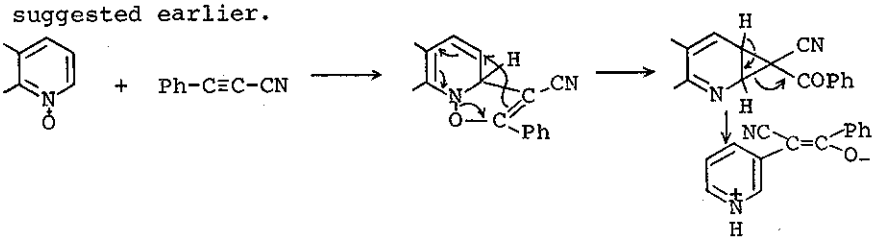
The reaction of isoquinoline N-oxide gives its N-ylide, apparently via the initial 1,3-dipolar addition and subsequent aziridine-ring-closure followed by the ring opening, as shown below.[71]



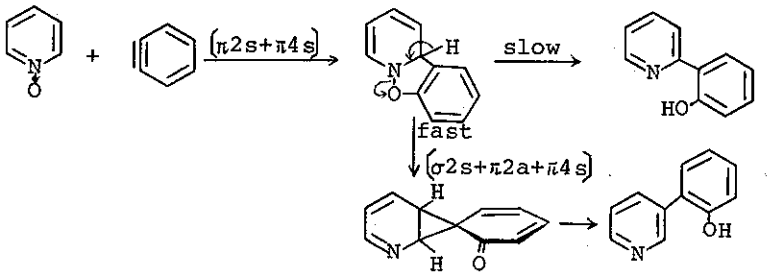
In the reaction of pyridine N-oxide with phenylpropiononitrile, Abramovitch et al. isolated only a small amount of the N-ylide but also 1,3-sigmatropic rearrangement products.[72]



Quinoline N-oxide reacts similarly and the reaction was suggested by Abramovitch et al. to proceed via symmetry-allowed ($\sigma 2s+\pi 2a+\pi 4s$) process, shown below,[73] instead of incipient formation of carbene species, suggested earlier.

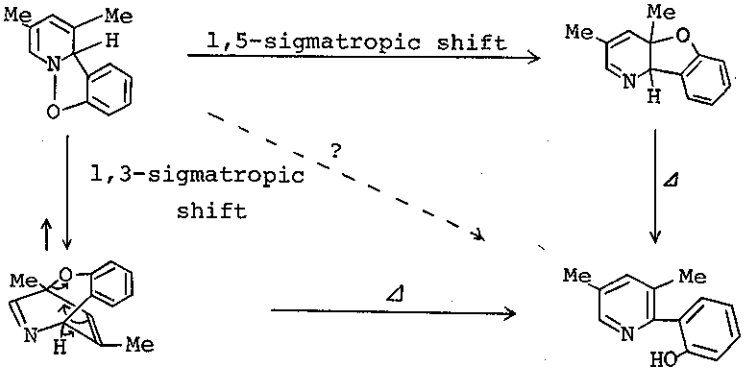


A similar reaction between pyridine N-oxide and benzyne gives 2- and 3-(o-hydroxyphenyl)pyridines.

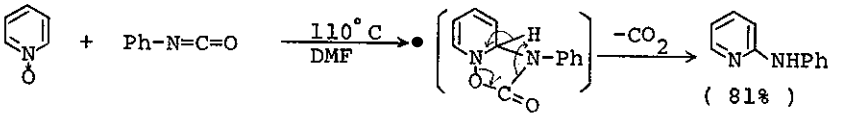


(main product)

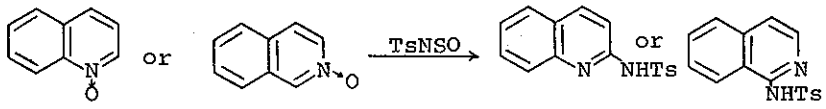
The reaction of 3,5-lutidine N-oxide with benzyne also gives 2-(o-hydroxyphenyl)-3,5-lutidine under the normal reaction condition, however under a very mild condition two dihydropyridine derivatives, i.e., 1,3- and 1,5-sigmatropic shift products can be isolated. These two were transformed to the final product as shown below.



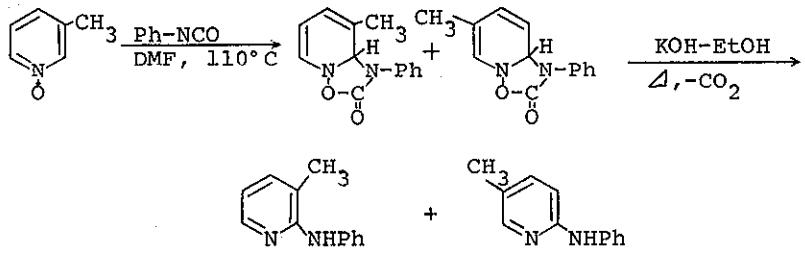
Pyridine N-oxide is known to react with the isocyanate[74] or the N-sulfinyl compound[75] via 1,3-dipolar addition as shown below.



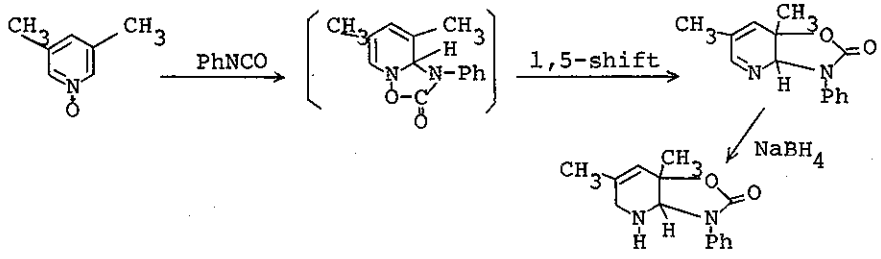
(81%)



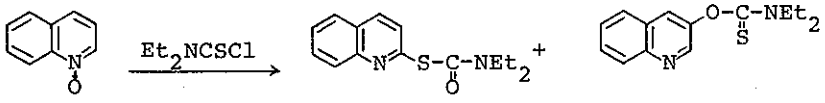
The reaction with phenylisocyanate was reexamined with 3-picoline N-oxide[76] and 1,2-dihydropyridine derivative, 1,3-dipolar addition intermediate, was isolated and shown to give the final products after decarboxylation in the presence of a base, in this case potassium hydroxide and in the earlier case perhaps pyridine N-oxide.

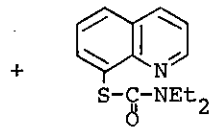


In the reaction of 3,5-lutidine N-oxide, 1,5-sigmatropic shift product, 2,3-dihydro derivative, was isolated, identified by NMR and further reduced for structural assignment.[67]

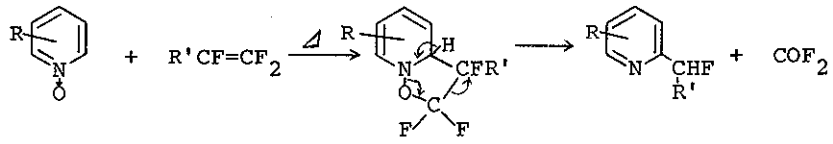


Similar reactions were found with N,N-diethylthiocarbamoyl chloride[77] and also with perfluoroolefins[78], as shown below.

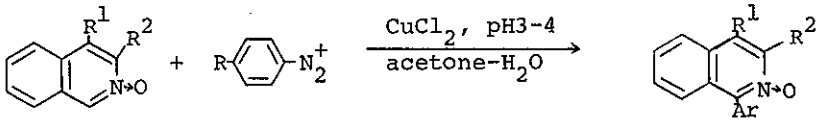




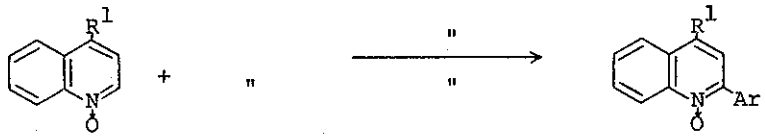
(only in the presence of base)



Decomposition of aromatic diazonium salts with heteroaromatic N-oxides in the presence of cuprous chloride proceeds via a homolytic path and gives α-arylated N-oxide, shown below.[79]

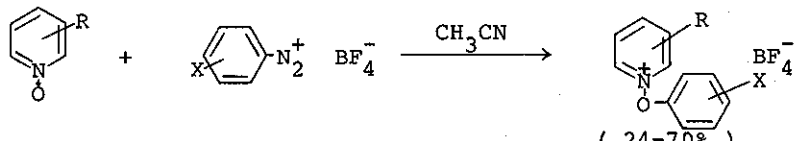


(16-42%)



R^1, R^2 = H, Me ; R = H, MeO, NO_2, CO_2Me

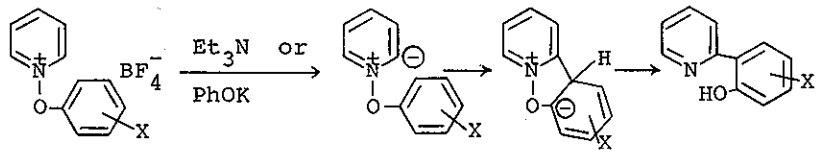
In the reaction of pyridine N-oxide with aryldiazonium tetrafluoroborates bearing strong electron-withdrawing substituents in acetonitrile, N-aryloxy salts were successfully isolated by Abramovitch et al..[80]



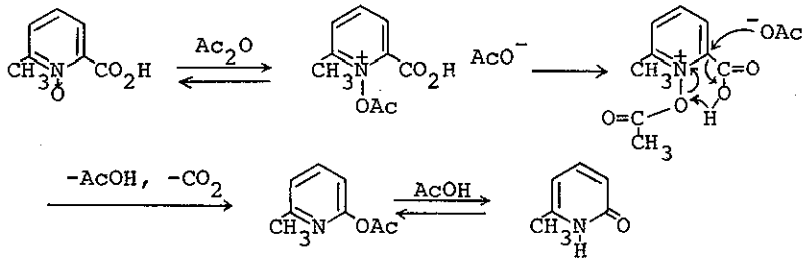
(24-70%)

X = p-NO_2, p-CN, p-CF_3, o-CF_3
o-NO_2 and m-NO_2

The same salts were synthesized by the use of diaryl iodonium tetrafluoroborate and shown to give the α-rearranged product, i.e., 2-(o-hydroxyphenyl)pyridine in high yields upon treatment with bases.



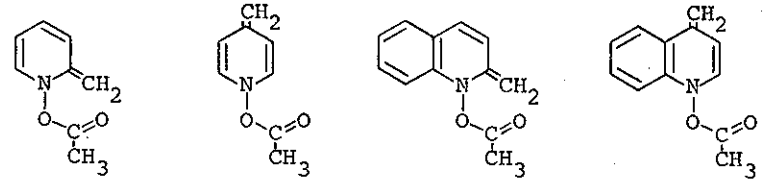
2-Pyridinecarboxylic acid N-oxide undergoes decarboxylation either upon heating[81] or by reaction with acetic anhydride.[82] Recently the reaction of 6-methyl-2-pyridinecarboxylic acid N-oxide with acetic anhydride was examined[83] and shown to give a small amount of 6-methylpyridine besides the normal rearrangement product, i.e., 2-acetoxy-6-methylpyridine. The following mechanism was suggested for the abnormal reaction.



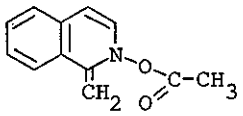
4. Reactions with Acylating Agents : Rearrangements to Alkyl Side-Chain

α- or γ-picoline and quinoline or lepidine N-oxides react with acetic anhydride to give α- or γ-acetoxymethylpyridine and quinoline, as the major products, via the formation of following " anhydrobases ", as the intermediates prior to the rearrangement.

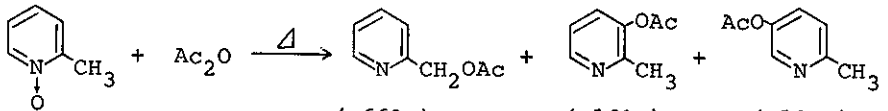
Actually the rearrangement is not limited to the alkyl side-chain alone.



anhydrobase

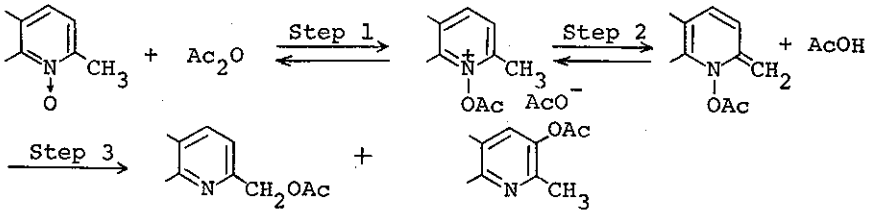


For example, the reaction of α-picoline N-oxide with acetic anhydride gives not only 2-acetoxymethylpyridine but also 3-acetoxy-2-picoline and 5-acetoxy-2-picoline as shown below.



(66%) (16%) (18%)

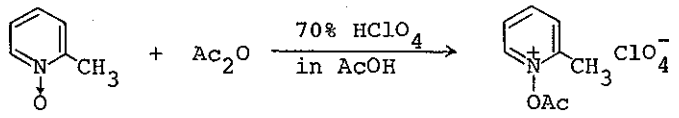
However, all the three products are presumed to be formed from the common intermediate, " anhydrobase ". The general scheme of the rearrangement is now believed to be as shown below, after many years of intensive studies on ^{18}O and D tracer and kinetic experiments, analyses of hydrogen kinetic isotope effects and product distributions, besides solvent effects since the discovery of the original reaction by Kobayashi and Furukawa[84] and Boekelheide and Lin[85] in early fifties.



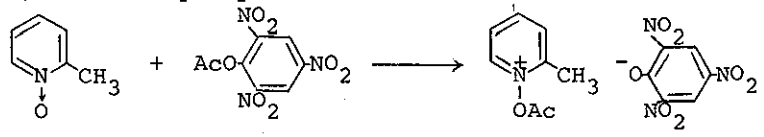
By the end of sixties, the existence of " anhydrobase " as the key intermediate was experimentally proved and each step of the overall reaction has been well established. Thus, each step of the reaction will be carefully examined in the light of mechanistic considerations.

Step 1

The initial step (Step 1) involves acetylation of the N-oxide function to form N-acetoxypicolinium acetate which can be converted to the perchlorate when acetylation with acetic anhydride is conducted in the presence of perchloric acid.[86)]

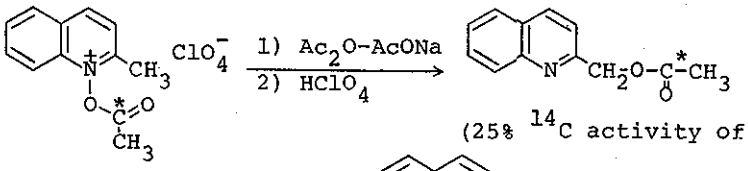


A similar salt of picrate was obtained with α-picoline N-oxide and 2,4,6-trinitrophenyl acetate as shown below.[87)]



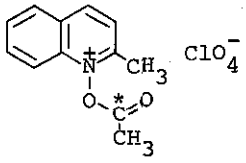
These salts give the same rearrangement products upon treatment with a base such as sodium acetate, triethylamine or even sodium cyanide, thus depicting clearly that acetoxypicolinium ion is the initial intermediate in this rearrangement. Furthermore, successful recovery of the original N-oxide upon treatment of the salt in alkaline media, and formation of 2-butyroxymethylpyridine as the major product upon heating the salt with n-butyric anhydride indicate that the acylation step is an equilibrium reaction. Muth and his co-workers[86a,86b)] treated N-acetoxyquinaldinium

perchlorate, ^{14}C-labeled at carbonyl group, with a mixture of acetic anhydride and sodium acetate, quenched the reaction mixture during the reaction and recovered N-acetoxyquinaldinium salt together with the rearranged ester. Both the rearranged product and the recovered salt were found to retain rather small percentages of ^{14}C activities, supporting the initial acetylation step to be an equilibrium.



(25% ^{14}C activity of the salt)

+

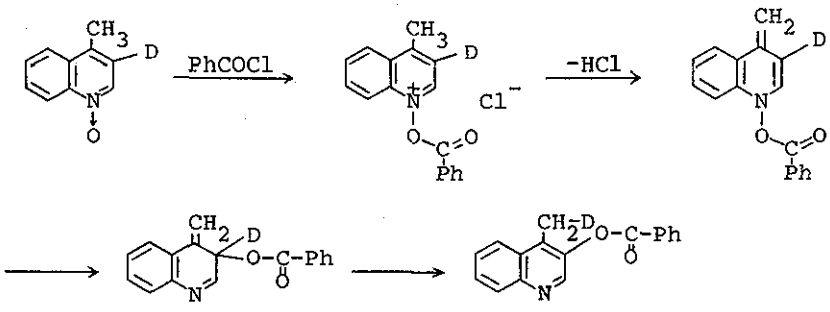


(10% of ^{14}C activity of original salt)

Step 2

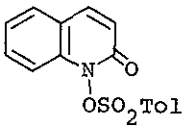
This step involves proton-removal from N-acetoxypicolinium ion by a weak base, in this case acetate ion, to form " anhydrobase ". The importance of the proton-removal can be understood if one considers that there is no rearrangement when N-acetoxypicolinium perchlorate alone is heated. However, " anhydrobase " intermediate cannot be isolated or identified by any spectroscopic analysis. The most evident support for the anhydrobase was obtained by the deuterium tracer experiment by Oae's group. The kinetic observation of Traynelis et al. on the reaction of 2-(α,α-dideuterated)-benzylpyridine N-oxide also suggests the proton-removal to be important and irreversible, supporting the anhydrobase formation.[87]

Oae, Tamagaki and Kozuka used the reaction between lepidine N-oxide and benzoyl chloride to give 3-benzoyloxylepidine (major product) and 4-benzoyloxymethylquinoline (minor product), paying their attention especially on the former major product which could be formed by a direct acyloxy-migration without involving " anhydrobase " intermediate.[88] When 3-deuterated lepidine N-oxide was treated with benzoyl chloride in benzene, 3-benzoyloxylepidine was found to be incorporated with deuterium at 4-methyl group over 90% of the original D-label at 3-position. Thus, the following mechanism involving the anhydrobase is strongely supported. The rather exclusive 1,3-deuterium migration to exo-methylene group appears strange, however this kind of base-catalyzed α,γ-allylic shift is known to proceed predominantly via an intramolecular path.[89]

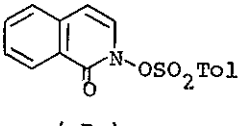


The formation of the incipient key intermediate, " anhydrobase ", during the reaction and the subsequent α,γ-acyloxy-migration are also keeping with the formation of anhydrobase-like chloride addition intermediate in the reaction of isoquinoline N-oxide with tosyl chloride and the successful isolation of other anhydrobase-like intermediate, N-tosyloxycarbostyril (A) and N-tosyloxyisocarbostyril (B) both of which give the

corresponding α,γ-rearranged products upon heating.

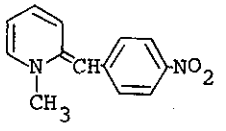


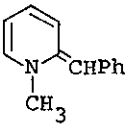
(A)



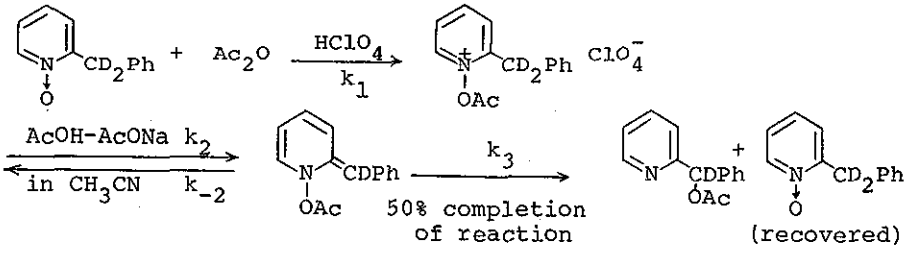
(B)

As models of " anhydrobase ", Traynelis and his co-worker[90] attempted to synthesize the following two compounds for spectroscopic comparision but were unsuccessful.





Then they carried out the reaction of 2-benzyl-d_2-pyridine N-oxide with acetic anhydride to 50% completion and recovered the original N-oxide together with the rearranged product. While the original N-oxide did not lose any deuterium, the rearranged ester was also found to retain exactly one deuterium atom per molecule. This observation clearly indicates that $k_3 \gg k_{-2}$ in the following equation and the N-O bond cleavage and the subsequent rearrangement after the formation of " anhydrobase ", are very fast.

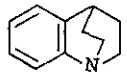


The H-D kinetic isotope effect of this reaction at 30°C was measured by Oae, Tamagaki et al. and found to be large, $k_H/k_D = 7.6$. Those of the reactions of 2-picoline and 4-picoline N-oxides are also large, i.e., $k_H/k_D = 6.3$ and 6.2, respectively,[91] clearly

depicting that the rate-determining step in all these reactions is the proton-removal from N-acetoxy-α, or γ-alkylpyridinium salts to form " anhydrobase " while the subsequent reactions are quite fast.

On the other hand, the hydrogen-deuterium kinetic isotope effect in the reaction with quinaldine N-oxide, trideuterated at methyl group, at 30° was found to be rather small (k_H/k_D = 2.0) [92,93] and a substantial portion of deuterium was found to be lost when the original deuterated quinaldine N-oxide was recovered.[93] A small value of H-D kinetic isotope effect (k_H/k_D = 3.5 at 30°) was observed in the reaction of 1-methyl-d_3-isoquinoline N-oxide and a similar hydrogen isotope exchange was found during the reaction, unlike in the case of picoline N-oxide. Furthermore, the rates of the reactions of these benzopicoline N-oxides were found to increase markedly in the polar media and by electron-donating substituents at 6-position of quinaldine N-oxide while electron-withdrawing groups at 6-position retard the rate. All these observations reveal clearly that the formation of " anhydrobase " by proton-removal is an equilibrium and the subsequent N-O bond cleavage is the rate-determining step of the reaction for these benzopicoline N-oxides series.

This different behaviors of benzopicoline N-oxides from those of picoline N-oxides, can be well understood when one considers the strong electron-withdrawing nature of benzo-group attached to pyridine ring, as is well illustrated in the comparison of basicities of the following two quinuclidines.[94]

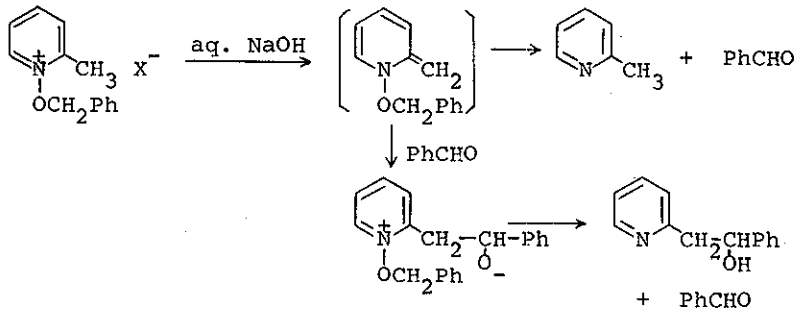


pKa 7.79

10.58

The methyl-proton of N-acetoxyquinaldinium ion, a benzopicolinium ion, should be markedly more acidic than that of N-acetoxypicolinium ion, thus reducing the energy-barrier of proton-removal while the same strong electron-withdrawing effect of benzo group will make the N-O bond cleavage of N-acetoxyquinaldinium ion more difficult than that of N-acetoxypicolinium ion, thus the N-O bond cleavage being the rate-determining step in the reactions of benzopicoline N-oxides.

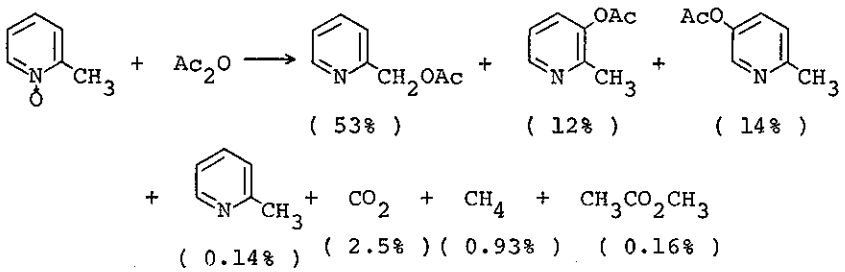
A slightly different but related reaction would be the following example, studied by Traynelis.[95]



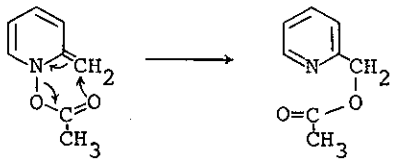
Step 3

This step involves two consecutive reactions, namely, N-O bond cleavage of " anhydrobase " intermediate and subsequent recombination of acetoxy group with either methylene or ring carbon. Earlier, a radical-chain mechanism was proposed for this reaction based on the observations that there are formations of small amounts of CO_2, methane after an induction period, while styrene polymerizes in this reaction system.[96]

Products formed in a typical run is shown below.

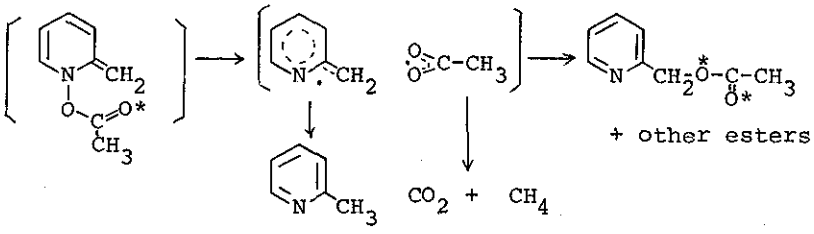


A concerted sigmatropic-type cyclic mechanism through an intramolecular six-membered cyclic transition state shown below was also proposed without any experimental support,[97] but was later ruled out by the ^{18}O tracer studies of Oae's group.[98]



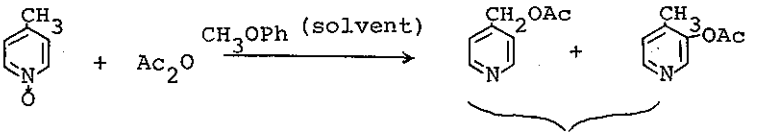
Although the free radical-chain mechanism was disfavored based upon the observation that the reaction of picoline N-oxide and acetic anhydride proceeds to form the rearranged esters regardless of either presence or absence of a radical scavenger such as m-dinitrobenzene, a radical cage mechanism shown below, was considered quite reasonable for sometime because of several partinent observations. The formation of β-phenethylpyridine in the reaction of 2-picoline N-oxide and phenylacetic anhydride[99] and that of alkylpyridine in the reaction of 4-picoline N-oxide and n-butyric anhydride[100] can be rationalized as cage-recombination geminal products after homolytic cleavage of N-O bond of " anhydro-base ". Meanwhile, an appreciable amount of carbon dioxide in the latter reaction can also derived from the decomposition of n-butyroxy radical, formed by homolysis of the N-O bond of the

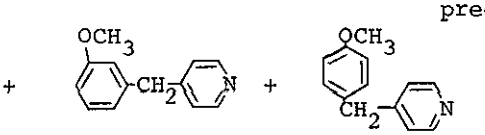
" anhydrobase ". The reaction between 2-picoline N-oxide and ^{18}O-labeled acetic anhydride gave 2-acetoxymethylpyridine which contains only a half of ^{18}O-concentration of that of ^{18}O-labeled acetic anhydride, while both carbonyl and ether oxygen atoms are incorporated with ^{18}O. Thus, the following homolytic process was suggested.[98-100]



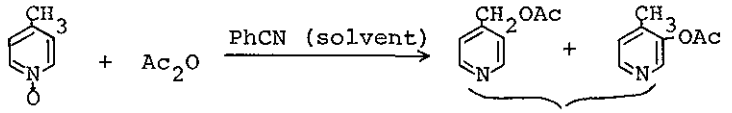
Later, however, a more precise mass-spectroscopic determination has become possible to analyze the ^{18}O-contents of both carbonyl and etheral oxygens and the ^{18}O-distribution between these two functions was found not equal. Thus, the mechanism involving the homolytic cleavage of N-O bond of " anhydrobase " was abandoned and substituted by that involves heterolytic cleavage of the N-O bond.[101] Recently Iwamura[102] examined CIDNP emission and enhanced absorption signals of NMR in the reaction of 4-picoline N-oxide and acetic anhydride and free radicals formed were suggested to be due to a minor process, while the major path appears to be the heterolysis of the N-O linkage. Like in the thermal decomposition of diacyl peroxides,[103] both homolytic and heterolytic processes are competing in this step. However, in view of the markedly uneven distribution of ^{18}O in the resulting esters and the incorporation of only a half of ^{18}O from acetic anhydride suggested strongly that the major reaction proceeds via an " intimate " or a " tight " ion

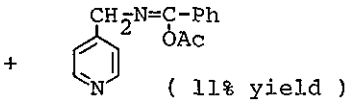
pair and the recombination is quite rapid. Meanwhile, Cohen and Deets[104] obtained a small amount of mixture of picolylanisoles, apparently formed by trapping 4-picolyl-cation by solvent anisole, besides normal rearranged esters, when the reaction of 4-picoline N-oxide with acetic anhydride was conducted in a large amount of anisole. A similar trapped product was also isolated though in a low yield when they carried out the same reaction in benzonitrile, but there was no detectable amount of 4-picolylbenzonitrile which would be formed if 4-picolyl radical would be the attacking species in benzonitrile.





(20% yield of a mixture of picolylanisoles)
m/p = 0.25
(cf. m/p=5.6-1.4 in common free radical substitution)

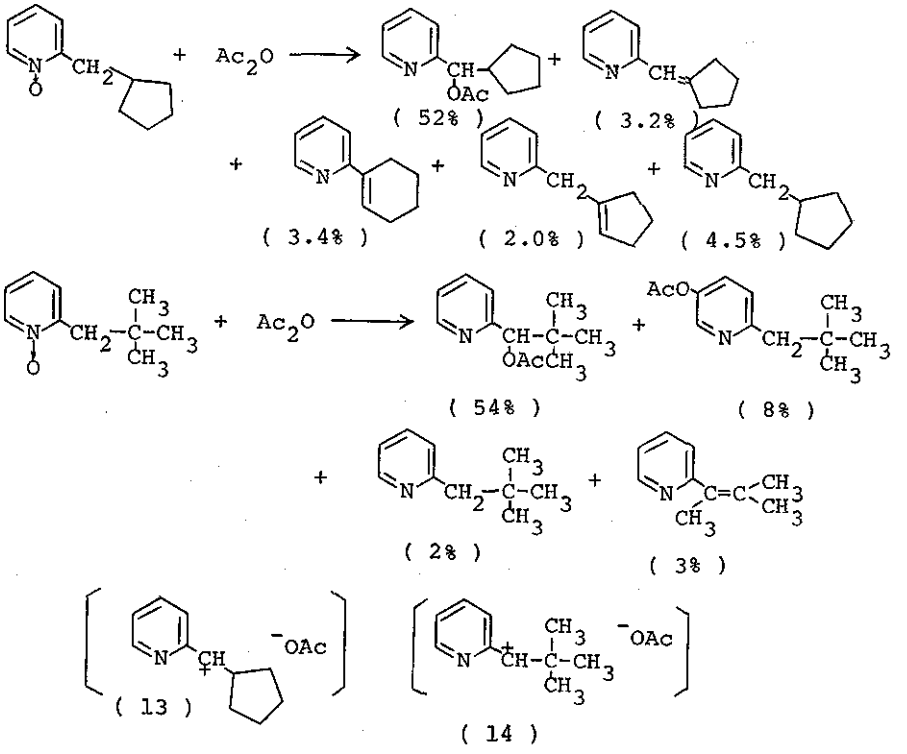




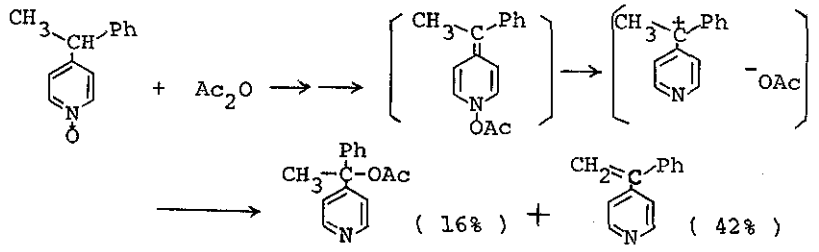
(11% yield)

Bodalski and Katritzky[105] carried out the reactions of 2-cyclopentylmethylpyridine and 2-neopentylpyridine N-oxides with acetic anhydride and obtained small amounts of Wagner-Meerwein

rearrangement products along with normal rearranged esters as shown below, revealing clearly that 2-picolyl cation analogs are the incipient intermediates (13) and (14) in these reactions.



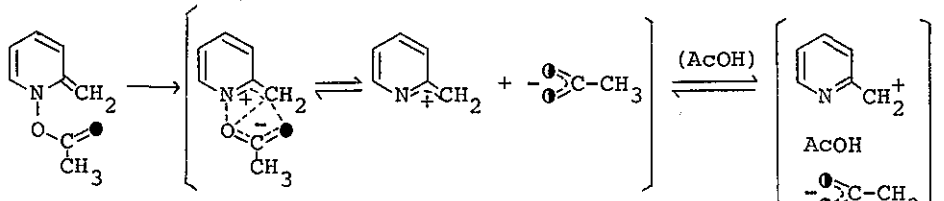
Traynelis, Yamauchi and Kimball[106] also carried out the reaction of 4-phenethylpyridine N-oxide and obtained, along with the normal product, an elimination product, formed apparently from 4-pyridylalkylcarbonium ion as shown below.



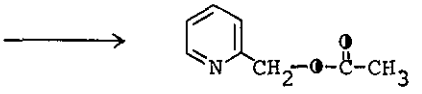
In the reaction of quinaldine N-oxide in which k_H/k_D was found to be small, i.e., ca. 2.0 and the proton-removal, i.e., Step 2, is not the rate-determining, the rate was found by Oae's group to be accelerated markedly in polar media, depicting that the N-O bond cleavage now becomes the rate-determining step of the rearrangement of the benzopicoline N-oxide.[93]

Mode of Rearrangement of Anhydrobase

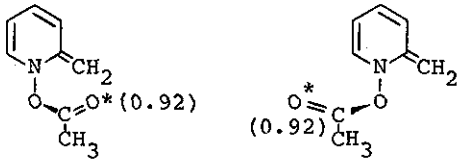
Although the dissociation of the N-O bond is now believed to be heterolytic rather than homolytic, suggested earlier, while the rearrangement is shown to be intramolecular on the basis of ^{18}O tracer experiments of Oae's group, the mode of the ester formation by acyloxy migration has not been discussed yet. Like in the solvolysis, according to Winstein's definitions, there are three possible ion pairs which would give the final ester products, namely intimate ion pair (15), solvent separated ion pair (16) and dissociated ion pair (17). Among these, the mechanism involving " solvent separated ion pair (17)" can be ruled out because of the lack of ^{18}O scrambling with solvent acetic acid in the resulting esters. If the acyl migration would take place via " dissociated ion pair (16) ", ^{18}O contents of both oxygen atoms in the resulting ester should be identical because oxygen atoms of dissociated acetate ion should be completely scrambled.



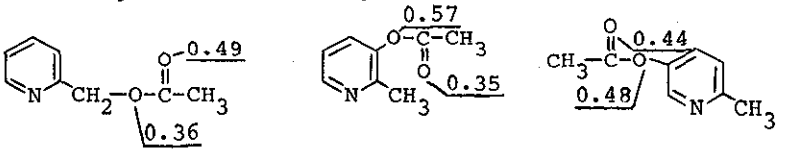
(15) (16) (17)



However, careful analyses of ^{18}O-distributions in the resulting esters[91,93,101] revealed that ^{18}O-incorporations are unevenly distributed in both carbonyl and etheral oxygen atoms and the oxygen atom closer to the combining site of the anhydrobase of the most stable conformer appears to have a better chance to combine with the combining site than the other which is slightly more remote from the recombination site. For example, among the following two conformers of anhydrobase from 2-picoline N-oxide, the comformer at right hand is more stable than that at left hand.



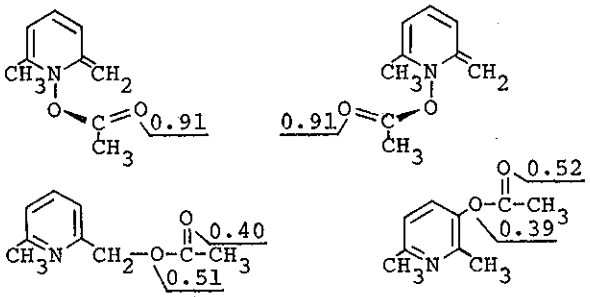
Thus, the N-oxide oxygen atom in the right hand-side conformer has a better chance to recombine with methylene carbon or 3-position of pyridine ring in the resulting esters as shown below.



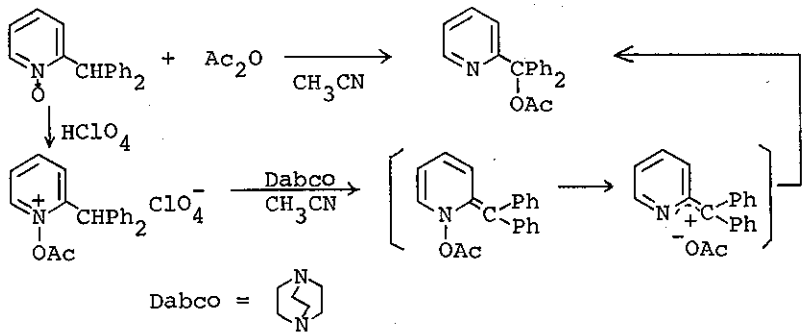
In other words, once N-O bond is cleaved, the subsequent recombination is extremely rapid and conformationally controlled.

In the anhydrobase from 2,6-lutidine N-oxide, the conformer at left hand side is considered to be slightly more stable than that at right hand side, thus carbonyl oxygen has a better chance to

recombine with methylene carbon but not with 3-carbon in the ring in the formations of esters as shown below.

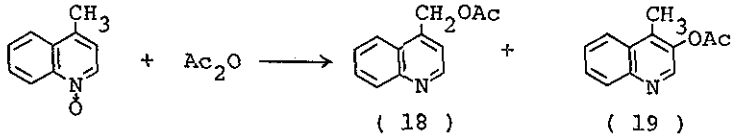


Intramolecular nature of the rearrangement was illustrated in the recent work of Markgraft et al.[106a] with 2-diphenylmethylpyridine N-oxide, which would give a stable carbonium ion intermidiate and is considered to live long forming either a "dissociated" or a "solvent separated" ion pair. In the usual ^{18}O tracer experiment, however, the resulting ester was found to contain only a half of ^{18}O of acetic anhydride, while Dabco can substitute acetate ion as the proton-removing base in acetonitrile.



The reaction of lepidine N-oxide with acetic anhydride gives two ester products and the ratio of the two products changes with solvent.[93] Since the carbonium ion of the ion pair formed from

the " anhydrobase " derived from " benzopicoline N-oxide " is considered to be more stable than that from monocyclic picoline N-oxide, it would be more susceptible to the effect of solvation.



	neat	benzene	dioxane	$CHCl_3$	CH_3CN
(18)/(19)	0.73	0.32	0.32	0.26	0.16

Thus, the ratio of the two products is believed to be effected by the change of the polarity of solvent. Here again, however, the rearrangement proceeds undoubtedly via " intimate ion pair " in view of the ^{18}O tracer experimental results.

Energy Profiles

Up to now, the main discussion was focussed on each step of the reaction and the rate-determining step of the reaction was only briefly mentioned. However, one would already have noticed that the reaction of monocyclic picoline N-oxides and that of benzopicoline N-oxides, such as quinaldine N-oxide, are somewhat different energetically. Therefore, the reactions of these two N-oxides will be dealt separatedly.

In the reactions of monocyclic picoline N-oxide derivatives with acetic anhydride, the pseudo-first order rate constant increases in the following order: 2-ethylpyridine $\approx$ 2-picoline $<$ 4-picoline $<$ 2,6-lutidine $<$ 2-phenyl-6-methylpyridine $<$ 2-benzylpyridine N-oxides. Thus, it appears that both initial O-acylation equilibrium, namely the basicity of N-oxide function, and the

subsequent proton-removal have to be taken into consideration for the discussion of the rate-determining step. However, the large hydrogen-deuterium isotope effects, i.e., $^{k}H/k_{D}$ = 6.3 at 60°C for 2-picoline N-oxide, $^{k}H/k_{D}$ = 6.2 at 60°C for 4-picoline N-oxide and $^{k}H/k_{D}$ = 7.6 at 30°C for 2-benzylpyridine N-oxide, together with the observation that there was no deuterium loss in the recovered 2-benzyl-d_2-pyridine N-oxide at half-completion of reaction, support strongly that the proton-removal is not an equilibrium but the rate-determining step of the overall reaction. Thus, the energy profile can be illustrated as shown below.(Fig.A)

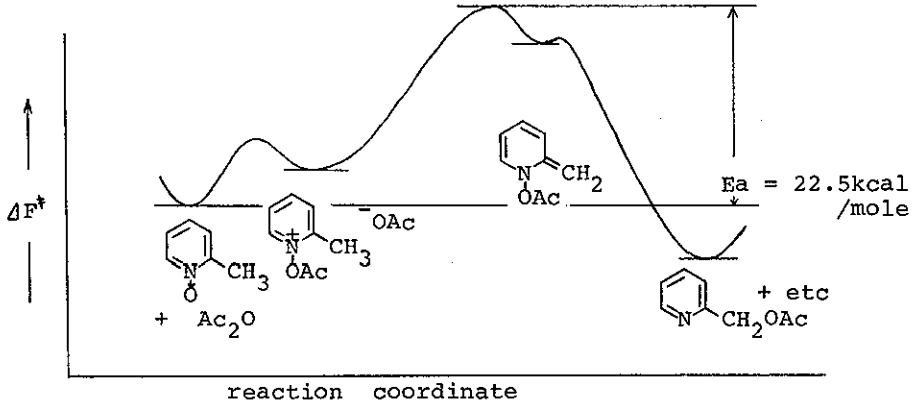


Fig. A. Energy Profile of the Reaction of Picoline N-Oxide with Ac_2O

Among few steps involved in the reaction, the proton-removal requires the highest energy for picoline N-oxides (Ea for 2-picoline N-oxide = 22.5 kcal/mole, 4-picoline N-oxide Ea = 22.5 kcal/mole) and even for 2-benzylpyridine N-oxide which reacts markedly faster (Ea = 14.8 kcal/mole).

In the bonzopicoline N-oxides series, the pseudo-first order rate falls in the following order: lepidine < quinaldine < 1-methyl-

isoquinoline N-oxides. The size of hydrogen-deuterium kinetic isotope effect fluctuates substantially from the largest k_H/k_D = 7.9 at 30 C°for lepidine N-oxide to k_H/k_D = 2.0 at 30° C for quinaldine N-oxide and again to k_H/k_D = 3.5 at 10° C for 1-methyl-isoquinoline N-oxide. Only in the case of lepidine N-oxide, the proton-removal is the rate-determining step and not an equilibrium. With the latter two benzopicoline N-oxides, the proton-removal is an equilibrium reaction, and the rate-determining step is believed to be the N-O bond cleavage, while the pseudo-first order rate constants increase markedly by the addition of lithium perchlorate into the system and also in polar media, e.g., k_1 in CH_3CN / k_1 in dioxane = ca. 3. When the reaction of trideuterated quinaldine and 1-methyl-d_3-isoquinoline N-oxides were stopped at a half completion of the reaction, the recovered N-oxides were found to have lost appreciable percents of deuterium. Thus the proton-removal is not the rate-determining but an equilibrium reaction. However, the energy barriers of both proton-removal and N-O bond cleavage are considered to be of comparable magnitude. Even with quinaldine N-oxide, substitution at 6 position changes the size of kinetic isotope effect. For example, k_H/k_D for 6-methylquinaldine N-oxide is 7.4, depicting that the proton-removal is the rate-determining step, whereas k_H/k_D for 6-chloro-derivative and unsubstituted quinaldine N-oxide are 2.2 and 2.0, respectively. An electron-withdrawing group reduces basicity of N-oxide function, increases acidity of methyl proton and strengthenes the N-O linkage, thus retarding the initial acetylation, facilitating the proton-removal at the second step and making the

cleavage of the N-O bond hard.

The energy profiles for the reactions of three typical benzopicoline N-oxides are illustrated in Fig. B.[93]

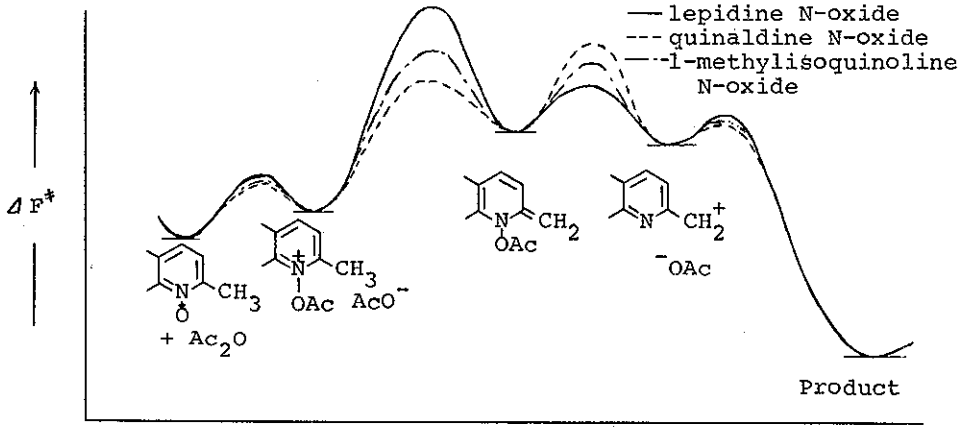
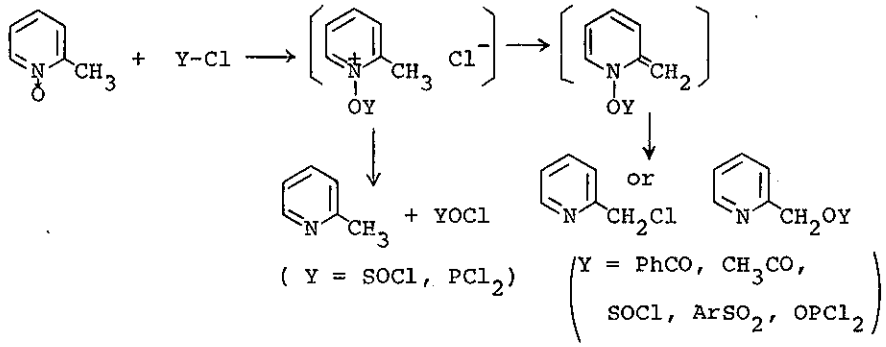


Fig. B. Energy Profiles of the Reactions of Benzopicoline N-Oxides with Ac_2O

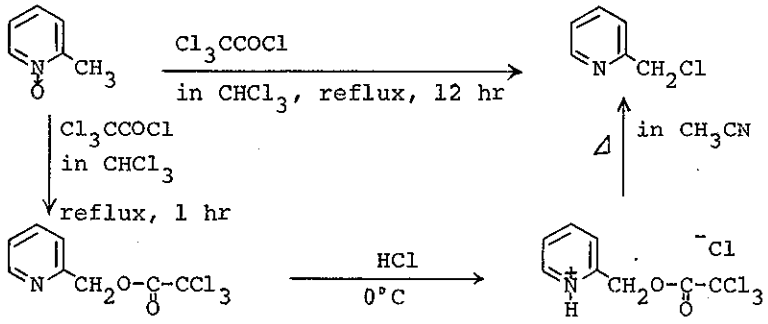
In the case of lepidine N-oxide, the highest energy barrier is the proton-removal (Ea = 16.9 kcal/mole) and in both quinaldine N-oxide (Ea = 13.7 kcal/mole) and 1-methylisoquinoline N-oxide (Ea = 10.9 kcal/mole), the N-O bond cleavage requires the highest energy. Apparently there is an energy minimum, corresponding to the ion pair, which in the recombination stage collapses differently in different solvents, thus changing the ratio of ester isomers.

Similar Reactions

The reaction of picoline N-oxide with arenesulfonyl chloride or phosphorous oxychloride to form 2-chloromethylpyridine is also considered to proceed via " anhydrobase ".[107]

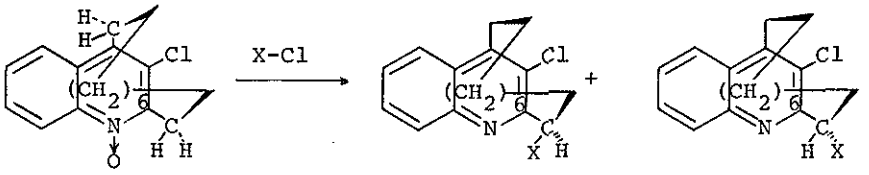


Koenig and his co-worker[108] carried out the reaction of 2-picoline N-oxide with trichloroacetyl chloride in refluxing chloroform for many hours and obtained 2-chloromethylpyridine. However, when they stopped the reaction only after one hour of refluxing, they could isolate 2-trichloroacetoxymethylpyridine, which upon heating in acetonitrile underwent decarboxylation and gave 2-chloromethylpyridine. Thus, the final product is believed to be formed by the nucleophilic attack of chloride ion on 2-trichloroacetoxymethylpyridine.



Parham and his co-workers[109] conducted reactions of 12,13-benzo-16-chloro(10)(2,4)pyridinophane N-oxide, a cyclophane derivative of 2,4-dimethyl-3-chloroquinoline N-oxide, with acetic

anhydride and other acyl chlorides and obtained corresponding esters of both syn- and anti-forms. In the reaction with tosyl chloride, however, only the syn-isomer was found to be formed.



syn anti

syn. a. OAc (32%) anti. a. OAc (26%)

b. OCOPh(26%) b. OCOPh (46%)

c. OSO_2Tol(73%) c. OSO_2Tol(0%)

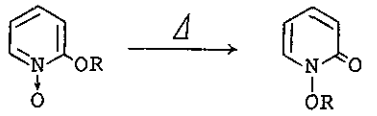
d. $OPOCl_2$

e. Cl

In a model reaction with 2,4-dimethyl-3-chloroquinoline N-oxide, only 2-chloromethyl derivative, but no ester was formed. Therefore, the formation of esters with the cyclophane N-oxide is quite interesting and may give some clue for understanding the energetic relation between " anhydrobase ", N-O bond cleavage and subsequent recombination. The formation of only syn-isomers with tosyl chloride and phosphorous oxychloride appears to suggest that such poor nucleophiles as tosylate and dichlorophosphate ions have rather low polarizabilities and recombine as soon as they can find any nearby cationic center, which happens to lead to the syn ester formation. The formation of esters again indicates that the rearrangement is intramolecular and takes place within " anhydrobase " and the chloromethyl derivatives are formed by the nucleophilic attack of chloride ion on the esters formed earlier.

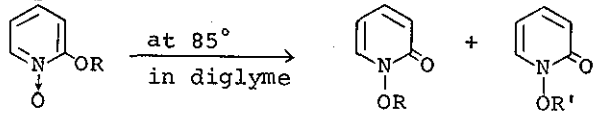
5. Other Related Rearrangements of Heteroaromatic N-Oxides

Dinan and Tieckelmann[110] found that thermolyses of 2-alkoxypyridine N-oxides give the corresponding N-alkoxypyridones in high yields and the yield is better with allylic or benzylic than with methyl or ethyl group at low temperatures.



R =		
$-CH_2CH=CH_2$	100°	83%
$-CH_2Ph$	100°	92%
$-CH_3$	140°	89%

For the rearrangement of allylic group, Thyagarajan[111] proposed earlier a mechanism involving a seven-membered cyclic transition state in contrast to the Meisenheimer rearrangement, however, such a possibility was ruled out by Tieckelmann[112] in the following experiments.

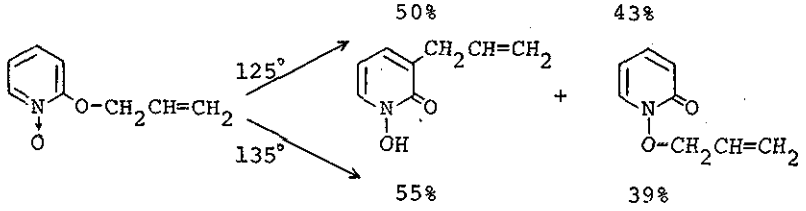


R =			
$-CH_2CH=CH_2$	$-CH_2CH=CH_2$		100%
$-CH_2CH=CH-CH_3$	$-CH_2CH=CH-CH_3$		98%
	$-CH(CH_3)-CH=CH_2$		2%
$-CH_2$-cyclopropyl	$-CH_2$-cyclopropyl		96%
	cyclobutyl		4%
$-CH(CH_3)-CH=CH_2$	$-CH(CH_3)-CH=CH_2$		80%
	$-CH_2CH=CH-CH_3$		10%

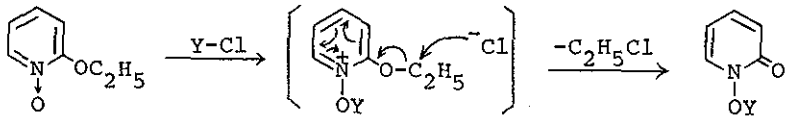
At relatively low temperatures (r.t. to 85°C) only a very small portion (ca. 2%) of alkenyl group undergoes 1,3-allylic shift

while 98% retains its skeleton during the rearrangement, while optically active 2-(α,γ-dimethylallyloxy)pyridine N-oxide gives, upon heating, an optically active N-allyloxypyridone (though the structure is not well confirmed). The cross-over experiment with two different allyloxypyridine N-oxides revealed that over 80% of the thermal rearrangement proceed via an intramolecular route. Conversion of cyclopropylcarbinyl group to cyclobutyl group, though only in 4%, still indicates that the contribution of heterolytic process is important at the transition state.

At higher temperatures (125-135°C), however, another product, formed via Claisen type rearrangement, namely, 3-alkenyl-N-hydroxy-2-pyridone is formed together with the normal rearrangement product.

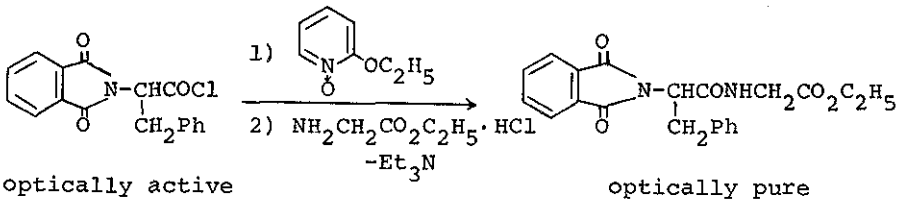


An interesting, but somewhat different reaction is that between 2-ethoxypyridine N-oxide and acylating agents to afford N-acyloxy-2-pyridone and ethyl chloride.[113]



Y = Ac, ArCO, CH_3SO_2, $ArSO_2$

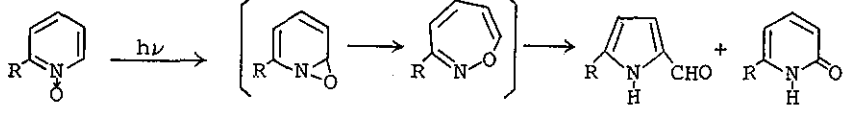
This reaction was applied for the stereoselective synthesis of peptides and following is an example of dipeptide synthesis without racemization.[114]



optically active optically pure

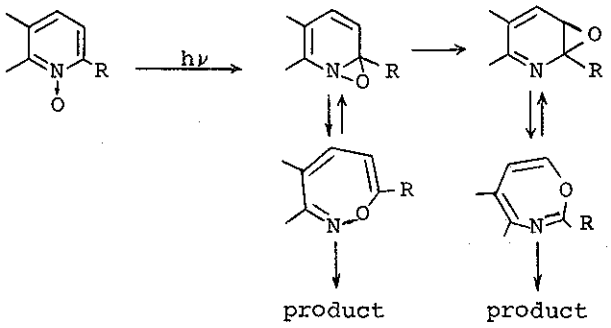
Photochemical deoxygenative reduction, ring contraction and expansion to other hetero-rings, ring cleavage and other photochemically interesting reactions of heteroaromatic N-oxides are many and well-covered in a few exellent reviews by Katritzky,[2] Taylor et al.[115] and Kaneko.[116] Therefore, we have no intention to duplicate the subject but will cover only recent works briefly.

Photolysis of pyridine and 3-picoline N-oxides in gaseous phase gives deoxygenated pyridine and 3-picoline.[117] Whereas, photolysis of gaseous 2-picoline N-oxide with 2537 Å light (π- π^* excitation) leads to deoxygenation by N-O bond cleavage and that with 3266 Å (n- π^* excitation) gives 2-pyridinemethanol as the main product.[118] Photolysis of pyridine N-oxide in aromatic hydrocarbon, such as benzene, gives both phenol and deoxygenated pyridine, in a high quantum yield.[119] In other solvents, ring contraction is the main course of the photolysis, forming 2-formylpyrrole.[120]

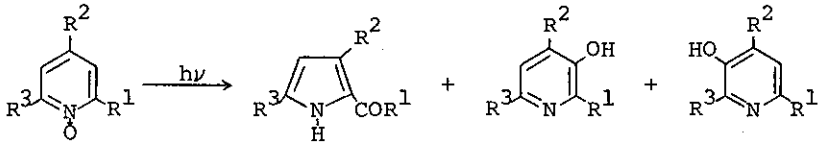


R = H, CH_3 R=H;10%
R=CH_3;8%

Following is believed to be the general route for the product formation in the photolysis of pyridine N-oxide.

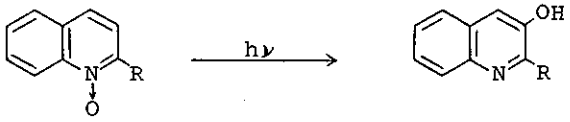


In the photolyses of heteroaromatic N-oxides, various intermediates have been suggested and many of them were actually isolated. These examples are listed in the following equations.



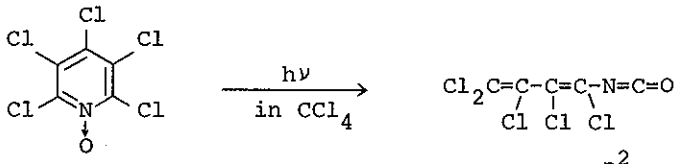
121)

R^1, R^2, R^3 = H, Me

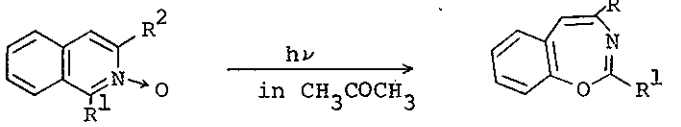


122)

R = CN, Ph

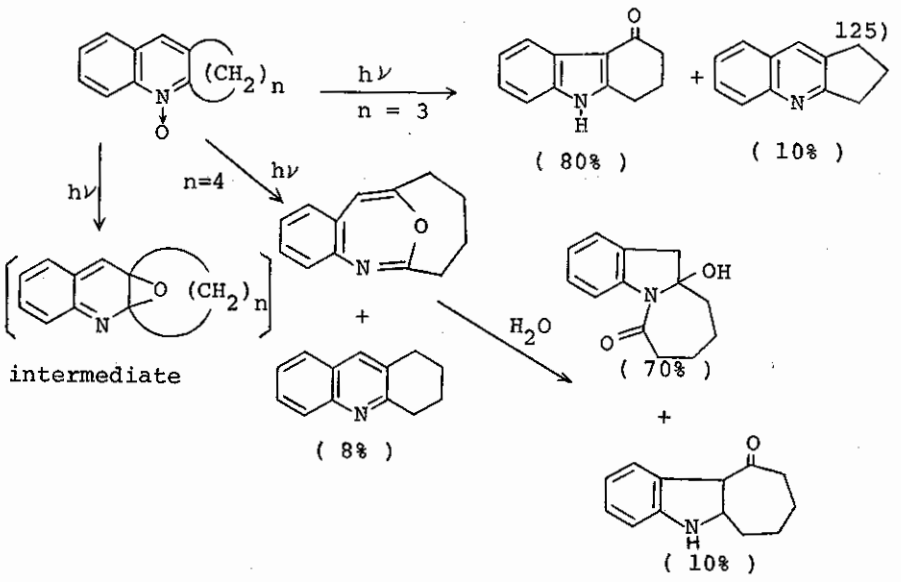


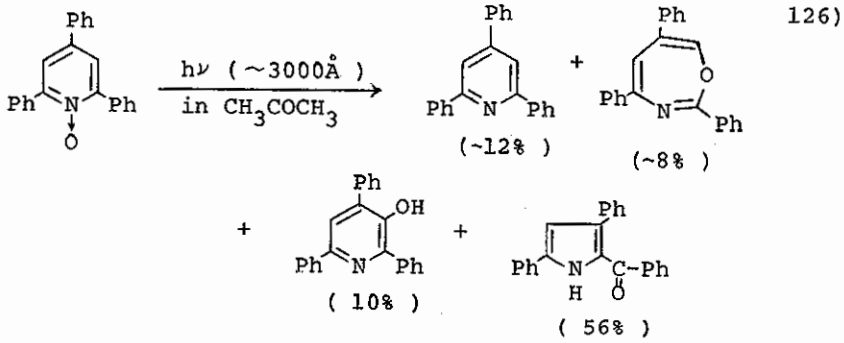
123)



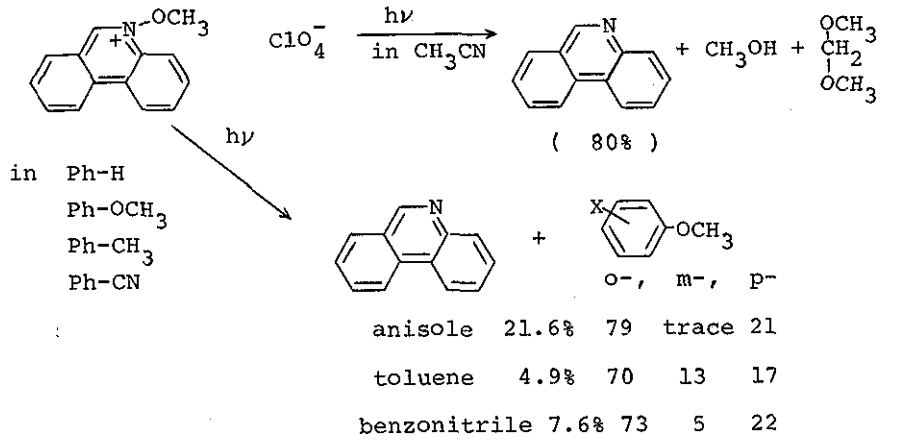
124)

R^1 = Ph, CN ; R^2 = H, Me



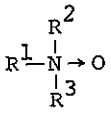


In the photolysis of N-methoxyphenanthridinium perchlorate in aromatic hydrocarbons, Taylor and his co-workers [127] observed that methoxy radical, formed by the cleavage of the N-O bond, attacks aromatic solvent to give o-, m- and p-anisole derivatives while the N-oxy compound is reduced back to the original base in a good yield.

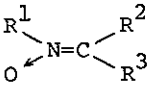


6. Reactions of Non-Heteroaromatic N-Oxides with Acylating Agents ; Aliphatic t-Amine Oxides, Nitrones and Azoxybenzenes

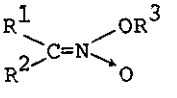
Apart from heteroaromatic N-oxides, following are other tertiary amine oxides which can undergo rearrangements or other interesting reactions.



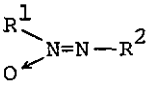
aliphatic t-amine oxides



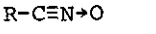
nitrones



nitronic esters



azoxy compounds

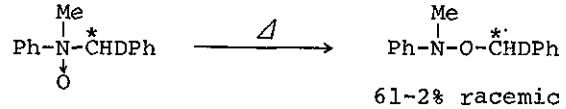


nitrile oxides

a). Aliphatic t-Amine Oxides

Aliphatic t-amine oxides may undergo the Meisenheimer rearrangement,[128] the Cope elimination, if there is at least one β-hydrogen in the molecule, and also dealkylation such as the Polonovski reaction. There are many examples of these reactions.

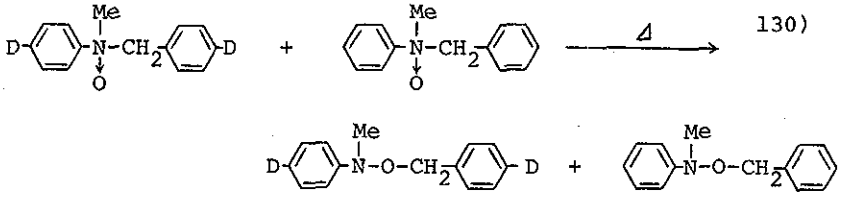
Intramolecular nature of the Meisenheimer rearrangement was depicted by the following experiments, shown below, with an optically active t-amine[129] and also by a cross-over tracer experiments between deuterated and undeuterated t-amine oxides.[130]



129)

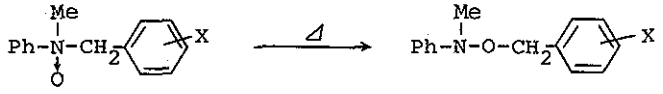
optically active

61-2% racemic



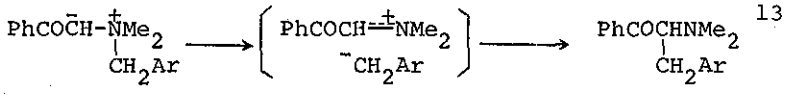
130)

The reaction is kinetically unimolecular, i.e., first order with the concentration of t-amine oxide while the ease of alkyl group to rearrange is allyl ⟩⟩ benzyl.[131] With substituted benzyl groups, the Hammett plot with σ values gave $\rho = 0.9$ which is substantially small than that ($\rho = 3.4$) for the Stevens rearrangements of phenacyl(subst.-benzyl)methylammonium salts.



132)

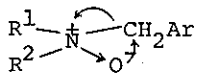
X = H, p-CH_3, m-CH_3, p-Cl, m-Cl, p-F, m-F, m-Br, p-NO_2



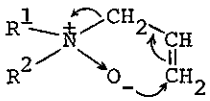
133)

Relatively small electronic effect and the activation parameters (Ea = 33-40 kcal/mole, $\Delta S^{\ddagger}$ = +19.2~+41.2 e.u.) seem to suggest that the Meisenheimer rearrangement does not proceed via a cyclic

such as S_Ni or S_Ni' transition state but via an initial N-C bond cleavage and subsequent C-O bond formation.

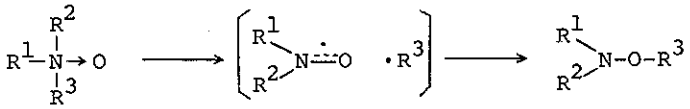


S_Ni

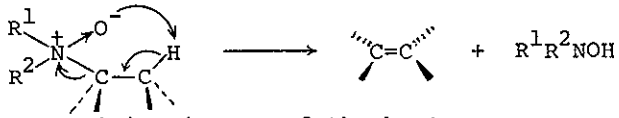


S_Ni'

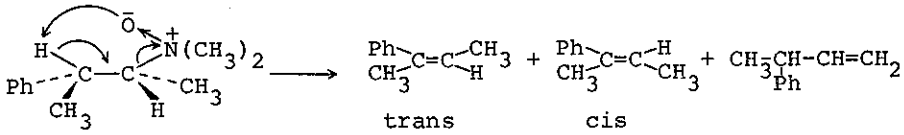
Indeed, it is now believed to be a free radical cage reaction as shown below.[128]



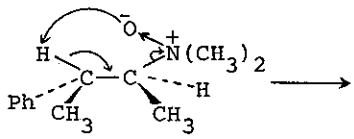
The Cope elimination reaction is a typical Ei reaction which proceeds via 5-membered transition state shown below, and has a wide application in the syntheses of olefins.



The stereoselectivity is one of the best among many similar Ei reactions that proceeds via 5-membered transition state, as is illustrated by the following examples.[134]

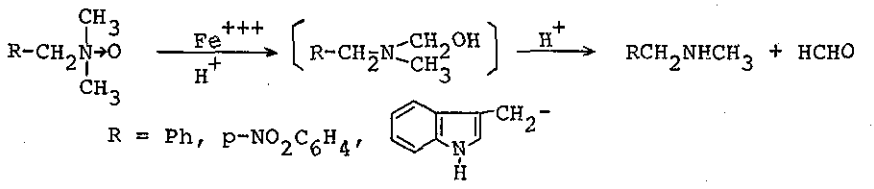


	trans	cis	
erythro	90%	3%	7%



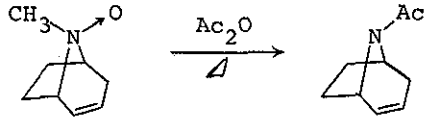
threo	1-2%	93%	7%

One example of dealkylation of tertiary amine oxides is ferric ion-catalyzed or dichromate ion-catalyzed reaction which gives hydroxymethylamine derivative at the initial stage as shown below.[135]

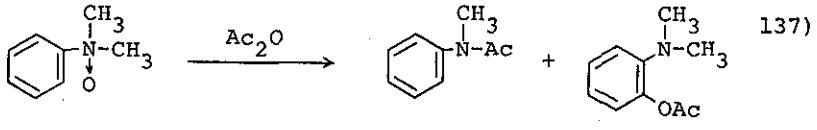


R = Ph, p-$NO_2C_6H_4$,

Following are interesting dealkylation reactions by treatment with acylating agent and called "Polonovski reaction". In the reaction of dimethylaniline N-oxide, the ratio of the two products, i.e., rearranged ester and demethylated amide varries with the polarity of the solvent used.[138]



136)

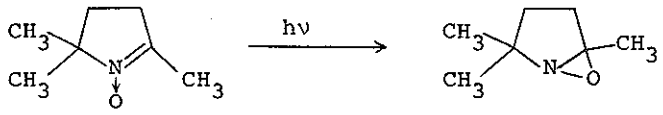


137)

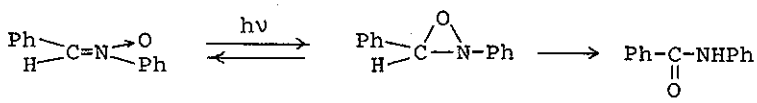
The rearranged product predominates in water and also in acetic anhydride, while the amide is the major product in less polar or non-polar media such as THF and benzene. Earlier, a free radical solvent cage mechanism was proposed by Oae's group based on a crude ^{18}O tracer experiment,[137] however, was questioned later by a recent CIDNP observation.[139] The renewed ^{18}O tracer experiment indicates that the reaction is intramolecular but the ^{18}O-distribution among the two oxygen atoms of the rearranged ester is not equal, suggesting the reaction to proceed via another ion-pair process.[140]

b). Nitrones

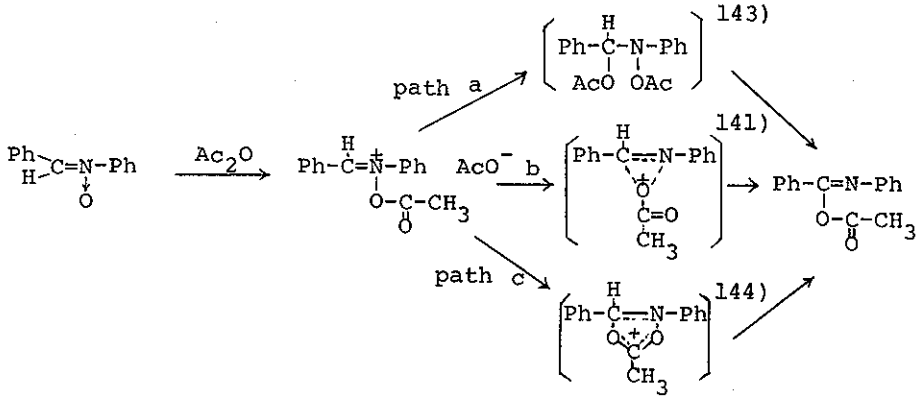
Photolyses of nitrones usually give three-membered oxaziranes which are unstable and transformed back to nitrones, leading to cis-trans isomerization or eventually isomerizing to the corresponding stable carboxylamides.[141)]



142)



The reactions with acylating agents usually give acylamides. A typical example is the reaction between α,N-diphenylnitrone with acetic anhydride and the following three mechanistic routes have been suggested.



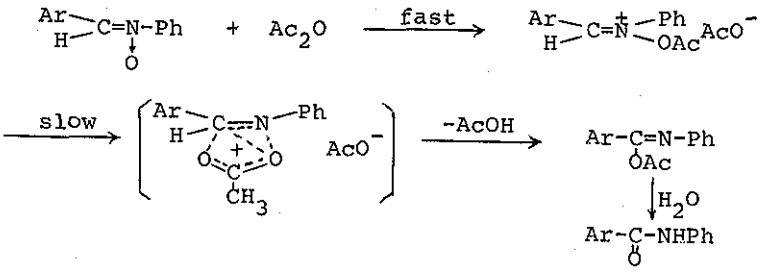
143)

141)

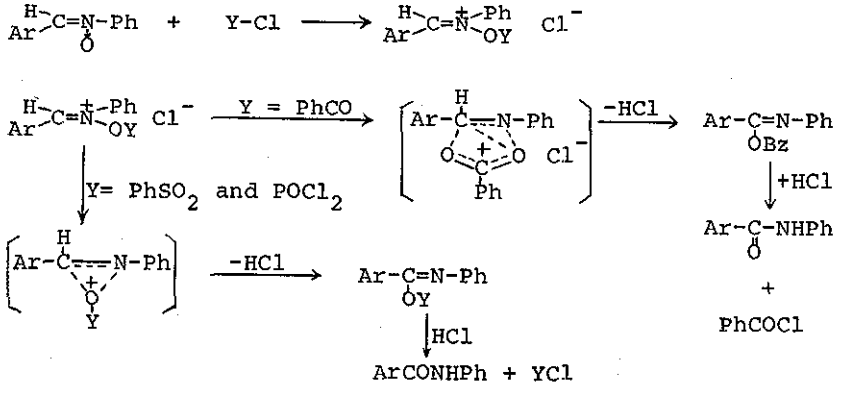
144)

Path a involves the attack of external acetate ion, while both path b and c are intramolecular shifts of acetoxy group, and the ^{18}O tracer experiments with ^{18}O-labeled acetic anhydride can easily discriminate path a from the other two. Thus, the usual ^{18}O tracer study was conducted by Tamagaki and Oae[145)] and the possibility of

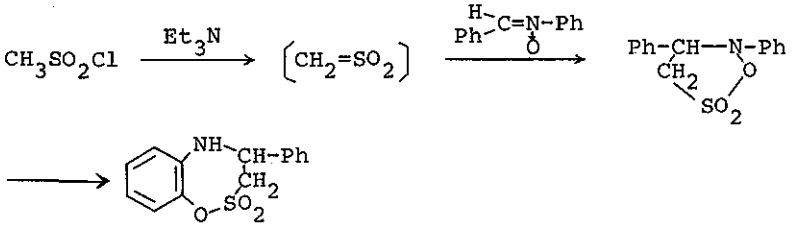
path a was ruled out. Meanwhile, the usual kinetic study on the reaction of α-aryl-N-phenylnitrone with acetic anhydride gave activation parameters of Ea = 10.9 kcal/mole and $\Delta S^{\ddagger}$ = -59.6 e.u. and the Hammett linear correlation with σ^{+} values and $\rho_{\sigma^{+}}$value of -0.8. Thus the following mechanism, which includes participation of both path b and path c, has been suggested as most plausible.[145]



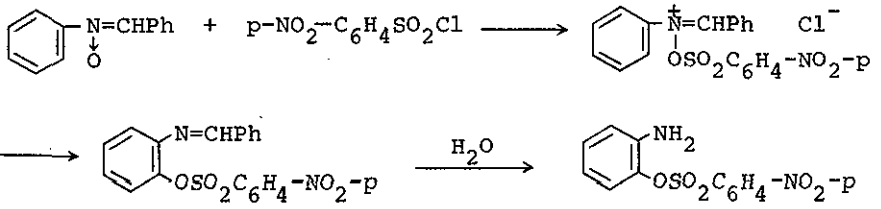
The similar reactions with benzoyl and benzenesulfonyl chloride and also with phosphorus oxychloride were investigated by Tamagaki and Oae[146] through their usual ^{18}O tracer technique, which suggested that the reaction with benzoyl chloride proceeds intramolecularly via both " oxygen bridged " and " cyclic " routes while those with the sufonyl chloride and phosphorus oxychloride undergo through " oxygen bridged " transition state, shown below.



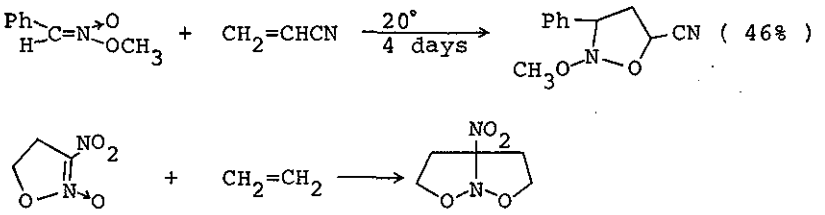
In the reaction with methylenesulfene, α,N-diphenylnitrone gives a heterocyclic sulfone, apparently an intramolecular rearrangement product.[147]



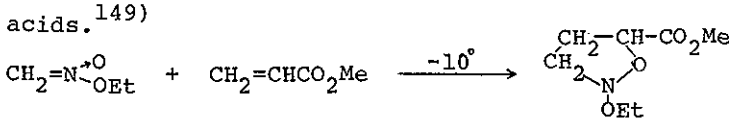
The reaction with arenesulfonyl chloride bearing an electron-withdrawing substituent such as p-nitro group, also gives an ortho-rearranged product.[148]

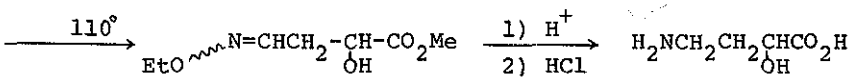


As for the reactions of nitronic esters, Nielsen summarized many examples of various kinds,[149a] and a few of them are shown below.

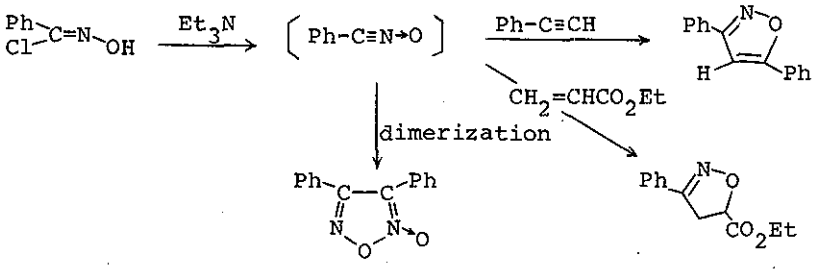


This addition reaction was applied to the synthesis of α-hydroxy-ω-amino acids.[149]



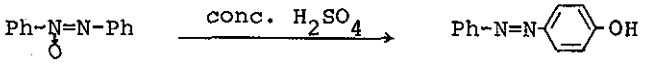


Nitrile oxides also give cycloaddition products together with dimerized heterocycles, presumably via 1,3-dipolar addition, according to Huisgen.[150]

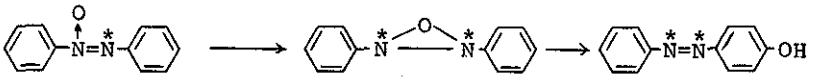


c). Azoxybenzenes

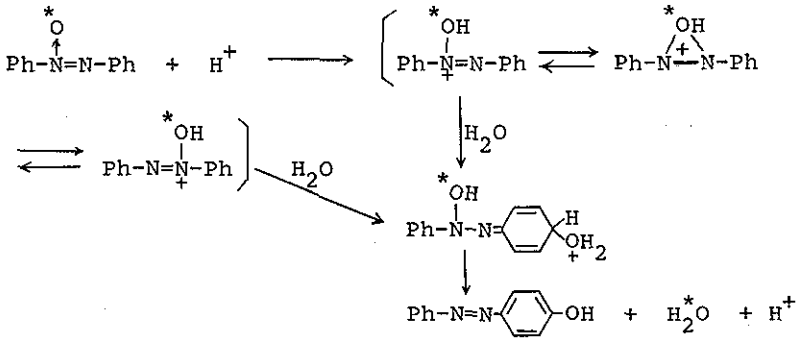
Aromatic azoxy compounds undergo rearrangement in the presence of strong acids. For examples, treatment of azoxybenzene with conc. sulfuric acid gives p-hydroxyazobenzene and this rearrangement is known as the Wallach rearrangement, which has received considerable attentions in the past.[151]



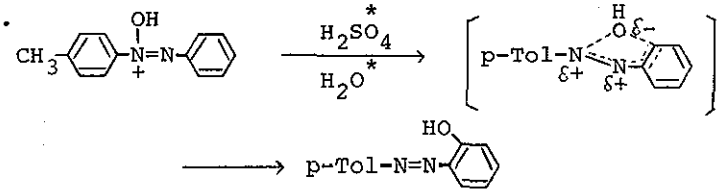
Shemyakin and his co-workers[152], based on their ^{15}N and ^{18}O tracer experiments, proposed the following mechanism involving the N,N-oxide intermediate, shown below.



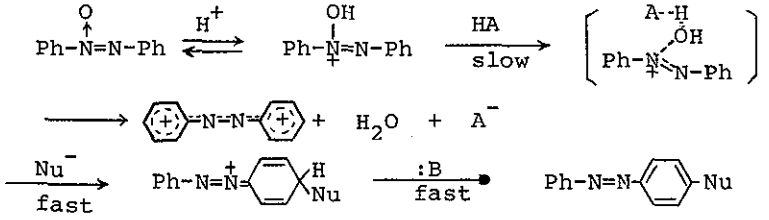
Oae, Fukumoto and Yamagami also carried out the rearrangement of ^{18}O-labeled azoxybenzene and found the resulting p-hydroxyazobenzene to have lost ^{18}O. Thus, the following mechanism was suggested.



As to the rearrangement to ortho-position, Oae et al.[153] suggested the following intramolecular rearrangement via an intimate ion pair, based on their observation that ^{18}O-label of the medium was not incorporated in the resulting ortho hydroxy group of the rearranged product.

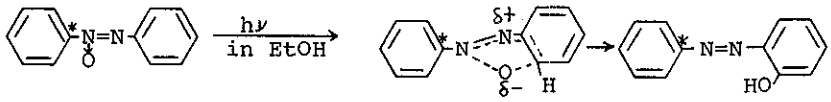


Kinetic studies of the rearrangement in various concentrations of sulfuric acid have been carried out and the mechanism involving " dicationic intermediate " was also proposed,[154] however the mechanism appears to change with the change of concentration of sulfuric acid. At higher acid concentrations, the dication intermediate is considered to be formed.[155]



The reaction looks quite simple, yet it involves oxygen migration not only between N and O, and p-carbons of both benzene rings but also between the two nitrogen atoms, thus complicating the whole mechanism. Further studies are now underway at several laboratories and will clarify the detailed mechanism.

Photo-Wallach rearrangement is known to be intramolecular and involves the shift of hydroxy group to ortho-position,[151] however, a question has remained as to which benzene ring hydroxy group migrates. In order to shed light on this problem, Oae et al.[156] conducted the reaction with azoxybenzene-1-^{14}C and determined the location of the ^{14}C by the reductive cleavage of o-hydroxyazobenzene. The result indicates that the photo-Wallach rearrangement leads to no significant delocalization of the isotopic ^{14}C during the ortho rearrangement, shifting oxygen to the unlabeled benzene ring to the extent of 87%. Thus the following mechanism was suggested.

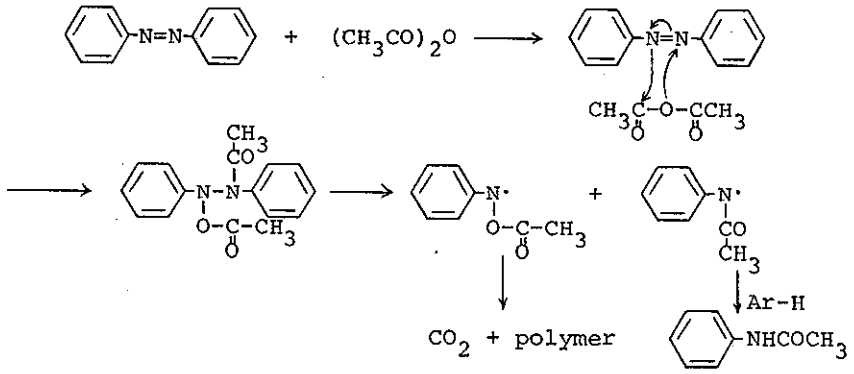


Since the basicity of azoxybenzene is very small (pKa = 6.45), as compared to other common tertiary amine oxides, by factors of 5-10 pKa units, the reaction of azoxybenzene with acetic anhydride is considered to be sluggish. The reaction, however, did occur under prolonged heating at 190°C in an autoclave and a mixture of azobenzene, acetanilide and acetic acid was obtained along with such gaseous products as carbon dioxide, carbon monooxide and methane.[157]

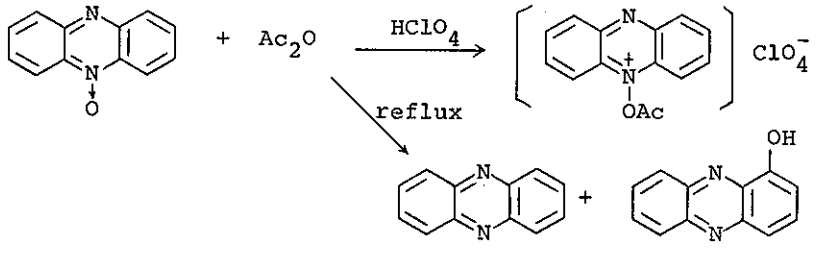
$$\mathrm{Ph\text{-}\overset{\overset{\displaystyle O}{\downarrow}}{N}\text{=}N\text{-}Ph} + Ac_2O \xrightarrow[15\ hr.]{190^\circ C} \underset{(\ 60\%\ )}{Ph\text{-}N\text{=}N\text{-}Ph} + \underset{(\ 13\%\ )}{PhNHAc} + \underset{(\ 63\%\ )}{CH_3COOH}$$

$$+ \underset{(\ 95\%\ )}{CO_2} + \underset{(\ 14\%\ )}{CO} + \underset{(\ 2\%\ )}{CH_4}$$

Acetanilide obtained is considered to be formed via azoxybenzene. Treatment with an excess acetic anhydride gave acetanilide in a high yield. The formation of acetanilide was inhibited by the addition of such radical scavengers as iodine, hydroquinone and nitrobenzene. Thus a free radical mechanism was suggested for the acetanilide formation.



Oae, Maeda and Kozuka[157] also found that phenazine N-oxide undergoes a similar reaction in refluxing acetic anhydride.



(71%) (5%)

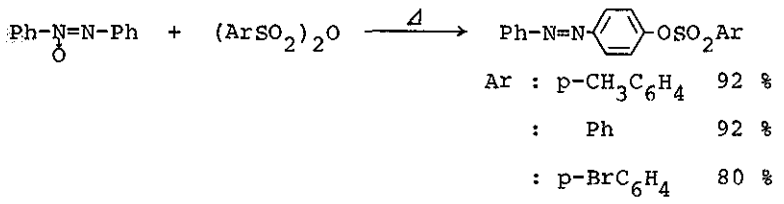
+ $CH_3CO_2CH_3$ + CH_3CO_2H + CO_2 + CH_4

(4.7%) (10.1%) (64%) (5%)

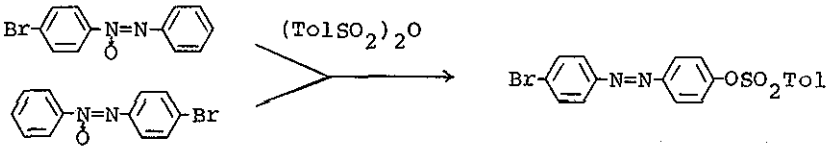
Since the N-acetoxy salt can be isolated as perchlorate, the initial step is undoubtedly the acylation, however, the subsequent step seems to be homolytic fission of the N-O bond, in view of the large

amounts of the reduced phenazine, methane, carbon dioxide and methyl acetate.

Azoxybenzene was found by Oae and Maeda[158] to react smoothly with arenesulfonic anhydride and yielded p-arenesulfonoxyazobenzene in high yields.



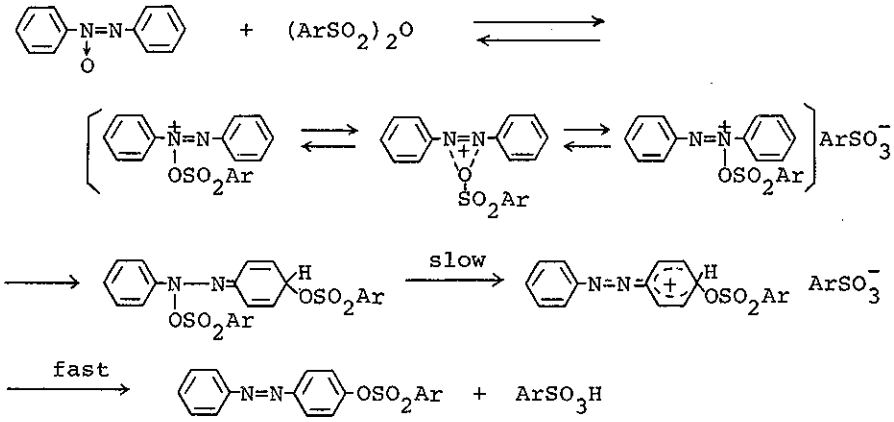
In this reaction, both isomers of bromoazoxybenzene gave the same rearrangement product, suggesting the oxygen transfer during the reaction.



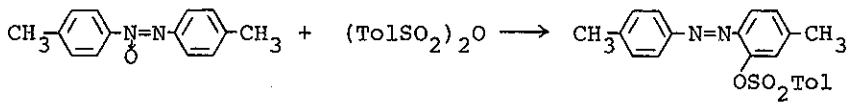
The usual ^{18}O tracer experiment with ^{18}O-labeled benzenesulfonic anhydride revealed that all the oxygen atoms in the resulting benzenesulfonoxyazobenzene was completely scrambled, showing that migration of the benzenesulfonoxy group proceeds through a completely intermolecular pathway. Meanwhile a ^{14}C tracer experiment with azoxybenzene-1-^{14}C, which involves reductive cleavage of p-hydroxyazobenzene with sodium hydrosulfide to p-aminophenol and aniline, revealed that the intermolecular attack of the sulfonate was slightly favored at phenyl group of the azo side (4-position) as compared to the azoxy side (4'-position) in the ratio of 57 to

43%. However, the result of this ^{14}C tracer experiment clearly depicts that there is a definite oxygen-migration between the two nitrogen atoms during the process.

Kinetic experiments with substituted benzenesulfonic anhydride in acetonitrile gave a good Hammett correlation with σ-values and the ρ-value was calculated as + 1.3, while, with p-substituted azoxybenzene, the Hammett correlation with σ values gave ρ-value of - 1.5. The activation parameters are Ea = 22.4 kcal/mole and $\Delta S^{\ddagger}$ = - 14.2 e.u. The hydrogen-deuterium kinetic isotope effect, measured with azoxybenzene-d_{10} was as nil, i.e., k_H/k_D = 1.00. Based on these observations, Oae and Maeda presented the following mechanism which involves the cleavage of N-O bond at the rate-determining step.

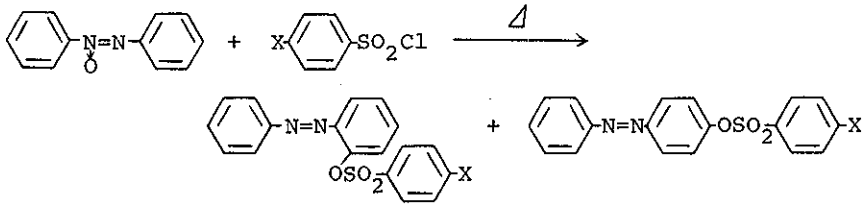


When both para-positions are substituted, the rearrangement occurs at an ortho position, for example.

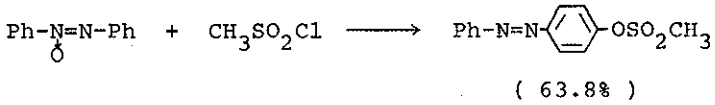


Like many other ortho-rearrangements, this migration of the sulfonoxy group to ortho position is considered to be intramolecular.

The reaction of azoxybenzene with arenesulfonyl chlorides gives both orhto- and para-arenesulfonoxyazobenzenes in different ratios depending upon the substituents, thus proceeding apparently via a somewhat different mechanistic route from that with arenesulfonic anhydride.[156)]



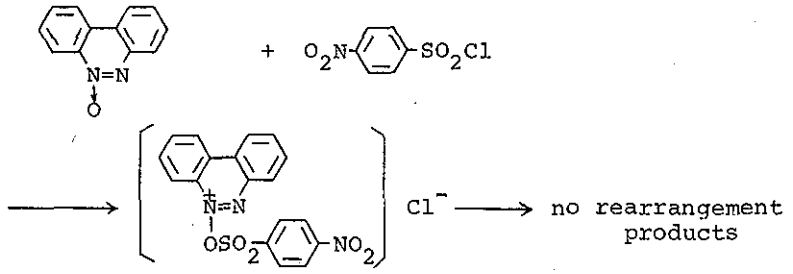
X = p-NO_2	59.7 %	24.8 %
p-Br	28.8	36.8
p-CH_3	0.6	61.4



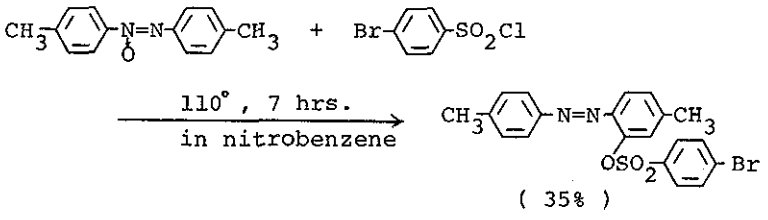
(63.8%)

The reaction is quite sluggish as compared to that with arenesulfonic anhydride, but the yields of the rearranged products are pretty good. A few characteristic features are followings. 1) There are formations of both ortho- and para-rearrangement products while the formation of ortho-derivative is favored with benzenesulfonyl chloride bearing an electron-withdrawing substituent and disfavored with that having an electron-releasing substituent. 2) In the reaction of sterically twisted benzocinnoline N-oxide with p-nitrobenzenesulfonyl chloride, no rearranged product was obtained because of the steric hindrance of the attack of chloride ion on the azo group after the arene-

sulfonylation of the N-oxy function.

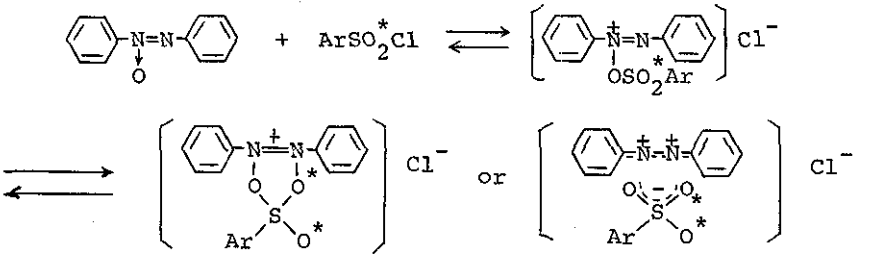


3) When both para-positions are blocked by substituents, as in the case of p,p'-dimethylazoxybenzene, the rearrangement to ortho position occurs,as shown below.



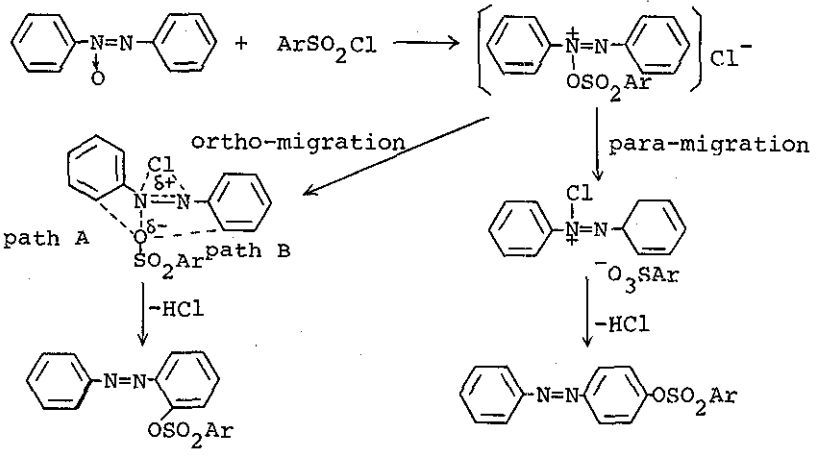
4) The reaction proceeds smoothly in polar media such as nitrobenzene but becomes sluggish without solvent. 5) The usual ^{18}O tracer experiment with ^{18}O-labeled p-bromobenzenesulfonyl chloride revealed that all oxygen atoms of p-brosyloxyazobenzene are completely scrambled, suggesting an intermolecular nucleophilic process for the para migration while o-brosyloxyazobenzene retains the original oxygen atoms of azoxybenzene implying an intramolecular oxygen-bridged ion-pair process for the ortho migration. 6) The small excess of ^{18}O found in the recovered azoxybenzene seems to suggest that there is a pre-equilibrium of oxygen atoms between the azoxybenzene and arenesulfonyl groups prior to the rearrangement via either (20) or (21), though in a very minor extent.

7) The ^{14}C-tracer experiment of azoxybenzene-1-^{14}C with p-nitrobenzenesulfonyl chloride revealed that the ratio of the sulfonoxy migration to the phenyl ring attached to the azoxy side (path A) to that attached to the azo side (path B) is 1 to 2 for the ortho rearrangement.



(20) (21)

Based on all these observations, the following mechanism was suggested by Oae and Maeda as most plausible.

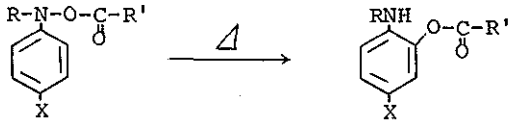


c). N-Hydroxylamines

There are a few interesting rearrangement reactions of N-hydroxylamines which are related to those of t-amine oxides.

Lwowski et al.[159] studied the reaction of N-arylhydroxylamines

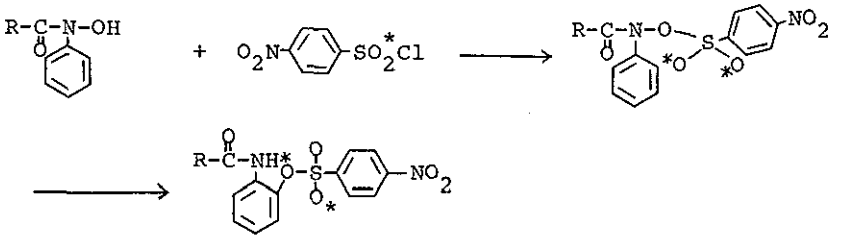
and benzoyl or arenesulfonyl chloride and isolated o-benzoyloxy- or arenesulfonyloxyanilines.



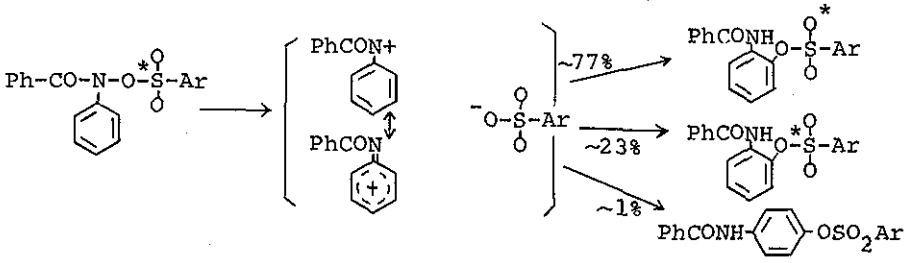
R = CH_3CO, R' = $CHCl_2$

R = R' = Ph

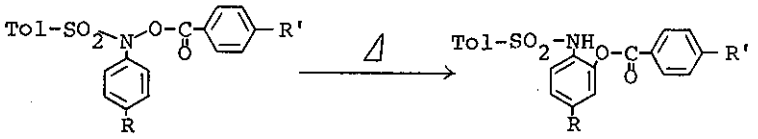
In the case of o-sulfonyloxy-migration, the etheral oxygen atom of the resulting ester was found to be incorporated with ^{18}O exactly as much as that of the sulfonyl chloride used. Thus, the following intramolecular cyclic mechanism was suggested for the rearrangement.



A little later, a careful ^{18}O-tracer study was conducted by Gutschke and Heesing,[160] changing the reaction temperature and the solvent while varying the substituent. The results indicated that there is a partial scrambling of ^{18}O in the resulting ester, while electron-withdrawing substituents accelerate the rate. Thus the following mechanism was suggested for the rearrangement.



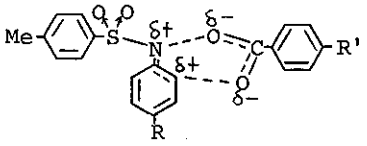
Oae and Sakurai found that O-(p-substituted benzoyl),N-(tosyl)-N-arylhydroxylamines rearrange thermally and give o-acyloxy-p-tosylanilides in another 1,3-migration.[161]



R = CH_3, H, Cl

R' = NO_2, Cl, H, CH_3, OCH_3

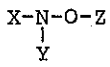
The usual ^{18}O tracer experiment with ^{18}O-labeled benzoyl chloride was carried out and the etheral oxygen was found to be originated nearly completely from the carbonyl oxygen. Thus, this reaction is considered to be the first example of intramolecular concerted process among similar reactions. The kinetic study revealed that the value of entropy of activation is unusually large and negative, e.g., - 25 e.u. for unsubstituted compound (cf. $\Delta S^{\neq}$ = + 13.4 for N-arenesulfonoxy-isocarbostyril[65]), and a good Hammett correlation with σ-values of substituent, R', gives ρ-value of + 1.5, while the effect of solvent on the rate of rearrangement is very small. Based on these observations, the rearrangement is considered to involve the rate-determining N-O bond cleavage within the following rigid structure of the ionic transition state (22).



(22)

It is interesting to examine the general mode of 1,3-acyloxy

migration in open systems, focusing attention mainly on the effect of substituents, X, Y, and Z on the rearrangements of the hydroxylamines (23).



(23)

The results obtained by Oae and others are tabulated in the following Table A.

Table A. Survey of 1,3-acyloxy migrations of the hydroxylamines  (23)

	X	Y	Z	mechanism	ref.
1.	CH_3CO	Ph	Cl_2CHCO	^{18}O-scrambling	162
2.	PhCO	Ph	CF_3CO	^{18}O-scrambling	162
3.	Ph	Ph	PhCO	^{18}O-scrambling	163
4.	PhCO	Ph	PhCO	Cyclic with partial ^{18}O-scrambling	161
5.	PhCO	Ph	Tos*	^{18}O-scrambling	160
6.	Tos*	Ph	PhCO	Cyclic	161
7.	Tos*	p-$CH_3C_6H_4$	PhCO	Cyclic with partial ^{18}O-scrambling	161

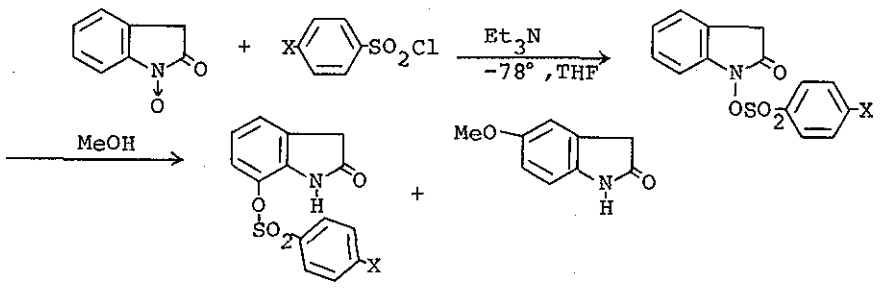
Tos* = p-$CH_3C_6H_4SO_2$-

Data in Table A reveal that replacement of sulfonyl or benzoyl group by phenyl group for the substituent X alters the mechanistic route from the cyclic path to the scrambling path when substituents Y and Z are phenyl and benzoyl group, respectively, (line 3, 4 and 6). As the leaving ability of the migrating group, i.e., OZ increases,

the oxygen scrambling increases even though the substituent X suppresses the heterolytic cleavage of the N-O bond, since the 1,3-acyloxy migration of (23) bearing dichloroacetoxy or arenesulfonoxy groups proceeds via the scrambling path, while the introduction of benzoyloxy group with poor leaving ability for OZ resulted in an exclusive cyclic process during the rearrangement (line 2, 4 and 5). Furthermore, a partial scrambling of ^{18}O was observed when Me group was introduced to the para-position of the phenyl ring as substituent Y (line 6 and 7). Comparison of lines 1 and 2 indicates that the mode of 1,3-acyloxy migration is not affected by the change from benzoyl to acetyl groups for the substituent X of (23) when a good leaving group such as trifluoroacetoxy or dichloroacetoxy is the OZ group.

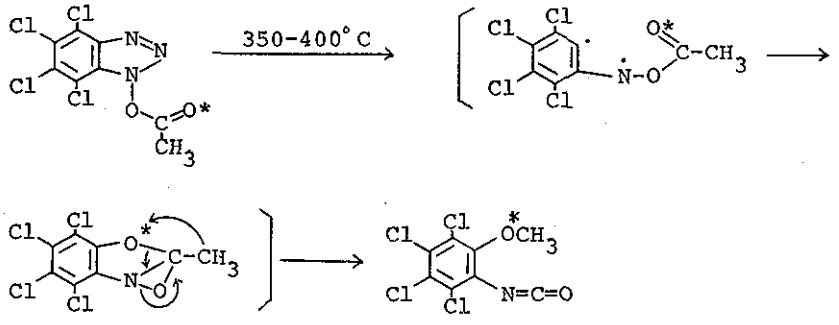
These observations suggest that the oxygen scrambling in the 1,3-acyloxy migration tends to increase by substituents, X, Y, and Z which promote the heterolytic cleavage of the N-O bond by stabilizing the cation or the anion formed by the heterolytic cleavage of the N-O bond. On the other hand, the 1,3-acyloxy migration involving a concerted cyclic transition state becomes predominant when the substituents X, Y and Z suppress the heterolytic cleavage of the N-O bond. Thus, the mechanism of the 1,3-acyloxy migration of the hydroxylamine (23) can reasonably be explained in terms of electronic effects of substituents, X, Y and Z on the heterolytic cleavage of the N-O bond.

An interesting 1,3-sulfonyloxy migration of N-hydroxy oxyindole, shown below, was found by Gassman et al.[164)]



X = p-CH_3	34 %	42 %
p-NO_2	30 %	52 %

Another modification is the thermolysis of 1-acetoxybenzotriazole, done by Leonard et al.[165] who found the intermediate to be a biradical species before yielding the final rearranged product.



Note and Acknoledgement:

Soon after the World War II, one of the auther (S.O.) started to follow the brilliant synthetic works of late Professor Eiji Ochiai and dreamed to carry out mechanistic investigations of various reactions, he and his co-workers discovered. However, the first mechanistic study we undertook was nearly fifteen years later when we started using ^{18}O tracer technique extensively at Radiation Center of Osaka Prefecture. Our first three works on " Rearrangements of t-Amine Oxides " which appeared later on J. Am. Chem. Soc., 84, 3359, 3362 and 3366 (1962) apparently drew the attention of late Professor Ochiai, whose warm-hearted encouragement pushed our further investigations for nearly fifteen years which crystallized into about fifty publications. Prof. Ochiai suggested S.O. to write up a review on whats we have done on the Rearrangements of t-Amine Oxides. However, the serious personal trouble of S.O. during the last few years at his former place retarded the actual writing schedule nearly three years. Thus, this manuscript could not be shown to Professor Ochiai before he passed away. During the brief association with him, however there have been many warm-hearted encounters, exchanges and supports not only from him but also with his former co-workers such as Professors M. Hamana, T. Kato, M. Ikehara and Dr. H. Tanida whom we would like to express our sincere thanks. We are also most grateful to Dr. Kenichi Takeda of Shionogi Pharm. Co., one of the earliest associates of late Prof. E. Ochiai who enabled us to continue ^{18}O tracer works at Osaka City University. One of the authors, S.O., would also like to acknowledge warm friendship in exchanging ideas with late Professor

Vincent J. Traynelis and Professor Hodge Markgraf who really have contributed so much on this chemistry despite their inconvenience for research. He treasures warm-hearted inter-visitations with Professor Alan Katritzky, intimate discussions with Professor Tom Koenig and a brief but intimate discussion with Professor Ted Cohen. All through our investigations on " Rearrangements of tertiary Amine Oxides ", quite a few outstanding organic chemists participated earnestly. Those who really made major contributions are Professor Teijiro Kitao of Osaka Pref. University, Dr. Y. Kitaoka of Kyoto University, Dr. Seizi Kozuka, Seizo Tamagaki and Kenji Ogino of Osaka City University, Dr. Tetsuo Maeda of Yamanouchi Pharm. Co. and Dr. Tadamitsu Sakurai of Univ. Wisconsin, without whose devotions, this work would not have been materialized.

References

1) E.Ochiai, "Aromatic Amine Oxides", Elsevier Pub., Amsterdum (1967).

2) A.R.Katritzky and J.M.Lagouski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, London (1971).

3) R.A.Abramovitch and J.G.Saha in "Advanced in Heterocyclic Chemistry", edited by A.R.Katritzky and A.J.Boulton, Vol. 6, p. 229, Academic Press, New York (1966).

4) V.J.Traynelis, "Rearrangement of O-Acylated Heterocyclic N-Oxides" in "Mechanisms of Molecular Migrations", edited by B.S.Thyagarajan, Vol. 2, p. 1, Interscience Pub., New York (1969).

5) S.Oae and K.Ikura, Bull. Chem. Soc. Japan, 38, 59 (1965).

6) S.Oae and K.Ikura, Tetrahedron Lett., 1968, 3791.

7) S.Oae and K.Ikura, Bull. Chem. Soc. Japan, 59, 1306 (1966).

8) S.Oae and S.Tamagaki, "Kangen-Hanno" (Reduction Reactions), Maruzen, Tokyo (1975).

9) C.Rüchardt, S.Eichler and O.Kratz, Tetrahedron Lett., 1965, 2331.

10) T.Cohen, I.H.Song and J.H.Fager, ibid., 1965, 2371, T.Cohen and J.H.Fager, J. Am. Chem. Soc., 87, 5701 (1965).

11) T.Koenig, Tetrahedron Lett., 1965, 3127.

12) C.Rüchardt and O.Kratz, ibid., 1966, 5915.

13) T.Koenig, ibid., 1967, 2751.

14) T.Cohen and I.H.Song, J. Org. Chem., 31, 3058 (1966).

15) H.Sliwa and A.Tartar, ibid., 41, 160 (1976).

16) N.Kornblum, W.J.Jones, G.J.Anderson, J.W.Powers, H.O.Larson, O.Levard and W.M.Weaver, J. Am. Chem. Soc., 79, 6562 (1957); See also S.Oae, "Organic Chemistry of Sulfur", Chapter 8, Plenum, New York (1977).

17) A.R.Katritzky and E.Lunt, Tetrahedron, 25, 4291 (1969).

18) R.E.Manning and F.M.Schaefer, Tetrahedron Lett., 1975, 2131.

19) W.N.Marmer and D.Swern, ibid., 1969, 531, J. Am. Chem. Soc., 93, 2719 (1971).

20) B.Bobranski, L.Kochansko and A.Kowalewska, Chem. Ber., 71, 2385, (1938).

21) I.W.Elliott,Jr. and R.B.McGriff, J. Org. Chem., 22, 514 (1957).

22) E.Ochiai, ibid., 18, 549 (1953).

23) M.Henze, Chem. Ber., 69, 1566 (1936).

24) T.Okamoto and H.Tani, Chem. Pharm. Bull.(Tokyo), 7, 130, 925 (1959); F.Feely and E.M.Beavers, J. Am. Chem. Soc., 81, 4004 (1959).

25) For a review, see Mosettig, Org. Reactions, 8, 218-257 (1954).

26) M.Hamana, J. Heterocyclic Chem., 1, S-51 (1972).

27) M.Hamana and O.Hoshino, Yakugaku Zasshi, 84, 35 (1964).

28) L.Bauer and K.F.King, J. Org. Chem., 36, 1641, 3749 (1971); B.A.Mikrut, K.K.Khullar, P.Y.P.Chan, J.M.Kokosa, L.Bauer and R.S.Egan, J. Heterocyclic Chem., 2, 713 (1974).

29) M.Hamana and H.Noda, Chem. Pharm. Bull.(Tokyo), 11, 1331 (1963), 13, 912 (1965).

30) M.Hamana and M.Yamazaki, ibid., 11, 415 (1963).

31) R.A.Abramovitch, M.Saha, E.M.Smith and R.T.Coutts, J. Am. Chem. Soc., 89, 1537 (1967); R.A.Abramovitch, E.M.Smith, E.E.Knaus and M.Saha, J. Org. Chem., 37, 1690 (1972).

32) R.A.Abramovitch, E.M.Smith and R.T.Knaus, J. Org. Chem., 37, 3584 (1972).

33) R.A.Abramovitch, J.Campbell, E.E.Knaus and S.Silhankova,Jr., J. Heterocyclic Chem., 9, 1367 (1972).

34) See ref. 33).

35) R.A.Abramovitch and E.E.Knaus, J. Heterocyclic Chem., 6, 989 (1969).

36) R.A.Abramovitch and E.E.Knaus, ibid., 12, 683 (1975).

37) See ref. 36); R.A.Abramovitch and G.M.Singer, "Pyridine and its Derivatives: A Supplement", Part I, R.A.Abramovitch, Ed., Wiley-Interscience, New York, Chapter 1A, p. 1 (1974).

38) M.E.C.Biffin, J.Miller and D.B.Paul, Tetrahedron Lett., 1969, 1019.

39) V.J.Traynelis and K.Yamauchi, ibid., 1969, 3619.

40) E.E.Schweizer, G.J.O'Neil and J.N.Wample, J. Org. Chem., 29, 1749 (1964).

41) E.E.Schweizer and G.J.O'Neil, ibid., 28, 2460 (1963).

42) R.A.Abramovitch, C.S.Menon, M.Munter and E.M.Smith, J. Chem. Soc. Chem. Commun., 1974, 693.

43) C.W.Muth, R.S.Darlak and J.C.Patton, J. Heterocyclic Chem., 9, 1003 (1972).

44) C.W.Muth, J.C.Patton, B.Bhattacharya, D.L.Giberson and C.A.Ferguson, ibid., 9, 1299 (1972).

45) C.W.Muth and R.S.Darlak, J. Org. Chem., 30, 1909 (1965).

46) M.Katada, Yakugaku Zasshi, 67, 51 (1947).

47) E.Ochiai and T.Okamoto, Yakugaku Zasshi, 68, 88 (1948).

48) J.H.Markgraf, H.B.Brown,Jr.,S.C.Mohr and R.C.Peterson, J. Am. Chem. Soc., 85, 958 (1963).

49) S.Oae and S.Kozuka, Tetrahedron, 20, 2691 (1964).

50) S.Oae and S.Kozuka, ibid., 21, 1970 (1965).

51) J.H.Markgraf and M.Ahn, J. Am. Chem. Soc., 86, 2699 (1964).

52) J.H.Markgraf and C.G.Carson, J. Org. Chem., 29, 2806 (1964).

53) S.Oae, S.Kozuka, Y.Sakaguchi and K.Hiramatsu, Tetrahedron, 22, 3143 (1966).

54) J.H.Markgraf, M.K.Ahn, C.G.Carson,III and G.A.Lee, J. Org. Chem., 35, 3983 (1970).

55) T.Cohen and G.L.Deets, ibid., 37, 55 (1972).

56) M.Murakami and E.Matsumura, Nippon Kagaku Zasshi, 70, 393 (1949); 72, 509 (1951).

57) E.Ochiai, T.Watanabe and S.Suzuki, ibid., 76, 1421 (1956).

58) E.Ochiai and M.Ikehara, Chem. Pharm.Bull.(Tokyo), 3, 454 (1955).

59) S.Oae, T.Kitao and Y.Kitaoka, Tetrahedron, 19, 827 (1964).

60) S.Oae, K.Ogino, S.Tamagaki and S.Kozuka, ibid., 25, 5761 (1969).

61) M.Hamana and K.Funakoshi, Yakugaku Zasshi, 84, 28 (1964).

62) H.Tanida, Chem. Pharm. Bull.(Tokyo), 7, 887 (1959).

63) H.Tanida, Yakugaku Zasshi, 78, 611 (1958).

64) M.Hamana and M.Yamazaki, Chem. Pharm. Bull.(Tokyo), 11, 415 (1963).

65) K.Ogino, S.Kozuka and S.Oae, Tetrahedron Lett., 1969, 3359; K.Ogino and S.Oae, Tetrahedron, 27, 6037 (1971).

66) R.Huisgen, Angew. Chem., 75, 604 (1963).

67) R.A.Abramovitch and I.Shinkai, Accounts Chem. Res., 9, 192 (1976).

68) a. R.A.Abramovitch and R.B.Rogers, Tetrahedron Lett., 1971, 1951;
b. R.A.Abramovitch and G.M.Singer, J. Org. Chem., 39, 1795 (1974);
c. R.A.Abramovitch and R.B.Rogers, ibid., 39, 1802 (1974);
d. R.A.Abramovitch, R.B.Rogers and G.M.Singer, ibid., 40, 41 (1975).

69) W.E.Parham and K.B.Sloan, Tetrahedron Lett., 1971, 1947.

70) S.Takahashi and H.Kano, ibid., 1963, 1687.

71) R.Huisgen, H.Seidl and J.Wulff, Tetrahedron Lett., 1963, 2023; Chem. Ber., 102, 915 (1969).

72) R.A.Abramovitch, G.Grins, R.B.Rogers, J.L.Atwood, M.D.Williams and S.Crider, J. Org. Chem., 37, 3383 (1972).

73) R.A.Abramovitch and I.Shinkai, J. Am. Chem. Soc., 96, 5265 (1974).

74) a. E.Hayashi, Yakugaku Zasshi, 81, 1030 (1961).
b. E.Hayashi and E.Oishi, ibid., 86, 576 (1966);
c. B.A.J.Clark and J.Pavick, J. Chem. Soc. Perkin I, 1974, 2270.

75) T.Onaka, Itsuu Kenkyusho Nempo, No. 15, 29 (1968); Chem. Abstr., 72, 90231q (1969).

76) T.Hisano, S.Yoshikawa and K.Muraoka, Org. Prep. Proced. Int., 5, 95 (1973); Chem. Pharm. Bull.(Tokyo), 22, 1611 (1974).

77) M.Hamana and K.Muraoka, Heterocycles, 1, 241 (1973).

78) a. E.A.Mailey and L.R.Ocone, J. Org. Chem., 33, 3343 (1968);
b. R.E.Banks, R.N.Haszeldine and J.M.Robinson, J.C.S. Perkin I, 1226 (1976).

79) M.Natsume, S.Kumadaki and R.Tanabe, Itsuu Kenkyusho Nempo, No. 16, 25 (1971); Chem. Abstr., 77, 61765g (1972).

80) R.A.Abramovitch, S.Kato and G.M.Singer, J. Am. Chem. Soc., 93, 3074 (1971).

81) P.Haake and J.Manteon, ibid., 86, 5230 (1964).

82) a. V.Boekeiheide and W.L.Lin, J. Org. Chem., 26, 428 (1961);
b. M.Hamana and M.Yamazaki, Yakugaku Zasshi, 81, 574 (1961).

83) Y.Murakami and J.Sunamoto, Bull. Chem. Soc. Japan, 42, 335 (1969).

84) G.Kobayashi and S.Furukawa, Chem. Pharm. Bull.(Tokyo), 1, 347 (1953).

85) V.Boekelheide and W.J.Lin, J. Am. Chem. Soc., 76, 1286 (1954).

86) a. C.W.Muth, R.S.Darlak, W.H.English and A.T.Hamner, Analytical Chem., 34, 1163 (1962);

b. C.W.Muth and R.S.Darlak, J. Org. Chem., 30, 1909 (1965);

87) a. V.J.Traynelis and P.L.Pacini, J. Am. Chem. Soc., 86, 4917 (1964).

b. V.J.Traynelis, A.I.Gallagher and R.F.Martellow, J. Org. Chem., 26, 4365 (1961).

88) S.Oae, S.Tamagaki and S.Kozuka, Tetrahedron Lett., 1966, 1513.

89) D.J.Cram and L.Gosser, J. Am. Chem. Soc., 86, 2950 (1964).

90) V.J.Traynelis and P.L.Pacini, ibid., 86, 4917 (1964).

91) S.Oae, S.Tamagaki, T.Negoro and S.Kozuka, Tetrahedron, 26, 4051 (1970).

92) C.W.Muth,R.S.Darlak and G.F.Chovanec, J. Org. Chem., 33, 2762 (1968).

93) S.Tamagaki, K.Ogino, S.Kozuka and S.Oae, Tetrahedron, 26, 4675 (1970).

94) B.Wepster, Rec. Trav. Chim., 71, 1159, 1171 (1952).

95) V.J.Traynelis and J.P.Kimball, J. Org. Chem., 40, 2365 (1975).

96) V.Boekelheide and D.L.Harrington, Chem. & Ind.(London), 1955, 1423.

97) T.J.Pachter, J. Am. Chem. Soc., 75, 3026 (1953).

98) S.Oae, T.Kitao and Y.Kitaoka, ibid., 84, 3359 (1962).

99) V.J.Traynelis and A.I.Gallagher, ibid., 87, 5710 (1965).

100) S.Oae, Y.Kitaoka and T.Kitao, Tetrahedron, 20, 2685 (1964).

101) S.Kozuka, S.Tamagaki, T.Negoro and S.Oae, Tetrahedron Lett., 1968, 923.

102) H.Iwamura, M.Iwamura, T.Nishida and S.Sato, J. Am. Chem. Soc., 92, 7476 (1970).

103) S.Oae and K.Fujimori, Tetrahedron, 28, 5327 (1972); 29, 65 (1973); U.S.-Japan Seminar on Organic Peroxide, Boulder, Colorado, Aug. 1976.

104) T.Cohen and G.L.Deets, J. Am. Chem. Soc., 89, 3939 (1967).

105) R.Bodalski and A.R.Katritzky, Tetrahedron Lett., 1968, 257.

106) V.J.Traynelis, K.Yamauchi and J.P.Kimball, J. Am. Chem. Soc., 96, 7476 (1974).

106a) J.H.Markgraf, S.R.Berryhill, L.R.Groden, W.M.Hensley, G.G.Spence and W.J.McMurray, J. Org. Chem., 40, 417 (1975).

107) a. E.Matsumura, Nippon Kagaku Zasshi, 76, 363 (1953);
b. T.Kato, Yakugaku Zasshi, 75, 1239 (1955);
c. J.F.Vozza, J. Org. Chem., 27, 3856 (1962).

108) T.Koenig and J.S.Wieczocek, J. Org. Chem., 33, 1530 (1968).

109) a. W.E.Parham, R.W.Davenport and J.B.Biasotti, ibid., 35, 3775 (1970);
b. W.E.Parham, K.B.Sloan, K.R.Reddy and P.E.Olsen, ibid., 38, 927 (1973).

110) F.J.Dinan and H.Tieckelmann, J. Org. Chem., 29, 1650 (1964).

111) B.S.Thyagarajan, Advanced Heterocyclic Chem., 8, 143 (1961).

112) J.E.Litster and H.Tieckelmann, J. Am. Chem. Soc., 90, 4361 (1968).

113) L.A.Paquette and T.R.Phillips, J. Org. Chem., 30, 3883 (1965).

114) L.A.Paquette, J. Am. Chem. Soc., 87, 1407, 5186 (1965).

115) G.G.Spence, E.C.Taylor and O.Buchardt, Chem. Revs.,70, 231 (1970).

116) C.Kaneko, Kagaku-no-Ryoiki, Spec. Ed., 93, 235 (1970).

117) N.Hata, Bull. Chem. Soc. Japan, 34,1440, 1444 (1961).

118) N.Hata and I.Tanaka, J. Chem. Phys., 36, 2072 (1962).

119) a. J.Strieth, B.Danner and C.Sigwalt, J.C.S. Chem. Commun., 1967, 979.

b. H.Igeta, T.Tsuchida, M.Yamada and H.Arai, Chem. Pharm. Bull. (Tokyo), 16, 767 (1968).

120) J.Strieth and C.Sigwalt, Tetrahedron Lett., 1966, 1347.

121) J.Strieth and C.Sigwalt, Bull. Soc. Chim. France, 1157 (1970).

122) S.Yamada and C. Kaneko, Chem. Abstr., 73, 98765h (1970).

123) E.Ager, G-E.Chivers and H.Suschitzky, J.C.S. Chem. Commun., 1972, 505.

124) O.Buchardt, L.Lóbse, A.M.Dufield and C.Djerassi, Tetrahedron Lett., 1967, 274.

125) C.Kaneko, S.Yamada, I.Yokoe and M.Ishikawa, ibid., 1967, 1873.

126) P.L.Kumler and O.Buchardt, J.C.S. Chem. Commun., 1968, 1321.

127) J.D.Mee, D.W.Heseltine and E.C.Taylor, J. Am. Chem. Soc., 92, 5814 (1970).

128) R.A.W.Johnstone, in "Mechanisms of Molecular Migrations", Ed. by B.S.Thyagarajan, Vol. 2, p. 249, Interscience Pub., New York (1969).

129) V.Schöllkoph and H.Schäfer, Ann. Chem., 683, 42 (1965).

130) V.Schöllkoph, V.Ludwig, M.Patsch and W.Franken, ibid., 703, 77 (1967).

131) A.H.Wragg, T.S.Stevens and D.M.Ostle, J. Chem. Soc., 1958, 4057.

132) See ref. 130) and also 128).

133) T.Thomson and T.S.Stevens, J. Chem. Soc., 1952, 69.

134) D.J.Cram, M.R.V.Sahyun and G.R.Knox, J. Am. Chem. Soc., 84, 1734 (1962).

135) G.A.Russell and G.J.Mikol, in "Mechanisms of Molecular Migrations", Ed. by B.S.Thyagarajan, Vol. 1, p. 157, Interscience Pub., New York (1968).

136) A.C.Cope, E.Ciganek and J.Lazar, J. Am. Chem. Soc., 84, 2591 (1962).

137) S.Oae, T.Kitao and Y.Kitaoka, J. Am. Chem. Soc., 84, 3366 (1962).

138) R.Huisgen, F.Bayerlein and W.Heydkarp, Chem. Ber., 92, 3223 (1959).

139) H.Iwamura, M.Iwamura, T.Nishida and I.Miura, Bull. Chem. Soc. Japan, 43, 1914 (1970).

140) S.Oae, N.Asai and K.Fujimori, unpublished data.

141) M.Lamchen, in "Mechanisms of Molecular Migrations", ed. by B.S.Thyagarajan, Vol. I, p.1, Interscience Pub., New York (1968).

142) L.S.Kominsky and M.Lamchen, J. Chem. Soc.(C), 1966, 2300.

143) F.Kroehnke, Ann. Chem., 604, 203 (1957).

144) B.Umesawa, Chem. Pharm. Bull.(Tokyo), 8, 698, 967 (1960).

145) S.Tamagaki, S.Kozuka and S.Oae, Tetrahedron, 26, 1795 (1970).

146) S.Tamagaki and S.Oae, Bull. Chem. Soc. Japan, 44, 2851 (1971).

147) W.E.Truce, J.R.Norell, R.W.Campbell, D.G.Brady and J.W.Frieldhouse, Chem. & Ind.(London), 1965, 1870.

148) F.L.Honer and H.Steppan, Ann. Chem., 606, 47 (1957).

149) H.Sato, T.Kusumi, K.Imaye and H.Kakizawa, Chem. Lett., 1975, 965.

149a) A.T.Nielsen, in "The Chemistry of Nitro and Nitroso Groups", ed. by H.Feuer, Part 1, p. 417, Interscience Pub., New York (1969).

150) R.Huisgen, Angew. Chem. Int'l. Ed., 2, 565 (1963).

151) a. E.Buncel in "Mechanisms of Molecular Migrations", ed. by B.S.Thyagarajan, Vol. I, p. 61, Interscience Pub., New York (1968);

b. H.J.Shine, in "Aromatic Rearrangements", p. 272, Elsevier, New York (1967).

c. D.L.H.Williams, in "Comprehensive Chemical Kinetics", ed. by C.H.Bamford and C.F.H.Tippes, Vol. 13, p. 465, Elsevier, Amsterdum (1972).

d. R.A.Cox and E.Buncel in "The Chemistry of the Hydrazo, Azo and Azoxy Groups", ed. by S.Patai, Part 2, p. 808, John Wiley & Sons, London (1975).

152) M.M.Shemyakin, V.I.Maimind and B.K.Vaichunaite, Zh. Obshch. Khim., 28, 1708 (1958); Chem. Abstr., 53, 1201 (1959); M.M.Shemyakin, V.I.Maimind and B.K.Vaichunaite, Chem. & Ind. (London), 1958, 755.

153) S.Oae, T.Fukumoto and M.Yamagami, Bull. Chem. Soc. Japan, 36, 601 (1963); 36, 728 (1963).

154) P.H.Core, Chem. & Ind.(London), 1959, 191.

155) a. E.Buncel and W.M.J.Strachan, Can. J. Chem., 48, 377 (1970);

b. E.Buncel and B.T.Lawton, ibid., 43, 862 (1965).

156) S.Oae, T.Maeda, S.Kozuka and M.Nakai, Bull. Chem. Soc. Japan, 44, 2495 (1971).

157) S.Oae, T.Maeda and S.Kozuka, ibid., 44, 442 (1971).

158) S.Oae and T.Maeda, Tetrahedron, 28, 2127 (1972).

159) G.T.Tisue, M.Gassmann and W.Lwowski, ibid., 29, 999 (1968).

160) D.Gutschke and A.Heesing, Chem. Ber., 106, 2379 (1973).

161) a. S.Oae, T.Sakurai, H.Kimura and S.Kozuka, Chem. Lett., 1974, 671.

b. S.Oae and T.Sakurai, Tetrahedron, 32, 2289 (1976).

162) A.R.Cox and M.F.Dunn, Abstracts, 152nd Meeting of the A.C.S., Abstr. 162, New York (1966).

163) D.B.Denney and D.Z.Denney, J. Am. Chem. Soc., 82, 1389 (1960).

164) P.G.Gassman and G.A.Campbell, J.C.S. Chem. Commun., 1971, 1437.

165) N.J.Leonard and K.Golankiewiz, J. Org. Chem., 34, 359 (1969).

Received, 3rd February, 1977