SOLVENT EFFECTS ON THE PHOTOCHEMISTRY OF PYRIDINECARBOXYLIC ACID N-OXIDES AND THEIR ESTERS

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE GRADUATE SCHOOL OF THE

TEXAS WOMAN'S UNIVERSITY

COLLEGE OF NATURAL AND SOCIAL SCIENCES

BY

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MAY, 1979

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April 23 19 79

We hereby recommend that the dissertation prepared under our supervision by Jo-Anne Blair Campbell entitled "Solvent Effects on the Photochemistry of Pyridinecarboxylic Acid N-oxides and their Esters."

be accepted as fulfilling this part of the requirements for the Degree of Doctor of Philosophy.

Committee:

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ACKNOWLEDGMENTS

I would like to express my appreciation to Professor Lyman R. Caswell for his patient direction of this research. His support, encouragement and guidance made completion of this investigation possible.

I would like to thank the members of my committee, Drs. L. R. Caswell, N. G. Foster, J. E. Johnson, W. L. Mecay and C. T. Wendel. Their many suggestions furthered the completion of this work. Their availability for discussions on numerous occasions was extremely helpful.

A special note of thanks for Dr. G. H. Stewart is in order. His invaluable recommendations and assistance with the High Pressure Liquid Chromatographic separations is deeply appreciated.

Valuable financial support provided by The Robert A. Welch Foundation and the Texas Woman's University is gratefully acknowledged.

A special thank-you to my husband, Charles F. Campbell, for his personal support through out the course of this study.

DEDICATION

Dedicated to the memory of my father, Donald D. Blair

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CHAPTER I

INTRODUCTION

In general, the photolysis of a pyridine N-oxide in a nonparticipating solvent will give any or all of the following types of reactions: (a) deoxygenation of the N-oxide to give the parent pyridine base; (b) migration of the oxygen atom either to the 2-position (forming a derivative of 2-1H-pyridone) or the 3-position (forming a derivative of 3-pyridinol) or (c) contraction of the ring to form a 2-acylpyrrole (1,2).

Nonparticipating solvents for these photolyses are saturated aliphatic hydrocarbons and ethers. Benzene and other arenes in some cases are nonparticipating (3). In most cases, they are oxidized to phenols (1). Primary alcohols have been reported (4) to undergo oxidation to aldehydes when they are used as solvents for the photolysis of pyridine 1-oxide.

A study (5,6) of the photolyses of N-oxides of pyridinecarboxylic acids and pyridinecarboxamides provides evidence that the course of the reaction may be influenced by hydrogen-bonding effects. Such effects may result from interaction with hydroxylic solvents, or in the case of the N-oxides of 2-pyridinecarboxylic acid and 2-pyridine-

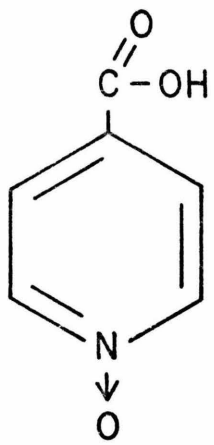
carboxamide, by intramolecular hydrogen bonding. Evidence provided by melting points (5), infrared spectra (6,7), and mass spectra (8) clearly show intramolecular hydrogen-bonding in 2-pyridinecarboxylic acid 1-oxide and 2-pyridinecarboxamide 1-oxide.

Influence of intramolecular hydrogen-bonding on the vapor phase photolysis of 2-methylpyridine 1-oxide has been suggested (9). The quantum yield of 2-methylpyridine in the irradiation of 2-methylpyridine 1-oxide at 2537 Å is temperature dependent. This indicates the existence of an energy of activation for the photolytic deoxygenation of 2-methylpyridine 1-oxide. In the irradiation of pyridine 1-oxide (10) and 3-methylpyridine 1-oxide (11) at 2537 Å, the quantum yields of the respective products (pyridine and 3-methylpyridine) are temperature independent. When pyridine 1-oxide (10) and 3-methylpyridine 1-oxide (11) are irradiated at 3261 Å, the parent base is obtained; but the irradiation of 2-methylpyridine 1-oxide (9) at this wavelength produces 2-pyridinemethanol.

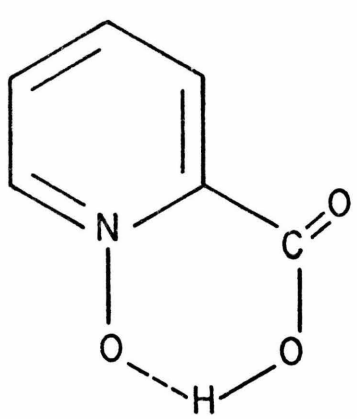
The evidence for hydrogen-bonding effects on the photolyses of N-oxides of pyridinecarboxylic acids is insufficient to be fully convincing, or to define the extent of hydrogen-bonding influences. The purpose of this investigation is clarification of the influence of hydrogen-bonding on the photochemistry of pyridinecarboxylic acid

N-oxides by a quantitative examination of solvent effects on the photochemistry of pyridinecarboxylic acid N-oxides, with special attention to the deoxygenation process.

4-Pyridinecarboxylic acid 1-oxide and 2-pyridinecarboxylic acid 1-oxide (Figure 1) were chosen for this investigation since photolysis reaction times are much shorter with these compounds than with 3-pyridinecarboxylic acid 1-oxide (6). The solvents used in this investigation include: (a) water, ethanol, and 2-propanol, which are hydrogen-bond donors; (b) 2-methyl-2-propanol, a hydroxylic solvent which does not as readily form hydrogen bonds; (c) dioxane, which is a strong hydrogen-bond acceptor; and (d) acetonitrile, a polar aprotic solvent.



4-Pyridinecarboxylic Acid N-Oxide
(Isonicotinic Acid N-Oxide)



2-Pyridinecarboxylic Acid N-Oxide
(Picolinic Acid N-Oxide)

Figure 1

CHAPTER II

HISTORICAL

The photochemistry of aromatic amine N-oxides has been extensively reviewed by Bellamy and Streith in 1976 (12) and by Spence, Taylor, and Buchardt in 1970 (1).

The excited states leading to photochemical reactions in aromatic amine N-oxides apparently result from $\pi \rightarrow \pi^*$ transitions. The long wavelength absorption of these compounds had been classified as $n \rightarrow \pi^*$ on the basis of the blue shift of this band when the polarity of the solvent is increased (13). It is now apparent that the $\pi \rightarrow \pi^*$ transitions of aromatic N-oxides are also blue shifted with increasing solvent polarity. Thus, it is not possible to distinguish between the $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of aromatic N-oxides on the basis of blue shifts observed in protic solvents (14).

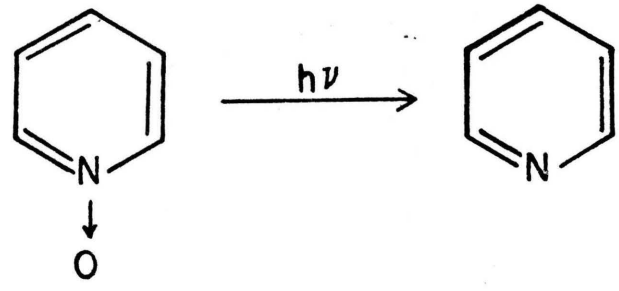
A semi-empirical study (CNDO-CI method) of the ground state and excited state properties of pyridine N-oxide indicated that the lowest energy transition, observed at 3.81 eV (325 nm) is a $\pi \rightarrow \pi^*$ transition (15). The probability of finding an $n \rightarrow \pi^*$ transition at about 3 eV (416 nm) is very small. Indeed, such a transition is not experimentally observed. The observed solvent effects upon the spectrum

of pyridine N-oxide can be explained by the overall dipole moments for the first excited singlet states. A decrease of the total dipole moment of the excited states induces a blue shift of the type observed. In the two $\pi \rightarrow \pi^*$ states of lower energy the dipole moment is strongly reduced. Calculations for the lowest triplet states indicate that they too arise from $\pi \rightarrow \pi^*$ transitions. These calculations are in agreement with the experimentally observed absorption spectra of pyridine N-oxide determined by the technique of high-pressure oxygen perturbation (16). The effect of electron-donating substituents on the electronic spectrum of pyridine N-oxide also indicates that the bands at 325 and 280 nm are due to $\pi \rightarrow \pi^*$ transitions. Substitution on pyridine N-oxide by electron-donating substituents, in the 3- and 4-positions, leads to a red shift of the 325 and 280 nm absorption bands; rather than the blue shift expected for spectral bands arising from $n \rightarrow \pi^*$ transitions (14).

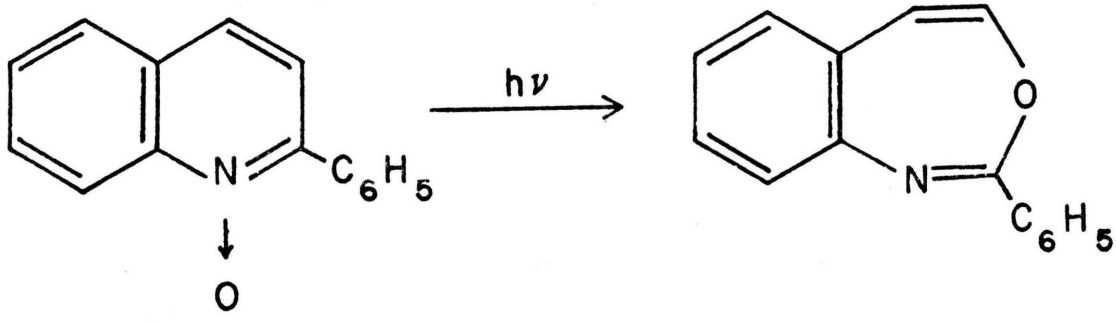
Structure and distribution of the products resulting from the photochemical treatment of aromatic N-oxides are dependent on irradiation conditions. In order to simplify the picture presented by the wide variety of products observed in the irradiation of various aromatic amine N-oxides, Spence, Taylor, and Buchardt (1) distinguished between primary photoproducts and secondary thermal products.

The primary photoproducts include:

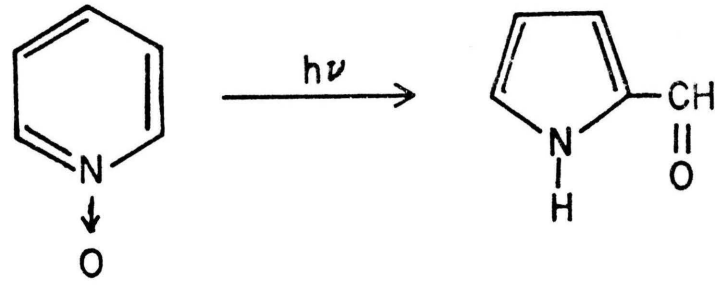
(a) parent bases by deoxygenation,



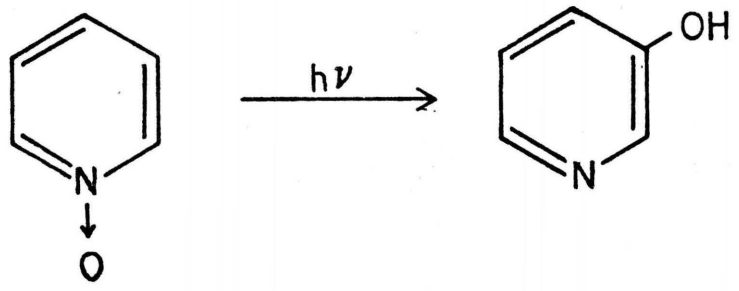
(b) 7-membered rings by ring expansion,



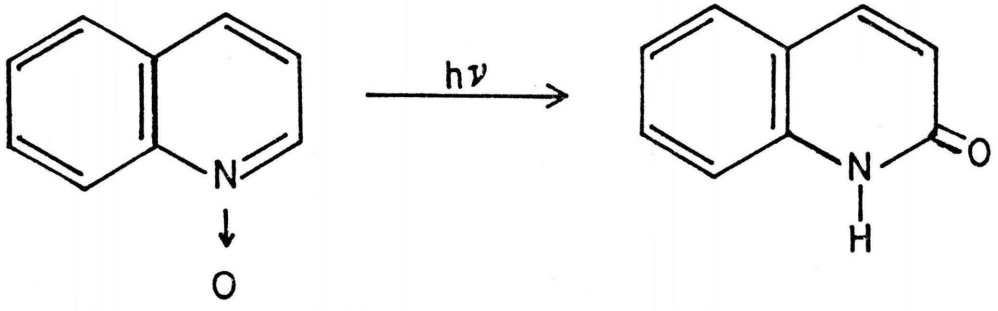
(c) 5-membered rings by ring contraction



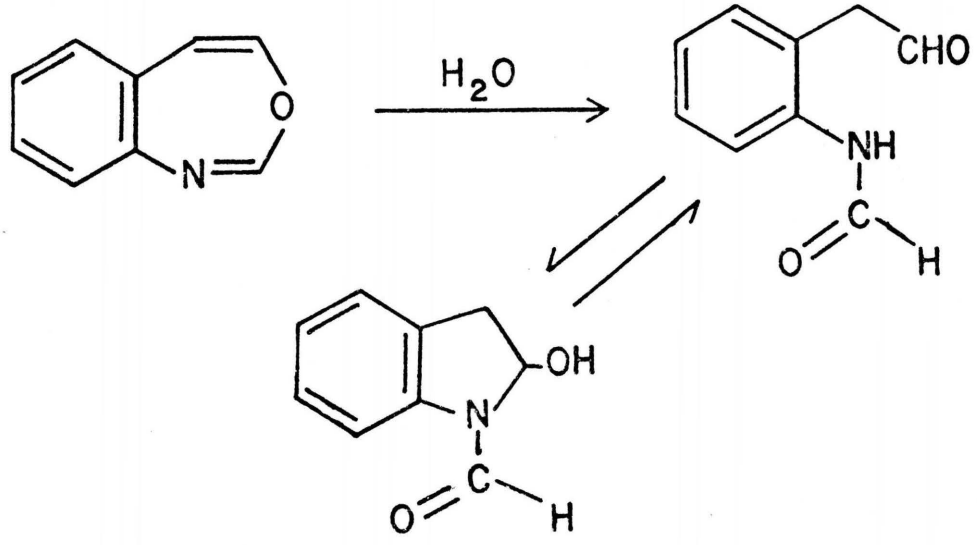
(d) 3-hydroxy derivatives by oxygen migration,



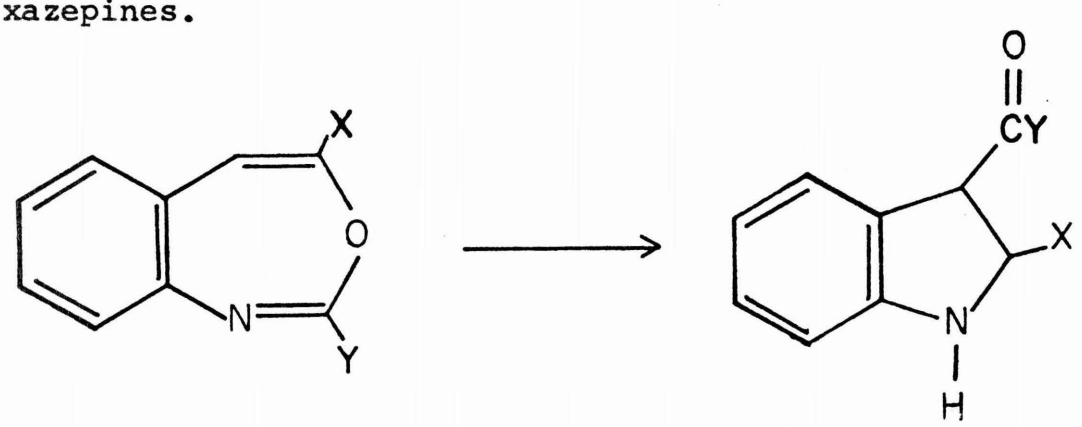
(e) and lactams by oxygen migration.



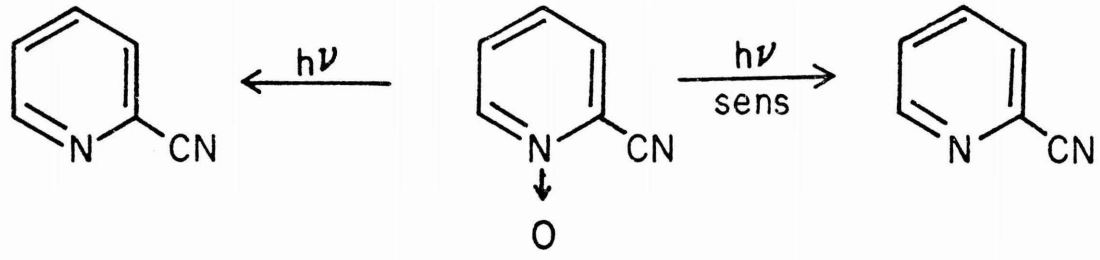
The secondary thermal products arise from 7-membered ring compounds. These are hydrolysis products, which sometimes undergo further reactions:



and products from the ring contraction of benz [d] [1,3]-oxazepines.



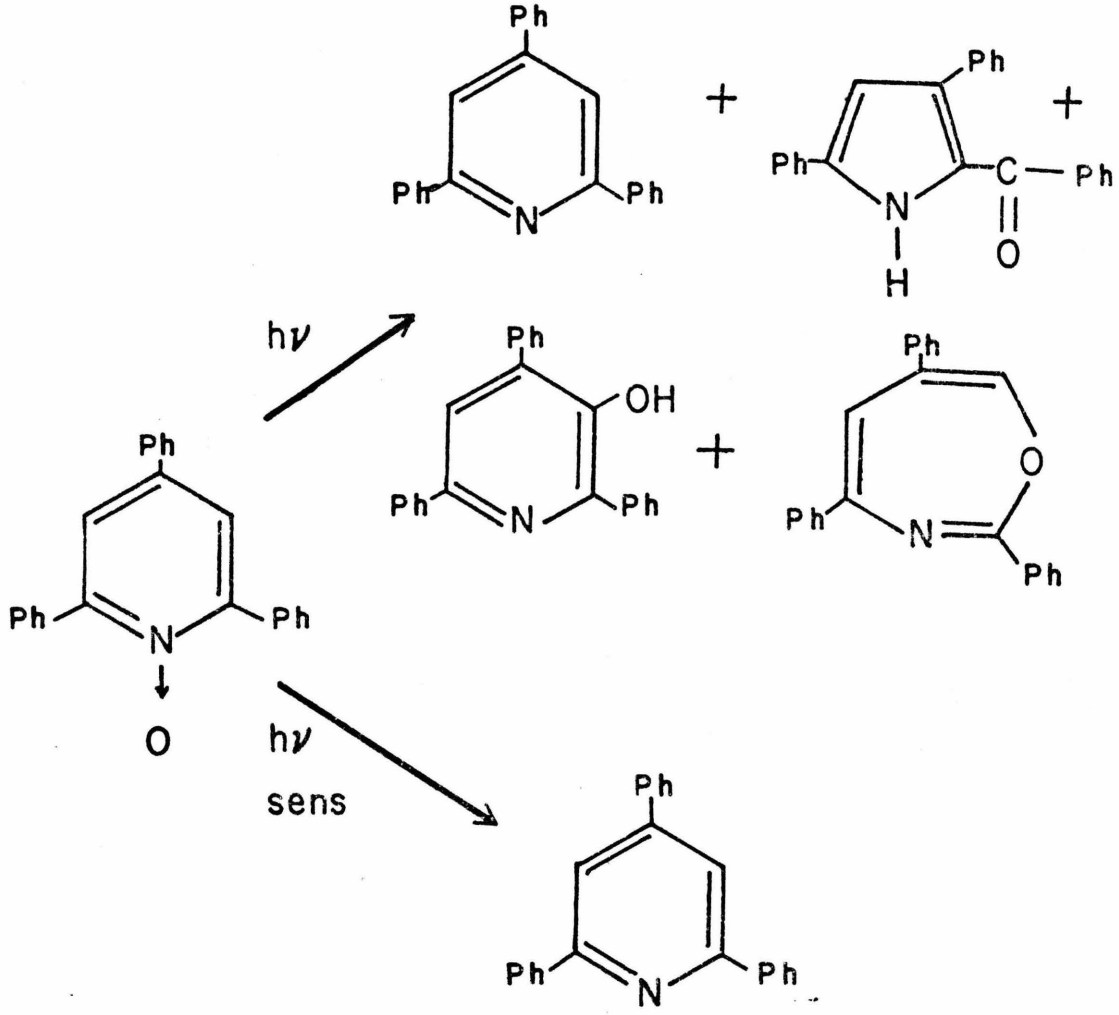
Although deoxygenation to the parent base takes place in most cases, it is much more extensive with pyridine N-oxides than with other aromatic amine N-oxides. It has been demonstrated in a few cases that deoxygenation seems to occur from excited triplet states. Irradiation of 2-cyanopyridine N-oxide results in the formation of the parent base, 2-cyanopyridine. The yield of 2-cyanopyridine is increased by the addition of a triplet sensitizer (17).



47·3%

57·6-71·7%

The major product from the irradiation of 2,4,6-triphenylpyridine N-oxide is 2-benzoyl-3,5-diphenylpyrrole, with minor amounts of the parent base and other products. Addition of benzophenone as a sensitizer results in a dramatic increase in the yield of the parent base, 2,4,6-triphenylpyridine. The other products are not observed in the sensitized reaction (18).



It has been established that the triplet state is responsible for deoxygenation of quinoline N-oxides, isoquinoline N-oxides (19), pyridazine N-oxides, and phthalazine N-oxides (12).

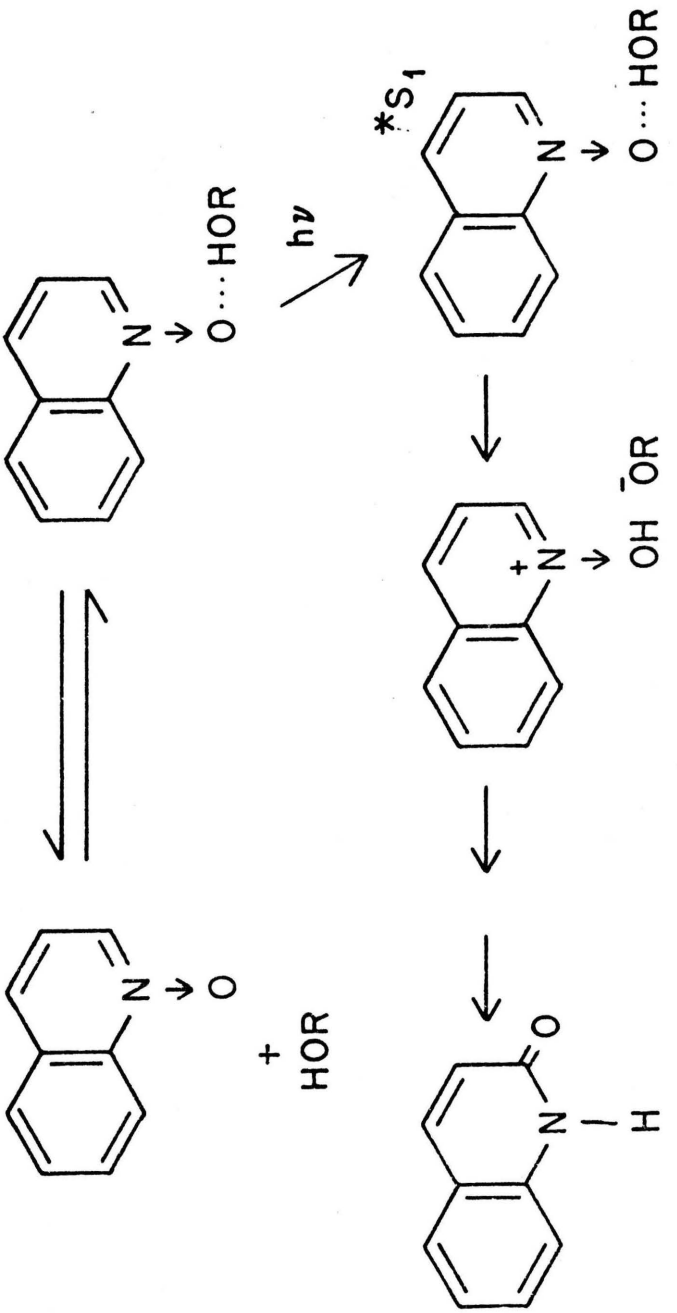
In some cases the yield of parent base depends on the wavelength of the incident light, the nature of the solvent, and the pH of the reaction medium. The quantum yield of pyridine formed in the irradiation of gaseous pyridine N-oxide is wavelength dependent. Furthermore, the quantum yield of pyridine is temperature dependent when pyridine N-oxide is irradiated at 326 nm (87.3 kcal/mole), whereas at 254 nm (117 kcal/mole) the quantum yield of pyridine is temperature independent. These results are in good agreement with the N-O bond energy which has been estimated at 110 kcal/mole from infrared studies and dipole moment considerations (10). Analogous behavior has been observed with 3-methylpyridine N-oxide (11). Irradiation of 2-methylpyridine N-oxide at 254 nm results in the formation of 2-methylpyridine, while irradiation at 326 nm results in the formation of 2-pyridinemethanol. The quantum yield of both products is temperature dependent (9). Irradiation of benzene solutions of 2,3,5,6-tetraphenylpyridine N-oxide leads to the deoxygenated product (11% at 350 nm; 25% at 254 nm). The yield of parent base generally decreases with

increasing solvent polarity. All other conditions being equal, the photochemistry of pyridine N-oxide leads to 30% pyridine in ether and to 2% pyridine in water. Similar effects are observed with other aromatic amine N-oxides. Acidity of the reaction medium also plays a role; as demonstrated in the case of pyridine N-oxide, where lowering the pH increases the yield of pyridine (12). A similar pH effect has been observed for some azanaphthalene N-oxides (19).

The photochemical isomerization and rearrangement processes, observed for most aromatic amine N-oxides, are apparently derived from excited singlet states. Oxaziridines are generally postulated as the first intermediates formed in photorearrangement processes of aromatic amine N-oxides, although they have never been detected by any physical means. Semi-empirical quantum mechanical calculations indicate that although the formation of the isomeric oxaziridine is highly improbable from the ground state, it is very likely from the first excited singlet state of the N-oxide (20). Other evidence, which would seem to support the formation of oxaziridine intermediates, is the analogy between the chemical behavior of some aromatic N-oxides upon irradiation and the reactivity of aliphatic oxaziridines (12). However, studies with some azanaphthalene N-oxides indicate that lactams are not formed from an oxaziridine intermediate.

Quinoline N-oxides and isoquinoline N-oxides undergo two types of photorearrangement. In polar hydroxylic solvents the photoproducts are lactams, and in nonpolar solvents 1,3-benzoxazepines are formed. Flash photolysis studies and quantum yield measurements of isoquinoline N-oxide indicate that the excited singlet state is the last species common to lactams and oxazepines. Furthermore, oxaziridines are not intermediate in the formation of the lactam (21). This conclusion is supported by studies in which quinoline N-oxides and isoquinoline N-oxides were irradiated in the presence of iodide, which is oxidized by oxaziridines (leading to the liberation of iodine and formation of the parent base of the N-oxide). Under conditions which normally lead to oxazepines, iodine was formed in quantity and no oxazepine was detected, indicating that oxazepines are formed through a powerful oxidant (probably oxaziridine). On the other hand, iodide has no effect on the course of photorearrangement under conditions which normally lead to lactam formation. This process apparently proceeds via photoexcitation of a hydrogen-bonded N-oxide. The excitation of the hydrogen-bonded N-oxide may lead to a rapid protonation of the N-O group to give an excited ion-pair through which the lactam is formed (Scheme I) (22,23).

SCHEME I



The proposed mechanisms for the formation of the various photoisomerization products are well described by Spence, Taylor, and Buchardt (1). The photorearrangement products from aromatic amine N-oxides have been tabulated by Bellamy and Streith (12).

CHAPTER III

EXPERIMENTAL

A. Preparation and Purification of Compounds

1. Isonicotinic acid N-oxide

Isonicotinic acid N-oxide was generously contributed by the Reilly Tar and Chemical Company. It was recrystallized from water. The melting point of the recrystallized material was 267-269°, in agreement with the reported value (6).

2. Isonicotinic acid

Isonicotinic acid (Aldrich Chemical Company, Inc.) was recrystallized from water. The melting point was 318-319°; the reported value is 319°.

3. Methyl isonicotinate

Commercial methyl isonicotinate (Aldrich Chemical Company, Inc.) was used following distillation under vacuum.

4. Methyl isonicotinate N-oxide

Methyl isonicotinate N-oxide was synthesized by Ochiai's (25) general method for the preparation of aromatic amine N-oxides. A solution of 35 g (0.27 m) methyl isonicotinate in 300 ml glacial acetic acid was prepared.

Thirty percent aqueous hydrogen peroxide (50 ml) was added to the solution. The mixture was heated in a water bath at 70-80° for four hours, after which more hydrogen peroxide solution (35 ml) was added. The water bath was maintained at 70-80° for an additional nine hours. The mixture was allowed to stand overnight. The mixture was then concentrated to about 100 ml under vacuum, diluted with 100 ml water, then concentrated as far as possible under vacuum. The residue was strongly alkalized with anhydrous sodium carbonate. The resulting white suspension was shaken with approximately 250 ml chloroform and allowed to stand overnight. The resulting sodium acetate and sodium carbonate were collected on a filter. The filtrate was dried for 24 hours over anhydrous sodium sulfate. The solvent was removed in a rotary evaporator. The crystalline product was recrystallized from toluene. The melting point was 119-121°; the reported value is 121-121.5° (26). The yield was 35 g (89% of theoretical).

5. Picolinic acid N-oxide

Picolinic acid N-oxide (Aldrich Chemical Company, Inc.) was recrystallized from water. The melting point was 155-156°, in agreement with the literature (6).

6. Picolinic acid

Picolinic acid (Sigma Chemical Company) was recrystallized from water. The melting point was 136-137°, in agreement with the reported value (23).

7. Solvents

Photochemical reactions were performed in distilled water (uv cut-off: 190 nm), distilled 95% ethanol (uv cut-off: 200 nm), 2-propanol, 2-methyl-2-propanol, dioxane and acetonitrile. Spectrophotometric grade 2-propanol (uv cut-off: 203 nm) and "Certified" 2-methyl-2-propanol (uv cut-off: 210 nm) were purchased from Fisher Scientific Company. Spectrophotometric grade dioxane (uv cut-off: 210 nm) was purchased from Aldrich Chemical Company. Acetonitrile (uv cut-off: 200 nm) was purchased from Burdick and Jackson Company. The uv cut-offs were measured in this laboratory. 2-Propanol, 2-methyl-2-propanol, dioxane and acetonitrile were stored over type 4A molecular sieves.

Methylene chloride and methanol for high-pressure liquid chromatographic analysis were purchased from Burdick and Jackson Company. All solvents were used without further purification.

B. Photochemical Studies

The photochemical reactions were conducted in a Rayonet "Merry-go-round" reactor equipped with sixteen

75 watt mercury vapor lamps. The reactor has a capacity of eight sample tubes which fit in a rotating disk positioned in the center of the reactor. The sample tubes are 15 x 150 mm Pyrex test tubes.

1. Irradiation of isonicotinic acid N-oxide and isonicotinic acid

Solutions of isonicotinic acid N-oxide and of isonicotinic acid in distilled water, 95% ethanol, 2-propanol, 2-methyl-2-propanol, dioxane and acetonitrile were prepared for irradiation. The concentrations of the solutions were such that the ultraviolet absorbance was at least 2.0 at 300 nm, but varied according to the solubilities of isonicotinic acid N-oxide and isonicotinic acid in various solvents.

The results from the analyses of the irradiated solutions of isonicotinic acid N-oxide are listed in Table 2.

a. Water

A 1.5×10^{-2} M solution of isonicotinic acid N-oxide in water was de-aerated by boiling for approximately 15 minutes and cooling to room temperature under nitrogen flow. Portions of the cooled solution were placed in each of five Pyrex test tubes. They were irradiated for eight hours. Three tubes containing 2.3×10^{-3} M isonicotinic acid solutions prepared in the same manner were irradiated simultaneously. Following photolysis, the solutions were

kept in sealed test tubes, in the dark until they were analyzed.

The solutions were individually analyzed by high pressure liquid chromatography (HPLC). A μ Porasil column (Waters Associates Part #27477) was used with 95:10:0.3:0.1 methylene chloride:methanol:water:acetic acid at a flow rate of 1 ml/min. Peaks for isonicotinic acid N-oxide (k' = 3.6), isonicotinic acid (k' = 2.4), and three unidentified components (k' = 1.1, 1.4, 1.6) were detected in the analysis of the irradiated isonicotinic acid N-oxide solutions. A sample of the de-aerated solution of isonicotinic acid N-oxide, which had not been irradiated was also analyzed by HPLC to insure that none of the deoxygenation resulted from the de-aeration process. The HPLC chromatogram of the de-aerated solution indicated the presence of isonicotinic acid N-oxide only. No change occurred in the chromatograms of isonicotinic acid upon irradiation under the described conditions.

Isonicotinic acid and isonicotinic acid N-oxide (identified by melting points, infrared spectra and mass spectra) were isolated from irradiated solutions of isonicotinic acid N-oxide in water, in the following manner. The irradiated solutions of isonicotinic acid N-oxide were combined and the volume reduced by half under reduced pressure. A white precipitate was collected by suction

filtration and recrystallized first from 95% ethanol, then from acetone. This substance was identified by its infrared and mass spectra as isonicotinic acid N-oxide. IR: (KBr) 3450 cm^{-1} (O-H), 3110 cm^{-1} (aromatic C-H), 1710 cm^{-1} (acid C=O), 1600, 1470, 1431 cm^{-1} (ring vibrations for 6-membered heterocyclic aromatic rings (26)), 1280 cm^{-1} (aromatic N-oxides N-O), 1184, 1150 cm^{-1} (C-O-H acid), 846 cm^{-1} (out-of-plane mode for 6-membered heterocyclic aromatic rings with H at 2,3,5,6 (26)). Mass spectrum: 139 (M^+), 123, 122, 121, 108, 80, 53, 46, 42 (base peak). The filtrate was evaporated to dryness. The residue was a dark brown powder, a portion of which was acetone soluble. The acetone-soluble portion was identified as isonicotinic acid after several recrystallizations from acetone and ethyl acetate. IR: (KBr) 3420 cm^{-1} (O-H), 1709 cm^{-1} (acid C=O), 1609, 1404 cm^{-1} (ring vibrations for 6-membered heterocyclic aromatic rings (26)). Mass spectrum: m/e 123 (M^+), 107, 76, 46, and 42 (base peak). The acetone-insoluble portion did not melt below 359°; but some sublimate was observed in the melting point capillary tube. The infrared spectrum of the acetone-insoluble substance was superimposable on that of isonicotinic acid, as was that of the white sublimate from this substance. The mass spectrum and melting point of the sublimate were also the same as those of isonicotinic acid. The black residue from the sublimation of the acetone-insoluble

substance did not melt below 359°and was insoluble in all common solvents. The infrared spectrum (KBr pellet) was the same as the spectrum of a blank KBr pellet. No other substances were isolated, although they could be detected by HPLC and thin-layer chromatography (TLC).

TLC analysis was performed on a silica gel chromatogram sheet (Eastman-Kodak 13181 with fluorescent indicator #6060). The chromatogram was developed with a solvent composed of 90:10:0.5 ethanol:acetone:acetic acid and examined under ultraviolet light. Isonicotinic acid N-oxide (R_f = 0.40), isonicotinic acid (R_f = 0.51) and a substance (R_f = 0.34) which exhibits blue fluorescence were detected in addition to substances which did not migrate.

b. Ethanol

A 1.7×10^{-2} M solution of isonicotinic acid N-oxide in 95% ethanol was prepared for irradiation as described for isonicotinic acid N-oxide in water. The concentration of isonicotinic acid in ethanol solution was 1.5×10^{-3} M. The solutions were individually analyzed by HPLC on a μ Porasil column with 95:10:1:0.1 methylene chloride:methanol:water:acetic acid at 1 ml/min.

Peaks for isonicotinic acid N-oxide and isonicotinic acid were detected along with unidentified components (k' = 1.4, 1.5, 1.7, 1.8, 2.0) in the photolyzed

solutions of isonicotinic acid N-oxide in ethanol. Isonicotinic acid did not undergo photolysis in ethanol.

c. 2-Propanol

A 1.5×10^{-2} M solution of isonicotinic acid N-oxide in 2-propanol was de-aerated and irradiated as described for isonicotinic acid N-oxide in water. The isonicotinic acid in 2-propanol solution was 1.2×10^{-3} M. The solvent system used in the HPLC analysis was 90:10:1:0.5 methylene chloride:methanol:water:acetic acid at 1 ml/min.

The chromatogram of the photolyzed solutions of isonicotinic acid N-oxide contained three unidentified peaks (k' = 1.3, 1.5, 4.1) in addition to those observed for isonicotinic acid and the N-oxide. Isonicotinic acid did not undergo photolysis under these conditions.

A 9.0×10^{-3} M solution of isonicotinic acid N-oxide in 2-propanol was irradiated for twenty-four hours under the same conditions as the eight hour irradiations. The chromatograms of these photolyzed solutions contained one unidentified peak (k' = 1.3) in addition to those observed for isonicotinic acid and the N-oxide.

d. 2-Methyl-2-propanol

An 8.0×10^{-3} M solution of isonicotinic acid N-oxide in 2-methyl-2-propanol was treated in the manner

described for isonicotinic acid N-oxide in water. The isonicotinic acid in 2-methyl-2-propanol solution was 9.9 x 10^{-4} M. The same analysis conditions as those used for the photolyzed 2-propanol solutions were used for the 2-methyl-2-propanol solutions.

Ultraviolet light had no effect on isonicotinic acid under these conditions. In addition to the peaks detected for isonicotinic acid N-oxide and isonicotinic acid, two unidentified peaks (k' = 1.3, 1.6) were observed in the chromatograms.

e. Dioxane

A 5.0 x 10^{-3} M solution of isonicotinic acid N-oxide in dioxane was irradiated in the same manner described for isonicotinic acid N-oxide in water. The isonicotinic acid in dioxane solution was 1.6 x 10^{-3} M. Precipitation occurred during the photolysis of isonicotinic acid N-oxide in dioxane. The precipitate was dissolved by the addition of four milliliters of methanol to each tube immediately before HPLC analysis. The analysis was performed with 95:10:0.5:0.25 methylene chloride:methanol:water:acetic acid on a μ Porasil column.

In addition to the peaks observed for the starting material and isonicotinic acid, three peaks (k' = 1.2, 1.8, 1.9) were observed in the chromatograms of the photo-

lyzed dioxane solution of isonicotinic acid N-oxide. Two of these peaks (k' = 1.2, 1.8) were also observed in the photolyzed dioxane solutions of isonicotinic acid.

A 5.2×10^{-3} M solution of isonicotinic acid N-oxide in dioxane was irradiated for four hours under the same conditions as the eight hour irradiations. The chromatograms of these photolyzed solutions contained three peaks (k' = 1.2, 1.8, 1.9) in addition to those observed for isonicotinic acid and the N-oxide.

f. Acetonitrile

A 2.3×10^{-3} M solution of isonicotinic acid N-oxide in acetonitrile was de-aerated and irradiated in the same manner as described for isonicotinic acid N-oxide in water. The concentration of isonicotinic acid in the acetonitrile solution was 9.1×10^{-4} M. Five milliliters of methanol was added to each photolysis tube, to dissolve the precipitate formed during the reaction, immediately prior to HPLC analysis with 95:10:1:0.25 methylene chloride: methanol:water:acetic acid.

The chromatograms of the photolyzed solutions of isonicotinic acid N-oxide contained two unidentified peaks (k' = 1.0, 1.6) as well as those identified for isonicotinic acid and its N-oxide. The unidentified peaks were also

present in the chromatograms (k' = 1.0, 1.6) of the photolyzed isonicotinic acid solutions.

The precipitate formed during the photolysis of isonicotinic acid N-oxide in acetonitrile was isolated from irradiated solutions by suction filtration. This substance was identified as isonicotinic acid by a mixed melting point measurement.

2. Irradiation of methyl isonicotinic N-oxide and methyl isonicotinate

Solutions of methyl isonicotinate N-oxide (9×10^{-3} M) in distilled water, 95% ethanol, 2-propanol, 2-methyl-2-propanol, dioxane and acetonitrile were prepared for irradiation. The solutions were de-aerated by boiling for approximately 15 minutes and cooling to room temperature under nitrogen flow. Portions of the solutions were placed in Pyrex test tubes for irradiation. To ascertain if any of the photoproducts attributed to methyl isonicotinate N-oxide were actually secondary products from the parent base, solutions of methyl isonicotinate were prepared for irradiation in the same manner. For a given solvent, five tubes containing methyl isonicotinate N-oxide solution and three tubes containing methyl isonicotinate solution were irradiated simultaneously in a Rayonet "Merry-go-round" reactor.

Following irradiation the solutions were analyzed by HPLC on a reverse phase column (Whatman Partisil PXS 10/25 ODS-2) with a 95:5 acetonitrile:methanol solvent system at a 1 ml/min flow rate. Methyl isonicotinate did not undergo photolysis in any solvent. The results from the analysis of the irradiated solutions of methyl isonicotinate N-oxide are listed in Table 2.

In water, peaks were observed for methyl isonicotinate N-oxide (k' = 3), methyl isonicotinate (k' = 2), and an unidentified substance (k' = 1.5). In ethanol, 2-propanol, and 2-methyl-2-propanol peaks were observed for methyl isonicotinate N-oxide, methyl isonicotinate and an unidentified substance (k' = 1.3). Three peaks were observed in the chromatograms of the photolyzed dioxane and acetonitrile solutions; methyl isonicotinate, and two unidentified substances (k' = 1.3, 1.5).

The unidentified substance with k' = 1.3 was isolated from reactions of methyl isonicotinate N-oxide in 2-methyl-2-propanol. The irradiated solution was reduced in volume in a rotary evaporator until precipitation occurred. The yellow precipitate was collected by suction filtration under an inert atmosphere since the compound tended to decompose rapidly upon exposure to air. The compound shrank at 127°, darkened at 137° and bubbled at 168°.

No further changes were observed when the temperature was further elevated. The molecular weight obtained from the mass spectrum was 153. IR: (KBr) 1718 cm^{-1} (C=O), 1255 cm^{-1} (C-O-C). NMR: (CD_3OH, TMS as an internal reference) 1.2 δ, singlet (2H); 3.0 δ, multiplet (1H); 4.0 δ, singlet (1H); 4.7 δ, singlet (3H). Mass spectrum: m/e 153 (M^+), 137 (-O), 106, 78, and 59 (base peak; due to ester group, $C_2H_3O_2^+$). From the spectral data it is suggested that the compound, isolated from the irradiation of methyl isonicotinate N-oxide in 2-methyl-2-propanol, was not aromatic and that the methyl ester group was intact.

3. Irradiation of picolinic acid N-oxide

A 1.1×10^{-2} M solution of picolinic acid N-oxide in water was de-aerated by boiling and cooling to room temperature under nitrogen flow. Portions of the solution were placed in each of eight Pyrex test tubes and irradiated in a Rayonet "Merry-go-round" reactor. One tube was removed from the reactor every hour for eight hours and analyzed by thin-layer chromatography. The photolyzed solutions were spotted along with solutions of picolinic acid N-oxide, picolinic acid, and a mixture of picolinic acid N-oxide and picolinic acid on a silica gel chromatogram sheet (Eastman-Kodak 13181 with fluorescent indicator #6060). The chromatogram was developed with a solvent composed of

75:25:1 acetone:methanol:acetic acid and examined under ultraviolet light. Picolinic acid (R_f = 0.09) was not formed during the photolysis. Picolinic acid N-oxide (R_f = 0.03) was completely consumed in eight hours. Three unidentified spots (R_f = 0.34, 0.54, 0.63) were observed in the chromatograms of the photolyzed solutions. The chromatograms of the solutions irradiated for less than eight hours also exhibited a spot corresponding to picolinic acid N-oxide.

Attempts to isolate the photoproducts from several irradiations of picolinic acid N-oxide by extraction were unsuccessful. The extraction procedure involved removing the solvent from the photolyzed solutions under reduced pressure. The resulting gummy black residue was extracted successively with chloroform, acetone, ethyl acetate, ethanol, methanol, and water. TLC analysis of the extracts indicated that no separation was achieved by this process. Each extract contained all three components of the mixture.

Column chromatographic separation was equally unsatisfactory. The residue from the photolysis mixture was dissolved in methanol and placed on a silica gel column and eluted with several solvent systems. TLC analysis of the eluted fractions indicated the presence of all three components of the mixture in the fractions.

A 1.0×10^{-2} M solution of picolinic acid N-oxide in acetonitrile was de-aerated and irradiated in the same manner as described for picolinic acid N-oxide in water. Thin-layer chromatographic analysis of the reaction mixture indicated that no deoxygenation occurred during the reaction. There were three spots, other than that for the starting material, detected by TLC.

C. High Pressure Liquid Chromatography

A Waters' M6000 pump and U6K injection system was used for high pressure liquid chromatography of the mixtures. A Varian Vari-Chrom variable wavelength detector was used. The detector wavelength was 272 nm for isonicotinic acid N-oxide and isonicotinic acid, and 290 nm for methyl isonicotinate N-oxide and methyl isonicotinate. The peak integration was done by a Columbia Scientific Industries Supergrator 3.

The sensitivity of the detector, for the compounds to be analyzed, varied according to the ultraviolet absorbance of the compounds. It was therefore necessary to calibrate the detector for each photolysis system.

1. Isonicotinic acid N-oxide and isonicotinic acid

The high pressure liquid chromatographic analyses of the photolyzed solutions of isonicotinic acid N-oxide

and isonicotinic acid were performed on a μ Porasil column (Waters Associates Part #27477). The solvent system used for these analyses consisted of methylene chloride and methanol with traces of water and glacial acetic acid. The amounts of water and acetic acid in the solvent system varied depending on the photolysis solvent. Slight adjustments in the separation solvent were necessary to accomplish the separation of the unknown components of the photolysis mixtures. The separation of the isonicotinic acid from the isonicotinic acid N-oxide was not sacrificed for improved separation of unknown components.

The solvent system was developed using standard solutions of isonicotinic acid N-oxide and isonicotinic acid. Methanol elutes both components of the mixture without separation. Isonicotinic acid N-oxide and isonicotinic acid are completely retained on the column if pure methylene chloride is used as the eluting solvent. The most useful separation was attained by using 95 parts methylene chloride to 10 parts methanol. The water and acetic acid were used to reduce peak tailing. The addition of water eliminated tailing on the isonicotinic acid peak. The isonicotinic acid N-oxide peak was sharpened by the addition of acetic acid. Separation was greatly reduced if more than one part water or acetic acid was added to the solvent system. Calibration

runs were made using known concentrations of isonicotinic acid N-oxide and isonicotinic acid each time an analysis was performed. Factors were computed for each compound and used in the computation of results. A sample calculation is shown in Appendix A.

The void volume of the system with the μ Porasil column was 3.3 ml. Thus, for this system:

$$k' = \frac{\text{retention volume of system}}{3.3 \text{ ml}}$$

2. Methyl isonicotinate N-oxide and methyl isonicotinate

A standard solution of methyl isonicotinate N-oxide and methyl isonicotinate was used to develop an appropriate solvent system for the analyses of the photolyzed solutions. The separation was accomplished on a reverse phase column (Whatman Partisil PXS 10/25 ODS-2), using a solvent system consisting of acetonitrile and methanol. Both components of the mixture were eluted with methanol. Methyl isonicotinate was partially retained and methyl isonicotinate N-oxide was completely retained by the column when acetonitrile was used as the mobile phase. Addition of small amounts of methanol to acetonitrile caused the elution of methyl isonicotinate N-oxide. A good separation was achieved by using 95 parts acetonitrile to 5 parts methanol.

Calibration runs were made using known concentrations of methyl isonicotinate N-oxide and methyl isonicotinate for each photolysis solvent. Factors were computed by the Supergrator 3 and used in the computation of results.

The void volume for the system with the reverse phase column was 2.0 ml. Thus, for this system:

$$k' = \frac{\text{retention volume of sample}}{2.0 \text{ ml}}$$

D. Determination of Spectra

1. Infrared spectra

The infrared spectra were recorded on a Perkin-Elmer 225 infrared spectrophotometer. The spectra of the samples were determined as potassium bromide pellets (1×10^{-4} - 1×10^{-3} g sample/ 1×10^{-1} g KBr), which were prepared by a Carver Laboratory Press Model K.

2. Ultraviolet spectra

A Cary Model 15 spectrophotometer was used to determine the ultraviolet absorption spectra. The concentrations of the isonicotinic acid N-oxide and methyl ester solutions were 2×10^{-5} to 6×10^{-5} molar and 2×10^{-5} to 9×10^{-5} molar respectively. The concentrations of the solutions of the parent bases were 1×10^{-4} to 2×10^{-4} molar.

3. Nuclear magnetic resonance spectra

The nuclear magnetic resonance spectra were obtained from a Varian A-60A Spectrometer with tetramethylsilane as an internal reference. Deuterated methanol was used as solvent.

4. Mass spectra

The mass spectra were obtained from a Consolidated Electrodynamics Corporation (CEC) model 21-104 single-focus mass spectrometer with an electron multiplier detector. The operating conditions were as follows:

Inlet system temperature: 170°C

Source temperature: 250°C

Ionizing voltage: 70, 12, 10, 8, eV

Anode current: 10 microamps

Accelerating voltage: 3500 volts-nominal

Magnet current: 7.3 amps

Slit width: 4 mil

Electrostatic scanning rate: Position 9

Recording chart rate: 0.25 in/sec

The samples were injected into the liquid inlet system after dissolution in methanol.

CHAPTER IV

DISCUSSION

A. General

It has been demonstrated that the photolysis of the N-oxides of quinoline and isoquinoline follows two pathways. In nonpolar solvents, oxazepines are formed, while polar hydroxylic solvents favor the formation of lactams. It had been widely maintained, until recently, that an oxaziridine was an intermediate common to both processes (1,27). Recent investigations (21,22,23) indicate that the oxazepines are formed from one intermediate (probably an oxaziridine) and lactams originate from another (a hydrogen bonded excited singlet state of the N-oxide). In most instances, deoxygenation has been observed as a minor reaction.

It is more difficult to generalize the photochemical processes involved in the irradiation of pyridine N-oxides because they have not been investigated as extensively as the quinoline and isoquinoline N-oxides. Furthermore, the products expected from the irradiation of many pyridine N-oxides are unstable. Oxazepines have been isolated from a number of reactions conducted in aprotic solvents, where electron withdrawing groups exert a stabilizing influence on the seven-membered ring (3,12,18,28). A

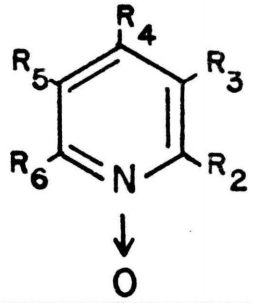
number of products of the photolysis of pyridine N-oxides (mainly acylpyrroles) have been classified as secondary products resulting from the collapse of oxazepines. Lactams have been isolated in a few instances (12). Thus, although the processes involved in the photochemistry of pyridine N-oxides have not been elucidated to as great an extent as have those for the N-oxides of quinoline and isoquinoline, it is the general contention that the photochemical processes for the two systems are essentially the same, but that the relative importances of competing processes are different (1,12). Generally, deoxygenation occurs with more frequency and to a greater extent for pyridine N-oxides than for azanaphthalene N-oxides, although the degree of deoxygenation is greatly dependent on the reaction solvent and ring substituents (Table 1).

B. Results of Photochemical Studies

Since it is evident that the nature of the photolysis solvent is a factor in determining the mode of photochemical reactions, isonicotinic acid N-oxide and methyl isonicotinate N-oxide were irradiated in a number of solvents. In order to clarify the significance of hydrogen bonding in the photochemical processes of pyridinecarboxylic acid N-oxides, several hydroxylic

Table 1

Deoxygenation of Pyridine N-oxides[a]

Substituents[b] 	Percent deoxygenation product	Solvent	Reference
	6.8	EtOH	4
$R_2 = R_3 = R_5 = R_6 = C_6H_5$	13-19	EtOH	3
$R_2 = R_4 = R_6 = C_6H_5$	≈12	MeCOMe	18
$R_2 = R_3 = R_5 = R_6 = C_6H_5$	14-16	MeCOMe	3
$R_2 = CN$	47.3	CH_2Cl_2	17
$R_2 = R_6 = CN$	12	CH_2Cl_2	29
$R_2 = R_6 = CN$, $R_4 = CH_3$	36	CH_2Cl_2	29
	30	Et_2O	2
$R_4 = CH_3$	35	Et_2O	2
$R_2 = R_5 = CH_3$	5	Et_2O	2
$R_2 = R_4 = CH_3$	3.3	Et_2O	2
$R_2 = R_3 = R_6 = CH_3$	4	Et_2O	2
$R_2 = R_3 = R_5 = R_6 = C_6H_5$	10-15	C_6H_6	3
$R_2 = R_6 = 4MeC_6H_4$, $R_3 = R_5 = C_6H_5$	19	C_6H_6	3
$R_2 = R_6 = 4ClC_6H_4$, $R_3 = R_5 = C_6H_5$	9	C_6H_6	3
$R_2 = R_6 = 4BrC_6H_4$, $R_3 = R_5 = C_6H_5$	17	C_6H_6	3
$R_2 = R_3 = R_4 = R_5 = R_6 = C_6H_5$	17	C_6H_6	3
$R_2 = R_3 = R_5 = R_6 = C_6H_5$, $R_4 = 4BrC_6H_4$	20	C_6H_6	3

a) Lists only cases where percent deoxygenation is given for irradiation at $\lambda > 300$ nm.; b) Unless otherwise stated R = H.

solvents with varying degrees of hydrogen-bonding capability (water > ethanol > 2-propanol > 2-methyl-2-propanol) were used in the investigation. Dioxane, a hydrogen bond acceptor, was chosen for the study with the expectation that it might participate in the photochemical process by interacting with the hydroxyl group of the carboxylic acid functional group. Acetonitrile was used as a non-participating solvent since isonicotinic acid N-oxide is insoluble in the nonpolar solvents. Isonicotinic acid N-oxide and methyl isonicotinate N-oxide were irradiated at wavelengths greater than 300 nm for eight hours in all solvents. Isonicotinic acid N-oxide was also irradiated for twenty-four hours in 2-propanol and for four hours in dioxane.

As illustrated by the data in Table 2, the degree to which isonicotinic acid N-oxide reacts, as well as the mode of the photochemical reaction is influenced by the nature of the solvent. It is apparent that isonicotinic acid N-oxide, is stabilized by hydrogen-bonding solvents: In strongly hydrogen bonding solvents, 65-78% of the starting material was consumed; whereas, the reaction proceeds essentially to completion in the same time period in the weakly hydrogen-bonding solvent, 2 methyl-2-propanol, and in the non-hydrogen bonding solvents. In fact the photolysis

Table 2[a]

Photolyses of Isonicotinic Acid N-Oxide and Methyl Isonicotinate N-Oxide

Solvent	Isonicotinic acid N-oxide				
	Percent N-oxide consumed	Percent N-oxide forming isonicotinic acid	Percent N-oxide forming other products	Number of other products	Irradiation time (hrs)
Water	76 ± 2	38 ± 2	62 ± 2	3	8
Ethanol (95%)	78 ± 3	24 ± 2	76 ± 2	5	8
2-Propanol	65 ± 2	17 ± 3	83 ± 3	3	8
	100	37 ± 3	63 ± 3	1	24
2-Methyl-2-propanol	97.0 ± 0.5	27 ± 4	73 ± 4	2	8
Dioxane	96 ± 1	38 ± 4	62 ± 4	3[b]	8
	99.96 ± 0.04	37 ± 3	63 ± 3	3[b]	4
Acetonitrile	98 ± 2	77 ± 5	23 ± 5	2[c]	8

Solvent	Methyl isonicotinate N-oxide				
	Percent N-oxide consumed	Percent N-oxide forming methyl isonicotinate	Percent N-oxide forming other products	Number of other products	Irradiation time (hrs)
Water	96.5 ± 0.7	30 ± 1	70 ± 1	1	8
Ethanol (95%)	99.9 ± 0.1	19 ± 2	81 ± 2	1	8
2-Propanol	98 ± 1	15.2 ± 0.9	85 ± 2	1	8
2-Methyl-2-propanol	94.7 ± 0.4	16.4 ± 0.3	83.6 ± 0.4	1	8
Dioxane	100	16 ± 1	84 ± 2	2	8
Acetonitrile	100	13 ± 2	87 ± 2	2	8

a) Sample calculations are given in Appendix A.

b) Two of the three other products were detected in the photolysis of isonicotinic acid in dioxane.

c) These products were also detected in the photolysis of isonicotinic acid in acetonitrile.

of isonicotinic acid N-oxide in dioxane was essentially complete in four hours. This phenomenon was initially attributed to the variation in the ultraviolet absorption of isonicotinic acid N-oxide in these solvents. See Figures 1 and 2 for the absorption spectra of isonicotinic acid N-oxide. The absorption maxima and molar absorptivities are tabulated in Appendix B. The long wavelength absorption band is blue shifted in the hydrogen bonding solvents. Since the solutions were irradiated through a Pyrex filter (uv cut-off, 300 nm), a smaller portion of the absorption band was exposed to the light in hydrogen bonding solvents.

This interpretation is not in agreement with the photochemical behavior of methyl isonicotinate N-oxide in the same solvents. Although the blue shift of the long wavelength absorption band is not as pronounced as it is for isonicotinic acid N-oxide, it is nevertheless significant. The absorption spectra of methyl isonicotinate N-oxide are shown in Figures 3 and 4. The absorption maxima and molar absorptivities are tabulated in Appendix B. That these variations do not affect the extent of the photolysis is shown by the data in Table 2. The reaction goes to greater than 90% in completion in all six solvents. Thus

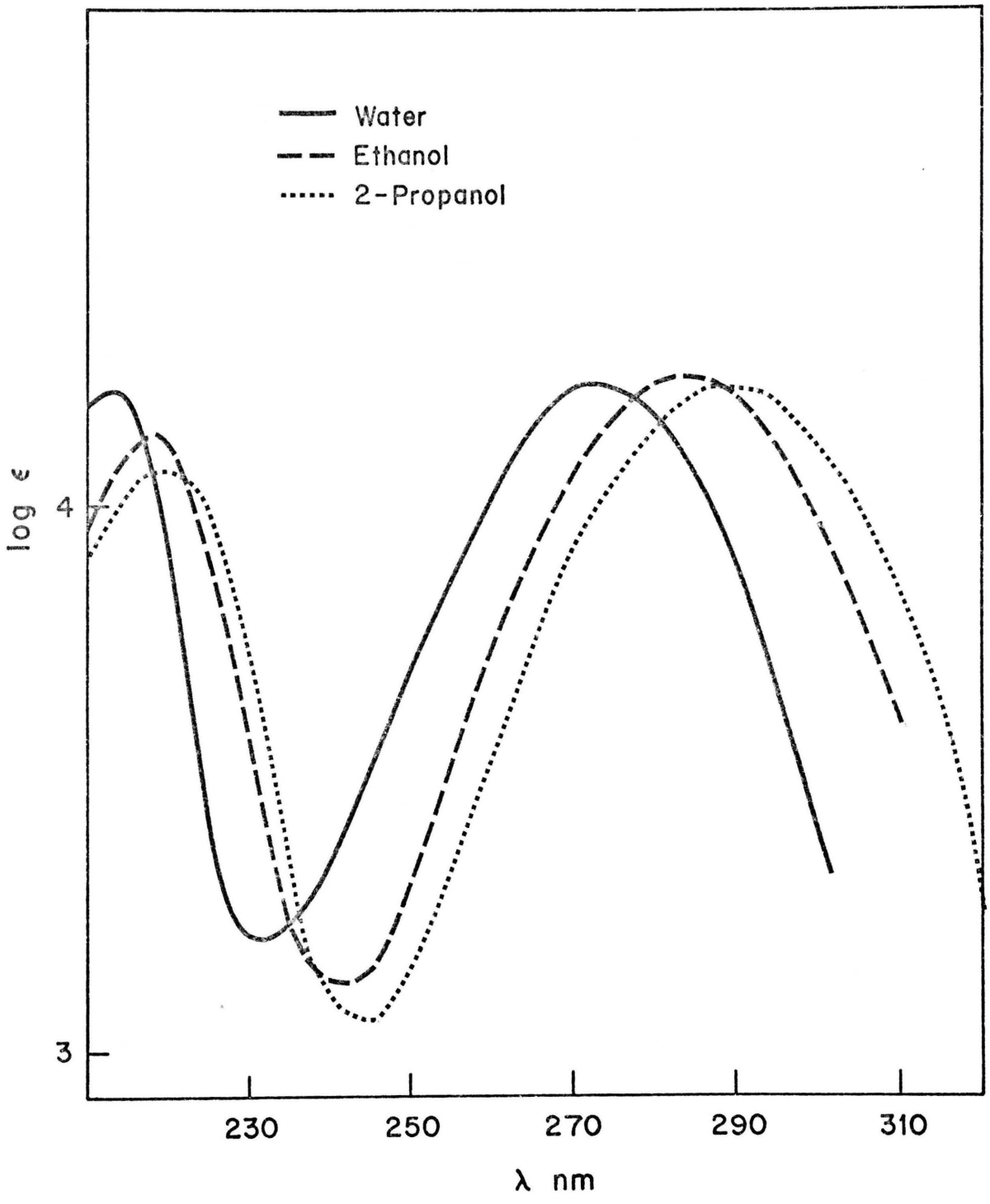


Figure 2: Ultraviolet Absorption Spectra of Isonicotinic Acid N-Oxide

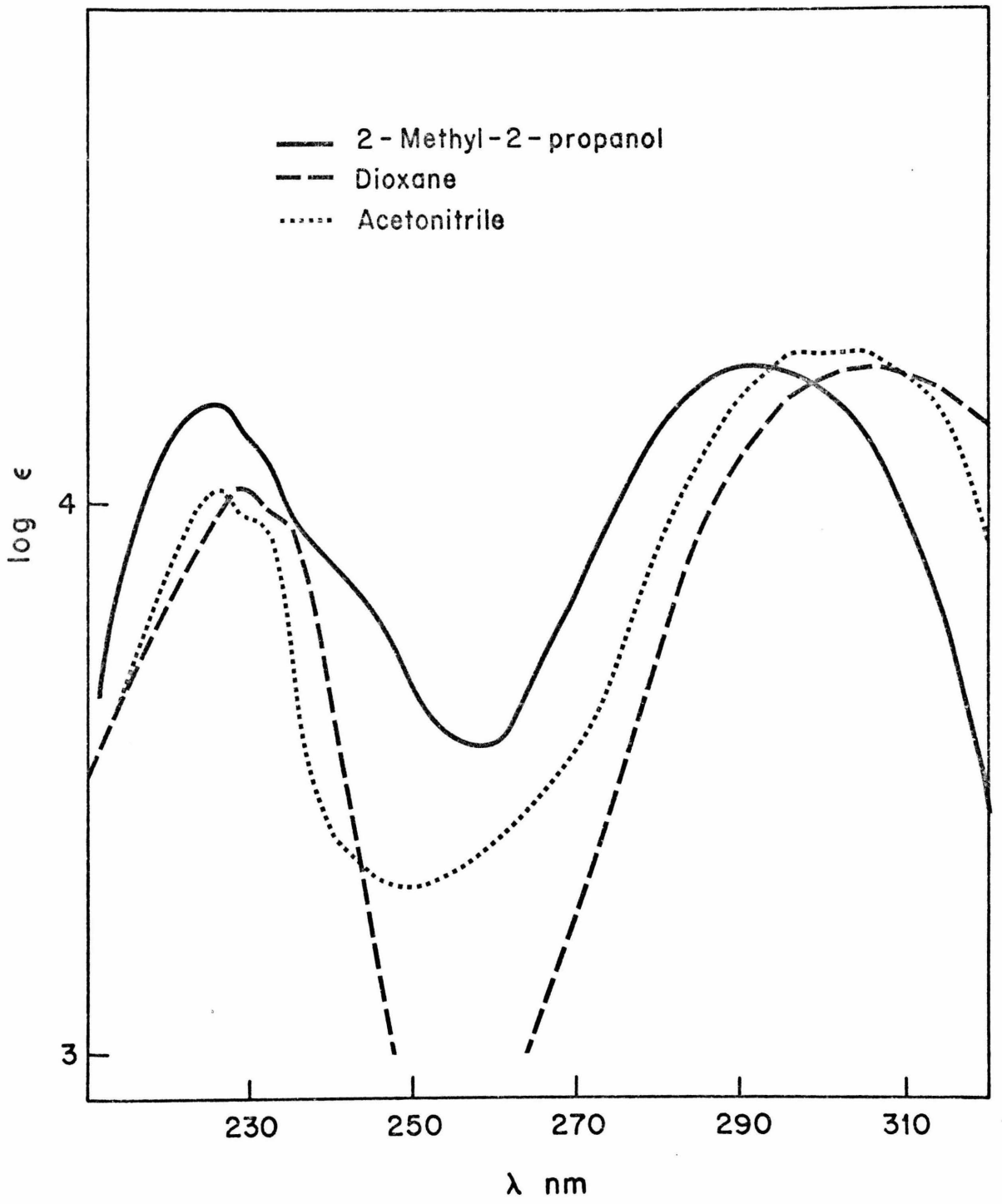


Figure 3: Ultraviolet Absorption Spectrum of Isonicotinic Acid N-Oxide

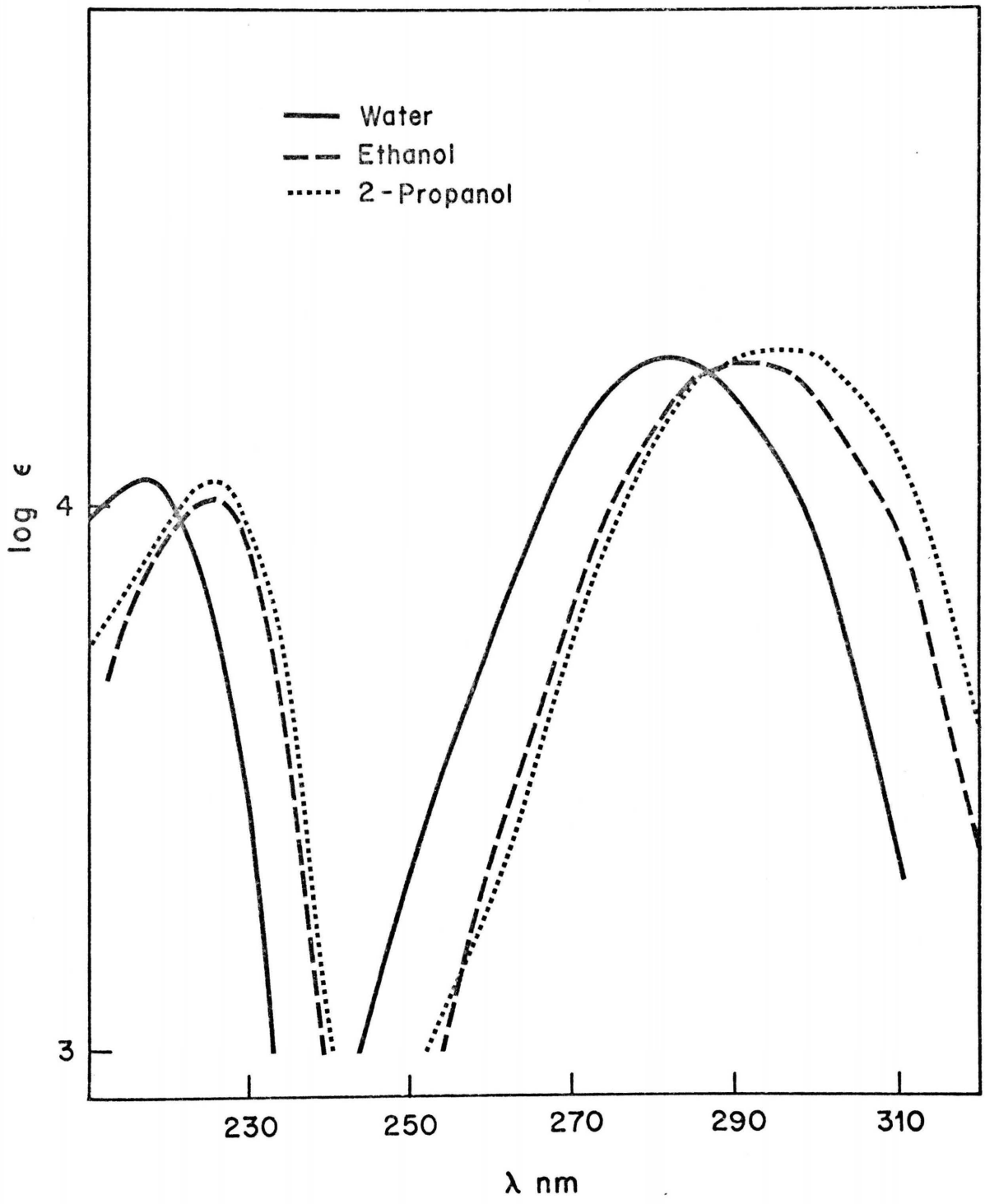


Figure 4: Ultraviolet Absorption Spectra of Methyl Isonicotinate N-Oxide

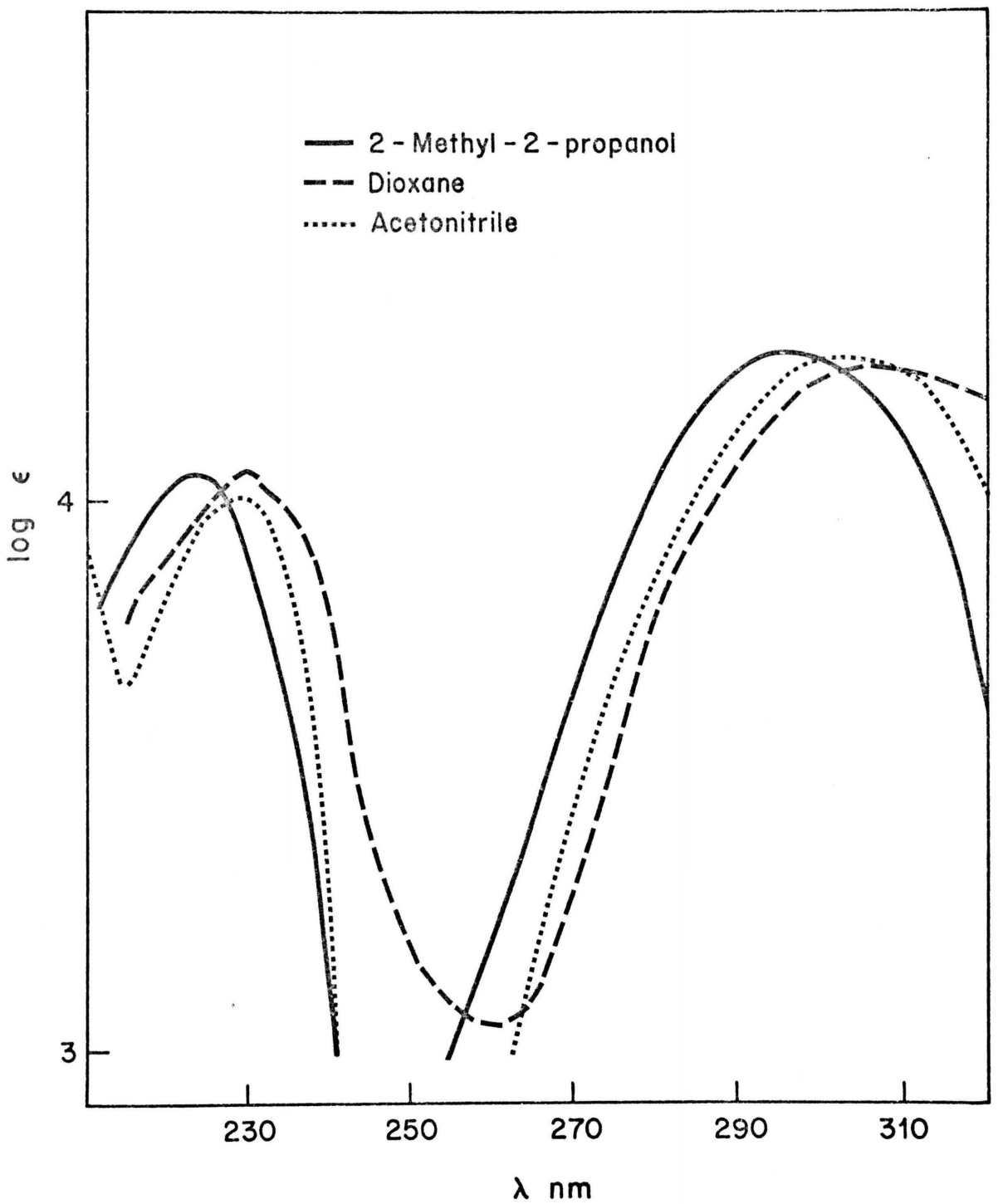


Figure 5: Ultraviolet Absorption Spectra of Methyl Isonicotinate N-Oxide

it appears that the influence of solvent on the reactivity of isonicotinic acid N-oxide is not a spectral effect.

The differing solvent effects on the photochemical reactivity of the N-oxides of isonicotinic acid and of methyl isonicotinate may be related to the ionization of isonicotinic acid N-oxide. The hydroxylic solvents, in which ionization should be more extensive, stabilized isonicotinic acid N-oxide, while no stabilization occurred in the non-ionizing solvents. Methyl isonicotinate N-oxide was not stabilized in any solvent since it cannot undergo ionization.

The predominant process in the photolysis of isonicotinic acid N-oxide was deoxygenation (Figure 5), although the total percentage of N-oxide forming other products was greater in most solvents. Comparison of the data from the experiments in which isonicotinic acid N-oxide was irradiated for eight hours indicates that the extent of deoxygenation was greatly dependent on the nature of the solvent. In the hydroxylic solvents, the extent of deoxygenation decreased with decreasing solvent polarity (and hydrogen bonding ability) then increased sharply for the low hydrogen bonding hydroxylic solvent, 2-methyl-2-propanol. The amount of isonicotinic acid N-oxide converted to isonicotinic acid decreased from approximately

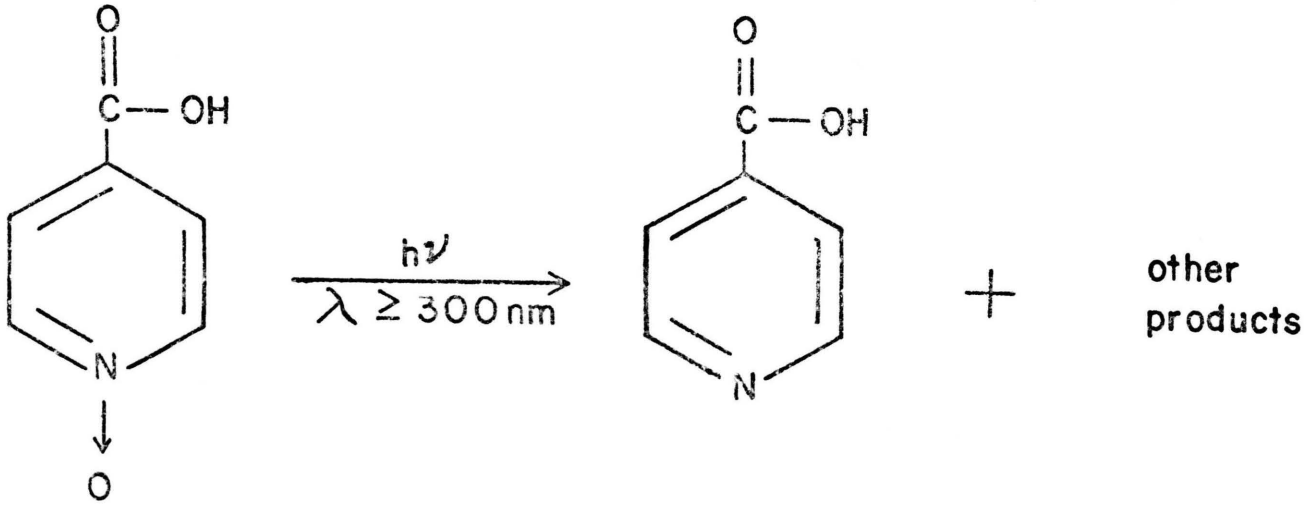


Figure 6

38% in water solution to about 17% in 2-propanol solution, then increased to approximately 27% in 2-methyl-2-propanol. In dioxane, approximately 38% of the isonicotinic acid N-oxide was converted to isonicotinic acid. The extent of deoxygenation was greatest in the non-participating solvent, acetonitrile, with about 77% conversion to isonicotinic acid. Deoxygenation is an even more significant photolytic process in dioxane and acetonitrile than the figures would seem to indicate.

In dioxane, the following evidence shows that two of the three other products were secondary products of isonicotinic acid. Irradiation of isonicotinic acid in dioxane under the same conditions as those used in the photolysis of the N-oxide leads to the formation of two products with the same retention volume as two of the products obtained in the photolysis of the N-oxide. About 50% of the isonicotinic acid was consumed in the formation of these secondary products. Thus the actual amount of isonicotinic acid N-oxide which was converted to isonicotinic acid was approximately 76% instead of the 38% observed. In the cases in which acetonitrile was used as the reaction solvent, similar evidence indicates that both of the other products were secondary products derived from isonicotinic acid. All of the isonicotinic acid N-oxide was therefore

initially converted to isonicotinic acid. Isonicotinic acid was not photolyzed upon irradiation in the hydroxylic solvents. The differing photochemical behavior of isonicotinic acid in the solvents cannot be attributed to spectral effects since the ultraviolet absorption spectrum of isonicotinic acid is essentially the same in the six solvents used for the investigation.

The photolysis of isonicotinic acid N-oxide in 2-propanol was essentially complete in twenty-four hours. It should be noted, however, that the product distribution was different. In eight hours 17% of the isonicotinic acid N-oxide consumed formed isonicotinic acid, while 83% formed three other products. In twenty-four hours 37% of the isonicotinic acid N-oxide consumed formed isonicotinic acid while 63% formed one other product. This indicates that at least part of the isonicotinic acid was a secondary product from one or both of the other products observed in the eight-hour reaction. The photolysis of isonicotinic acid N-oxide in dioxane was essentially complete in four hours. The product distribution was the same for four and eight hour irradiation times.

As these data indicate, the nature of the solvent exerts a substantial influence on the extent of photochemical deoxygenation of isonicotinic acid N-oxide. The

photolytic cleavage of the N-O bond was inhibited by hydrogen bonding solvents and enhanced by polar aprotic solvents. The extent of deoxygenation was greater in dioxane, which may act only as a hydrogen bond acceptor, than in the hydroxylic solvents. However, the greatest extent of deoxygenation was observed in the case of acetonitrile, a solvent in which carboxyl groups do not appear to be involved in any kind of hydrogen bonding (30).

Although a number of products were detected in the irradiated solutions of isonicotinic acid N-oxide, the deoxygenation product, isonicotinic acid, was the only one which was identifiable. As shown in Table 2, the number of products detected was dependent on the reaction solvent. In the hydroxylic solvents, all of these products were derived from isonicotinic acid N-oxide. In water three products, other than isonicotinic acid, were detected by high-pressure liquid chromatography (HPLC). One of these products exhibited a blue fluorescence, as observed by thin layer chromatography (TLC). The only substance isolated, other than isonicotinic acid N-oxide and isonicotinic acid, was a black powder. This substance did not melt below 359^{o} and was insoluble in all common solvents. The infrared spectrum (KBr pellet) of this substance was the same as

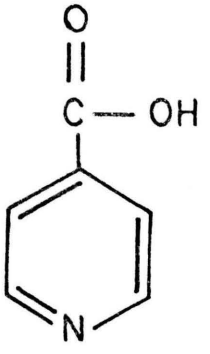
the spectrum of a blank KBr pellet. In ethanol five products other than isonicotinic acid were detected by HPLC. In the eight hour irradiation of isonicotinic acid N-oxide in 2-propanol, three products in addition to isonicotinic acid were detected. Upon irradiation for twenty-four hours in 2-propanol, only one other product was observed, accompanied by an increase in the percent isonicotinic acid N-oxide converted to isonicotinic acid. This indicates that two of the products observed in the eight hour irradiation are intermediates in the formation of isonicotinic acid and in the formation of the other product detected in both the eight and twenty-four hour irradiations of isonicotinic acid N-oxide in 2-propanol. Irradiation of isonicotinic acid N-oxide in 2-methyl-2-propanol resulted in the formation of isonicotinic acid and two other products.

In dioxane, three products in addition to isonicotinic acid were detected. However, two of these substances are secondary products, derived from isonicotinic acid. In acetonitrile, two products other than isonicotinic acid were detected. Both of these substances derive from isonicotinic acid. Attempts at isolation and identification of these components of the mixture were unsuccessful.

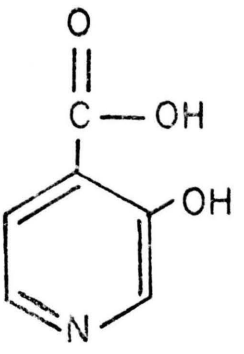
At least eight compounds are possible products of the photolysis of isonicotinic acid N-oxide. The

structures of these products are given in Figures 6 and 7. These compounds fall into three categories: (a) the primary photoproducts (isonicotinic acid, 2-1H-pyridone-4-carboxylic acid, 2-formyl-3-pyrrolecarboxylic acid, and 1,3-oxazepine-5-carboxylic acid); (b) products which may be derived from either isonicotinic acid N-oxide or 1,3-oxazepine-5-carboxylic acid (3-hydroxyisonicotinic acid and 3-pyrrolecarboxylic acid); and (c) secondary products derived from 1,3-oxazepine-5-carboxylic acid (1-formyl-3-pyrrolecarboxylic acid and 1-formyl-5-hydroxy pyrroline-4-carboxylic acid). The deoxygenation product, isonicotinic acid which has been isolated and identified, has already been discussed. Although it was not isolated, there is evidence that 3-hydroxyisonicotinic acid was formed in the photolysis of isonicotinic acid N-oxide in water. As mentioned before, a substance which exhibited a blue fluorescence was detected by thin layer chromatographic analysis. 3-Hydroxypyridine exhibits this type of fluorescence (34).

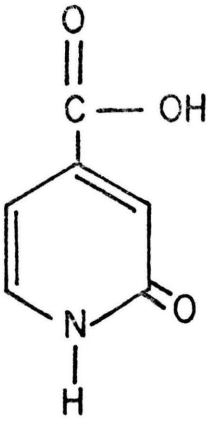
If the photochemical processes in pyridine N-oxides correspond to those in the N-oxides of quinoline and isoquinoline, the formation of the pyridones should be greatly enhanced by hydrogen bonding between the N-oxide functional group and the solvent. The formation of the



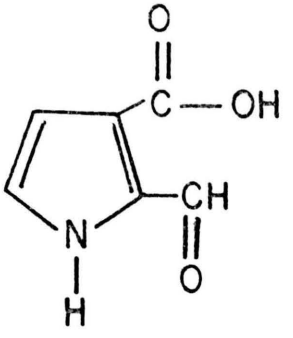
Isonicotinic acid



3-Hydroxyisonicotinic acid

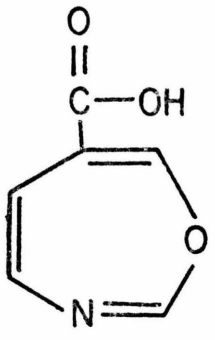


2-1H-pyridone-4-carboxylic acid

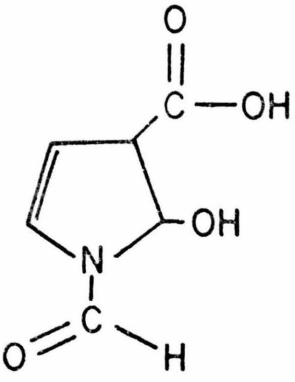


2-Formyl-3-pyrrole-carboxylic acid

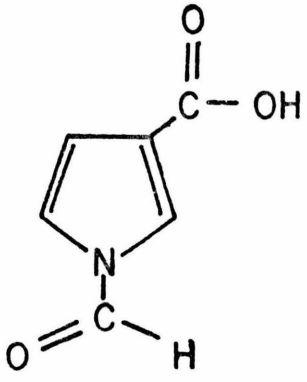
Figure 7



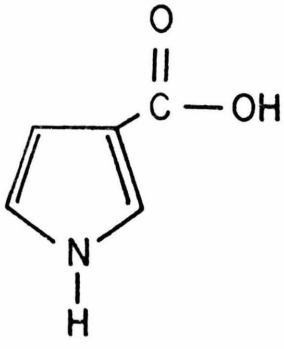
1,3-Oxazepine-5-carboxylic acid



1-Formyl-5-hydroxy pyrroline-4-carboxylic acid



1-Formyl-3-pyrrole-carboxylic acid



3-Pyrrolecarboxylic acid

Figure 8

1,3-oxazepines would be favored in aprotic solvents. Continuous and flash illumination studies of isoquinoline N-oxide (21,22) and quinoline N-oxide (22) indicate that the lactams are formed preferentially in hydroxylic solvents while 1,3-oxazepine formation is favored in aprotic solvents. The introduction of a strongly electron-withdrawing group in the 2-position of quinoline N-oxide, which greatly reduces the ability of the N-oxide function to form hydrogen bonds, results in the enhancement of 1,3-oxazepine formation regardless of the nature of the solvent (22,23).

Since the electronic effect of substitution at the 4-position should be similar to the effect of the substitution at the 2-position, substitution of pyridine N-oxide with an electron withdrawing group, such as the carboxyl group, in the 4-position may be expected to enhance the formation of the 1,3-oxazepine in the photolysis of isonicotinic acid N-oxide in hydroxylic and nonhydroxylic solvents. However, it probably would not be possible to isolate 1,3-oxazepine-5-carboxylic acid even if it were formed, since it would be very unstable. Instead the secondary products derived from 1,3-oxazepine-5-carboxylic acid would be expected.

Thus 2-formyl-3-pyrrolecarboxylic acid, 3-hydroxyisonicotinic acid, 1-formyl-3-pyrrolecarboxylic acid and

3-pyrrolecarboxylic acid may be possible in all solvents, in addition to isonicotinic acid. 1-Formylpyrrole-2-carboxamide has been isolated from the photolysis of picolinamide N-oxide in water (5,6). The formation of 2-1H-pyridone-4-carboxylic acid would be expected only in the hydroxylic solvents. The formation of 1-formyl-5-hydroxypyrroline-4-carboxylic acid would only be possible in aqueous solutions since it results from the addition of water to 1,3-oxazepine-5-carboxylic acid.

The effect of solvent on the deoxygenation of methyl isonicotinate N-oxide (Figure 8) was much less pronounced than was the effect on the photolysis of the acid. The amount of methyl isonicotinate N-oxide converted to methyl isonicotinate was essentially the same for all the solvents (13-19%) except water (30%). Unlike isonicotinic acid, which was photolyzed in dioxane and acetonitrile, methyl isonicotinate did not undergo further photolysis in any of the solvents.

As mentioned before, most of the methyl isonicotinate N-oxide was consumed upon irradiation in the six solvents used in this investigation. The formation of products other than the deoxygenation product was more extensive for the ester than it was for the acid. Methyl isonicotinate was the least abundant product detected in

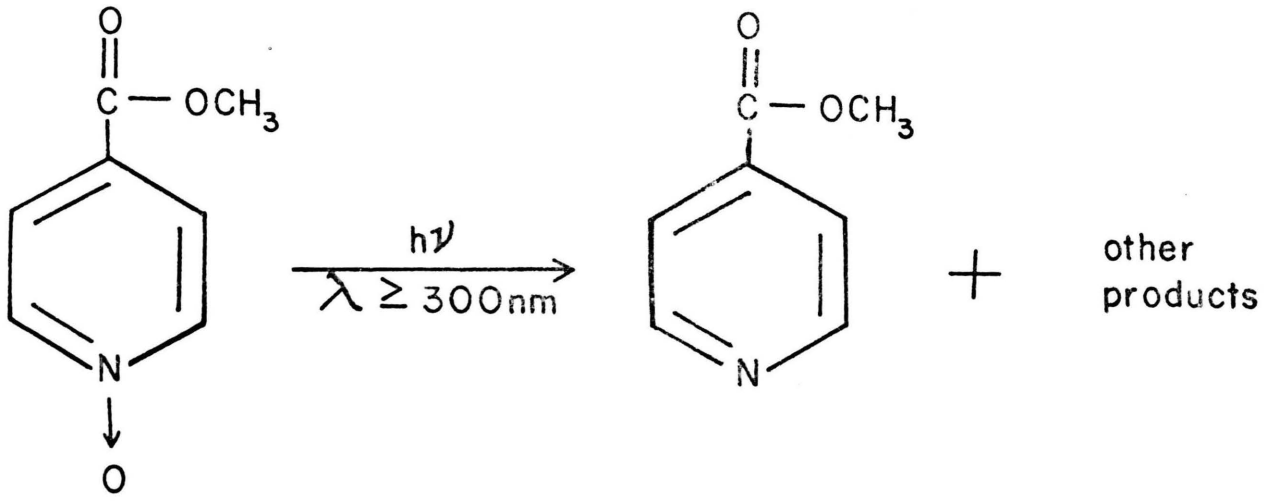


Figure 9

each solvent. The second product (Table 2) detected in ethanol, 2-propanol, and 2-methyl-2-propanol all exhibited the same chromatographic retention volume. This substance was isolated from 2-methyl-2-propanol reaction mixtures. Spectral data indicates that this compound is a non-aromatic isomer of methyl isonicotinate N-oxide in which the ester group remains intact during the photolysis. The ester group was identified by the carbonyl (1718 cm^{-1}) and ester (1255 cm^{-1}) absorption bands in the infrared spectrum, the methyl ester signal (a singlet which integrates for 3 H at 4.7 δ) in the nuclear magnetic resonance spectrum, and the base peak due to the methyl ester group (m/e 59) in the mass spectrum. The NMR signals (1.2 δ, singlet (2 H); 3.0 δ multiplet (1 H); 4.0 δ, singlet (1 H); 4.7 δ singlet (3 H)) which account for seven hydrogens were too far upfield to be attributed to an aromatic compound, a pyrrole(6), or an oxazepine (31).

The only photoproducts resulting from ring openings of pyridine N-oxides which have been reported are an isocyanide from pyridine N-oxide (Figure 9) under aqueous basic conditions (32) and an isocyanate, reported for pentachloropyridine N-oxide (Figure 10) in anhydrous carbon tetrachloride (33).

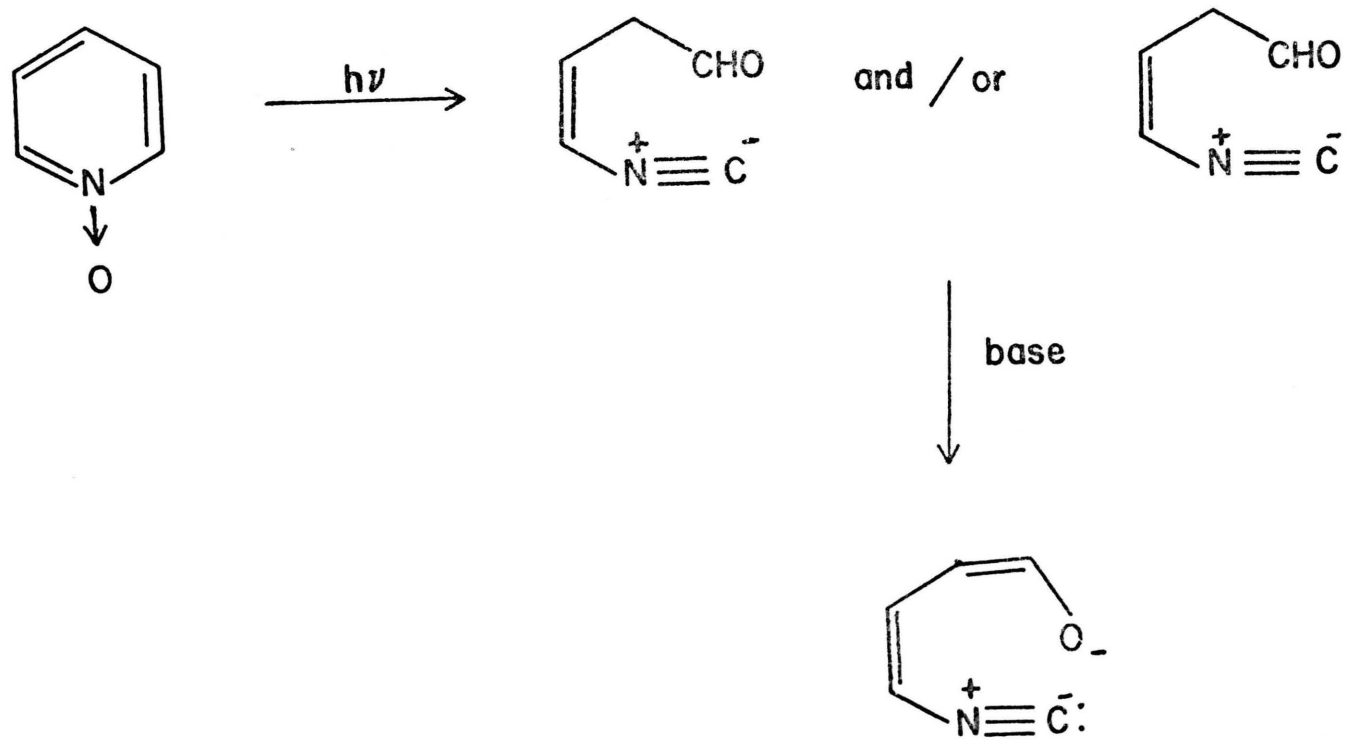


Figure 10

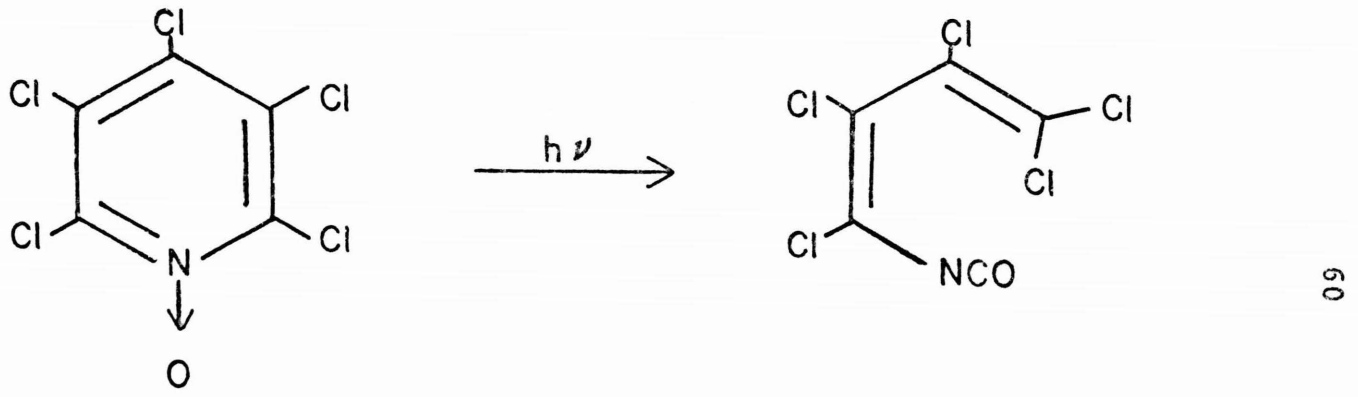


Figure 11

There is no evidence for the isocynate or isocyanide group in the infrared spectrum or the mass spectral fragmentation pattern of the product of this study. There was also no evidence for an aldehyde group in any of the spectra. A product with a different retention volume was detected in the water reactions. Two products other than methyl isonicotinate were detected in the reaction mixtures resulting from the irradiation of methyl isonicotinate N-oxide in dioxane and acetonitrile. In both cases, one of the components had the same retention volume as the compound detected in the water reaction and the other had the same retention volume as the compound detected in the three alcohols.

Picolinic acid N-oxide, which forms intramolecular, hydrogen bonds, was irradiated in water and acetonitrile for eight hours. Three products were detected by TLC analysis. None of these substances has been identified. The deoxygenation product, picolinic acid, was not formed in either reaction. Analysis of photolyzed aqueous solutions of picolinic acid N-oxide at one-hour intervals indicates that picolinic acid is not formed during the course of the reaction. As mentioned before, the influence of intramolecular hydrogen bonding on the vapor-phase photolysis of 2-picoline N-oxide has been demonstrated by

Hata (9). Although irradiation of pyridine N-oxide (10) and 3-picoline N-oxide (11) leads to the formation of pyridine and 3-picoline respectively, deoxygenation does not occur in the case of 2-picoline N-oxide.

CHAPTER V

SUMMARY

Isonicotinic acid N-oxide and methyl isonicotinate N-oxide were irradiated in water, ethanol, 2-propanol, 2-methyl-2-propanol, dioxane and acetonitrile. The results indicate that the mode of the photochemical reaction as well as the degree to which isonicotinic acid N-oxide reacts is very solvent sensitive. Isonicotinic acid N-oxide was stabilized by hydrogen bonding solvents. This stabilization may be related to the ionization of isonicotinic acid N-oxide. Stabilization occurred in the hydroxylic solvents, in which ionization should be more extensive. Isonicotinic acid N-oxide was not stabilized in the non-ionizing solvents.

Although the predominant process in the photolysis of isonicotinic acid N-oxide was deoxygenation in all solvents, the percent conversion to isonicotinic acid varied greatly with the nature of the solvent. The deoxygenation process was enhanced in the aprotic solvents and inhibited in the hydroxylic solvents. A number of other products were detected in the irradiated solutions of isonicotinic acid N-oxide in all solvents, but none of these were isolated or identified.

In contrast, the photochemistry of methyl isonicotinate N-oxide was relatively insensitive to the nature of the solvent. The photochemical reaction proceeded essentially to completion regardless of the nature of the solvent. The extent of deoxygenation, which was a minor process in the case of methyl isonicotinate N-oxide, was almost unaffected by the nature of the solvent.

Although the formation of products other than the deoxygenation product was more extensive for methyl isonicotinate N-oxide than for isonicotinic acid N-oxide, fewer of these products were formed. The spectral properties of the only isolated product, other than methyl isonicotinate, indicate that it is a non-aromatic substance in which the ester group remains intact.

Picolinic acid N-oxide, which forms intramolecular hydrogen bonds, was irradiated in water and acetonitrile. In each case, three products were detected. None of these substances were identified. The deoxygenation product, picolinic acid, was not formed in either reaction. This result is consistent with the data obtained from the irradiations of isonicotinic acid N-oxide which indicate that deoxygenation is inhibited by hydrogen bonding interactions.

CHAPTER VI

SUGGESTIONS FOR FURTHER INVESTIGATION

A. Isolation and Identification of the Photochemical Products of Isonicotinic Acid N-Oxide and Methyl Isonicotinate N-Oxide

Although the deoxygenation products of isonicotinic acid N-oxide and methyl isonicotinate N-oxide were identified, none of the other photochemical products were identified. The isolation and identification of these other products would be helpful in the elucidation of the types of photochemical rearrangements which occur in pyridine N-oxides. It should be possible to achieve the isolation of the components of the mixtures by preparative HPLC, using the same type of column and solvent systems used in the analysis of the reaction mixtures.

B. The Photolysis of Metal Salts of Pyridinecarboxylic Acid N-Oxides

It has been found that copper (II) complexation enhances the formation of 2-formylpyrrole and 3-substituted 2-formylpyrroles in the irradiation of pyridine N-oxide and 4-substituted pyridine N-oxides respectively (17, 35). Cobalt (II), nickel (II), zinc (II) and iron (III) complexes of the N-oxides, irradiated under the same experimental conditions had no effect on the yield of 2-formylpyrroles. The counter ion of the compound which

provided the copper (II) also had some influence on 2-formylpyrrole formation. The greatest enhancement occurred with copper (II) sulfate and copper (II) perchlorate, while copper (II) chloride was the least effective. It is proposed that the photochemistry of the copper (II) salts of pyridinecarboxylic acid N-oxides be investigated.

C. The Deoxygenation Process in the Photochemistry of Pyridine N-Oxides

It is the general contention that deoxygenation of aromatic amine N-oxides takes place from the triplet state while the other processes proceed through an excited singlet state. The major supportive evidence for this contention is derived from triplet sensitization experiments. In the photolysis of 2,4,6-triphenylpyridine N-oxide, the deoxygenation process was greatly enhanced by the addition of a triplet sensitizer (18). The photoinduced deoxygenation of 2-cyanopyridine N-oxide was increased by triplet sensitizers. The extent of deoxygenation was reduced in the presence of oxygen, which has a high triplet quenching efficiency (17). Decreasing the oxygen concentration present during the irradiation of quinoline N-oxides results in a decrease in deoxygenation (36), which would seem to suggest a singlet state in this case. However, caution should be exercised in interpreting oxygen quenching

results (1).

Although triplet sensitization experiments are supportive of the contention that deoxygenation of aromatic amine N-oxides takes place from the triplet state, they by no means provide conclusive evidence. If deoxygenation occurred from the triplet state only, a triplet quencher should completely inhibit the formation of the parent amine of the N-oxide. Since the results of oxygen quenching experiments must be approached with caution, it is suggested that triplet quenching experiments be performed on some simple pyridine N-oxides.

Generally, the deoxygenation process is believed to involve the formation of atomic oxygen by photolytic cleavage of the N-O bond. Atomic oxygen has been generated in the vapor phase photolyses of pyridine N-oxide and its methyl derivatives (9,10,11). Irradiation of pyridine N-oxides in the presence of benzene leads to the formation of phenol. This has been interpreted as being indicative of an electrophilic oxidizing entity, atomic oxygen (2,37). Studies with some aliphatic amine N-oxides indicate that N-O bond rupture is homolytic, leading to the conclusion that the oxygen leaves as the oxygen radical anion or its conjugate acid, the hydroxyl radical. It was concluded that the oxygen reactive species in the irradiated N-oxide

solutions is the hydroxyl radical (38). Flash photolytic techniques and radical trapping experiments would be helpful in clarifying the nature of the oxygen moiety removed in the deoxygenation of pyridine N-oxides.

D. Substituent ans Solvent Effects on the Photochemistry of Pyridine N-Oxides

In general, it is supposed that there are two major photochemical processes, other than deoxygenation, involved in the photochemistry of pyridine N-oxides. This conclusion is, for the most part, based on the assumption that the photochemistry of pyridine N-oxides is analogous to that of the azanaphthalene N-oxides. A number of investigations (21,22,23,28) of the photochemistry of the N-oxides of quinolines and isoquinolines indicate that hydrogen bonding interactions between the N-oxide function and the solvent are essential for lactam formation, while 1,3-oxazepine formation is enhanced in situations where hydrogen bond formation is impossible. Although it was originally assumed that both of these products originated from the same intermediate, oxaziridine; flash photolytic investigations indicate that the last intermediate common to both processes is the excited singlet state. Lactam formation proceeds through a hydrogen bonded excited singlet state while 1,3-oxazepines are formed from a powerful oxidizing

agent, probably an oxaziridine (21,22,23).

Although pyridine N-oxides are considered to behave in a similar manner, analogies must be drawn with caution because the photochemical processes in these compounds are generally more complex (1,12). A detailed investigation of the effect of substituents and solvents on the photochemistry of pyridine N-oxides would be of great interest. If pyridine N-oxides are analogous to azanaphthalene N-oxides, pyridone (lactam) formation should be enhanced in hydrogen bonding solvents and inhibited by strongly electron withdrawing substituents in the 2-position. The formation of 1,3-oxazepines would be enhanced in aprotic solvents and by electron withdrawing substituents in the 2-position. Indications of 1,3-oxazepine formation would probably have to come from their secondary products since they would probably be unstable. In azanaphthalene N-oxides, the intermediate to oxazepine fromation is a strong oxidizing agent. If iodide ion is added to the reaction mixture under conditions which normally lead to oxazepine formation, iodine is liberated with the formation of the parent amine. Iodide ion has no effect when the process for lactam formation is favored (22). Since isolation of the 1,3-oxazepines expected from most pyridine N-oxides is unlikely, this information might supply an alternative method of determin-

ing if this reaction process is in effect. Flash photolysis studies may also supply insight into the nature of the reaction intermediates.

It is proposed that these studies be conducted in an alcohol, acetonitrile and cyclohexane; with a series of 2-substituted pyridine N-oxides. The following substituents would be useful: methyl, fluoro or chloro, nitro, amino or dimethylamino, methoxy and cyano.

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APPENDIX A: SAMPLE CALCULATIONS

A. Isonicotinic Acid N-Oxide in Water, Ethanol, 2-Propanol, and 2-Methyl-2-propanol

The calculations used in determining the percent isonicotinic acid N-oxide consumed and the percentages of isonicotinic acid and unidentified products formed from the isonicotinic acid N-oxide in water, ethanol, 2-propanol, and 2-methyl-2-propanol are demonstrated using the results from a photolyzed solution of isonicotinic acid N-oxide in ethanol. Prior to analysis of the photolyzed solutions in a given solvent, 2 µl of a standard solution containing isonicotinic acid N-oxide and isonicotinic acid was injected into the chromatographic system to determine sensitivity factors. The standard solution was 4.353×10^{-3} M in isonicotinic acid N-oxide and 4.878×10^{-3} M in isonicotinic acid.

From the standard solution:

Isonicotinic acid N-oxide peak area = 1284896 µV-sec

Isonicotinic acid N-oxide sensitivity factor = 1.233

$$\text{Corrected area} = \frac{1284896}{1.233} = 1042089 \text{ µV-sec}$$

$$\frac{\text{moles Isonicotinic acid N-oxide}}{\text{µV-sec}} = \frac{(2 \times 10^{-6} \text{l})(4.353 \times 10^{-3} \text{ m/l})}{1042089 \text{ µV-sec}}$$

$$= 8.354 \times 10^{-15} \text{ m/µV-sec}$$

Isonicotinic acid peak area = 924816 μV-sec

Isonicotinic acid sensitivity factor = 0.792

$$\text{Corrected area} = \frac{924816}{0.792} = 1167697 \text{ μV-sec}$$

$$\frac{\text{moles Isonicotinic acid}}{\text{μV-sec}} = \frac{(2 \times 10^{-6})(4.878 \times 10^{-3} \text{m/l})}{1167697 \text{ μV-sec}}$$

$$= 8.355 \times 10^{-15} \text{ m/μV-sec}$$

Photolysis solution:

Initial concentration = 1.72×10^{-2} M

Isonicotinic acid N-oxide in 2 μl sample =

$$(2 \times 10^{-6} \text{l})(1.72 \times 10^{-2} \text{m/l})$$

$$= 3.44 \times 10^{-8} \text{ m}$$

Isonicotinic acid N-oxide peak area = 1121792 μV-sec

Isonicotinic acid peak area = 602080 μV-sec

$$\text{Moles Isonicotinic acid N-oxide} = \frac{(8.354 \times 10^{-15} \text{m})(1121792)}{(\text{unit area})(1.233)}$$

$$= 7.601 \times 10^{-9} \text{ m}$$

Moles Isonicotinic acid N-oxide consumed =

$$(3.44 \times 10^{-8} \text{m}) - (7.601 \times 10^{-9} \text{m})$$

$$= 2.680 \times 10^{-8} \text{ m}$$

$$\% \text{ Isonicotinic acid N-oxide consumed} = \frac{(2.680 \times 10^{-8})}{(3.44 \times 10^{-8})} 100$$

$$= 77.91 \simeq 78\%$$

$$\text{Moles Isonicotinic acid formed} = \frac{(8.355 \times 10^{-15} \text{m})(602080)}{(\text{unit area})(0.792)}$$

$$= 6.351 \times 10^{-9} \text{m}$$

% Isonicotinic acid N-oxide consumed forming isonicotinic acid = $\frac{(6.351 \times 10^{-9})}{(2.680 \times 10^{-8})} 100$

$= 23.70 \simeq 24\%$

Moles Isonicotinic acid N-oxide consumed forming unidentified products = $(2.680 \times 10^{-8}) - (6.351 \times 10^{-9})$

$= 2.045 \times 10^{-8}$ m

% Isonicotinic acid N-oxide consumed forming unidentified products = $\frac{(2.045 \times 10^{-8})}{(2.680 \times 10^{-8})} 100$

$= 76.31 \simeq 76\%$

The values listed in Table 2 are averages obtained from the analysis of five solutions in each solvent.

B. Isonicotinic Acid N-Oxide in Dioxane and Acetonitrile

The calculations used in determining the percent isonicotinic acid N-oxide consumed and the percentages of isonicotinic acid and unidentified products formed from the isonicotinic acid N-oxide in dioxane and acetonitrile are essentially the same as those used for isonicotinic acid N-oxide in the other four solvents. The addition of methanol to the photolyzed solutions, to dissolve the precipitate formed during irradiation, required some adjustment in determining the amount of isonicotinic acid N-oxide in a 2 µl sample. This is demonstrated with a dioxane solution of isonicotinic acid N-oxide.

Photolysis solution:

Initial concentration = 5.011×10^{-3}M

Initial volume = 15.0 ml

Volume methanol added = 4.0 ml

$$\text{Final concentration} = \frac{(15.0 \text{ ml})(5.011 \times 10^{-3}\text{M})}{(19.0 \text{ ml})}$$

$$= 3.956 \times 10^{-3}\text{M}$$

Isonicotinic acid N-oxide in 2 µl sample =

$$(2 \times 10^{-6}\text{l})(3.956 \times 10^{-3}\text{m/l})$$

$$= 7.912 \times 10^{-9}\text{M}$$

The remaining calculations were performed as described in section A.

C. Methyl Isonicotinate N-Oxide

The calculations used in determining the percent methyl isonicotinate N-oxide consumed and the percentages of methyl isonicotinate and unidentified products formed from the N-oxide in water, ethanol, 2-propanol, 2-methyl-2-propanol, dioxane, and acetonitrile are the same as those described in section A.

APPENDIX B: ULTRAVIOLET ABSORPTION SPECTRA OF ISONICOTINIC ACID N-OXIDE AND METHYL ISONICOTINATE N-OXIDE

Table 3

Ultraviolet Absorption Spectra of Isonicotinic Acid N-Oxide

Solvent	λmax (nm)	log ε
Water	274	4.22
	212	4.21
Ethanol	284	4.23
	218	4.14
2-Propanol	289	4.22
	219.5	4.07
2-Methyl-2-propanol	293	4.25
	245.5[a]	3.81
	225.5	4.18
Dioxane	307	4.24
	235	3.98
	230	4.03
Acetonitrile	305	4.27
	298	4.27
	232[a]	3.98
	226.5	4.03

(a) Shoulder

Table 4

Ultraviolet Absorption Spectra of Methyl Isonicotinate N-Oxide

Solvent	λmax (nm)	log ε
Water	282	4.27
	216.5	4.07
Ethanol	293	4.26
	225	4.01
2-Propanol	296	4.28
	232[a]	3.86
	224.5	4.05
2-Methyl-2-propanol	296	4.29
	224.5	4.07
Dioxane	312[a]	4.24
	305.5	4.26
	300[a]	4.24
	235[a]	3.99
	229	4.06
Acetonitrile	301.5	4.27
	232[a]	3.95
	228	4.02

(a) Shoulder