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PHOTOCHEMISTRY OF PYRIDINE *N*-OXIDES

CHRISTIAN LOHSE,[a] LINDA HAGEDORN,[a] ANGELO ALBINI,[b]
and ELISA FASANI[b]

(a) Department of Chemistry, The University,
Campusvej 55, DK-5230 Odense M, Denmark

(b) Department of Organic Chemistry, The University,
V. Taramelli 10, I-27100 Pavia, Italy

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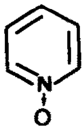
Abstract - Photolysis of pyridine *N*-oxide (**1a**) in aqueous basic solution yields the anion of 5-hydroxypentadienenitrile (**2a**). Kinetic data are obtained from flash photolytic measurements. The reaction is extended to twenty substituted pyridine *N*-oxides, including deuterated derivatives, as well as 10 other experimental conditions (amines as the base in organic solvents).

The results can be rationalized as involving primary photorearrangement to open-chain nitrene **11** (τ 63 msec in water for **11a**), which rearranges in low yield to 2-formylpyrrole or undergoes polymerization to tars. In the presence of bases, this intermediate is efficiently deprotonated to anion **2** (k = 690 $M^{-1}s^{-1}$ for the reaction of **11a** with OH^-). The relation of this new rearrangement to other photoprocesses of heterocyclic *N*-oxides is discussed.

Numerous reports on the photolysis of aromatic amine oxides have shown two basic pathways of reaction.[1] One results in the formation of lactams, the other in the formation of oxazepines. The lactam formation is the main process for most *N*-oxides in a protic solvent, whereas oxazepine formation seems to be enhanced by a non polar aprotic solvent. Generally an excellent material balance can be obtained for the photolysis of *N*-oxides, and these processes are in several cases by far the best synthetic way to important new compounds.

The mechanistic results so far presented all show that lactam formation as well as 1,3-oxazepine formation occur from the lowest excited singlet state. No conclusive evidence for a common intermediate for these two types of products has been published. On the contrary, some evidence from nanosecond flash photolytic experiments suggests that these are two independent rearrangements.[2]

The main exception to this general picture is, however, pyridine *N*-oxide (**1a**).

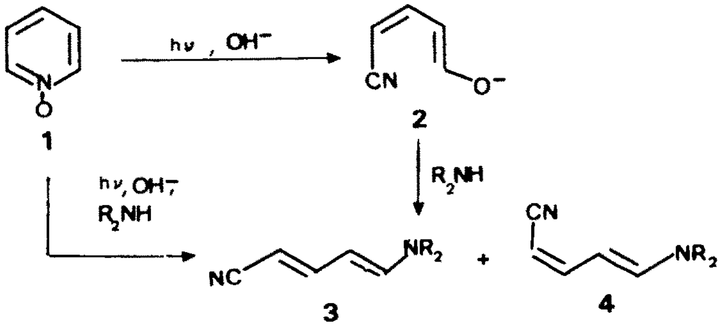


1a

This is rather unfortunate because of the simplicity and fundamental properties of this compound compared to all other aromatic *N*-oxides. In nearly all reports on the photolysis of pyridine *N*-oxide a very low material balance has been obtained, and a reasonable explanation for these fact has not yet been presented[3] (note, however, that on photolysis in water in the presence of copper salts moderate yields of 2-

formylpyrrole are obtained).[4] Thus, in the case of pyridine N-oxide either a different mechanism is operative, or, if the reaction occurs through pathways already known from other N-oxides, the products are unstable and decompose under the working conditions.

In sharp contrast with the above findings, it has been reported that when pyridine N-oxide is irradiated in basic aqueous solutions the anion 2 is obtained in high yield. This can be isolated as a salt or can be converted with amines into the enaminonitriles 3-4 (mixture of trans and cis isomers)[5] (Scheme 1).



Scheme I

Obtaining these enaminonitriles is preparatively interesting, but the mechanism of the ring-cleavage is as yet unclear.

The purpose of this paper is to explore the scope of the reaction by extending it to other substrates and to other experimental conditions, as well as to gather new experimental evidence towards the elucidation of the mechanism, in particular flash photolytic measurements.

1. Photolysis of Pyridine N-oxide in basic aqueous solution

Steady state irradiation of (1a) in aqueous sodium hydroxyde solution yields anion (2a) and formation of the product can be conveniently monitored at 323 nm. The rate of reaction depends on the strength and the concentration of the base, e.g. quantum yield for the formation of (2a) in 0.1 M NH_3 is only 15% of that in 0.1 M NaOH. Furthermore, the base must be present during photolysis. Addition of NaOH to a freshly irradiated solution of (1a) in NH_3 does not affect the yield of (2a).

Photolysis of a series of 10^{-4} M aqueous solutions of (1a) containing NaOH in concentrations between 1 M and 10^{-3} M shows a decrease in the relative quantum yield of (2a) from 1 to 0.06. A plot of the quantum yield against the concentration of NaOH follows an S-shaped curve, and the yield in a 10^{-2} M solution is one half of that in 1 M NaOH. The absolute quantum yield could not be accurately measured because of the uncertainty about the extinction coefficient of (2a).

Under exactly the same reaction conditions the quantum yield for the consumption of the starting material (1a) was found to be constant and independent of the NaOH concentration.

Anion (2a) is formed in a relatively slow reaction, and the rate of the process could be measured using the flash photolytic technique. 10^{-5} M aqueous solutions of (1a) containing NaOH in concentrations between 1 M and 10^{-3} M were flashed with a high energy discharge lamp. In all experiments the formation of (2a) was observed as a permanent increase in absorption at 323 nm. The rate of formation of (2a) obeys a first order kinetic at all concentrations of NaOH. The pseudofirst order rate is not proportional to NaOH concentration, as it is relatively too fast at low base concentration. A detailed kinetic investigation showed all measured rate constants to obey the following expression:

$$\text{measured rate} = k_1 + k_2|\text{NaOH}|$$

with $k_1 = 3.91\ s^{-1}$ and $k_2 = 680\ M^{-1}s^{-1}$. Thus, anion (2a) is formed by reaction with water through a relatively slow process ($k_1 = 3.91\ s^{-1}$, pseudofirst order, or $k_1' = 0.07\ M^{-1}s^{-1}$ second order) and addition of NaOH enhances its formation by introducing a new fast process ($k_2 = 680\ M^{-1}s^{-1}$). In 1 M NaOH solution the rate is determined by the latter reaction.

Since steady state irradiation shows no change in the quantum yield for the consumption of (1a) with NaOH concentration (see above), a third process consuming (1a) and not leading to (2a) must be taken into account, and the minimum kinetic scheme is:

$$(1a) \xrightarrow[k_1]{H_2O} (2a)$$

$$(1a) \xrightarrow[k_2]{OH^-} (2a)$$

$$(1a) \xrightarrow[k_3]{} \text{Other Products}$$

k_3 is the sum of the rates of processes not yielding (2a), i.e. essentially polymerization leading to tars.

The quantum yield for the formation of (2a), Φ_a, is:

$$\Phi_a = \Phi_t \times \frac{k_1 + k_2\ |OH^-|}{k_1 + k_2\ |OH^-| + k_3}$$

where Φ_t is the total quantum yield for the consumption of (1a), a constant. At high $|OH^-|$ $\Phi_a = \Phi_{a(lim)}$ and at a concentration for which $k_1 + k_2\ |OH^-| = k_3$, $\Phi_a = \frac{1}{2}\ \Phi_{a(lim)}$. Hence k_3 can be evaluated, and is found to be $11\ s^{-1}$.

2. Photolysis of substituted pyridine N-oxides in basic aqueous solution

Twenty substituted pyridine N-oxides were studied under similar conditions (see Table 1 for the numbering of the derivatives). Formation of a new absorption maximum at 325-330 nm is observed under steady state irradiation and by flash photolysis.

In every case is a pseudofirst order reaction with the base observed. In some cases a longer lived component is also observed, e.g. with the 4-t-butylpyridine N-oxide, which can be easily attributed to the cis-trans isomerization of the unsatured anion slowed down in these cases by the bulky substituent.

The rate depends on the structure of the N-oxide, but the change observed is limited. Most observed rates are within an order of magnitude. Substituents in position 2 decrease the rate of reaction independently from their nature. A free α position is required for the reaction to occur. Thus, 2,6-disubstituted pyridine N-oxides, e.g. 2,6-lutidine N-oxide, show no new absorption in the expected region, nor do they yield enaminonitriles of type 3,4 in preparative experiments (see below). Deuteration at the α position also slows down the process.

Thus, 2,6-dideuteropyridine N-oxide (1e) reacts 4 times slower than perprotiopyridine N-oxide. For comparison, 2-deuteropyridine N-oxide (1f) was prepared, and showed a two components decay, one corresponding to the rate observed with 1a and one to that observed with 1e.

As for substituents in position 3 and 4, aryl and acyl substituents appear to increase, alkyl substituents to decrease the observed rate.

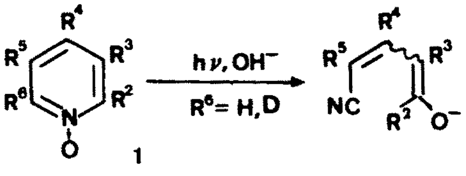


Table 1. Rate constants for the photoreaction of substituted pyridine N-oxides with aqueous NaOH.

	Substituent	$k_2, M^{-1}s^{-1}$		Substituent	$k_2, M^{-1}s^{-1}$
1a	H	680	1k	4-Ph	981
1b	4-tBu	197 and 1.7	1l	4-PhCH$_2$	607
1c	2-Me	329	1m	4-PhCO	2760
1d	2-Ph	289	1n	4-CN	478 and 3.3
1e	2,6-diD	178	1o	2,3-diMe	335
1f	2-D	655 and 143	1p	2,4-diMe	155
1g	2-PhCH$_2$	335	1q	2,5-diMe	262
1h	3-Me	359	1r	2,6-diMe	no reaction
1i	3-Ph	1350	1s	3,4-diMe	151
1j	4-Me	351	1t	3,5-diMe	249
			1u	2,4,6-triMe	no reaction

3. Photolysis of pyridine N-oxides in organic solvents

The irradiation of pyridine N-oxides was investigated also in organic solvents with amines acting as bases. The reaction was carried out in a protic (ethanol) and in an aprotic (ethyl acetate) solvent. Under these conditions enaminonitriles of type 3,4 are formed.

Preparative yields obtained from the irradiations of 10^{-2} M N-oxide solutions in the presence of 0.2 M diethylamine and following Kugelrohr distillation are low (15-33%) (Table 2) but this is probably due to decomposition during work up, since spectrophotometric experiments at lower N-oxide concentration revealed a higher yield in these products. In contrast, 2,6-lutidine N-oxide does not undergo this reaction.

Flash-photolysis experiments were also carried out. Formation of a maximum at 305-335 nm with pseudofirst order kinetics is revealed also in this case and the rate observed is lower than in aqueous sodium hydroxide (Table 3).

Table 2. Photoproducts from Pyridine N-oxides in the presence of Diethylamine 0.2 M.

Starting Material	Substituent	Solvent	Yield of Aminonitriles 3,4
1a	H	EtOH	3a,4a (17%)
		AcOEt	3a,4a (21%)
1l	4-CH_2Ph	EtOH	3l,4l (25%)
		AcOEt	3l,4l (15%)
1k	4-Ph	EtOH	3k,4k (33%)
		AcOEt	3k,4k (23%)
1r	2,6-diMe	EtOH	None
		AcOEt	None

Table 3. Rate constants (k_2, $M^{-1}s^{-1}$) for the reaction of substitute pyridine N-oxides with Et_2NH in organic solvents.

	1k	1l
Water	194	217
Ethanol	115	35
AcOEt	28	70
Benzene	24	not observed

MECHANISTIC DISCUSSION

The data reported here show that the photochemical cleavage to yield the pentadienenitriles derivatives 2, 3, and 4 is a fairly general reaction among pyridine N-oxides by irradiation in the presence of bases, provided that there is at least one α position free. This process takes place under a variety of conditions, including dilute amine solution in organic solvents.

The reaction obviously involves abstraction of a proton from the α position. However, the kinetic data reported here clearly exclude the hypothesis that an excited state is involved in the reaction with the base, since the decomposition quantum yield of N-oxides does not depend on the base concentration, there is no effect of dissolved oxygen and the rate of product formation is too slow to involve an excited state.

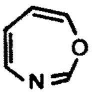
The reaction rather involves interaction of the base with the primary photoproduct from pyridine N-oxides, and the three rate constants measured by flash photolysis refer to this intermediate. Since the chemical yield of the pentadienenitriles is high ($\geq$ 80% from spectrophotometric measurements in most cases even if isolation procedures lead to consistent losses), it can be assumed that the excited singlet undergoes virtually a single chemical process and the intermediate thus formed reacts further to tars, unless it is trapped by bases.

The intervention of an intermediate has been previously suspected, e.g. in order to rationalize the spectrum observed by photolysis in matrix,[5a] but the larger amount of chemical and kinetic data now available allows a detailed discussion.

As mentioned before, this intermediate has an extrapolated lifetime in water (leaving out the reaction with bases) of $\ln 2/k_3$ = 63 ms and undergoes proton abstraction by OH^- with a rate k_2 = 690 $M^{-1}s^{-1}$.

Different structural hypotheses can be considered. The observed intermediate can be either a saturated molecule or an unsaturated species. Among saturated molecules the 1,2-oxazepine 6, the 1,3-oxazepine 7, and the oxaziridine 8 can be considered.

The first type of compound is obtained as stable photoproduct from some acridine N-oxides, the second is, as it has been already mentioned, commonly observed in the photochemistry of N-oxides, the third has been often postulated as an intermediate. Other types of photoproducts, such as pyridones or 2-formylpyrroles, are stable molecules under this condition and need not to be considered.



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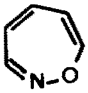

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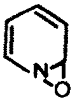

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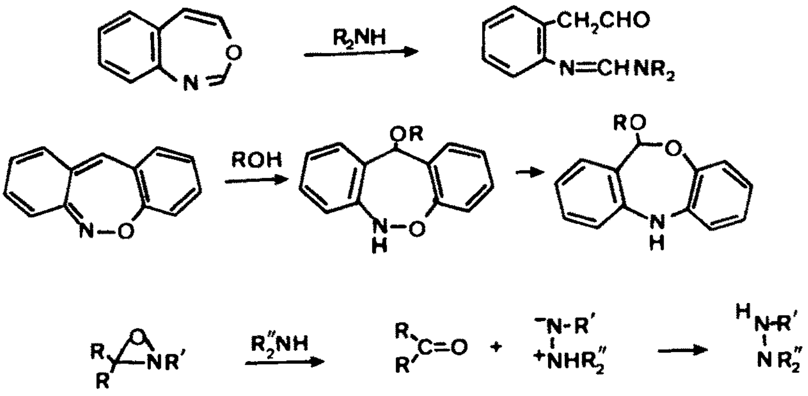


Scheme 2

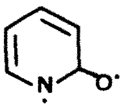
The known chemistry of compounds 6-8 is summarized in Scheme 2. 1,3-Oxazepines are known to be cleaved by amines, but the products obtained are, as expected, carbamates[6] and it is difficult to imagine a modification of the process that could give rise to nitriles.

1,2-Oxazepines are not stable in protic media, readily adding the solvent, and also are not expected to cleave to nitriles.[7]

Benzoxaziridines such as compound 8 are not known. Not condensed oxaziridines are cleaved by amines, however, the processes observed are again different from the present ones.[8]

In summary, compounds of type 6-8 undergo nucleophilic addition rather than proton abstraction, and furthermore the reaction we observe is too rapid for a thermal reaction and the rate shows a limited variation with the solvent polarity, at most little more than an order of magnitude in going from benzene to water in the case of 4-phenylpyridine N-oxide. This fits poorly with the idea of a reaction from a saturated molecule and much better for an unsaturated species reacting so fast that solvent polarity has little effect.

Thus, the hypothesis of a saturated formula for the intermediate is abandoned, and unsaturated species are discussed. Diradicalic or zwitterionic formulae can be, and have been, considered as intermediates in the photochemistry of N-oxides.[1]



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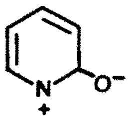

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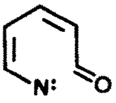

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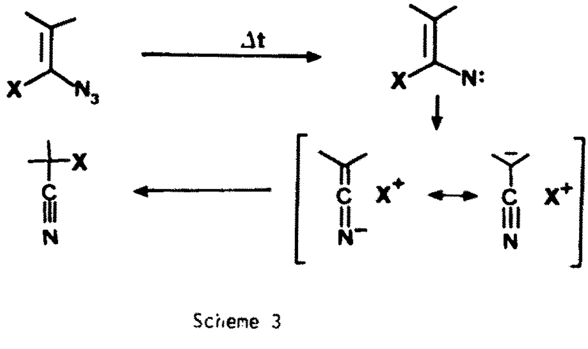
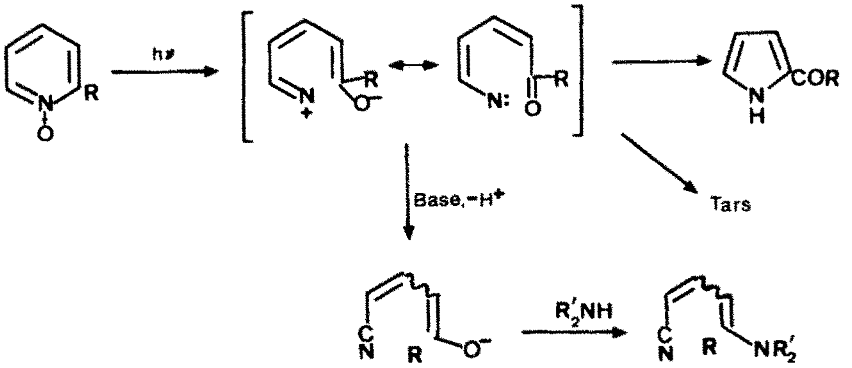
However, the lifetime (63 ms) of the species intercepted by amines appears to be too long for species such as 9 and 10, except possibly than when a strongly stabilizing group is present, which is not the case here. Another intermediate which has been considered to rationalize the formation of 2-acylpyrroles from pyridine N-oxides is the nitrene 11.[4] This appears more promising because the conjugated nitrene 11 could reasonably have a longer lifetime than intermediates such as 9 and 10. Taking a closer look to the literature, a precise analogy is found. In fact, vinylazides bearing in α a group X which is capable of stabilizing a positive charge, thermally decompose to nitrenes that cleave to unsaturated nitriles, following Scheme 3.[9]



Scheme 3

The group X can be a hydrogen.[10] In the present case a base promoted proton abstraction occurs, and the known facts can be rationalized on the basis of Scheme 4. Nitrene 11 is the logical precursor of 2-formylpyrroles and of polymeric tars (which contain, as it has been noted, a cyano group[5a] and thus arise through polymerization of the diene moiety) and is deprotonated to the stable anion 2. It appears reasonable that proton transfer is the only reaction sufficiently fast to trap the nitrene and the observed deuterium effect[11] and the dependence of the rate on the base strength fits in the expected range. Another way to trap the nitrene is, as previously reported, metal complexation leading to enhanced yield of acylpyrroles.[4]



Scheme 4

We consider nitrene 11, the primary photoproduct. It is apparent that the formation of this species requires a complex molecular rearrangement, and the reaction can be visualized as a sequence of steps including the oxaziridine 8 and the 1,2-oxazepine 6, but to none of these stages is a significant stability associated. It appears likely, as it has been previously suggested,[2b] that the entire rearrangement takes place on the excited state surface, or either that there is no minimum in the ground state corresponding to intermediate stages. A funnel form the excited surface to the lowest one is practicable only at a configuration corresponding to the nitrene in which the bond $N-C_\alpha$ is already broken. Thus, only factors which affect the nitrene stability influence the rate of reaction (thus for example a substituent in 6 affects the reaction as a ketone rather than an aldehyde group is now present in the nitrene).

This does not exclude that in other cases configurations precurring the nitrene can play a role, e.g. in heavily substituted pyridine N-oxides where 1,3-oxazepines are the end products. This work recognizes the open-chain nitrene as a new type of primary photoproduct from N-oxides, and shows that the reaction extends to many substituted pyridine N-oxides. On the other hand, this is simply another variation in the general scheme of the photorearrangement of N-oxides, where the most significant minimum, from which crossing to the ground state takes place, happens to correspond to the nitrene geometry, rather than to the related 1,2-oxazepine or 1,3-oxazepine geometry. In the absence of detailed calculations, effects of the structure on the pathway chosen are impossible.

EXPERIMENTAL

The N-oxides were prepared by standard peracid oxidation. Spectroscopic grade solvents and extra pure grade diethylamine were used as received. UV spectra were registered on a Cary 19 spectrophotometer, IR spectra on a Perkin-Elmer 297 spectrophotometer, NMR spectra on a Bruker 80 instrument, mass spectra on Du Pont DU2 instrument, elemental analyses were carried out by means of a Carlo Erba automatic analyzer.

Preparative Photochemical Reactions

Solutions of the N-oxides (10^{-2} M) were irradiated in an immersion well apparatus at 17°C by means of a 500 W medium pressure mercury arc. No difference was observed between nitrogen flushed and air equilibrated solutions. After that 50% or more of the starting N-oxide had reacted, the irradiation was quenched and the solution was extracted by cyclohexane and benzene in the case of aqueous solutions. The solvent was then evaporated and the residue chromatographed on silica gel (Merck 0.063-0.2 mm, eluting with cyclohexane-ethyl acetate mixtures) or, in separate experiments, bulb to bulb distilled by means of a Büchi GKR-50 instrument under reduced pressure ($< 10^{-2}$ Torr). The enaminonitriles 3-4 were obtained as a mixture and identified on the basis of elemental analysis and comparison of their spectroscopic properties with previously described derivatives of similar structure.[5c,d] The ratio of the two isomers was determined on the basis of the NMR spectrum of the mixture. The structure of the new enaminonitriles will be discussed together with the revision of the photochemistry of the N-oxides 1k and 1l in a later paper.

Flash photolysis

The flash photolysis equipment was of conventional design for kinetic measurements. The samples were contained in a 10 cm optical path cuvette, and the analyzing light beam was passed through a monochromator before entering the sample cell. This setup prevented photolysis of the N-oxides by the analyzing light beam. A second monochromator after the sample compartment protected the photomultiplier from the flash light. The flash energies were typical between 200 and 400 J. The flash lamp was made from an air filled quartz tube, with a stainless steel electrode in each end. One of the electrodes was hollow. The flash was triggered by evacuating the quartz tube.

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