THE PHOTOCYCLIZATION OF N-ACYL-2-NITRODIPHENYLAMINES TO PHENAZINE N-OXIDES: SCOPE AND MECHANISM §

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Abstract - The photocyclization of N-acyl-2-nitrodiphenylamines to phenazine N-oxides is extended to several dinitro derivatives and a pyridine analogue obtaining N-oxides of otherwise difficult access. In the presence of some additives, the reaction takes a different course. Thus, with acids deacylation occurs, with triphenylphosphine a N-phosphoranylidene amine is formed and with 2,6-di-ter-butylphenol the corresponding nitrosodiphenylammine is obtained. A mechanism starting from the nitroamide triplet and involving several discrete intermediates is proposed in order to account for such observations.

A large number of synthetic methods for nitrogen heterocycles involve an intramolecular cyclization through the electrophilic attack of a low-valency nitrogen functionality, e.g. a nitrene, onto a neighboring aromatic ring. As far as phenazines are concerned, a typical such synthesis is the cyclization of 2-nitrodiphenylamines under either basic or acidic conditions by treatment with hydrazine and a catalyst[1] or by reduction with metal or salts.[2-5] A mixture of the base and the N-oxide is formed in some cases, and their ratio as well as the overall yield change greatly according to substrate and conditions. Some years ago, Maki et al reported that N-acyl-2-nitrodiphenylamines are

§ Dedicated to Professor Masatomo Hamana on the occasion of his 75th birthday

photochemically converted to phenazine N-oxides.[6] The product yields depend on the structure, and only in some cases are satisfactory. However, this synthesis deserves attention both in view of the mild conditions used and of the fact that the pure N-oxides, rather than these products mixed with the phenazines, are formed, and such substrates present a large potentiality for elaboration, apart from the simple deoxygenation to the azines.[7]

Previous authors investigated the photochemistry of N-phenyl-2-nitroacetanilides carrying an OMe, SMe, or COOMe group in position 2', as well as of some analogues containing a π-excessive heterocycle, viz 5-(1-methyl-4-nitropyrazolyl) and 3-(5-acetyl-2-nitrothienyl).[6] The aim of the present study is twofold, first to check the scope of the reaction, and accordingly we report the photochemistry of some dinitrodiphenylacylamines and of a pyridine analogue, and second, to obtain a deeper insight in the mechanism, in order to rationalize synthetic choices.

RESULTS

We first checked the occurrence of the reaction on parent 2-nitrophenylacetanilide (**1a**). Indeed, the amount of phenazine-N-oxide (**2a**) formed was almost 100% of the consumed **1a** when the irradiation of dilute solutions (10^{-4}M) was interrupted at a 25% conversion of **1a**. (Table 1, Scheme 1). Thus, the 5% yield of **2a** previously reported at total conversion is due to the well known secondary photodecomposition of **2a**,[8] as it had correctly been assumed.[6] Indeed, we checked that the products present at high conversion are those arising from the rearrangement of **2a**.

2,4-Dinitrodiphenylacetamide (**3**) was cleanly converted into 2-nitrophenazine 10-oxide (**4**) upon irradiation in benzene, dichloromethane, acetonitrile or methanol. A lower yield was obtained in 2-propanol. Because of the known photostability[9,10] of N-oxide (**4**) the yield did not decrease when the reaction was carried out until complete conversion of the substrate was reached, and the photochemical synthesis could be conveniently carried out on a 0.5 g scale.

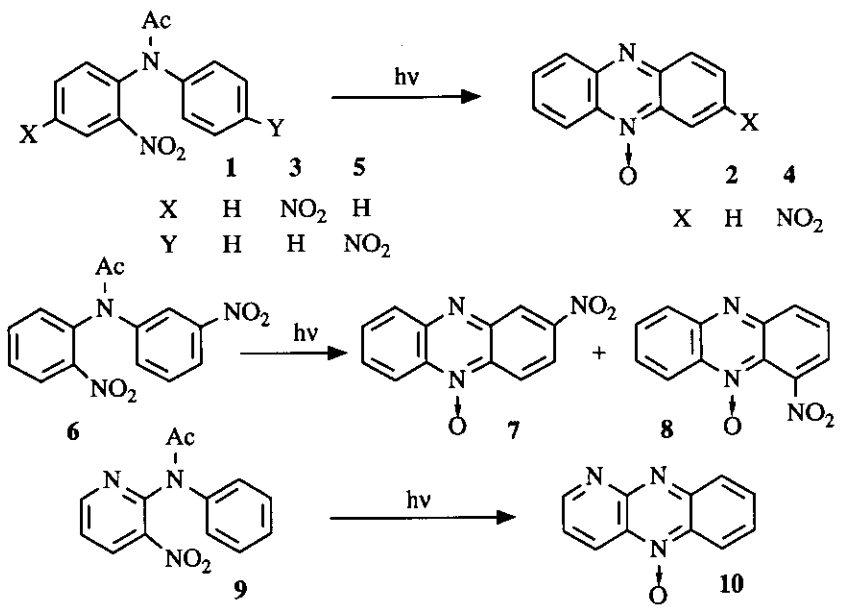
The N-oxide (**4**) was likewise obtained, again in good yield, by irradiation of 2,4'-dinitrodiphenylacetamide (**5**).

The two expected nitrophenazine N-oxides (**7**) and (**8**) were obtained from 2,3'-dinitrodiphenylacetamide (**6**) in roughly equal amounts. These were recognized by phosphorous trichloride deoxygenation to 2-nitro- and 1-nitrophenazines, respectively.

Table 1. Products from the Preparative Irradiation of Diphenylacetamides[a]

Substrate	Solvent	Irradiation Time	Substrate Conversion (%)	Products (% Yield)
1	Benzene[b]	5 min	25	**2**(80)
3	Benzene[b]	35 min	95	**4**(95)
3	Benzene[b,d]	35 min	95	**4**(98)
3	Acetonitrile[b]	35 min	95	**4**(95)
3	Benzene[b,e]	30 min	90	**4**(85)
5	Benzene[c]	19 h	90	**4**(88), **11**(5)
6	Benzene[c]	21 h	73	**7**(34), **8**(40)
9	Benzene[c]	30 h	78	**10**(40)

a. Deaerated solution, unless otherwise stated. B Irradiation by Pyrex-filtered light (see Experimental). c Irradiation by phosphor-coated lamp at 350 nm (see Experimental). d Air equilibrated solution. e In the presence of 10^{-2}M benzophenone.



Scheme 1

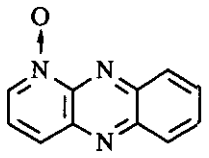
When N-acetyl-3-nitro-2-phenylaminopyridine (**9**) was irradiated in benzene, an analogous cyclization took place and pyrido[2,3-b]quinoxaline 5-oxide (**10**) was obtained. Irradiation of compound (**10**) in acetone converted it to the parent base. An attempt to reobtain **10** by 3-chloroperbenzoic acid oxidation of the pyridoquinoxaline revealed that the preferred position of oxidation was by far position 1 (to yield N-oxide (**10'**), see Experimental for spectroscopic characteristics) rather than position 5.

Encouraged by the satisfactory results of preparative irradiation, we carried out some trapping experiments aimed to obtain mechanistic information. Though the reaction was in general not strongly dependent on the medium characteristics (e.g. it resulted to be largely independent of solvent polarity and on its protic or nonprotic nature, and furthermore it was not affected by the presence of dissolved oxygen, see an example in Table 1), some selective trapping experiments were successful (Table 2). Thus, when the irradiation of amide (**5**) was carried out in the presence of 10^{-2} M CF_3COOH (TFA), the conversion of the starting material proceeded at about the same rate but it gave a much lower yield of the N-oxide and 90% yield of the amine (**11**). Similarly, the other amides when irradiated under these conditions underwent deacetylation to yield the amines (**12-14**) with corresponding reduction of the amount of cyclization products.

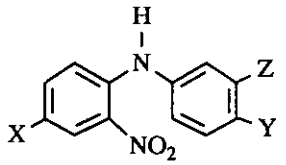
Table 2. Products from the Irradiation of Diphenylacetamides in Benzene in the Presence of Trapping Agents.[a]

Substrate	Additive, 10^{-2}M	Products (% Yield on Converted Amide)
1	TFA	**2**(25), **12**(57)
3	TFA	**4**(13), **13**(85)
5	TFA	**4**(5), **11**(90)
	TPP	**4**(3), **15**(9)
	DTBP	**4**(11), **16**(70)
6	TFA	**7**(8), **8**(10), **14**(78)

a. Irradiation by phosphor-coated lamps at 350 nm (see Experimental)



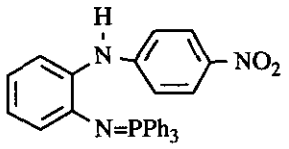
10'



	11	12	13	14
X	H	H	NO_2	H
Y	NO_2	H	H	H
Z	H	H	H	NO_2

The addition of triphenylphosphine (TPP) likewise caused an important change. From the amide(**5**)the yield of the cyclized product (**4**) strongly decreased and a new product was obtained as a yellow crystalline material. This was analyzed correctly for $C_{30}H_{24}N_3O_2P$, in accordance with the molecular peak at m/z 489 in the mass spectrum. Thus, the acetyl group was eliminated and one triphenylphosphine molecule was incorporated. In view of these and other spectroscopic evidences (see Experimental) which fit with known examples of N-phosphoranylidene amines[11] structure (**15**) was attributed to this compound.

Yet another successful trapping was obtained by using 2,6-di-tert-butylphenol (DTBP). Again, the yield of **4** from **5** decreased and a new product was formed. This appeared as a red-brown solid, giving an orange-red solution in ethanol which turned deep brown in the presence of bases. It was analyzed for $C_{12}H_9N_3O_3$ and was trasformed into 2,4'-dinitrodiphenylamine (**11**) by treatment with basic hydrogen peroxide. On this basis, and in accordance with the other spectroscopic properties (see Experimental) this compound was recognized as 2-nitroso-4'-nitrodiphenylamine (**16**).



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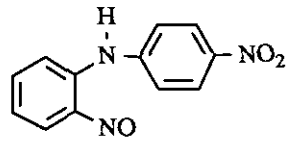

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Finally, some quantum yield measurements for the formation of the phenazine N-oxides from the amides were carried out (Table 3).

Table 3. Quantum Yields for the Formation of the N-Oxides in Benzene

Starting Amide	Φ (N-oxide) a	b	c
1	0.1	0.08	0.07
3	0.06	0.06	0.04
5	0.025	0.025	0.018

a. Degassed solution b. Air equilibrated solution c. Degassed solution containing 10^{-2}M benzophenone.

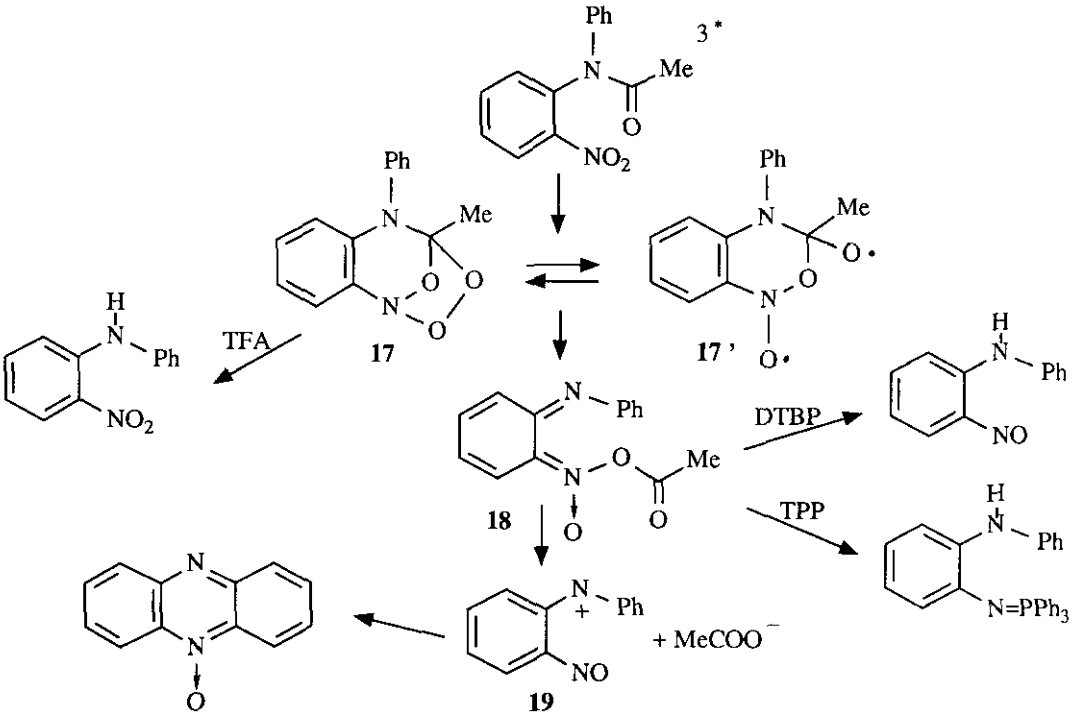
DISCUSSION

The results of this study, in conjunction with those previously reported by Maki[6] show that the photochemical cyclization of N-acyl-2-nitrodiphenylamines to phenazine N-oxides is a quite general process, relatively little affected by the presence of electron-donating or -withdrawing substituents. From the limited series of measurements we carried out, the quantum yield for the overall transformation also does not change much. Thus, this reaction is a general method which can be added to the other known cyclization methods from 2-nitrodiphenylamines and derivatives mentioned in the introduction. The limitation is in the well known photolability of N-oxides.[7,8,10] Indeed these compounds absorb at a longer wavelength than the starting substrate and react (in the case of parent phenazine N-oxide) with a similar quantum yield. Thus, it is difficult to carry the reaction to completion and to avoid extensive secondary photodecomposition. In this second reaction, the substituent effect is important, since it is known that the quantum yield of N-oxides rearrangement changes greatly according to the type and position of the substituent, though in a way that it is difficult to generalize. A rule that is possible to recognize, however, is that electron-withdrawing substituents strongly decrease the tendency to photorearrangement.[10] 2-Nitrophenazine 10-oxide is known to be quite photostable and apparently the other nitro N-oxides prepared here are also stable.

Thus the photoreaction of these substrates is preparatively useful. As shown in the

case of compounds (**7**) and (**8**), photocyclization offers a viable path for nitrophenazine N-oxides not accessible by nitration. Likewise, in the case of compound (**10**) a derivative not accessible by N-oxidation of the azine is obtained by cyclization. Notice further that the pyridoquinoxaline N-oxide (**10**) is photochemically deoxygenated rather than rearranged, a tendency known to increase with increasing aza substitution.[10] At any rate, deoxygenation of **10** is slow under the conditions of photocyclization of **9**, and the main product remains the N-oxide also in this case.

We consider now the mechanism of the amide photocyclization. The overall process involves elimination of acetic acid and formation of a new carbon-nitrogen bond, but this is obviously a multi-step process involving discrete intermediates. In our opinion, scheme 2 (referred to the parent substrate (**1**))adequately depicts the process. The Scheme in part incorporates previous proposals,[6] and is supported by the present trapping experiments.



Scheme 2

The reaction is initiated by the triplet state of the amide (see sensitization experiments); this has a radical character localized on the nitro group. This character of nitro aromatics in the triplet state is well known,[12] and there is a precedent for the attack of the nitro group onto the carbon-carbon double bond.[13] Thus, a fast (indeed not quenched by dissolved oxygen) intramolecular attack ensues, and leads to an "azaozonide" with strong diradical character (**17**). Accordingly, this collapses to the further intermediate (**18**), which can be considered a mixed anhydride of the nitro derivative in the aci form. In turn, **18** suffers heterolytic cleavage to yield the acetate anion (it is known that the corresponding acids are set free when similar amides are irradiated)[14] and the cation (**19**), which finally undergoes intramolecular electrophilic attack. Under our conditions an added acid (TFA) does not protonate the starting amides, but it is conceivable that intermediate (**17**), expected to be much more basic, is protonated and thus deacylation with conservation of the nitro group results. On the other hand, electron donors such as TPP and DTBP probably facilitate cleavage of intermediate (**18**). TPP has apparently a double function, viz deoxygenation and trapping of a nitrenic intermediate, as observed e.g. in the thermolysis of azides[11] and of 2,1-benzoxazole.[15] DTBP probably produces the 2-nitrosodiphenylamino radical and then transfers hydrogen to the same radical yielding the observed nitrosoamine.

In conclusion, the photocyclization of N-acyl-2-nitrodiphenylamides is a valuable method for the synthesis of phenazine N-oxides, and furthermore the present study shows that the reaction can be diverted to other products, also of potential synthetic interest.

EXPERIMENTAL

The starting amides were prepared by treatment of corresponding amines with acetic anhydride-zinc chloride[16] and the physical properties of amides (**1**, **3**, **5**) corresponded to literature data.[16,17] *2,3'-Dinitrodiphenylacetamide* (**6**) *and* *N-acetyl-3-nitro-2-phenylaminopyridine* (**9**) were analogously prepared from the amines.[18,19] Compound (**6**), almost colorless crystals, mp 125°C (MeOH). Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 55.81; H, 3.68, N, 13.95. Found: C, 56.02; H 3.72; N, 14.00. Compound (**9**), light yellow crystals, mp 112-13°C (EtOH). Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.69; H 4.31; N,16.34. Found: C, 60.85; H, 4.40; N, 16.25.

The spectra were taken with the following instruments. Ir: Perkin Elmer 287; nmr: Bruker 80 or 300 MHz; mass: Finnigan MAT; uv: Cary 19. Elemental analyses were

performed by means of a Carlo Erba microanalyzer.

Preparative irradiations. $5x10^{-3}$M solutions of the amides were reacted in either of the following ways: 1) 250 ml of solution in benzene or other solvents (see text) in a cylindrical vessel fitted with a Pyrex immersion well were brought to boil and then cooled to 17°C under an Argon stream, and irradiated for 5-60 min (see Table I) by means of a Helios Italquartz 125 W medium-pressure mercury arc; or 2) 150 ml of solution in benzene or other solvents in a Pyrex tube were deoxygenated by flushing with Argon for 20 min, then serum capped and irradiated for 15-30 h (see Table I) by means of six external 15W phosphor-coated lamps (emission centered at 350 nm). Deoxygenation was omitted or benzophenone or an other additive was added when required. In all cases the progress of the reaction was monitored by tlc, the irradiated solution was evaporated at reduced pressure, and the residue was chromatographed on silica gel Merck 60 HR eluting with cyclohexane-ethyl acetate mixtures from 8:2 to 1:1. Two of the products obtained (see Table 1) were identical to authentic samples (compounds **2**, **4**).[20]

2-Nitrophenazine 5-oxide (**7**), yellow-orange crystals, mp 191°C ($EtNO_2$). Anal. Calcd for $C_{12}H_7N_3O_3$: C,59.75; H,2.93; N,17.42. Found: C, 59.57; H, 2.94; N, 17.24. Nmr ($CDCl_3$) δ 8.85 (d, J=9, 1H) 8.8 (d, J=1, 1H), 8.3 (dd, J = 9,1, 1H), 8.4-8.6 (m, 2H), 7.85-8.0 (m, 2H).

1-Nitrophenazine 10-oxide (**8**), bright yellow crystals, mp 200°C ($EtNO_2$). Anal. Calcd for $C_{12}H_7N_3O_3$:C, 59.75; H, 2.93; N, 17.42. Found: C, 59.65; H, 2.99; N, 17.15. Nmr ($CDCl_3$) δ 8.55-8.75 (m, 1H), 8.2-8.45 (m, 2H), 7.75-8.0 (m, 4H). Spectroscopic properties and admixed mp showed that this compound was different from the known 1-nitrophenazine 5-oxide.[20]

Pyrido[2,3-b]quinoxaline 5-oxide (**10**), yellow crystals, mp 200-202°C ($EtNO_2$). Anal. Calcd for $C_{11}H_7N_3O$; C, 67.00; H, 3.58; N, 21.31. Found: C, 67.21; H, 3.65; N, 21.25. Mass spectrum, m/z 197. Nmr see Table 4 and discussion below.

N-(Triphenylphosphoranyliden)-2-(4-nitrophenylamino)benzenamine (**15**), yellow crystals, mp 178-180°C (EtOH). Anal. Calcd for $C_{30}H_{24}N_3O_2P$: C, 73.61; H, 4.94; N, 8.58. Found: C, 73.80; H, 4.95; N, 8.75. Mass spectrum, m/z 489. Nmr ($CDCl_3$) δ 8.05 and 7.1 (AA'BB' system, J = 9,4H), 7.4-7.8 (m, 15 H), 6.5-6.8 (m, 4H); ir (KBr), 1595, 1300, 1105 cm^{-1}.

4-Nitro-2'-nitrosodiphenylamine (**16**), orange crystals, mp 175°C (toluene). Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28 Found: C, 58.70; H, 2.50; N, 16.82. Mass spectrum, 243 m/z (weak peak at m/z 259). Nmr, ($CDCl_3$) δ 8.55 (br d, J = 8,1H) 8.3 and 7.4 (AA'BB' system, J = 9, 4H), 7.5 (dd, J = 1,7, 1H), 7.6 (ddd, J = 1,7,8, 1H), 6.9

(br t, J = 8, 1H), 11.1 (br, exchangeable, 1H).

Table 4. ^{1}H Chemical Shifts (δ) for Pyrido [2,3-b]quinoxaline Derivatives in Chloroform

	2-H	3-H	4-H	6-9, 9-H	7-H, 8-H
Base	9.4	7.8	8.6	8.25, 8.38	7.9
5-oxide (**10**)	9.4	7.7	9.1	8.7, 8.4	7.75, 7.9
1-oxide (**10'**)	9.1	7.8	8.8	8.25, 8.6	7.8, 7.9

Thermal deoxygenations. N-Oxides (**7**) and (**8**) (30 mg 0.15 mmol) were refluxed with 0.3 ml (1.4 mmol) of PCl_3 for 3 h, then the mixture was diluted with water, neutralized with aqueous ammonia, and extracted with $CHCl_3$. The residue from the organic layer was purified by passing through a filter of activated alumina. Compound (**7**) gave 15 mg (55%) of 2-nitrophenazine and compound (**8**) gave 20 mg (73%) of 1-nitrophenazine, identical with authentic samples.[20,21]

Oxidation of compound (**16**). To the red solution of compound (**16**) (30 mg, 0.12 mmol) in MeOH (1 ml) NaOH (50 mg, 1.25 mmol) was added. The solution turned to deep brown. 30% Aqueous hydrogen peroxide (100 μl, 0.9 mmol) was added. The solution turned orange and a precipitate began to separate. After 1 h, dilution with water and filtration yielded an orange material which was identical to 2,4'-dinitrodiphenylamine (32 mg, quantitative yield).

N-oxidation of pyrido[2,3-b]quinoxaline. The title compound (100 mg, 0.55 mmol) in chloroform (5 ml) was treated with 55% 3-chloroperbenzoic acid (173 mg, 0.55 mmol). After 3 h the solution was shaked with aqueous 5% $NaHCO_3$ and water and then dried over $MgSO_4$. Evaporation and silica gel chromatography of the residue eluting with 1:1 cyclohexane-ethyl acetate gave unreacted starting material (30 mg), N-oxide (**10**) (2 mg, 3%) as well as a yellow crystalline material (15 mg, 20%), mp 138-142°C ($EtNO_2$). Anal.Calcd for $C_{11}H_7N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 66.75; H, 3.39; N, 21.15. This was recognized as pyrido[2,3-b]quinoxaline 1-oxide on the basis of the comparison of the nmr spectrum with those of the base and the 5-oxide (Table 4). Notice the marked shift to higher field of 2-H a d 4-H in the 1-oxide and to lower field of 4-H and 6-H in the 5-oxide. These shifts fit well with the predicted effect of the N→O group, as it has been previously established.[22]

Quantum yield measurements. Measurements were effected on benzene solution of the amides (10^{-4}M) in 1 cm optical path spectrophotometric cells. These were degassed by five freeze-thaw-degas cycles at 10^{-5} mm Hg and irradiated on an optical bench by means of a focalized high-pressure mercury arc (Osram 200 W HB) monochromatized at 366 nm through an interference filter. The incident flux was of ca. 0.6×10^{-6} Einstein min^{-1} cm^{-2}. The formation of the N-oxide was monitored spectrophotometrically.

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