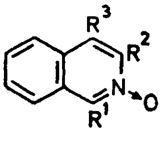
Primary Photoprocesses in Isoquinoline *N*-Oxides

By **Christian Lohse,*** Davy Faraday Research Laboratory of the Royal Institution, London W.1

The photoisomerization of isoquinoline *N*-oxides (I) in a variety of solvents was investigated by use of conventional and laser flash photolysis techniques, combined with fluorescence and quantum yield measurements. The formation of isoquinolones (II) in polar solvents and 1,3-benzoxazepines (III) in non-polar solvents proceeds *via* singlet excited states. A triplet excited state of isoquinoline *N*-oxides was observed and characterized, but was shown not to contribute to the photochemical reactivity. A possible oxaziridine intermediate could not be observed. Experiments with a laser flash showed that the isoquinolone was formed within 20 ns. Since the singlet lifetime is 1 ns, there is little time left for the formation of an intermediate. Parameters for the various modes of decay of the first excited singlet state (*e.g.* fluorescence quantum yields, radiative lifetimes, and quantum yield for product formation) were measured for reactions in various solvents. From these the rate constants of product formation were calculated. The rate of formation of isoquinolone is nearly solvent-independent: the rate of formation of oxazepine in polar solvents is 20 times slower than that of isoquinolone and 30 times greater in non-polar solvents.

THE photochemistry of heteroaromatic amine oxides has been the subject of a number of recent publications.[1-3] Quinoline *N*-oxide (IV) apparently undergoes only two main types of rearrangement. In polar hydroxylic solvents the photoproduct is the quinolone (V)[4-6] and in non-polar, non-hydroxylic solvents the photoproduct is 3,1-benzoxazepine (VI).[5,6] Furthermore, a small amount (2—5%) of the parent base, quinoline has been isolated in many cases.[1,5] Isoquinoline *N*-oxides have not been as fully investigated, but the available results[5,7,8] indicate that similar processes take place. The main photoproducts in polar solvents are isoquinolones, and in non-polar solvents, 1,3-benzoxazepines. This paper deals with some of the primary photoprocesses in the rearrangements of isoquinoline *N*-oxides.

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = Me$, $R^2 = R^3 = H$
c; $R^1 = R^2 = H$, $R^3 = Br$
d; $R^1 = PhCH_2$, $R^2 = R^3 = H$
e; $R^1 = PhCHMe$, $R^2 = R^3 = H$
f; $R^1 = R^3 = H$, $R^2 = Me$



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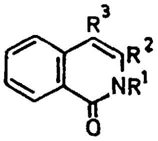

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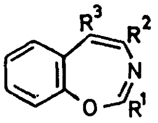

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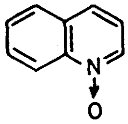

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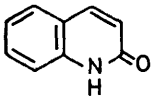

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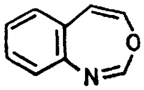

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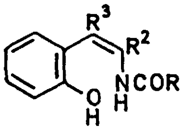

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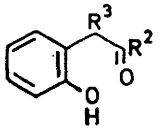

(VIII)

RESULTS AND DISCUSSION

Steady State Irradiations.—Irradiation of an isoquinoline *N*-oxide with either a hydrogen atom or an alkyl group in the 1-position in ethanol, gave the corresponding isoquinolone in high yield (Table 1). The yield of isoquinolone was significantly less when the *N*-oxides were irradiated in acetone. Furthermore, new photoproducts, derivatives of the phenol (VII) appeared. These are known[7] products of the hydrolysis of stable 1,3-benzoxazepines (the primary photoproduct from 1-cyano- and 1-phenyl-substituted isoquinoline *N*-oxides). This provides good evidence for the formation of 1,3-benzoxazepines as primary photoproducts in the photolysis of alkyl-substituted isoquinoline *N*-oxides in non-polar solvents.[8] Although the chemical yields from the irradiations do not account for all the *N*-oxide

TABLE 1

Starting material	Solvent (dielectric const.)	Product (%)
(Ia)	Ethanol (24·30)	(IIa) (67)
	Acetone (20·7)	(IIa) (8), (VIIa) (27)
(Ib)	Ethanol	(IIb) (74)
	Acetone	(IIb) (<10), (VIIb) (78)
(Ic)	Ethanol	(IIc) (90)
	Acetone	(IIc) (33)
(Id)	Ethanol	(IId) (82)
	Acetone	(IId) (<10), (VIId) (62)
(Ie)	Ethanol	(IIe) (49)
(If)	Water (80·30)	(IIf) (95)
	Ethanol	(IIf) (75)
	Acetone	(IIf) (26), (VIIf) (34), (VIIIf) (21)
	Ethylene chloride (10·65)	(IIf) (21)
	Ethyl acetate (6·02)	(IIf) (18)
	Benzene (2·28)	(IIf) (6·2)
	Carbon tetrachloride (2·24)	(IIf) (4·3)

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[1] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 231.

[2] C. Kaneko, S. Yamada, and M. Ishikawa, *Tetrahedron Letters*, 1970, 2329.

[3] J. Streith and P. Martz, *Tetrahedron Letters*, 1969, 4899.

[4] O. Buchardt, *Acta Chem. Scand.*, 1963, **17**, 1467.

[5] M. Ishikawa, S. Yamada, H. Hotta, and C. Kaneko, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1102.

[6] O. Buchardt, P. L. Kumler, and C. Lohse, *Acta Chem. Scand.*, 1969, **23**, 159.

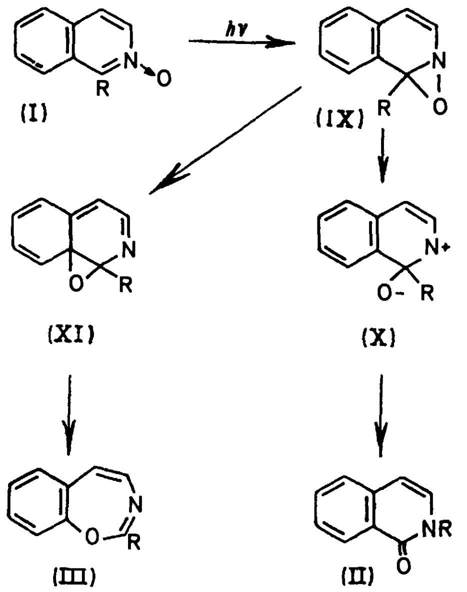
[7] O. Buchardt, C. Lohse, A. M. Duffield, and C. Djerassi, *Tetrahedron Letters*, 1967, 2741.

[8] C. Lohse, *Tetrahedron Letters*, 1968, 5625.

consumed, no isoquinolines were detected in the product mixture, in contrast to previous reports.[5]

In order to investigate the influence of the solvent further, 3-methylisoquinoline *N*-oxide was irradiated in a series of solvents with different dielectric constants. The results (Table 1) demonstrate a pronounced solvent effect. Comparison with the results for alkyl-substituted quinoline *N*-oxides [1] indicates strongly that a similar mechanism is operating.

The intervention of an oxaziridine intermediate has been suggested to explain the results in the photolysis of quinoline *N*-oxides.[1] If a similar reaction pathway is assumed to be operating in the photolysis of isoquinoline *N*-oxides the excited *N*-oxide will rearrange to give the oxaziridine (IX) (Scheme 1). In polar solvents, the next step involves the formation of the zwitterion (X), followed by a [1,2] shift of the alkyl group. In non-polar solvents, the pathway from the oxaziridine is formulated as a [1,5] sigmatropic shift to the epoxy structure (XI), followed by a new [1,5] shift to the oxazepine (III). This mechanism is attractive because the behaviour of alkyl-substituted *N*-oxides in different solvents can be explained in a convincing way.[1] But in spite of much work, oxaziridine intermediates have not so far been detected. We thought that conclusive evidence might be obtained by flash-spectroscopic studies.



SCHEME 1

Flash Photolysis.—By use of flash-spectroscopic techniques [9] it was possible to observe a short lived transient from a degassed solution of 1-methylisoquinoline *N*-oxide in ethanol (Figure 1). This transient is believed to be the triplet state of 1-methylisoquinoline *N*-oxide because (*a*) the decay is first order with a rate constant of $1{\cdot}3 \times 10^5$ s^{-1}; (*b*) it is quenched by oxygen; and (*c*) flashing of an ethanolic solution containing 1-methylisoquinoline *N*-oxide and anthracene through an anthracene filter permitted the observation of anthracene triplet–triplet absorption,[10] but not of the above transient.

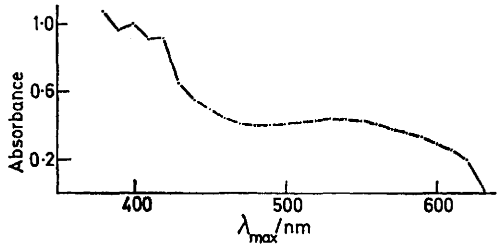


FIGURE 1 Triplet–triplet absorptions of 1-methylisoquinoline *N*-oxide, 4 μs delay

The triplet from 1-methylisoquinoline *N*-oxide as well as the triplet from other *N*-oxides were observed in different solvents (Table 2). The spectral region in which the absorption is observed and the absorption maxima and lifetimes are similar for all the observed transients. Since the photoproducts vary for these compounds, the possibility that the transients could be triplets of a photoproduct seems excluded. The conclusion was confirmed by flash photolysis of some isoquinolones. Transients were observed (Figure 2), but the absorption

TABLE 2

Triplet–triplet absorption of isoquinoline *N*-oxides

Compound	Solvent	Absorption region (nm)	First-order rate constant $10^{-5}k$/s^{-1}
(Ia)	Water	360—650, 389	4·9
	Ethanol	380—640, 396	1·3
	Cyclohexane	400—620, 418	2·8
(Ib)	Water	360—630, 388	1·3
	Ethanol	370—630, 395, 418	1·3
	90% Ethanol	370—640, 398	1·1
	Cyclohexane	400—620, 422	1·7
(Id)	Ethanol	380—620, 392	3·4
(Ic)	Water	370—650, 382	10·4
4-Bromo-1-cyano-isoquinoline *N*-oxide	Ethanol	410—620, 420	2·5
	Cyclohexane	420—650, 427	5·9

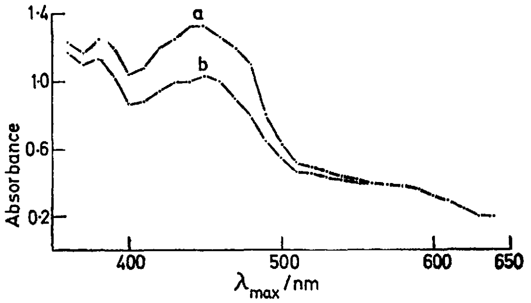


FIGURE 2 Transient from isoquinolone: a, 7 μs delay; b, 12 μs delay

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[9] G. Porter, 'Technique of Organic Chemistry,' ed. A. Weissberger, Interscience, New York, 1963, vol. 8, part II, p. 105

[10] G. Porter and M. W. Windsor, *Discuss. Faraday Soc.*, **1954**, **7**, 178.

spectra of these and their lifetimes were different from those of the corresponding *N*-oxides.

Table 3 shows the effect of degassing on the lifetime of the triplet from 3-methylisoquinoline *N*-oxide. Although the triplet is effectively quenched by oxygen, the quantum yield of product formation (Table 4) was found to be unaffected by degassing. Thus it is concluded that the observed photoproducts arise from an excited singlet state.

TABLE 3

Triplet lifetimes for 3-methylisoquinoline *N*-oxide

	First-order rate constant $10^{-5}k/\mathrm{s}^{-1}$	
Solvent	Degassed	Aerated
Cyclohexane	3·1	50
Ethyl acetate	2·5	62
Ethanol	2·2	62
Water	4·9	11

TABLE 4

Quantum yields (ϕ) for 3-methylisoquinoline *N*-oxide

Solvent	*N*-Oxide disappearance	Isoquinolone appearance	Oxazepine appearance (difference)	Yield of isoquinolone (%) Calc.	Found
Carbon tetrachloride	0·42	0·022	0·40	5·4	4·3
Ethyl acetate	0·31	0·035	0·27	12	17
Ethanol	0·19	0·15	0·035	76	75
Water	0·16	0·16	0	100	95
Cyclohexane	0·42	0·014	0·41		

The quantum yield for the disappearance of 1-methylisoquinoline *N*-oxide in cyclohexane and ethanol was found to be independent of the light intensity from the flash-lamps. Therefore, no photochemically formed intermediate is subject to a further photochemical reaction. The photoproducts are formed in two parallel reactions. If the number of photochemical steps in each is the same, the ratio of the quantum yields will be equal to the ratio of the chemical yields. This allows a calculation of the chemical yield from the quantum yield. Fair agreement is obtained between the calculated yields (Table 4) and those obtained by steady state irradiations. Although two or more photochemical steps could be involved in each of the photochemical rearrangements, the probability of only one photochemical step occurring, *i.e.* the excitation of the *N*-oxide, is high. Thus, there is good evidence for a monophotonic reaction.

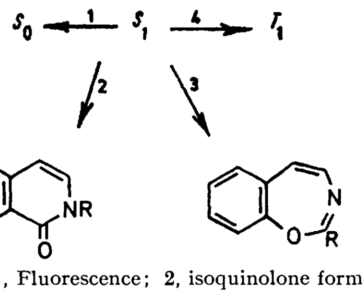
It was not possible to detect any common intermediates for the two photoproducts. On the contrary, there is evidence for the lack of such intermediates. Though no data could be obtained on the rate of formation of oxazepines, more informative results were obtained for the formation of isoquinolones. When a 5×10^{-5}M-solution of isoquinoline *N*-oxide in water was flash-photolysed, absorption bands identical with those of isoquinolone were observed after 4 μs, and their intensity did not change thereafter. Since isoquinolone is the only photoproduct from isoquinoline *N*-oxide in water the reaction is complete in 4 μs.*

A similar experiment using laser flash spectrophotometric measurements was unsuccessful because of a very low signal-to-noise ratio due to light absorption by the triplet and emission of fluorescence. However fluorescence measurements of solutions of isoquinoline *N*-oxide and isoquinolone in ethanol gave supplementary information. Both solutions were 5×10^{-4}M with the same optical density at 347 nm, the frequency doubled wavelength of the ruby laser pulse. The relative fluorescence intensities obtained by using a conventional fluorescence technique (*i.e.* low-intensity continuous excitation light source) were 0·299 for isoquinoline *N*-oxide and 1·00 for isoquinolone. However when identical solutions were excited with one *single* laser pulse (*e.g.* a high intensity light pulse) the fluorescence intensities were 0·450 and 1·00, respectively. The intensity of the laser pulse was 10^{14} times greater than that of the fluorimeter light source, and sufficiently intense to excite every single *N*-oxide molecule in the solution. Isoquinolone is however photostable under these conditions and the change in the ratio of the fluorescence intensities must therefore be due to a photochemical conversion of isoquinoline *N*-oxide during the light pulse.

Because isoquinolone is the main photoproduct from isoquinoline *N*-oxide in ethanol, and because the fluorescence of isoquinoline *N*-oxide changes significantly to resemble that of isoquinolone under the influence of a single laser pulse, it is inferred that the formation of isoquinolone takes place within the duration of one laser pulse, 20 ns.

The singlet lifetime of isoquinoline *N*-oxide is 1 ns.† The difference between this singlet lifetime and the apparent upper time limit for the formation of isoquinolone is not sufficient for the formation and subsequent thermal breakdown of any intermediate. It is thus concluded that there is no common intermediate giving rise to the two photoproducts.

Since the photochemical reaction takes place from the lowest excited singlet state, the parameters of this are important for a mechanistic discussion. Scheme 2



SCHEME 2 1, Fluorescence; 2, isoquinolone formations; 3, oxazepine formations; 4, triplet formations

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* If a 10^{-6}M-solution of isoquinoline *N*-oxide was flash-photolysed, a new transient with a lifetime of 60 μs appeared in the 310—640 nm region. This transient could not be observed for more concentrated solutions of isoquinoline *N*-oxide, but a transient with a similar lifetime and absorption was formed from a solution of isoquinolone (Figure 2).

† Measured with a pulse sampling fluorescence apparatus.[11] I thank Dr. G. S. Beddard for this measurement.

[11] L. Hundley, T. Coburn, E. Garwin, and L. Stryer, *Rev. Sci. Instr.*, 1967, **38**, 488.

shows the processes responsible for the decay of the first excited singlet state of 3-methylisoquinoline *N*-oxide. The quantum yields for processes 2 and 3 in five solvents are given in Table 4, and Table 5 shows the fluorescence quantum yields (ϕ_1), the reciprocal radiative lifetimes (k_1),* and the activation energies for the singlet decay ($E^{\ddagger}{}_{1\text{-}4}$). These values are sufficient to calculate the rate constants for product formation, k_2 and k_3 (Table 5).

TABLE 5

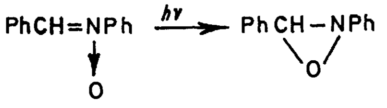
Parameters of the first excited singlet state of 3-methylisoquinoline *N*-oxide in various solvents [a]

Solvent	$10^3\phi_1$	$10^{-7}k_1$/ s^{-1}	$10^{-8}k_2$/ s^{-1}	$10^{-7}k_3$/ s^{-1}	$E^{\ddagger}{}_{1-4}$ cal
Water	3·8	1·07	4·51	<2·3	1410
Ethanol	5·2	1·66	4·66	14·4	1070
Ethyl acetate	1·1	2·17	6·92	536	2160
Cyclohexane	0·60	3·08	7·18	2100	1930
Carbon tetrachloride	0·43	3·14	17·0	3160	*ca.* 0

[a] Subscripts refer to processes shown in Scheme 2.

The change in the photoproduct distribution when changing from a polar to a non-polar solvent has previously been explained by the interaction of the solvent with a hypothetical oxaziridine intermediate.[1] However our experimental evidence indicates that the excited singlet state is the last species common to the two photoproducts. The solvent effect is clearly displayed in the magnitude of k_2 and k_3. These show that, whatever the mechanism might be, the rate of isoquinolone formation is largely independent of the solvent, and the solvent effect should be explained in terms of a change in the rate of oxazepine formation.

Many parameters in this reaction are very similar to those in the photochemical isomerization of *N*-benzylideneaniline *N*-oxide (XII) to diphenyloxaziridine



(XII) (XIII)

(XIII).[13] Both are singlet reactions,[14] the rates of product formation are of equal magnitude,[13] and the quantum yields change in a similar way from polar to non-polar solvents.[13] However, whereas it is well established that the primary photoproducts from nitrones are oxaziridines [$\tau_{1/2}$ (2,3-diphenyloxaziridine) *ca.* 2 h in ethanol [15]], the present work shows that a possible oxaziridine intermediate from isoquinoline *N*-oxides must have $\tau_{1/2} < 4$ µs (from the flash-photolysis results). This is a 10^9-fold decrease in the half-life, and the laser experiments indicate a 4×10^{11} times shorter half-life. Such a destabilization of an oxaziridine intermediate in the *N*-oxide rearrangements is difficult to explain by steric, or electronic considerations, and it seems likely that the mechanism in the photolysis of *N*-oxides is significantly different from that of nitrones.

EXPERIMENTAL

I.r. spectra were taken with a Perkin-Elmer Infracord and u.v. spectra with a Beckman DB instrument. Quantum yields were measured with a Perkin-Elmer 124 and fluorescence measurements were made with a Perkin-Elmer MPF-2A instrument. N.m.r. spectra were obtained with a Varian A60A instrument. G.l.c. was performed with a Varian Autoprep A 700 machine (SE 30 column). The spectroscopic flash photolysis apparatus was of standard design [9] and used with krypton–xenon filled lamps. The delay times were from 4 µs—5 s and were reproducible to ±10% or better. In flash experiments *N*-oxide concentrations from 5×10^{-4}—10^{-6}M were used. The kinetic laser flash photolysis apparatus has recently been described.[16] The *N*-oxide concentration in these experiments was adjusted until the optical density of the solution was 0·3—0·5 at 347 nm in a 1 cm cell.

1-*Methylisoquinoline* N-*Oxide*.—1-Methylisoquinoline (2·0 g) was heated with acetic anhydride (2 ml) and 35% hydrogen peroxide (6 ml) on a steam bath for 2 h, after which ice and sodium hydroxide were added. The homogeneous solution was extracted with chloroform, and the organic phase was dried ($MgSO_4$) and evaporated. The crude *N*-oxide was redissolved in dry ether (100 ml) and the solution was left in a water-saturated atmosphere at 4° for 4 weeks, after which 1-methylisoquinoline *N*-oxide dihydrate (2·7 g) was isolated, m.p. 28—30° (Found: C, 61·95; H, 6·3; N, 7·3. Calc. for $C_{10}H_{13}NO_3$: C, 61·55; H, 6·65; N, 7·2%).

Steady State Irradiations.—A 0·1% solution (w/v) of the *N*-oxide in ethanol or acetone was irradiated in argon until the *N*-oxide had been consumed. In general, photolysis was complete in 4—6 h for 250 mg samples. Evaporation of the solvent *in vacuo*, p.l.c. on silica gel, and crystallization yielded the products.

Identification of Photoproducts.—The isoquinolones (IIa),[17] (IIb),[18] and (IIf) [17] are known. Compound (IIc) was prepared from the oxide (Ic) by treatment with acetic anhydride. Compounds (IId) and (IIe) were prepared from the quinolone (IIa) by *N*-alkylation with benzyl bromide and 1-bromo-1-phenylethane, respectively. The identity of photochemical and synthetic isoquinolones was established by i.r. spectroscopy and mixed m.p.s.

Identification of N-(o-*Hydroxy-α-methylstyryl*)*formamide* (VIIf).—Hydrolysis of compound (VIIf) in M-hydrochloric acid yielded 2-methylbenzofuran,[19] ammonia, and formic acid. Hydrolysis in ethanol–water yielded 2-hydroxyphenylacetone.[20] Compound (VIIf) showed $\nu_{max.}$ (KBr) 3220 (NH), 2150, and 1650 (CHO) cm^{-1}, τ 0·16br (1H, s, OH), 0·82br (1H, s, NH), 1·65br (1H, s, CHO), 2·7—3·3 (4H, m, ArH), 4·25 (1H, m, HC=), and 7·85 (3H, d, *J* 1 Hz,

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* Calculated by use of the formula given by Bowen and Wokes.[12]

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Me). The structures of compounds (VIIa, b, and d) were assigned similarly.

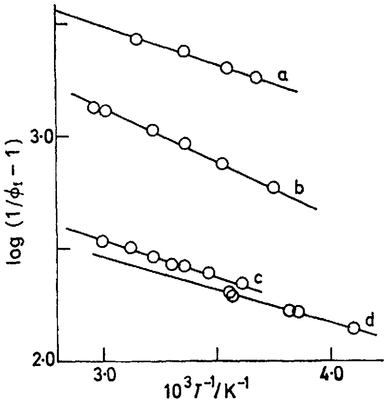

FIGURE 3 Temperature dependence of the fluorescence quantum yields of 3-methylisoquinoline *N*-oxide: a, cyclohexane; b, ethyl acetate; c, water; d, ethanol

Measurements.—The quantum yields were determined at 313 nm with a high pressure xenon lamp as source. The excitation part of a Perkin-Elmer spectrofluorimeter was used as monochromator. The half band width was 4 nm. Ferrioxalate was used as actinometer.[21] The disappearance of *N*-oxide was followed by u.v. spectroscopy. The appearance of isoquinolone was followed by emission spectroscopy, by comparing the fluorescence intensity of the irradiated solution with that of a standard solution of *N*-oxide and isoquinolone. The reaction was normally quenched at 10% conversion into photoproduct. Fluorescence quantum yields were found relative to anthracene. The procedure recommended by Parker was used.[22] From the temperature dependence of the fluorescence quantum yield (Figure 3) the activation energy for the singlet decay was calculated by use of the expression[23] $(1/\phi_f - 1) = k\exp(-E/RT)$. Phosphorescence could not be detected in a matrix at 77 K. Fluorescence lifetimes were measured with a pulse sampling fluorescence apparatus.[11]

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