Photochemistry of Quinoxaline 1-Oxide and Some of its Derivatives

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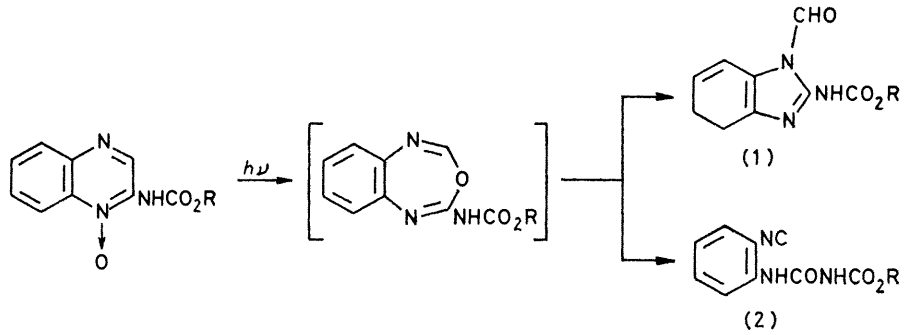
The solvent and substituent effects on the photoisomerization of quinoxaline 1-oxide were investigated. Irradiation in water afforded the corresponding quinoxalones if there was a hydrogen atom in position 2 or 3. However from 2,3-dimethylquinozaline 1-oxide the hydrolysis product of 3,4-dimethyl-3,1,5-benzoxadiazepine was isolated. 3,1,5-Benzoxadiazepines were formed as the main products under irradiation in cyclohexane from all the methyl derivatives, while the parent compound and 2-methoxyquinoxaline 1-oxide gave 2-isocyanophenyl derivatives. Both ring enlargement products and open-chain compounds have to be considered as primary photoproducts.

QUINOXALINE 1-OXIDE was the first aromatic amine *N*-oxide reported to isomerize on exposure to light.[1] However, information on the photochemistry of quinoxaline 1-oxide and its derivatives is limited, in contrast to the large number of papers concerning other azine *N*-oxides.[2] Both 2- and 3-phenylquinoxaline 1-oxides are known to give phenyl-3,1,5-benzoxadiazepine on irradiation in acetone or benzene,[3] while quinoxaline 1-oxide itself is known to give quinoxalone on irradiation in water.[1] Irradiation of some quinoxalinylcarbamate *N*-oxides yields benzimidazolylcarbamates or open-chain products, depending on the reaction conditions.[4] Burrel *et al.*[4] suggest that both compounds are secondary products formed from a 3,1,5-benzoxadiazepine which they postulate as the only primary photoproduct (Scheme 1).

It seemed worthwhile to proceed to a systematic examination of the photochemistry of quinoxaline *N*-oxides in order to ascertain whether the foregoing information is generally valid. In selecting the experimental conditions, the presence of substituent groups and the type of solvent (particularly whether protic or aprotic) were considered. It is well known that these have a major influence on the photochemistry of azine *N*-oxides, although it is not always clear whether this is an effect on the formation of primary photoproducts or on their stability.[2,5] The results described here concern the photochemistry, in water and in cyclohexane, of compound (3a) and of some of its derivatives (3b—e). All were unstable to irradiation with Pyrex-filtered light, after flushing with nitrogen. In all cases, products from processes involving rearrangement of the heterocyclic ring were found, with great differences according to the various substrates. A moderate yield of the parent azine was noticed in one case only (Scheme 2).



SCHEME 1

RESULTS

Irradiation in Water.—As shown in Table 1, the corresponding quinoxalones (4) were formed in almost quantitative yield in the cases with X = H [*e.g.* (3a) gave (4a) in 90% yield; lit. yield 20% [1]]. However, if a 2-methyl group was present, the shift of this group from C-2 to N was inefficient and if H was present at C-3 it was this H which was shifted (Scheme 3), while the substituent in position 2 was shifted to position 3. This process was previously observed in the case of 2-methylquinoline *N*-oxide.[6] If C-3 also bears a substituent, other processes predominate, *e.g.* from (3c), isomerization and hydrolysis take place to form (7c) as the main product.

Irradiation in Cyclohexane.—Under these conditions, products very unstable to moisture and heat were formed together with stable products such as (4) and (8). Chromatographic separation alone did not give satisfactory results as it yielded, besides the above-mentioned stable products, compounds formed by further thermal reaction of the unstable primary photoproducts. Therefore, the labile compounds were isolated first, usually by extraction and

[1] J. K. Landquist, *J. Chem. Soc.*, 1953, 2830.
[2] G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 231; F. Bellamy and J. Streith, *Heterocycles*, 1976, **4**, 1391.
[3] C. Kaneko, S. Yamada, Y. Yokoe, and M. Ishikava, *Tetrahedron Letters*, 1967, 1873.
[4] R. A. Burrel, J. M. Cox, and E. G. Savins, *J.C.S. Perkin I*, 1973, 2707.
[5] A. Albini, A. Barinotti, G. F. Bettinetti, and S. Pietra, *J.C.S. Perkin II*, 1977, 238.
[6] O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, 1963, **17**, 1461; M. Ishikava, S. Yamada, H. Hotta, and C. Kaneko, *Chem. and Pharm. Bull. (Japan)*, 1966, **14**, 1102.

crystallisation, and characterized spectroscopically. The reaction yield was then determined in further experiments using an appropriate spectroscopic technique directly on the irradiation mixture without separation (see Table 2).

TABLE 1

Yields of photoproducts of quinoxaline 1-oxides (3a—e) in water

Substrate	Products (%)
(3a)	(4a)(90), (7a)(5)
(3b)	(4b)(95)
(3c)	(4c)(13), (7c)(68), (8c)(8)
(3d)	(4d)(95)
(3e)	(4c)(15),* (7e)(38)

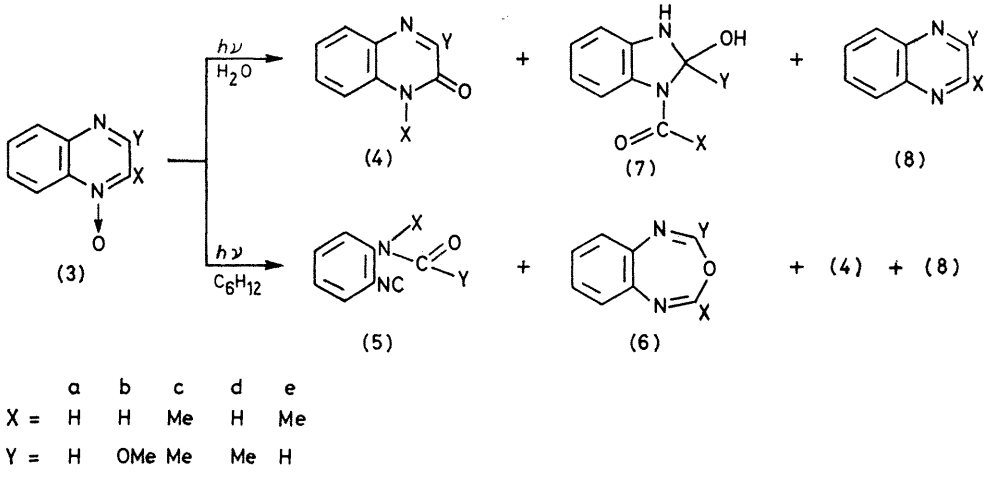
* Also a 45% yield of (4d).

Irradiation of the parent compound (3a) gave two products, one of which was insoluble in cyclohexane and was shown to be (4a). The other, the main product, was soluble in cyclohexane and could be crystallized from it as a low-melting solid, hygroscopic and with an unpleasant smell, and isomeric with the starting material. I.r. and n.m.r. spectra showed an isocyano and a formamido group to be present. These data and the reactivity of this compound showed it to be 2′-isocyanoformanilide (5a). Analogously, irradiation of the methoxy-derivative (3b) yields methyl (2-isocyanophenyl)carbamate (5b), a comparatively stable compound. As a shift of the methoxy group seems unlikely (see Scheme 2, Y = OMe), this shows that the C atom of the isocyano-group is C-2 while the O atom has shifted to C-3. This excludes the opposite hypothesis that the oxygen shifts to C-2 and a triple bond is formed between positions 5 and 6, which was also conceivable for the formation of (5a) from (3a). The methylquinoxaline *N*-oxides (3c—e) also gave very unstable products but of a different chemical nature; *e.g.* (3c) yielded only one product in addition to a small quantity of the deoxygenated product (8c). This compound is extremely soluble in hydrocarbons, hygroscopic, and gives off irritant vapours. It can be crystallized from light petroleum as a low-melting solid, isomeric with the starting material. In the n.m.r. spectrum all the aromatic proton signals coincide in a singlet at δ 7.1 and the methyl groups are equivalent; in the i.r. spectrum a strong band at 1 705 cm^{-1} is found, similar to that shown by the known benzoxadiazepines.[3] Therefore, this compound is identified as 2,4-dimethyl-3,1,5-benzoxadiazepine (6c). Both monomethylquinoxaline 1-oxides (3d and e) gave the same main product, which has properties analogous to (6c) and is therefore identified as 2-methyl-3,1,5-benzoxadiazepine (6d).

TABLE 2

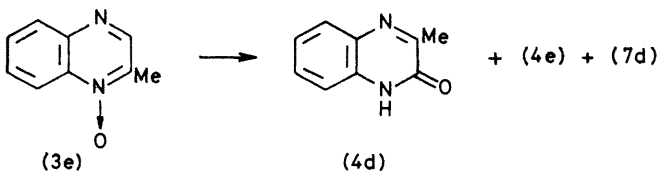
Yields of photoproducts of quinoxaline 1-oxides (3a—e) in cyclohexane

Substrate	Products (%)	
(3a)	(4a)(27), (5a)(65)	
(3b)	(5b)(80)	
(3c)		(6c)(90), (8c)(10)
(3d)	(4d)(23)	(6d)(70)
(3e)		(6e)(85)

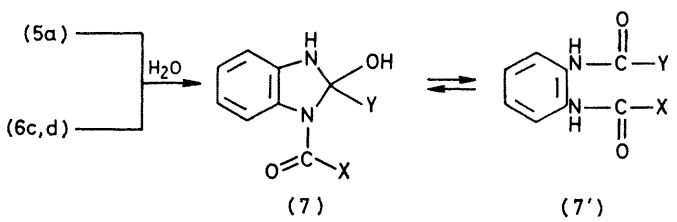


SCHEME 2

Chemical Properties of Compounds (5) *and* (6).—Benzoxadiazepines (6c and d) are extremely sensitive to moisture.



SCHEME 3

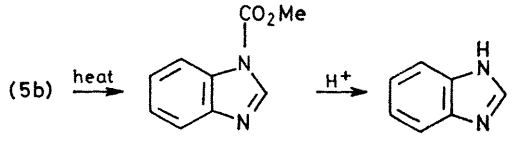


SCHEME 4

Compound (5a), which has a reactive isocyano-group, is also easily hydrated but less quickly. In each case *NN′*-diacylphenylenediamines (7′) or the corresponding cyclic tautomers, *i.e.* 1-acyl-2-hydroxydihydrobenzimidazoles (7) are formed (Scheme 4). These products, and not (5a) or (6c—d), are isolated if the reaction mixture is separated by chromatography. In connection with this work the

tautomerism (7) ⇌ (7′) has not been investigated more closely. However, in the case of (7a), n.m.r. and i.r. spectra are clearly asymmetric and are analogous to those of the known acyloxydihydroindoles; the u.v. spectra are also analogous.[7] Thus, the structure should be of type (7), at least in the tested conditions. In contrast, in the case of (7c), which has already been described as *NN′*-diacetylphenylenediamine,[8] the spectra are indeed symmetrical, and the structure should be of type (7′); (7d) has intermediate properties. As for (5b), it is more stable than (5a), and does not undergo hydration. However, this compound is thermally unstable and can only be crystallized in a quick operation. Otherwise, it reacts by insertion of the electron-deficient isocyano group into the amidic N–H bond to yield methyl benzimidazole-1-carboxylate (9) (Scheme 5), identified by its spectroscopic properties and its ready hydrolysis to benzimidazole.

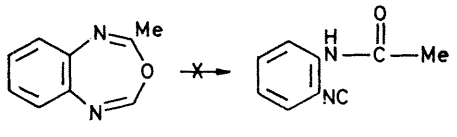
Possible Interconversion between Compounds (5) *and* (6).—It seemed important to investigate the possibility of interconversion between compounds (5) and (6), because when products similar to (5) were obtained from quinoxalylcarbamate *N*-oxides,[4] it was assumed that they were formed by acidolysis of an oxadiazepine, and furthermore because in the reactions described here (5) and (6) are never formed together. 2-Methyl-3,1,5-benzoxadiazepine (6d) was chosen to clarify this point as it can be considered



(9)

SCHEME 5

to be a reliable model of the chemical properties of the unknown unsubstituted benzoxadiazepine (6a) (the only difference being methyl group at C-2) and, having a hydrogen atom at position 4, could conceivably undergo the transformation to (5d) (Scheme 6). As the isocyano derivative (5a) is less unstable than the benzoxadiazepines (6c and d), we thought it should be possible to show the eventual formation of (5d). In fact, the formation of (5d) was not detected in the product from heating, hydrolysis, acidolysis, or further irradiation, although (5a) could be recovered from parallel experiments in a sufficient amount to be identified.



(6d) (5d)

SCHEME 6

DISCUSSION

The above results show a situation less simple than might have been anticipated for the photochemistry of quinoxaline *N*-oxides. As in the case of other azine *N*-oxides, the nature of the solvent has a dramatic effect on the formation of the photoproducts. Thus, quinoxalones (4) are mainly formed by irradiation in protic solvents if there is a H atom at C-2 or at least at C-3. However when both positions have a substituent compound (7), which can be considered as the product of direct hydration of a benzoxadiazepine, is formed predominantly. It appears that the preferential formation of quinoxalones in protic solvents requires an easily transferable H atom, otherwise the same rearrangement as in an aprotic solvent takes place. Conversely, appreciable amounts of quinoxalones are also formed by irradiation in aprotic solvents if a hydrogen atom is available at C-2. As for the photochemistry in aprotic solvents, 3,1,5-benzoxadiazepines (6), the expected ring-enlargement products, are indeed the main products in some cases. However, the open-chain products (5) also have to be considered as primary photoproducts, as it seems very unlikely that (5a) is formed *via* a hypothetical benzoxadiazepine (6a) if (6d) gives no open-chain products. Nevertheless it is obviously possible that the excited state of (3a) changes into (5a) *via* an oxadiazepine configuration without reaching the ground state in this configuration. In the light of these results

TABLE 3

Spectral data of photoproducts (5)—(7) and (9)

	N.m.r.[a]					
	H-3	H-4,-5	H-6	NH	CHO	I.r.[b] (cm^{-1})
(5a)	8.5(m)	7.4(m)		7.9(br)	8.6(s)	3 260m, 2 120s, 1 680s, 1 595s
(5b)	8.3(m)	7.4(m)	7.0(m)	7.5(br)		3 290m, 2 130s, 1 710vs
	ArH		H-2	Me		
(6c)	7.1(s)			2.2(s)		1 705vs
(6d)	7.1(s)		6.6(s)	2.2(s)		1 705vs, 1 645s
	ArH		H-2	NH, OH	CHO	
(7a)	7.3(m), 7.8(m)		8.4(d)	9.6(s)	8.3(s)	3 240s, 1 690s, 1 665s, 1 610m, 1 595m
(7c)	7.2(m), 7.6(m)			9.4(s)		3 220s, 1 670s, 1 620s
(7d)	7.2(m), 7.9(m)		8.4(d)	9.4(s)	8.3(s)	3 240s, 1 685s, 1 660s, 1 610m, 1 600m
	H-2	H-4	H-5, -6	H-7		
(9)	8.3(s)	8.0(m)	7.3(m)	7.8(m)		1 760vs, 1 610m

[a] Solvent CCl_4 for compounds (5) and (6), $(CD_3)_2SO$ for compounds (7), $CDCl_3$ for compound (9); internal standard $SiMe_4$. [b] Nujol mull.

[7] O. Buchardt, J. Becher, and C. Lohse, *Acta Chem. Scand.*, 1966, **20**, 2467.

[8] A. Bistrzycki and F. Ulffers, *Chem. Ber.*, 1890, **23**, 1876.

the mentioned effect of acids on the photoisomerization of quinoxalylcarbamate *N*-oxides [4] could possibly be attributed to a modification of the excited state rather than to decomposition of the primary photoproduct. The isolation of the benzoxadiazepines (6c and d) is the first example in which the photorearrangement azine *N*-oxide→1,3-oxazepine is actually proved in aza-naphthalene *N*-oxides not bearing a cyano- or a phenyl-group, although it has been postulated in many other cases.[2]

The substituent effect in the case described here is certainly remarkable: quinoxaline 1-oxide yields only the open-chain product (5) but the presence of a methyl group is sufficient to direct the reaction towards the exclusive formation of a ring-enlargement product. However, such a marked effect for a small structural change is typical of excited state reactions.

EXPERIMENTAL

U.v. spectra were recorded on a Perkin-Elmer 200 spectrophotometer, i.r. spectra on a Perkin-Elmer 257 spectrophotometer, and n.m.r. spectra on a Perkin-Elmer R12 instrument, using $SiMe_4$ as internal standard. Quinoxaline 1-oxide, 2-methoxyquinoxaline 4-oxide, and 2,3-dimethylquinoxaline 1-oxide were prepared and purified following literature methods.[9] Solvents were distilled before use (cyclohexane over Na).

Oxidation of 2-Methylquinoxaline.—Only poor yields of the two possible *N*-oxides were obtained by oxidation of this substrate, owing to the concurrent *C*-oxidation. 2-Methylquinoxaline (10.7 g),[10] 30% H_2O_2 (7.5 ml), and glacial acetic acid (80 ml) were heated together at 50 °C overnight. The mixture was basified, the precipitate collected, and the solution extracted with chloroform. The combined precipitate and extract were chromatographed on silica gel (eluant cyclohexane–ethyl acetate). The crude products were crystallized from cyclohexane to give 2-methylquinoxaline 1-oxide (3e) (0.9 g) and 2-methylquinoxaline 4-oxide (3d) (0.4 g), identified by comparison of their n.m.r. spectra [the signal of the H *ortho* to the *N*-oxide function group is shifted upfield: (3d), δ_{H-2} 8.3; (3e) δ_{H-3} 8.7]. This is consistent with a similar effect in other azine *N*-oxides.[11]

Photoreactions.—Solutions of (3) (4×10^{-3}M) were degassed by boiling and bubbling with nitrogen and irradiated with a medium-pressure, water-cooled mercury lamp (Hanau TQ 150) equipped with a Pyrex filter, until complete conversion of (3) had occurred. For the experiments in cyclohexane, the solvent was evaporated off at reduced pressure at room temperature, and the residue was treated in one of three ways. In one set of experiments, the residue was extracted with small amounts of cyclohexane (3a, b) or light petroleum (3c—e) and the unstable compounds (5a, b) and (6c and d) were crystallized. In a separate set of experiments, the residue was dissolved in CCl_4 and directly examined by n.m.r. and i.r. spectroscopy to determine the composition of the mixture. Only quinoxalones (4), if present, remained undissolved in these conditions. In a third set of experiments, the residue was chromatographed on silica gel. In this case only minimal, if any, amounts of compounds (5) and (6) were obtained. Instead, the hydration products (7), or the isomerisation product (9) in the case of (3b), were obtained in about the same yield, together with the stable products (4) and (8). For the experiments in water, the solutions were extracted with chloroform, the solvent was evaporated off, and the residue was chromatographed on silica gel.

Identification of the Photoproducts.—Products (4a—d) and (7c) were identical with authentic materials.[8,12] Elemental analyses of new compounds are listed in Table 4. Their identification was based on spectroscopic properties (the more relevant data are reported in Table 3) and on the chemical reactions reported below.

TABLE 4

Analytical data of new compounds

Compound	M.p. (°C) (solvent)	Found (%) C	H	N	Formula	Required (%) C	H	N
(3d)	90—92 (cyclohexane)	67.1	5.0	17.5	$C_9H_8N_2O$	67.5	5.0	17.5
(3e)	115—118 (cyclohexane)	67.5	5.1	17.4	$C_9H_8N_2O$	67.5	5.0	17.5
(5a)	82—84 (cyclohexane)	65.5	4.7	19.2	$C_8H_6N_2O$	65.8	4.1	19.2
(5b)	81—83 (petroleum)	61.3	4.7	15.9	$C_9H_8N_2O_2$	61.4	4.6	15.9
(6c)	71—73 (petroleum	68.5	5.8	15.8	$C_{10}H_{10}N_2O$	69.0	5.8	16.1
(6d)	53—55 (petroleum)	67.2	5.4	17.2	$C_9H_8N_2O$	67.5	5.0	17.5
(7a)	156—157 decomp. (water)	58.7	5.2	17.2	$C_8H_8N_2O_2$	58.5	4.9	17.1
(7d)	103—104 (water)	60.6	5.9	16.1	$C_9H_{10}N_2O_2$	60.7	5.7	15.7
(9)	90—91 (cyclohexane)	61.1	4.7	16.0	$C_9H_8N_2O_2$	61.4	4.6	15.9

Hydration of Compounds (5) *and* (6).—Compounds (5a and b) or (6c and d) (20 mg) were dissolved in water-saturated ether at room temperature. Compounds (5a) (1 h) and (6c and d) (10 min) were completely converted into the corresponding hydration products (7). In these conditions (5b) was converted (1 h) into its isomer (9).

Thermal Conversion of (5b).—(*a*) A sample of (5b) brought to its m.p. and immediately cooled was completely transformed into (9).

(*b*) (5b) (20 mg) was refluxed in cyclohexane (1 ml) for 3 h and was quantitatively isomerized into (9).

Hydrolysis of (9).—Compound (9) (20 mg) was refluxed in EtOH (1 ml) containing a trace of HCl. In 5 min (9) was quantitatively converted into benzimidazole, identical with an authentic sample.

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[10] R. W. Bostand and E. E. Towell, *J. Amer. Chem. Soc.*, 1948, **70**, 903.

[11] K. Tori, M. Ogata, and H. Kano, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 681.

[12] O. Hinsberg, *Annalen*, 1896, **292**, 245; G. W. H. Cheeseman, *J. Chem. Soc.*, 1955, 1804; F. Kehrmann and J. Messinger, *Ber.*, 1892, **25**, 1627; S. Ruhemann and J. Stapleton, *J. Chem. Soc.*, 1894, **77**, 249; O. Kühling and O. Kaselitz, *Ber.*, 1906, **39**, 1314.

Attempted Isomerisation of (6d) *to* (5d).—2-Methyl-3,1,5-benzoxadiazepine (6d) (20 mg samples) was subjected to the following treatment; (*a*) refluxing (10 min) in cyclohexane; (*b*) treatment with water-saturated ether at room temperature (5 min); (*c*) treatment with ether containing a trace of HCl at room temperature (5 min); (*d*) irradiation in cyclohexane solution (10 min). In none of these cases did the product obtained show the isonitrile band in the i.r. spectrum. In parallel experiments on (5a), sufficient amounts of unchanged compound could be recovered and identified after any of the above-mentioned treatments.

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