Photochemistry of Methoxy-substituted Quinoline and Isoquinoline *N*-Oxides

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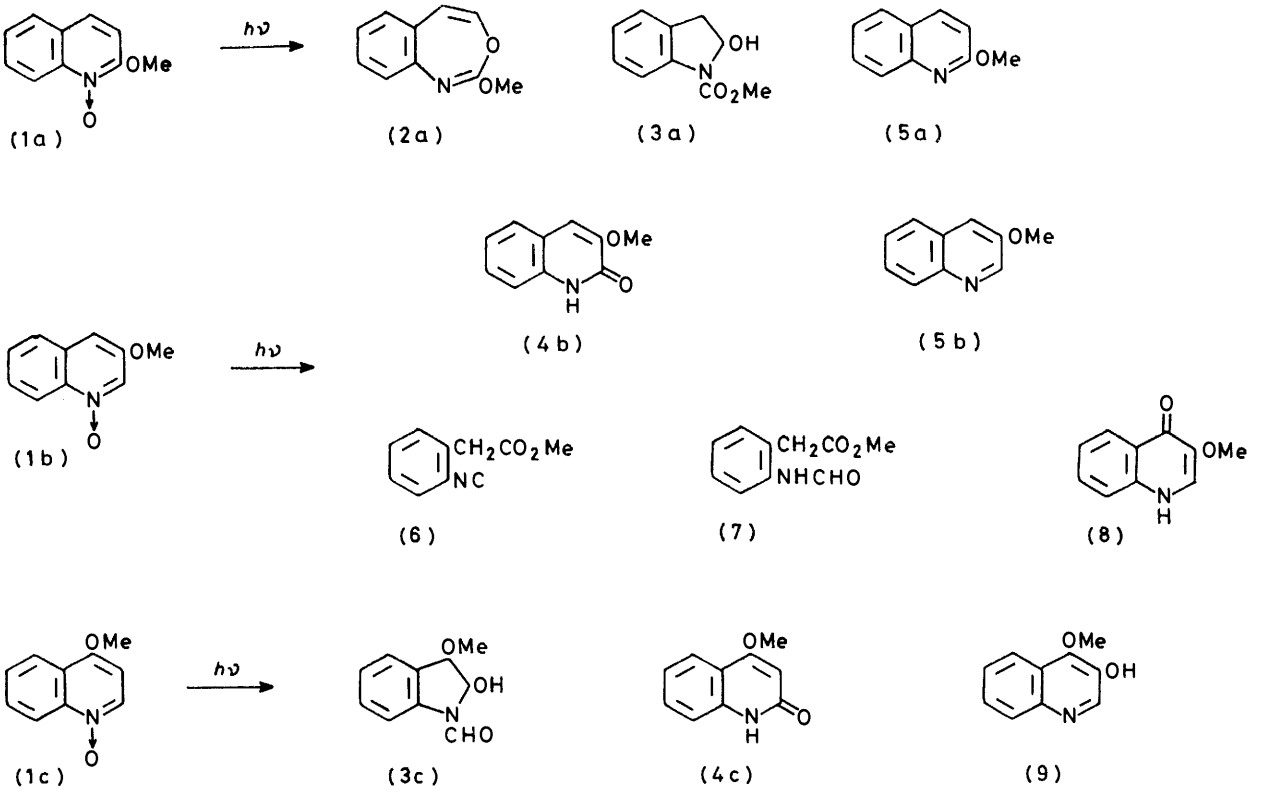
The photochemistry of quinoline 1-oxides and isoquinoline 2-oxides bearing a methoxy-group in the pyridine ring was investigated in protic and aprotic media. The formation of various photoisomers, *viz.* 3,1-benzoxazepines, 2(1*H*)-quinolones, *N*-(2-isocyanobenzyl)formamides, 4(1*H*)-quinolones, and 3-hydroxyquinolines from the different methoxyquinoline 1-oxides, and 1,3-benzoxazepines and 1(2*H*)-isoquinolones from the different methoxyisoquinoline 2-oxides, was observed along with deoxygenation and formation of products derived from hydration and decomposition of the primary products. The position of the methoxy-group has an important directing effect on the photoreactions.

RECENT investigations on the photochemistry of heteroaromatic *N*-oxides have shown the situation to be rather complicated, with different processes occurring for different heterocyclic systems.[1-4] Furthermore, introduction of substituents and the choice of solvent (particularly protic *vs.* aprotic solvents) may dramatically affect the course of the photochemical reactions. We have therefore embarked on a systematic study of the effect of the methoxy-group, which has hitherto been neglected. The present study is concerned with the effect on the photochemistry of quinoline 1-oxide and isoquinoline 2-oxide of the introduction of a methoxy-group into the pyridine ring. The substrates chosen are, from a photochemical point of view, two of the most intensively investigated heteroaromatic *N*-oxides.



SCHEME 1

RESULTS

Owing to the strong effect of protic solvents on the photoisomerization of heteroaromatic *N*-oxides, the photochemistry of the methoxyquinoline 1-oxides (1a—c) and of the methoxyisoquinoline 2-oxides (11a—c) was investigated under two extreme conditions: in an anhydrous hydrocarbon (cyclohexane or benzene) and in water.

Irradiation of 2-methoxyquinoline 1-oxide (1a) in cyclohexane gave almost quantitatively an oil, which was identified as 2-methoxy-3,1-benzoxazepine (2a) on the basis of spectroscopic evidence (strong i.r. absorption at 1 690

cm^{-1}; AB pattern for H-4 and -5 in the n.m.r. spectrum; mass spectrum characterized by an initial loss of *m/e* 30, then identical with that of 3,1-benzoxazepine).

Compound (2a) is less unstable and hygroscopic than 3,1-benzoxazepine and was partially recovered after chromatography on a short silica-gel column. Elution through a longer column completely decomposed (2a), yielding mainly a hydration product, methyl 2-hydroxyindoline-1-carboxylate (3a), as a crystalline solid. This kind of hydration is a general process among 3,1-benzoxazepines.[3-5] The rather complicated ABMX pattern in the n.m.r. spectrum of (3a) was simplified after exchange with D_2O.

Direct chromatography of the irradiation mixture also gave a high yield of (3a). This same compound was also obtained as the main product from the irradiation of (1a) in water.

TABLE 1

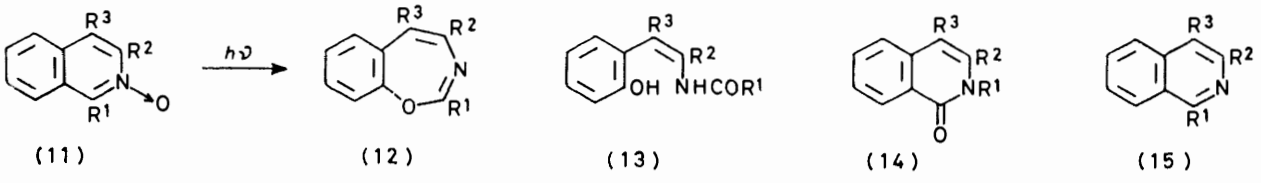
Photoproducts from quinoline *N*-oxides (1a—c)

Starting *N*-oxide	Solvent	Isolation Procedure [a]	Products [Yield (%)]
(1a)	C_6H_{12}	Extraction	(2a) [90]
(1a)	C_6H_{12}	Chromatog.	(3a) [64]
(1a)	H_2O	Chromatog.	(3a) [75]
(1b)	C_6H_{12}	Extraction	(6) [40]
(1b)	C_6H_{12}	Chromatog.	(5b) [17], (6) [40], (7) [24], (8) [26]
(1b)	H_2O	Chromatog.	(4b) [42], (7) [43]
(1c)	C_6H_{12}	Chromatog.	(3c) [45], (4c) [10], (9) [20]
(1c)	H_2O	Chromatog.	(4c) [95]

[a] See Experimental section.

The photolysis of (1b) in cyclohexane yielded a complex mixture. Chromatography afforded four main products, identified as (5b), (6), (7), and (8). Compound (6), an oil, was very soluble in cyclohexane. It is isomeric with the starting *N*-oxide, and was identified on the basis of its spectra, which showed the presence of an isonitrile group (i.r. absorption, and loss of *m/e* 26 from the parent ion in the mass spectrum), a carboxymethyl group, and a methylene group.

The formation of product (7) involves the addition of one molecule of water. Its structure was readily determined from its spectroscopic properties.

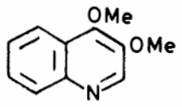


(11) (12) (13) (14) (15)

	R1	R2	R3
a;	OMe	H	H
b;	H	OMe	H
c;	H	H	OMe

SCHEME 2

Product (8), a crystalline material isomeric with the starting compound, showed a carbonyl absorption in its i.r. spectrum, but differed from the expected 2-quinolone (4b) (see below). The structure of 3-methoxy-4(1*H*)-quinolone was confirmed by the n.m.r. spectrum, which showed the NH group to be vicinal to a CH group, and also showed that the carbonyl group is in an α position, causing a strong deshielding of an aromatic proton in the carbocyclic ring. All these compounds were stable to chromatography on silica gel. Extraction of the residue from the irradiated solution using cyclohexane yielded only (6) and some (5b).



(10)

The photolysis of (1b) in water afforded two crystalline products, *viz.* the aforementioned (7) and 3-methoxy-2(1*H*)-quinolone (4b).

Irradiation of (1c) in cyclohexane gave likewise a complex mixture. Chromatography yielded some 4-methoxy-2(1*H*)-quinolone together with two more major products. The first, a hydration product, was identified as 2-hydroxy-3-methoxyindoline-1-carbaldehyde (3c) owing to the similarity of its properties with those of the analogous derivative

TABLE 2

Photoproducts from isoquinoline *N*-oxides (11a—c)

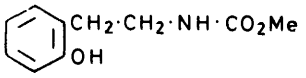
Starting *N*-oxide	Solvent	Isolation Procedure [a]	Products [Yield (%)]
(11a)	C_6H_{12}	Extraction	(12a) [40]
(11a)	C_6H_{12}	Chromatog.	(13a) [9], (15a) [38]
(11a)	H_2O	Chromatog.	(13a) [22], (15a) [22]
(11b)	C_6H_6	Extraction	(12b) [50]
(11b)	C_6H_6	Chromatog.	(14b) [16], (17) [8], (18) [16]
(11b)	H_2O	Chromatog.	(14b) [83]
(11c)	C_6H_6	Chromatog.	(14c) [14], (15c) [18]
(11c)	H_2O	Chromatog.	(14c) [20], (15c) [15]

[a] See Experimental section.

mentioned previously. The second, which was isomeric with the starting *N*-oxide, was identified as 4-methoxyquinolin-4-ol (9), its chemical and spectroscopic properties indicating the presence of a phenolic group. Compound (9) was methylated to yield compound (10), an *ortho*-dimethoxy-derivative (shown, *inter alia*, by subsequent losses of CH_3 and CO in its mass spectrum). Irradiation of (1c) in water yielded (4c) in almost quantitative yield.

Of the methoxy-substituted isoquinoline 2-oxides, 1-methoxyisoquinoline 2-oxide (11a) gave, on irradiation in benzene, a moisture-sensitive oil in good yield, isolated by

extraction of the irradiation mixture with a little cyclohexane, and identified as 2-methoxy-1,3-benzoxazepine (12a) (strong i.r. absorption at 1 665 cm^{-1}, AB n.m.r. pattern, mass fragmentation analogous to that of 2-cyano- and 2-phenyl-1,3-benzoxazepine). This product decomposed on chromatography, yielding the phenol (13a), whose formula was supported by its spectral characteristics. [As one of the olefinic signals in the n.m.r. spectrum was submerged under the aromatic signal, this compound was



(16)

hydrogenated to yield (16). The spectrum of this latter product could be assigned unambiguously, thereby confirming the proposed structure of (13a).]

Another important product from the irradiation in benzene of (11a) was 2-methoxyisoquinoline (15a). This product was also obtained, together with the phenol (13a), when the photolysis was carried out in water.

3-Methoxyisoquinoline 2-oxide (11b) gave on irradiation in benzene the moisture-sensitive benzoxazepine (12b). Chromatography of this product or of the irradiation mixture yielded a complex mixture from which, as the two main products, were isolated, methyl (2-hydroxyphenyl)-acetate (17) and 2-formylamino-2-methoxy-2,3-dihydrobenzofuran (18). Identification of the former was by direct comparison with an authentic sample, while that of the latter was on the basis of spectroscopic evidence, particularly the i.r. and the n.m.r. spectrum, which showed *inter alia* the presence of a methylene group with non-equivalent protons. As is often the case with formamide derivatives, the formyl proton gives two signals corresponding to the two rotameric conformations (that at lower field coupled with the NH proton). Formation of the amide acetal (18) and the hydrolysis product (17) is rationalized as involving the intermediacy of compound (13b), the expected hydration product of the benzoxazepine (12b).

Irradiation of (11b) in water yielded 3-methoxy-1(2*H*)-isoquinolone (14b), which was also obtained as a minor product in the photolysis in benzene.

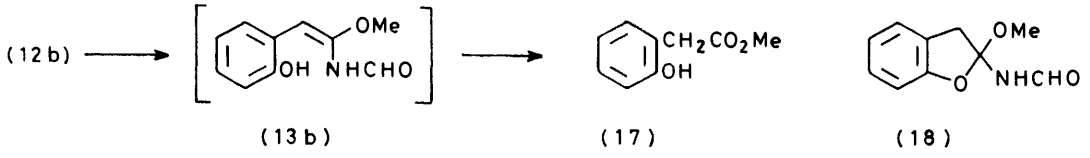
No solvent effect was observed for the photochemistry of 4-methoxyisoquinoline 2-oxide (11c); 4-methoxy-1(2*H*)-isoquinolone (14c) and 4-methoxyisoquinoline (15c) were obtained from irradiations in both benzene and water.

TABLE 3

Relevant spectroscopic data for photoproducts

Product	N.m.r.[a]	I.r.[b]
(2a)	6.35 (s, H-2), 5.75 (d, *J* 6, H-4), 5.55 (d, H-5) [c]	1 680vs, 1 640s
(3a)	6.1 (dd, *J* 6, 2, H-2), 3.35 and 3.2 (2 d, CH_2) [d,e]	3 430s, 1 680vs
(3c)	5.9 (s, H-2), 4 (s, H-3), 8.9 (s, CHO) [d,e]	3 250m, 1 670vs
(6)	3.66 (s, CH_2), 3.64 (s, OMe) [c]	2 125vs, 1 745vs
(7)	3.65 (s, CH_2), 8.5 (s, CHO), 8.55 (s, NH) [d]	3 200br, 1 740vs
(8)	7.85 (d, *J* 3, H-2), 8.1 (m, H-5), 8.75 (s, NH) [d]	3 250s, 1 670s
(9)	8.8 (s, H-2), 9.6 (s, OH) [d]	3 420s
(12a)	6.25 (d, *J* 9, H-4), 6 (d, H-5) [c]	1 665vs, 1 620vs, 1 610s
(12b)	6.55 (s, H-2), 5.45 (s, H-5) [c]	1 640s, 1 615s
(13a)	5.55 and 6.8 (2 d, olefinic) [d,e]	3 340vs, 3 230br, 1 700vs
(18)	3.55 and 3.4 (br, CH_2), 8.15 (s) and 8.42 (d, *J* 12) (CHO) [d]	3 240s, 1 700s, 1 670s

[a] Chemical shifts as δ values, coupling constants in Hz, tetramethylsilane as internal standard. [b] For neat liquids or Nujol mulls; $\nu_{max.}$ in cm^{-1}. [c] In CCl_4. [d] In $CDCl_3$. [e] After shaking with D_2O.



(12b) (13b) (17) (18)

SCHEME 3

DISCUSSION

In discussing the effect of substituents on the photoisomerization of heteroaromatic *N*-oxides, we must distinguish between the effects of substituents on the stability of the photoproducts, and the authentic directing effects of substituents on the course of the photochemical isomerisation. As an example, we consider the cases of quinoline and quinoxaline *N*-oxides. In aprotic solvents quinoline 1-oxide is photoisomerized to 3,1-benzoxazepine, a very unstable compound. The introduction of a cyano-group at position 2 makes the photoproduct much easier to be isolated, without changing the course of the photoreaction.[3,4] Under the same conditions, however, quinoxaline 1-oxide is photoisomerized to *N*-(2-isocyanophenyl)formamide, but if a cyano or a methyl group is introduced at positions 2 or 3, the isomerization is directed towards formation of the corresponding 3,1,5-benzoxadiazepines. These compounds are stable when a cyano-group is present, but they are very sensitive in the presence of a methyl group.[2] Thus, in this case, directing and product-stabilizing effects are clearly distinguished.

The present results show that introduction of a methoxy-group can affect the photochemistry of quinoline 1-oxide, the effect depending on the position of the substituent. Discussing first the photochemistry in aprotic solvents, it can be concluded that the presence of a methoxy-group at position 2 does not change the course of the photoreaction: the product is a 3,1-benzoxazepine, as is obtained from the parent compound. Furthermore, the methoxy-group has a marked stabilizing effect on the benzoxazepine. Thus, introduction of a methoxy-group at position 2 has the same effect as a phenyl or cyano-group at the same position. This effect appears to be general for all conjugating groups.

On the contrary, a methoxy-group at position 3

causes photoisomerization to different products, the isonitrile (6) and the 4(1*H*)-quinolone (8), the expected benzoxazepine (2b) not being formed. Analogous isonitrile derivatives formed by isomerization of quinoxaline 1-oxides have been demonstrated to be primary photoproducts, not derived from an oxazepine.[2]

In the case of methoxy-substitution at position 4, it is more difficult to distinguish whether a benzoxazepine is formed but not found owing to its excessive instability, or whether it is not formed at all, the hydration product (3c) being derived from some other source (the latter hypothesis seems more likely, as even unstable 3,1-benzoxazepines could be detected, even if not isolated, in previous cases). The formation of 4-methoxyquinolin-3-ol (9) from (1c) has precedent in an analogous photoreaction of 2-cyano-4-methoxyquinoline 1-oxide.[6]

It may be further discussed whether the formation of both the benzoxazepines and the other photoisomers occur through a common intermediate; this is, however, clearly a matter of speculation. All these photoisomerizations can be interpreted using the traditional hypothesis of a sequence of sigmatropic shifts and valence isomerizations from an initially formed oxaziridine.[3] However, if one takes into account the evidence from the photoisomerization of trinuclear heteroaromatic *N*-oxides, in which the C-2–C-3 axis becomes perpendicular to the original molecular plane during some of the photo-processes,[7,8] it is perhaps simpler to postulate that in this case also the molecule undergoes a strong deformation upon electronic excitation, allowing attack of oxygen at position 3 [which would account for the formation of the oxazepines (2), the isonitrile (6), and the quinolinol (9)] and even at position 4 [accounting for the formation of the 4-quinolone (8)], without formation of an intermediate oxaziridine being required.

In water, the photochemistry of the methoxyquinoline 1-oxides is, as is usually the case, markedly different, isomerization to 2(1*H*)-quinolones becoming important or even predominant, except for 2-methoxyquinoline 1-oxide. This is in accord with the generalization that these processes predominate in protic media, provided that an H atom or an alkyl group is present at position 2.

The effect of methoxy-substitution on the photochemistry of isoquinoline 2-oxide appears to be less pronounced. In aprotic media, 1,3-benzoxazepines, the same products as obtained from the parent *N*-oxide, are formed from 1- and 3-methoxyisoquinoline 2-oxides, although not from the 4-methoxy-isomer. While the unsubstituted 1,3-benzoxazepine is excessively elusive, the two methoxy-1,3-benzoxazepines are sufficiently stable to allow characterization, although they decompose more readily than the corresponding 3,1-benzoxazepines, a difference probably due to the propensity to polymerization of the dienic system present in 1,3-benzoxazepines.[5]

1(2*H*)-Isoquinolones are formed upon photolysis of the methoxyisoquinoline 2-oxides in water, unless the methoxy-group is in position 1. 4-Methoxyisoquinoline 2-oxide behaves somewhat anomalously, as the formation of the corresponding isoquinolone is the only photoisomerization observed both in protic and aprotic media. The deoxygenation to the corresponding isoquinolines appears to be more important than the analogous process from quinoline 1-oxides.

EXPERIMENTAL

N.m.r. spectra were obtained with a Perkin-Elmer R12 spectrometer. I.r. spectra were recorded on a Perkin-Elmer 257 spectrometer and mass spectra on a Du Pont spectrometer. Spectroscopic grade solvents were used as received. The methoxyquinoline *N*-oxides (1a)[9] and (1c)[10] were prepared and purified as described in the literature. Other *N*-oxides were prepared as follows.

3-*Methoxyquinoline* 1-*Oxide* (1b).—Quinolin-3-ol[11] (8.5 g) in methanol (200 ml) was treated with an excess of diazomethane. The solution was left overnight and then evaporated and treated with 2N-NaOH (30 ml). Extraction with chloroform, evaporation of the solvent, and steam-distillation yielded 3-methoxyquinoline[12] (4 g, 43%). After dissolution in acetic acid (6 ml) H_2O_2 (40%; 2 ml) was added and the mixture was heated at 70 °C for 4 h. Further H_2O_2 (40%; 1.5 ml) was then added and the heating was continued for a further 3 h. The mixture was cooled, basified with 10% NaOH, and extracted with chloroform. Evaporation yielded 3-*methoxyquinoline* 1-*oxide* (2.1 g, 43%) which was crystallised from benzene as colourless needles, m.p. 86—86.5 °C (Found: C, 62.1; H, 5.7; N, 7.2. $C_{10}H_9NO_2 \cdot H_2O$ requires C, 61.8; H, 5.8; N, 7.3%), δ($CDCl_3$) 8.4 (d, *J* 2.5 Hz, H-2) and 7.4 (d, H-4).

1-*Methoxyisoquinoline* 2-*Oxide* (11a).—In a round-bottomed flask fitted with a mechanical stirrer were mixed maleic anydride (6.3 g), H_2O_2 (40%; 6.8 ml) and chloroform (100 ml), and the mixture was stirred for 1 h while cooling with ice. 1-Chloroisoquinoline[13] (3.2 g) was then added while stirring. The flask was stoppered and left at 5 °C in the dark for 5 days. The precipitated maleic acid was filtered off and the filtrate was shaken with 40% NaOH. The organic layer was collected and the aqueous layer was extracted with $CHCl_3$ (25 ml). The combined extracts were dried and the solvent was evaporated off, yielding 1-*chloroisoquinoline* 2-*oxide* (3.1 g, 80%). Crystallisation from benzene–cyclohexane yielded the monohydrate as colourless needles, m.p. 113—115 °C (Found: C, 60.2; H, 3.4; N, 7.8; Cl, 19.8. $C_9H_6NOCl \cdot H_2O$ requires C, 60.4; H, 3.5; N, 8.0; Cl, 19.7%), δ($CDCl_3$) 8.2 (d, *J* 7.5 Hz, H-3).

The 1-chloroisoquinoline 2-oxide monohydrate (1.3) was dissolved in a solution of sodium methoxide (1 g) in methanol (30 ml). The solution was refluxed for 30 min. The solvent was evaporated off and the residue was treated with water and extracted with chloroform. Evaporation of the organic layer yielded 1-*methoxyisoquinoline* 2-*oxide* (11a) (0.8 g, 63%) which was recrystallised from benzene–cyclohexane to afford the monohydrate as colourless needles, m.p. 54—55 °C (Found: C, 62.2; H, 5.7; N, 7.3. $C_{10}H_9NO_2 \cdot H_2O$ requires C, 62.4; H, 5.8; N, 7.3%), δ($CDCl_3$ 8·05 (d, *J* 6·5 Hz, H-3). Several attempts to obtain this compound by direct *N*-oxidation of 1-methoxyisoquinoline were unsuccessful (see also ref. 14).

3-*Methoxyisoquinoline* 2-*Oxide* (11b).—A mixture of 3-chloroisoquinoline 2-oxide,[14] (1.5 g) sodium methoxide (2 g), and methanol (20 ml) was refluxed for 2 h and, after addition of further methanol (10 ml), refluxing was

continued overnight. The precipitated salt was filtered off and the filtrate evaporated. The residue was extracted with chloroform, and the solvent evaporated off to afford *3-methoxyisoquinoline 2-oxide* (11b) (0.5 g, 33%). Crystallisation from benzene–light petroleum yielded colourless needles, m.p. 166—169 °C (Found: C, 68.2; H, 5.2; N, 8.1. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%), δ($CDCl_3$) 8.85 (s, H-1) and 7.1 (s, H-4).

4-Methoxyisoquinoline 2-Oxide (11c).—A mixture of 4-methoxyisoquinoline [15] (1.4 g), H_2O_2 (40%; 2.2 ml), and acetic acid (4 ml) was heated at 75 °C for 7 h. The cooled solution was basified with 40% NaOH and extracted with chloroform. Evaporation yielded *4-methoxyisoquinoline 2-oxide* (1 g, 65%) (11c) which crystallised from benzene as colourless needles, m.p. 184—185 °C (Found: C, 68.9; H, 5.4; N, 8.2. $C_{10}H_9NO_2$ requires C, 68.2; H, 5.2; N, 8.0%), δ($CDCl_3$) 8.35 (d, *J* 2 Hz, H-1) and 7.7 (d, H-3).

Irradiations.—1—5 × 10^{-3}M-Solutions of the heteroaromatic *N*-oxides were irradiated by means of a Hanau TQ 150-W medium-pressure mercury vapour lamp at 15 °C through a Pyrex filter until complete conversion of the *N*-oxides had occurred. The progress of the reaction was followed by t.l.c. When anhydrous conditions were employed the solution (or the suspension) of the *N*-oxides (mostly containing water of crystallisation) was brought to boil under a slow stream of nitrogen in the irradiation vessel, the distillation being continued until perfectly clear solvent was collected (*ca.* 10% of the solvent had to be distilled off). The lamp was then fitted in and the solution was cooled down while maintaining a sufficient stream of nitrogen. For experiments performed in water the solutions were purged with nitrogen. The photolysed solutions were evaporated under reduced pressure and the residues either extracted with a little cyclohexane or chromatographed as described in ref. 2.

TABLE 4

Elemental analyses of photoproducts

		Found (%)				Required (%)		
Compd.	M.p. (°C)	C	H	N	Formula	C	H	N
(3a)	90—90.5 [a]	62.6	6.0	7.0	$C_{10}H_{11}NO_3$	62.2	5.7	7.3
(3c)	91—91.5 [b]	62.5	5.7	7.3	$C_{10}H_{11}NO_3$			
(7)	100—101 [a]	62.6	5.8	7.3	$C_{10}H_{11}NO_3$			
(8)	148—149 [c]	68.9	5.4	8.1	$C_{10}H_9NO_2$	68.6	5.2	8.0
(9)	161—162 [d]	68.7	5.2	7.9	$C_{10}H_9NO_2$			
(13a)	95.5—96 [c]	62.2	5.7	7.0	$C_{10}H_{11}NO_3$	62.2	5.7	7.3
(18)	69—71 [b]	62.5	5.8	7.2	$C_{10}H_{11}NO_3$			

[a] From cyclohexane. [b] From benzene. [c] From benzene–cyclohexane. [d] From toluene

Identification of Photoproducts.—Products (4b),[16] (4c),[17] (14b),[18] (14c),[19] and (17) [20] were identical with known compounds. New compounds were identified on the basis of their spectroscopic properties and elemental analyses or, in the case of liquids, mass spectroscopic formula determination. In some cases products were derivatised. Melting points and elemental analyses are shown in Table 4.

Methylation of 4-Methoxyquinolin-3-ol (9).—A solution of 4-methoxyquinolin-3-ol (9) (0.1 g) in diethyl ether (3 ml) was treated with an excess of diazomethane; reaction was instantaneous. Evaporation yielded 3,4-dimethoxyquinoline (10) (0.075 g, 70%), δ(CCl_4) 8.55 (s, H-2).

Hydrogenation of Methyl 2-Hydroxystyrylcarbamate (13a).—A solution of the ester (13a) (0.1 g) in ethanol (8 ml) was hydrogenated at room temperature in the presence of 5% Pd–charcoal for 1 h. The catalyst was filtered off and the solvent evaporated yielding *methyl 2-hydroxyphenethylcarbamate* (0.08 g, 80%) (16) as colourless needles, m.p. 104—105 °C from benzene–cyclohexane (Found: C, 61.3; H, 6.8; N, 7.5. $C_{10}H_{13}NO_3$ requires C, 61.5; H, 6.7; N, 7.2%), $\nu_{max.}$ 3 400s, 3 225br, and 1 690s, δ($CDCl_3$) 2.8 and 3.35 (2 t, CH_2CH_2), after shaking with D_2O.

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