CHEMISTRY LETTERS, pp. 133-136, 1974. Published by the Chemical Society of Japan

PHOTOCHEMICAL REACTION OF 2-CYANOQUINOLINE 1-OXIDES IN AN ACIDIC ALCOHOL. SYNTHESIS OF 6-ALKOXY-2-CYANOQUINOLINES[1)]

Chikara KANEKO*, Hiroshi HASEGAWA*[2)], Seiji TANAKA**, Kōsaku SUNAYASHIKI*[3)], and Sachiko YAMADA*

* Division of Chemistry, Research Institute for Medical Engineering, Tokyo Medical and Dental University, Surugadai, Chiyoda-ku, Tokyo 101

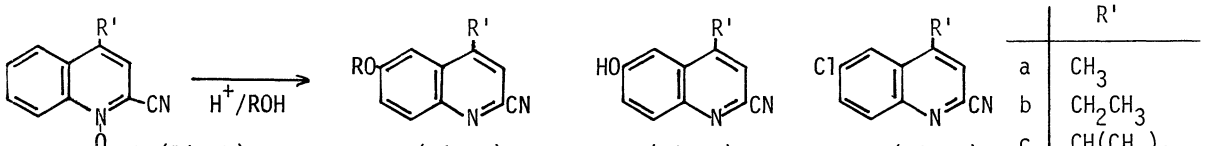
** Product Development Laboratories, Sankyo Co. Ltd., Hiromachi, Shinagawa-ku, Tokyo 140

The photolysis of 2-cyanoquinoline 1-oxide and its 4-methyl derivative in a variety of alcohols in the presence of conc. HCl gives the corresponding 6-alkoxy- and 6-chloroquinoline 2-carbonitriles, whose relative ratio depends on the concentration of the acid and the kind of alcohols. Similarly, the photolysis of these N-oxides in an alcohol in the presence of conc. H_2SO_4 gives 6-alkoxyquinoline 2-carbonitriles as the main substitution product.

A mechanism is postulated for this novel photo-alkoxylation reaction.

Recent experiments have established that photolysis of 2-cyanoquinoline 1-oxides in either hydroxylic or non-hydroxylic solvent causes isomerization to the corresponding 3,1-benzoxazepine-2-carbonitriles.[4)]

We now wish to report that irradiation of 2-cyanoquinoline 1-oxides (I and II) in an alcohol in the presence of strong acid gives 6-alkoxyquinoline 2-carbonitriles (III and IV).



I (R'= H)
II (R'=CH_3)

III (R'= H)
IV (R'=CH_3)

V (R'= H)
VI (R'=CH_3)

VII (R'= H)
VIII (R'=CH_3)

	R'
a	CH_3
b	CH_2CH_3
c	$CH(CH_3)_2$
d	$C(CH_3)_3$

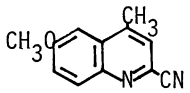
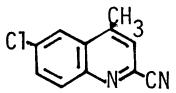
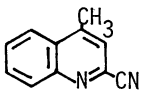
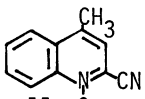
As a typical example, a solution of I (10^{-2} mol/L) in 500 ml of methanol in the presence of 200 g of sulfuric acid was irradiated with a 450W high pressure Hg lamp (Hanovia 679A-36) with a Pyrex filter for 3 hrs at room temperature.[5)] After careful work-up,[6)] the products were separated by silica gel chromatography. 6-Methoxyquinoline 2-carbonitrile (IIIa); mp. 176-177.5°[7)], was obtained in 59% yield. An appreciable amount (14%) of 6-hydroxyquinoline 2-carbonitrile (V); mp.218-

219°[8] was also obtained, together with 2-cyanoquinoline (IX, 2%) and the starting N-oxide (I, 13%).

The total amount of 6-methoxy- and 6-hydroxy-compounds decreased with decreasing concentration of the acid and thus, though the yield of IIIa did not change (61%) when the irradiation was performed in 550 ml of methanol and 100 g of sulfuric acid, the yield of V decreased to 7%. It is also noted that no starting N-oxide was recovered in this case. These facts indicate not only that the hydroxylation can occur only in very high concentration of the acid, but also that the consumption of the N-oxide is faster in a lower concentration of the acid. As lowering the acid concentration further, the products *via* the oxazepine[9] increased and only the oxazepine (80-90%) and the deoxygenated product (5%) were obtained if irradiation was carried out in pure methanol.[4b-i,ii]

The photo-alkoxylation reaction also occurred if conc. hydrochloric acid was used instead of sulfuric acid. In this case, however, 6-chloroquinoline 2-carbonitrile (VII); mp. 198-199°,[10] was also obtained in an appreciable amount. The yields of these two 6-substitution products again varied with the concentration of the acid. These results are summarized in Table 1.

Table 1. Results of Photochemical Reaction of 4-Methyl-2-cyanoquinoline-1-oxide (II) in an acidic medium.[a]

product / solvent	 IVa	 VIII	 X	 II O	indole derivatives (products *via* the oxazepine)
conc. HCl	-	-	-	80	-
conc. HCl: 1 vol. methanol: 5 vol.	35	41	7	-	-
conc. HCl: 1 vol. methanol: 17 vol.	45	15	4	-	15

a) Concentration of II = 1 x 10^{-2} mol/L. Light source; 450W high pressure Hg lamp with Pyrex filter. Irradiation was continued for 3 hrs. 6-Hydroxy-2-cyanoquinoline (VI) was not obtained in any significant yield.

This photo-alkoxylation reaction proceeds likewise in ethanol, isopropanol, or *t*-butanol. However, it is obvious that the alkoxylation is favoured in methanol, while the chlorination is favoured in *t*-butanol. Table 2 summarizes these results.

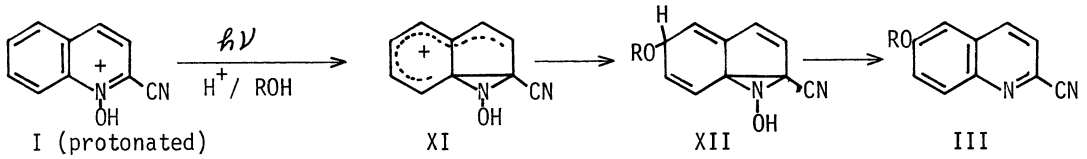
Table 2. Photolysis of 2-Cyanoquinoline 1-oxide (I) in conc. HCl (1 vol.) and an Alcohol (17 vol.).[a]

solvent / quinoline	methanol	ethanol	2-propanol	*t*-butanol
6-alkoxy-2-cyano- (III)	40-45	30-35	20-22	10
6-chloro-2-cyano- (VII)	10-15	15-25	32-35	40
2-cyano- (IX)	3-5	3-5	2-5	2
8-chloro-2-cyano-	±	1-2	2-3	6
products via the oxazepine	10-15	10-15	10-15	17

a) 6-Hydroxy-2-cyanoquinoline (V) was obtained in small amounts (<5%) in the experiments using 2-propanol or *t*-butanol.

It is noteworthy that irradiation in conc. HCl resulted in the recovery of the starting N-oxide (Table 1). This fact indicates not only the fact that the presence of an alcohol is the essential requisite of the above photo-alkoxylation reaction but also the fact that the isomerization reaction via the oxaziridine is inhibited by the presence of strong acids. The preliminary experiments show that this novel photo-alkoxylation also occurs in some quinoline 1-oxides having an electron-withdrawing group (e.g., COOR) and thus seems to have synthetic value.

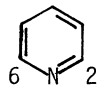
On the basis of MO calculation and by analogy of the photochemical formation of methy-ether of 6-methylazabicyclo[3.1.0]hex-3-en-2-exo-ol from 1-methylpyridinium ion in basic methanol reported by Kaplan et al.,[11] we postulate the mechanism shown below as the most reasonable one.

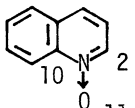


I (protonated) XI XII III

As shown in Table 3, the partial bond order between C_2 and C_{11} in the LVMO of quinoline 1-oxide (this value parallels with the ease of oxaziridine formation from the excited N-oxide[12]) decreased gradually, while the bond order between C_2 and C_{10} increased as in the order of A (free N-oxide), B, and C (protonated N-oxide). This result seems to support the intermediacy of the 2,10-bonded quinoline species (XI and XII) in the photolysis of the protonated N-oxide. The line of this thought predicts correctly the formation of Kaplan's product, since the partial bond order in the LVMO of pyridine between C_2 and C_6 also increased appreciably by the increment of the electron negativity of the nitrogen atom (this increment corresponds to the quaternization of the nitrogen atom).

Table 3. Partial Bond Order in LVMO of Pyridine and Quinoline 1-Oxide in Free or in Protonated Form by HMO Calculation[a]

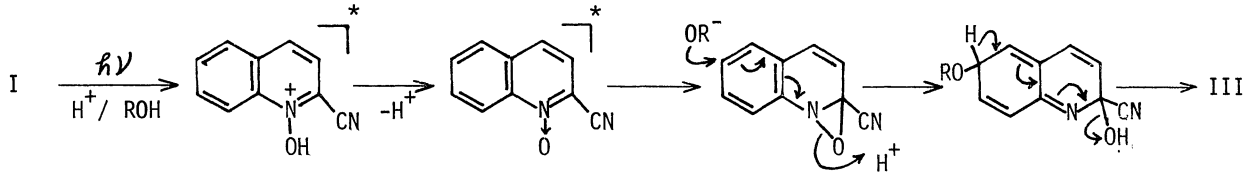




		free		protonated		A (free)	B	C (protonated)
parameter	α_N	$\alpha + 0.5\beta$	$\alpha + 1.0\beta$	$\alpha + 1.5\beta$	α_N	$\alpha + 1.6\beta$	$\alpha + 2.0\beta$	$\alpha + 2.4\beta$
					α_O	$\alpha + 0.8\beta$	$\alpha + 1.4\beta$	$\alpha + 2.0\beta$
					β_{NO}	1.0β	0.8β	0.6β
p^{LVMO}	2-6	0.134	0.179	0.215	2-11	0.116	0.074	0.040
					2-10	0.045	0.094	0.120

a) The parameter sets used are those of Kubota et al.; M. Yamakawa, T. Kubota, and H. Akazawa, Theoret. Chem. Acta (berl.), 15, 244(1969).

An alternative mechanism, in which the π-π^* excited state of the protonated N-oxide loses the proton to afford the oxaziridine via the excited state of the free N-oxide and then affords the



substitution product, is less probable by the following reason. That is, though it is known that the π-π^* excited state of the aromatic amine oxide is less basic than the ground state[13], the proton elimination would not occur efficiently from the excited N-oxide in such a high concentration of the acid (e.g., 200 g of sulfuric acid in 500 ml of methanol).

The application of this photo-alkoxylation reaction to the other type of aromatic amine oxides are now in progress, together with the verification of the mechanism.

The authors are grateful to Prof. T. Matsuura, Kyoto Univ., for very suggestive discussions to the mechanism and to Prof. M. Ishikawa of this institute for his warm encouragement.

References

1. Studies on the N-Oxides of Pi-Deficient N-Heteroaromatics. XXII. For XXI; I. Yokoe, M. Ishikawa, and C. Kaneko, Rept. Res. Inst. Med. Engi., Tokyo Medico-Dental Univ., 6, 18(1972). A part of this work was presented at the Symposium of Photochemistry held at Gumma, Japan, October, 1973.
2. A fellow of undergraduate training course from Kitasato University.
3. Present position; a graduate student of the Faculty of Pharmacutical Sciences, Hiroshima Univ.
4. a) C. Kaneko and S. Yamada, Chem. Pharm. Bull.(Tokyo), 14, 555(1966); see also C. Kaneko, S. Yamada, I. Yokoe, and M. Ishikawa, Tetrahedron Letters, 1967, 1873. b) For recent reviews on this topic: i) C. Kaneko, J. Synth. Org. Chem. Japan, 26, 758(1968); ii) M. Ishikawa and C. Kaneko, Kagaku no Ryoiki, Suppl. 92, 149(1970); iii) E.C. Taylor, G.G. Spence, and O. Buchardt, Chem. Rev., 70, 231(1970).
5 All of the N-oxide was consumed under these conditions, if the photolysis was done in an ordinary organic solvent or in the less acidic alcholic solvent.
6. To avoid the solvolysis of the nitrile group, the irradiated solution was directly neutralized by aq. KOH solution under ice-cooling, evaporated to dryness under a reduced pressure below 40° and extracted by CH_2Cl_2. 6-Hydroxy-2-cyanoquinolines were obtained from aq. layer by acidification.
7. E. Ochiai, M. Hamana, Y. Kobayashi, and C. Kaneko, Chem. Pharm. Bull.(Tokyo), 8, 487(1960).
8. Satisfactory elemental analyses and spectral data were obtained for all new compounds.
9. 2-Cyano-3,1-benzoxazepines was solvolyzed in hydroxylic solvents containing strong acids to indole derivatives; see refs. 1 and 4.
10. T. Takahashi, J. Okada, and Y. Hamada, Yakugaku Zasshi, 77, 1243(1957).
11. L. Kaplan, J.W. Pavik, and K.W. Wilzwach, J. Amer. Chem. Soc., 94, 3283(1972).
12. C. Kaneko, S. Yamada, I. Yokoe, and T. Kubota, Tetrahedron Letters, 1970, 2333; see also C. Kaneko, Kagaku Sōsetsu, 1, 131(1973).
13. E. Ochiai,"Aromatic amine Oxides", Elsevier Pub. Co., Amsterdam (1967).

(Received December 12, 1973)