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PHOTOCHEMICAL REACTION OF 2-CYANOQUINOLINE 1-OXIDES WITH AMINES: A NEW APPROACH TO N-AMINOCARBOSTYRILS[*1]

Chikara Kaneko, Ichiro Yokoe, and Masayuki Ishikawa
Research Institute for Medical Engineering, Tokyo Medical
and Dental University, Chiyoda-ku, Tokyo, Japan

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As a continuation of the photochemistry of aromatic amine N-oxides,[2] we should like to report a new route to N-aminocarbostyrils from 2-cyanoquinoline 1-oxides by irradiation of the latter compounds in a mixture of dichloromethane and amines (or their aqueous solutions).

In a typical run, a solution of 2-cyanolepidine 1-oxide (I) (1.00 g) in a mixture of 300 ml of CH_2Cl_2 and 50 ml of 40% methylamine solution[*2] was irradiated under stirring by 200W high-pressure mercury lamp[*3] with a Pyrex filter, until the disappearance of the starting N-oxide (6 hr). Concentration of the organic layer followed by recrystallization from ether gave colorless prisms melting at 143-144° as a major product (400 mg). The structure IIIa was assigned to this product unambiguously on the basis of the following evidences:

i) The infrared spectrum showed characteristic bands at 3270 and 1650 cm^{-1} attributed respectively to the NH and N-C=O function.

ii) The ultraviolet spectrum in EtOH exhibited the following absorption maxima at 233,273, 280, and 332 mμ (log ε ; 4.69, 3.81, 3.78, and 3.79) and was very similar to that of 4-methylcarbostyril[3] at 231, 269.5, 277, and 328 mμ (log ε; 4.58, 3.79, 3.75, and 3.81).

iii) The nuclear magnetic resonance spectrum in $CDCl_3$ exhibited the following peaks: A doublet centered at 7.52τ (3H, J=1.6 cps, methyl group attached to

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[*1] This paper is No. XI in the series entitled "Studies on the N-Oxides of π-Deficient N-Heteroaromatics". For the preceding paper X, cf. Ref. (1).

[*2] The whole reaction mixture should be shaken thoroughly to effect a complete distribution of the amine to both aqueous and organic layers before irradiation.

[*3] Hanovia immersion lamp and the lamp purchased from Ohsawa Electric Co., Tokyo, were used.

aromatic ring), doublet centered at 7.24 τ, which collapsed into a singlet by addition of D_2O (3H, J = 6 cps, methyl group on NH-CH_3), quartet centered at 4.0 τ, which disappeared by addition of D_2O (1H, J = 6 cps, a proton in $NHCH_3$), quartet centered at 3.35 τ (1H, J = 1.6 cps, due to an allylic proton neighboured by CH_3 group), and a multiplet ranging from 2.9-2.0 τ (4H, aromatic protons).

The yield of IIIa calculated from the consumed N-oxide was not affected by the duration of irradiation, and, without irradiation, the starting N-oxide was recovered quantitatively. The formation of IIIa suggested not only the utility of the afore-mentioned irradiation reaction to the synthesis of III-type compounds[*4] but also the unique nature of this reaction, since irradiation of I in CH_2Cl_2 alone has been known to give 6-methylbenz[d]-1,3-oxazepine-2-carbonitrile[*5] (IV) in a good yield.[2a,b,5a] It is noteworthy that IV under essentially the same condition as the present photolysis reacted with methylamine to give 2-methylamino-3-aminolepidine (Va) in almost a quantitative yield. This and the related reactions will be given in our subsequent communications.6) Since neither IV nor Va was detected in the irradiation mixture, it is reasonably assumed that the amine reacted with an unstable intermediate before it collapsed to IV. The strongest candidate for the possible intermediate in the above reaction is surely the corresponding oxaziridine (3-methyl-1a<u>H</u>-oxazirino[2,3-<u>a</u>]quinoline-1a-carbonitrile), (II), since most of the photolysis of aromatic amine N-oxides have now been rationalized to proceed via the corresponding oxaziridines as the unstable intermediates.1-3,5a,7) Considering these, one can now visualize the following pathway as the most probable one:

[*4] The sodium salt of carbostyril with chloramine has been reported to yield N-aminocarbostyril in ca. 7% yield, and this compound, to the best of the present authors' knowledge, is the only one example of III-type compound so far synthesized. Cf. Ref. (4).

[*5] Though the compound (IV) and the related photo-products were assumed to have the oxaziridine structure (i.e., II) in our earlier papers (2a-2c), the recent investigation revealed that the alternative benz[d]-1,3-oxazepine structure should be given to these photo-products on the basis of chemical and spectroscopical evidences. cf. Ref. (5). Dr. Buchardt at Copenhagen informed in his private communication to one of the authors (C. K.) dated July 20, 1967, that the X-ray crystallographic analysis of some of the photo-products also gave the same conclusion.

Table 1 shows a variety of amines that reacted with I and 2-cyanoquinoline 1-oxide (VI) under these conditions to give the corresponding N-aminocarbostyrils (IIIa - IIId and N-methylaminocarbostyril (VII)).

TABLE 1[a,b]

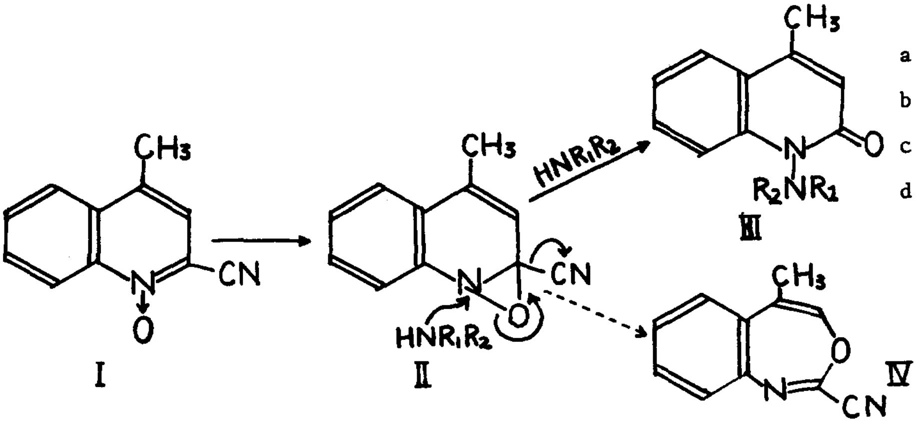
Starting N-oxide (g)	Amines (ml) used with 300 ml of CH_2Cl_2	Product		
		yield (mg)	m.p.	(solvent for recrystallization)
I (1.0)	40% aq. $MeNH_2$ (50)	IIIa (400)	143-144°	(ether)
I (1.0)	40% aq. Me_2NH (50)	IIIb (1000)	70-71°	(hexane)
I (1.0)	40% aq. $EtNH_2$ (50)	IIIc (290)	78-79°	(hexane)
I (1.0)	Et_2NH (20)	IIId (700)	109-110°	(ether)
I (1.0)	Et_3N (20)	IV[2a)] (750)	66-68°	(hexane)
I (1.0)	28% aq. NH_3[c] (50) or NH_3[c,d]	IV (700)	66-68°	(hexane)
VI (1.0)	40% aq. $MeNH_2$ (50)	VII (350)	100-101°	(ether)

a Satisfactory elemental analyses have been obtained for all the new compounds listed and spectroscopical properties (IR, UV, and NMR) were consistent with the postulated structures.

b Less than 5% of simple deoxygenated product (2-cyanolepidine from I and 2-cyanoquinoline from VI) was obtained from the irradiation mixture.

c With 6-hr. irradiation and immediate work up, IV was obtained as the main product. However, prolonged standing before work up caused the formation of 2,3-diaminolepidine[6)] at the expense of IV.

d Ammonia gas was passed through the irradiation mixture during irradiation.



	R_1	R_2
a :	Me	H
b :	Me	Me
c :	Et	H
d :	Et	Et

The inability of ammonia as a trapping agent may be due to its weak nucleophilic character.

The ease by which the above transformations may be accomplished recommends this new approach to the syntheses of N-aminocarbostyrils. The experiments designed to trap the intermediates (such as II) with other nucleophiles are in progress in order to ascertain the present supposition.

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REFERENCES

1. C. Kaneko and Sa. Yamada, Tetrahedron Letters, in press.
2. (a) C. Kaneko and Sa. Yamada, Chem. Pharm. Bull. (Tokyo), 14, 555 (1966); (b) Idem, Rept. Res. Inst. Dental Materials, Tokyo Medico-Dental Univ., 804 (1966); (c) C. Kaneko, I. Yokoe, Sa. Yamada and M. Ishikawa, Chem. Pharm. Bull. (Tokyo), 14, 1316 (1966); (d) C. Kaneko, Sa. Yamada and I. Yokoe, Tetrahedron Letters, 4729 (1966); (e) Idem, Chem. Pharm. Bull. (Tokyo), 15, 356 (1967); (f) C. Kaneko, I. Yokoe, and Sa. Yamada, Tetrahedron Letters, 775 (1967).
3. (a) M. Ishikawa, Sa. Yamada and C.Kaneko, Chem. Pharm. Bull. (Tokyo), 13,747 (1965); (b) M. Ishikawa, Sa. Yamada, H. Hotta, and C. Kaneko, Ibid., 14, 1102 (1966).
4. K. Hoegerle, Helv. Chim. Acta, 41, 539 (1958).
5. (a) C. Kaneko, Sa. Yamada, I. Yokoe, and M. Ishikawa, Tetrahedron Letters, 1873 (1967); (b) O. Buchardt, ibid., 6221 (1966).
6. C. Kaneko and I. Yokoe, Tetrahedron Letters, in press.
7. (a) J. Streith and C. Sigwalt, Tetrahedron Letters, 1347 (1966); (b) E. C. Taylor and C.G. Spence, Chem. Commun., 1966, 767; (c) M.J. Haddadin and C.H. Issidorides, Tetrahedron Letters, 753 (1967); (d) N. Ikekawa and Y. Honma, ibid., 1197 (1967).