Studies on the Reaction of Heterocyclic Compounds. VII.[1] Oxidative Cyanation of Heteroaromatic *N*-Oxides[2]

YOSHIRO KOBAYASHI,* ITSUMARO KUMADAKI, AND HARUO SATO

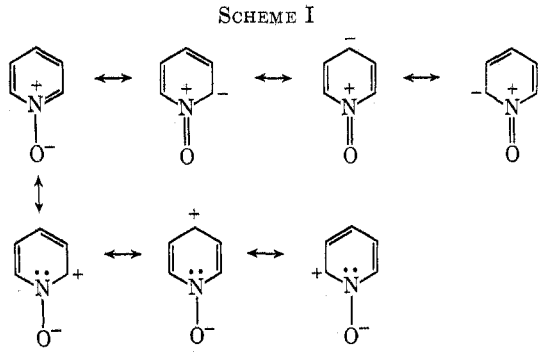
Tokyo College of Pharmacy, Shinjuku-ku, Tokyo, Japan

Received March 24, 1972

Most heteroaromatic *N*-oxides (*e.g.*, quinoline 1-oxide, isoquinoline 2-oxide, phenanthridine 5-oxide, acridine 9-oxide, 1,6-naphthyridine *N*-oxides, quinoxaline *N*-oxides, 1,6-phenanthroline *N*-oxides, and their substituted derivatives) were cyanated in their α position with potassium cyanide and potassium ferricyanide in protic solvents, especially in water. The merit of this reaction is that α-cyano heteroaromatic *N*-oxides are obtained from the *N*-oxides in one step. On the other hand, monocyclic heteroaromatic *N*-oxides (*e.g.*, pyridine 1-oxide, pyrazine 1-oxide, pyridazine 1-oxide, and pyrimidine 1-oxide) and α-substituted quinoline *N*-oxides did not react even at 130°. The reactivity of *N*-oxide for this reaction was estimated according to the reactivity index, "superdelocalizability," which was calculated from simple LCAO–MO.

Heteroaromatic *N*-oxides are very useful intermediates in the field of heterocyclic chemistry, since they are much more reactive to electrophilic and nucleophilic reagents than the free bases from which they are derived.[3] For example, pyridine 1-oxide is nitrated much more readily than pyridine, and quinoline 1-oxide is attacked by cyanide ion after quaternization with benzoyl chloride to give 2-cyanoquinoline. In other words, the *N*-oxide group increases or decreases electron density of carbon atoms in α and γ positions to it as shown in Scheme I.

SCHEME I



However, as in the case of quinoline 1-oxide, most nucleophilic reactions are followed by elimination of the *N*-oxide group, except in a few cases. This report will show new examples of nucleophilic reactions of heteroaromatic *N*-oxides without elimination of the *N*-oxide group, found in 1,6-naphthyridine *N*-oxides.[4]

As shown in our previous paper,[5] 1,6-naphthyridine 1,6-dioxide (**1**) reacted with aqueous potassium cyanide exothermally and decomposed to a tar, but treatment of this dioxide with methanolic potassium cyanide gave three compounds (**3**, **4**, and **5**) as shown in Scheme II.

This reaction seems to be initiated by the solvation at the *N*-oxide group and formation of an adduct, 2-cyano-1,2-dihydro-1,6-naphthyridine 1,6-dioxide (**2**). Therefore, we tried to oxidize this adduct and succeeded in obtaining α-cyano compound without elimination of the *N*-oxide group. Further, we found that this reac tion can be applied to other heterocyclic compounds.

Results

A solution of 1,6-naphthyridine 1,6-dioxide (**1**), dissolved in the aqueous solution of potassium cyanide and potassium ferricyanide at 0°, was stirred and the crystals that precipitated out were collected to afford 2,5-dicyano-1,6-naphthyridine 1,6-dioxide (**6**) in 17% yield. From the filtrate, 2-cyano- (**7**) and 5-cyano-1,6-naphthyridine 1,6-dioxide (**8**) were obtained in respective yields of 30 and 13%. In the same manner, 1,6-naphthyridine 1-oxide (**9**) treated at 20° afforded 2-cyano-1,6-naphthyridine 1-oxide (**10**) in a high yield of 57%. 1,6-Naphthyridine 6-oxide (**11**) gave 5-cyano-1,6-naphthyridine 6-oxide (**12**) by the same treatment at 25° in 26% yield (Scheme III).

The characteristic point of this cyanation was that the cyano group was introduced predominantly into the position α to the *N*-oxide group without elimination of the oxygen atom. This cyanation reaction gives α-cyanated heteroaromatic *N*-oxides in only one step from the parent *N*-oxides and may be called an "oxidative cyanation."

Application of this oxidative cyanation to many other heteroaromatic *N*-oxides was examined (Table I). Quinoline 1-oxide (**13**) and isoquinoline 2-oxide (**14**) underwent this oxidative cyanation at 75°, a much higher temperature than in the case of 1,6-naphthyridines, and afforded 2-cyanoquinoline 1-oxide (**15**) and 1-cyanoisoquinoline 2-oxide (**16**), respectively, both in 85% yield.

In contrast, pyridine 1-oxide (**17**) does not react even when the reaction temperature is raised to 130°. This reaction does not proceed with any diazine *N*-oxides [pyridazine 1-oxide (**18**), pyrazine 1-oxide (**19**), and pyrazine 1,4-dioxide (**20**)], but does so with diazanaphthalene *N*-oxides. As for other kinds of *N*-oxides, namely, benzoquinoline *N*-oxide, for example, acridine 9-oxide (**21**) and phenanthridine 5-oxide (**22**) gave 10-cyanoacridine 9-oxide (**23**) and 6-cyanophenanthridine 5-oxide (**24**) when treated at 70 and 50° in 35 and 58% yield, respectively, while benzo[*f*]quinoline 1-oxide (**25**) and benzo[*h*]quinoline 1-oxide (**26**) were recovered even when treated at 130°.

In these oxidative cyanation reactions, it is interesting that these *N*-oxides showed large difference in their reactivity. Acridine and phenanthridine *N*-oxides were more reactive than quinoline and isoquin-

(1) Paper VI: T. Kutsuma, K. Fujiyama, Y. Sekine, and Y. Kobayashi, *Chem. Pharm. Bull.*, **20**, 1558 (1972).

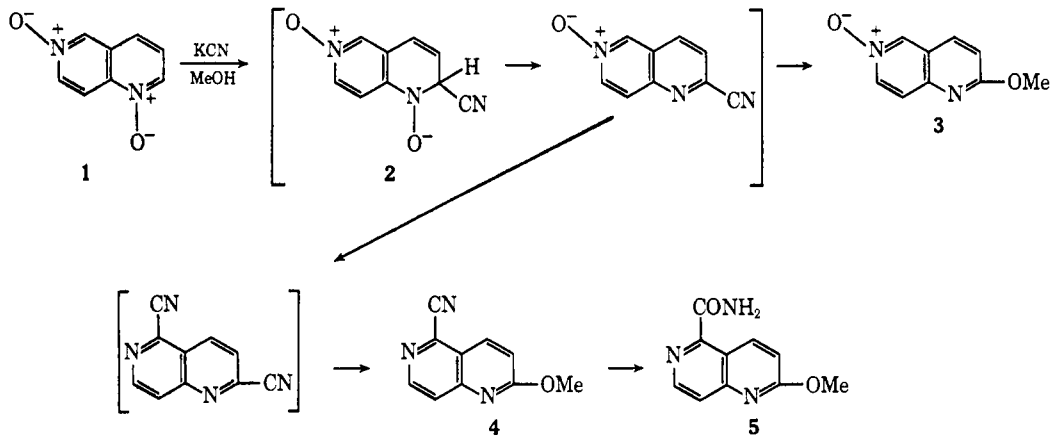
(2) Preliminary communication: Y. Kobayashi, I. Kumadaki, and H. Sato, *ibid.*, **18**, 861 (1970).

(3) E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, 1967.

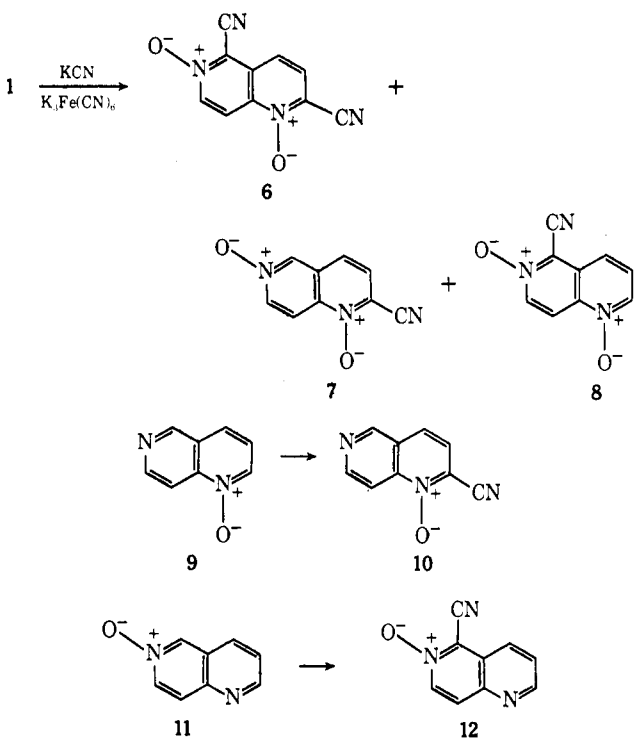
(4) Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.*, **17**, 1045 (1969).

(5) Y. Kobayashi, I. Kumadaki, and H. Sato, *ibid.*, **17**, 2614 (1969).

SCHEME II



SCHEME III



oline *N*-oxides, while pyridine 1-oxide and benzo[*f*]- and benzo[*h*]quinoline 1-oxides did not undergo this cyanation and the starting materials were recovered.

In this reaction mechanism, the rate-determining step was assumed to be the formation of a dihydro intermediate and, therefore, the reactivity of each *N*-oxide seemed to depend on the electrophilicity of the reaction site.

In order to elucidate the relationship between the reactivity of this oxidative cyanation and electrophilicity of *N*-oxides, the substituent effect was examined with a few derivatives of quinoline 1-oxides. Methoxyl was chosen as an electron-donating group and trifluoromethyl as an electron-attracting group. 3-(Trifluoromethyl)quinoline 1-oxide (**27**) and 4-(trifluoromethyl)-quinoline 1-oxide (**31**) gave their cyanated products (**28** and **32**) at a lower temperature than that in the case of quinoline 1-oxide; 4-methoxyquinoline 1-oxide (**29**) was treated at a higher temperature and gave 2-cyano compound (**30**) in poor yield. In this oxidative cyanation (trifluoromethyl)quinoline *N*-oxides were more reactive than quinoline *N*-oxide. Therefore, the readiness of their oxidative cyanation depends on the electronic effect of the substituent, and the rate-determining step is the first step when cyanide ion attacks.

2-(Trifluoromethyl)qunioline 1-oxide (**33**) does not undergo this cyanation even at 130°. This experiment suggests that the reaction proceeds selectively at the α position and quinoline 1-oxide affords 2-cyanoquinoline 1-oxide exclusively. The only exception is acridine 9-oxide, which affords a γ-cyanated product. This formation of a γ-cyanated product depends on higher reactivity of the γ position in the acridine ring than that of quinoline 1-oxide. With 3-(trifluoromethyl)quinoline 1-oxide, the trifluoromethyl group accelerates the reactivity of the γ position and, therefore, a trace of 4-cyano-substituted product is obtained in addition to the 2-cyano derivative as the major product.

From the above experiment, it is certain that oxidative cyanation is specific to the α position of the *N*-oxide and that the success of the reaction depends on the electrophilicity of that position. Since the reaction takes place with potassium cyanide and potassium ferricyanide, the question of the solubility in water of the starting material becomes important; *i.e.*, there are cases such as (trifluoromethyl)quinoline *N*-oxide where the α-cyano compound is not obtained in a good yield because of the low solubility in water, even though the reactivity of the α position is accelerated. In such a case mere raising of the reaction temperature would allow the hydroxide anion to attack the starting material or the cyanated compound, thereby preventing the selective attack of the cyanide ion from occurring; therefore, oxidative cyanation was attempted with diazanaphthalene *N*-oxides or diazaphenanthroline *N*-oxides, whose solubility in water is high and the electrophilicity of the α position is also high. As a result, 2-cyanoquinoxaline 1-oxide (**35**) was obtained from quinoxaline 1-oxide (**34**) and 2,3-dicyanoquinoxaline 1,4-dioxide (**37**) was obtained from quinoxaline 1,4-dioxide (**36**) at reaction temperatures below 0°.

However, in cases where the reactivity is as high as this, in accord with slight raising of the reaction temperature, the produced cyano compound is liable to be attacked by hydroxide anion and to decompose. Taking the above fact into consideration, this reaction was attempted with 1,6-phenanthroline 6-oxide[6]

(6) Y. Kobayashi, I. Kumadaki, and K. Morinaga, *Chem. Pharm. Bull.*, **17**, 1511 (1969).

TABLE I
REACTIONS OF HETEROAROMATIC *N*-OXIDES WITH $K_3Fe(CN)_6$ AND KCN[a]

Starting material	Reaction conditions: Temp, °C	Solvent	Product	Yield, %	Mp,[b] °C	Ir (KBr), cm^{-1}	Nmr
1	0	H_2O	6	17.3	248 dec (M)	2240 (C≡N)	8.56 (s, 2, C_7 H, C_8 H)
						1320 (NO)	8.27 (d, 1, J = 10 Hz, C_4 H)
							7.85 (d, 1, J = 10 Hz, C_3 H)[d]
			7	30.2	260 dec (M)	2250 (C≡N)	
						1300 (NO)	9.08 (d, 1, J = 2.5 Hz, C_5 H)
							8.33 (d, 1, J = 2.5 Hz, C_7 H, C_8 H)
							8.03 (d, 1, J = 10 Hz, C_4 H)
							7.74 (d, 1, J = 10 Hz, C_3 H)[d]
			8	13.5	257 dec (M)	2250 (C≡N)	8.68 (t, 1, J = 4 Hz, C_4 H)
						1300 (NO)	8.58 (s, 2, C_7 H, C_8 H)
							7.80 (d, 2, C_2 H, C_3 H)[d]
9	20	H_2O	10	57.7	235–236 dec (B)	2280 (C≡N)	9.40 (s, 1, C_5 H)
						1340 (NO)	8.92 (d, 1, J = 7 Hz, C_8 H)
							8.43 (d, 1, J = 7 Hz, C_7 H)
							7.84 (d, 1, J = 9 Hz, C_4 H)
							7.65 (d, 1, J = 9 Hz, C_3 H)[e]
11	25	H_2O	12	26.8	96.5 dec (B)	2290 (C≡N)	9.05 (d, 1, J = 5, 2.5 Hz, C_2 H)
						1320 (NO)	8.57 (d, 1, J = 7.5 Hz, C_7 H)
							8.27 (m, 2, C_8 H, C_4 H)
							7.85 (dd, 1, J = 5 Hz, C_2 H)[e]
13	75	H_2O	15	85.0	171 (B)		
14	75	H_2O	16	85.0	207 (B)		
17	130	H_2O	*c*				
18	90	H_2O	*c*				
19	90	H_2O	*c*				
20	70	H_2O	*c*				
21	70	30% EtOH	23	35.4	225 dec (M)		
22	50	30% EtOH	24	57.5	216–217 (M)		
25	130	H_2O	*c*				
26	130	H_2O	*c*				
27	50	30% EtOH	28	53.3	212 (M)	2240 (C≡N)	8.10–8.00 (m, 4, benzene ring)
						1140–1190 (CF)	8.80 (s, 1, C_4 H)[e]
						1340–1380	
						1260 (NO)	
29	90	H_2O	30	17.5	163 (M)	2280 (C≡N)	4.10 (s, 3, –OCH)
						1220 (NO)	7.30 (s, 1, C_3 H)
							8.80–7.50 (m, 4, benzene ring)[e]
31	35	20% EtOH	32	47.7	169 (M)	2260 (C≡N)	8.78 (m, 1, C_3 H)
						1350 (NO)	8.20 (m, 1, C_5 H)
						1240 (CF)	7.90–8.00 (m, 3, C_6 H, C_7 H, C_8 H)[e]
						1130–1160	
33	130	30% EtOH	*c*				
34	25	H_2O	35	30.0	135 (M)	2280 (C≡N)	8.87 (s, 1, C_3 H)
						1300 (NO)	8.55 (dd, 1, C_8 H)
							8.13 (dd, 1, J = 10, 2 Hz, C_5 H)
							8.00–7.80 (m, 2, C_6 H, C_7 H)[e]
36	0	30% EtOH	37	15.3	228 dec (B)	2280 (C≡N)	10.58 (q, 2, C_5 H, C_8 H)
						1270 (NO)	10.24 (q, 2, C_6 H, C_7 H)[d]
38	0	H_2O	39	82.5	218 (M)	2260 (C≡N)	9.10 (m, 2, C_2 H, C_{10} H)
						1240 (NO)	8.75 (m, 1, C_7 H)
							8.30 (dd, 1, C_4 H)
							7.80 (m, 2, C_8 H, C_9 H)
							7.70 (dd, 1, C_3 H)[e]

[a] Satisfactory analyses (±0.35% for C, H, N) were reported for **6**, **7**, **8**, **10**, **12**, **35**, **37**, and **39**: Ed. Exact mass spectral *m/e* values were reported for **28** and **32**. Compounds **15**, **16**, **23**, and **24** were identified with authentic samples by admixture and ir spectral comparison. [b] Recrystallization solvent: M, methanol; B, benzene. [c] Starting material was recovered. [d] Solvent $(CD_3)_2SO$. [e] Solvent $CDCl_3$.

(**38**), whose reactivity is fairly high and whose product is assumed to be stable; and 5-cyano 1,6-phenanthroline 6-oxide (**39**) was obtained in good yield as expected.

Discussion

The above experimental results show three characteristics of this cyanation. First, this cyanation does not proceed with either pyridine or diazine *N*-oxides. Second, many kinds of monoaza- or diazanaphthalene *N*-oxides reacted and afforded α-cyanated products predominantly and, in this case, an electron-donating group decreased the reactivity whereas an electron-attracting group increased it. Third, in the series of benzoquinoline oxides, some were more re-

TABLE II
SUPERDELOCALIZABILITY (Sr^N) VALUE OF HETEROAROMATIC *N*-OXIDES

N-Oxide	Position	Sr^N	Exptl result
Pyridine 1-oxide (**17**)	2	1.518	
	4	1.435	
Pyridazine 1-oxide (**18**)	3	1.627	
	6	1.545	
Pyrazine 1-oxide (**19**)	2,6	1.617	
	3,5	1.504	
Pyrazine 1,4-dioxide (**20**)		3.746	
Quinoline 1-oxide (**13**)	2	1.956	+
	4	2.020	
Isoquinoline 2-oxide (**14**)	1	2.199	+
	4	1.894	
Phenanthridine 5-oxide (**22**)	6	2.705	+
Acridine 9-oxide (**21**)	10	3.350	+
(Acridine)	10	1.912	+
Benzo[*f*]quinoline 1-oxide (**25**)	2	1.747	
	4	1.756	
Benzo[*h*]quinoline 1-oxide (**26**)	2	1.774	
	4	1.790	
Quinoxaline 1-oxide	2	2.342	+
	3	1.439	
Quinoxaline 1,4-dioxide	2,4	5.197	+
1,6-Naphthyridine 1-oxide (**9**)	2	2.117	+
	4	2.149	
1,6-Naphthyridine 6-oxide (**11**)	5	2.388	+
1,6-Naphthyridine 1,6-dioxide (**1**)	2	3.366	+
	5	4.346	+
1,6-Phenanthroline 6-oxide	5	2.787	+

active than quinoline 1-oxide, but the others did not react even at 130°.

These experimental results cannot be explained merely by electronic interpretation and, therefore, we applied molecular orbital theory for the interpretation. The simple LCAO–MO was calculated for each unsubstituted heteroaromatic *N*-oxide, utilizing the parameter[7] of *N*-oxide in a protic solvent, and superdelocalizability[8] (Sr^N value, introduced by Fukui to compare the reactivity in aromatic substitution reactions) was applied to examine the difference of reactivities among *N*-oxides.

The calculated data are listed in Table II. The experimental results agreed with the calculated results. The oxidative cyanation occurred when the value of Sr^N is more than *ca.* 1.8. This calculated result can explain the above three characteristics. First, pyridine and diazine *N*-oxides have Sr^N values lower than *ca.* 1.8. Second, the values of reactivity of benzoquinoline oxides can be divided with *ca.* 1.8 as the boundary and the high reactivity of diazanaphthalene can, therefore, be interpreted quantitatively. Third, the selectivity of this cyanation was explained by comparing the Sr^N value of each position in *N*-oxides. Finally, we must note that the difference in the reactivities of the 2 and 4 positions in quinoline 1-oxide cannot clearly be interpreted by Sr^N. Sr^N is 2.020 in the 4 position and 1.950 in the 2 position, but that this reaction proceeded in the 2 position seems to be partly affected by steric factors.

(7) T. Kubota, *Bull. Chem. Soc. Jap.*, **80**, 578 (1959).
(8) K. Fukui, T. Konezawa, and C. Nagata, *ibid.*, **27**, 423 (1954).

Experimental Section

General Procedure of Oxidative Cyanation.—To a saturated solution of $K_3Fe(CN)_6$ (1.2 molar equiv) and KCN (3–5 molar equiv) in H_2O or EtOH–H_2O, an heteroaromatic *N*-oxide was added and stirred at the designated temperature for 3 hr. The precipitate was collected by filtration, washed with H_2O, dried, and recrystallized from an appropriate solvent and afforded the cyanated product. The filtrate obtained above was extracted with $CHCl_3$ and was purified by silica gel chromatography when necessary.

Registry No.—**1**, 23616-34-4; **6**, 27182-21-4; **7**, 27182-22-5; **8**, 27182-23-6; **9**, 23616-39-9; **10**, 27182-24-7; **11**, 23616-37-7; **12**, 35657-55-7; **13**, 1613-37-2; **14**, 1532-72-5; **15**, 18457-79-9; **16**, 6969-11-5; **17**, 694-59-7; **18**, 1457-42-7; **19**, 2423-65-6; **20**, 2423-84-9; **21**, 10399-73-2; **22**, 14548-01-7; **23**, 10228-98-5; **24**, 27182-26-9; **25**, 17104-69-7; **26**, 17104-70-0; **28**, 35666-36-5; **30**, 20473-17-0; **32**, 35666-38-7; **35**, 18457-81-3; **37**, 35666-40-1; **39**, 27182-25-8; acridine, 260-94-6; quinoxaline 1-oxide, 6935-29-1; quinoxaline 1,4-dioxide, 2423-66-7; 1,6-phenanthrodine 6-oxide, 25952-30-1.

Acknowledgments.—We express our sincere gratitude to Sankyo Company for elemental analyses and to Dr. C. Nagata and Dr. A. Imamura of National Cancer Center Research Institute, Tokyo, for letting us use their computer.