NITRATION OF 1-CYANOISOQUINOLINE 2-OXIDE AND ISOQUINOLINE 2-OXIDE

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The nitration of 1-cyanoisoquinoline 2-oxide (1) with potassium nitrate and sulfuric acid gave 5- and 6-nitro derivatives (2 and 3). The reaction was affected by the concentration of sulfuric acid, and only 3 was obtained from the reaction in 85% acid at 70°, though in a small yield. The nitration with fuming nitric acid (d=1.50) led to the formation of 3 in fairly good yields together with small amounts of 8-nitro derivative (7).

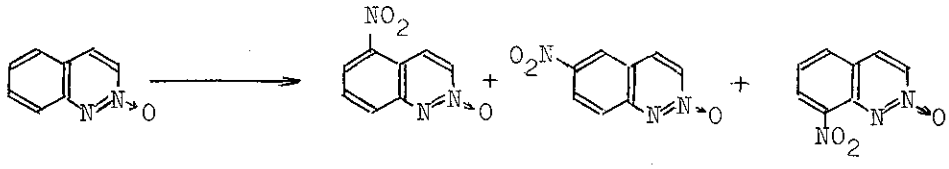
Further, the nitration of isoquinoline 2-oxide (9) with fuming nitric acid was found to give 5-, 6- and 8-nitro derivatives (10, 11 and 12). The orienting effect of the N-oxide function is apparently operative in the formation of 11 and 12.

Nitration of quinoline N-oxides is markedly affected by two factors, that is, the reaction temperature[1] and the concentration

of sulfuric acid[2]. For instance, the nitration of quinoline 1-oxide with potassium nitrate and conc. sulfuric acid at low temperatures gives 5- and 8- nitro derivatives, whereas the reaction at 65-70° produces 4-nitroquinoline 1-oxide as the main product. However, the effect of the concentration of sulfuric acid is rather more important for the direction of nitration, and the γ-nitration is promoted by the use of sulfuric acid of somewhat lower concentrations (85-75%).

While the nitration of isoquinoline 2-oxide with a mixture of conc. nitric and sulfuric acids affords 5- and 8-nitro derivatives in 90 and 5% yields, respectively[3], the orienting effect of its N-oxide function is not clarified at all.

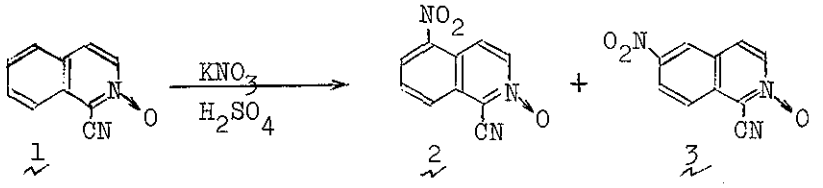
Suzuki et al. have obtained 5-, 6- and 8-nitro derivatives on the nitration of cinnoline 2-oxide with nitric and sulfuric acids. They have further examined the reaction in detail by varing the reaction temperature as well as the concentration of sulfuric acid, and concluded that the directive effect of the N-oxide group is transmitted to the 6- and 8-positions, especially markedly to the former[4]



These results prompted us to investigate nitration of 1-cyanoisoquinoline 2-oxide (1)[5] in expectation of obtaining 6-nitro derivative, because the polarization of 1 seems somewhat similar to that of cinnoline 2-oxide.

At first the nitration of 1 with potassium nitrate and sulfuric acid was examined under various conditions, and 1-cyano-6-nitroisoquinoline 2-oxide (3) was successfully obtained accompanied with other products in some cases (Table I).

Table I Nitration of 1-Cyanoisoquinoline 2-Oxide (1) with Potassium Nitrate and Sulfuric Acid



1 2 3

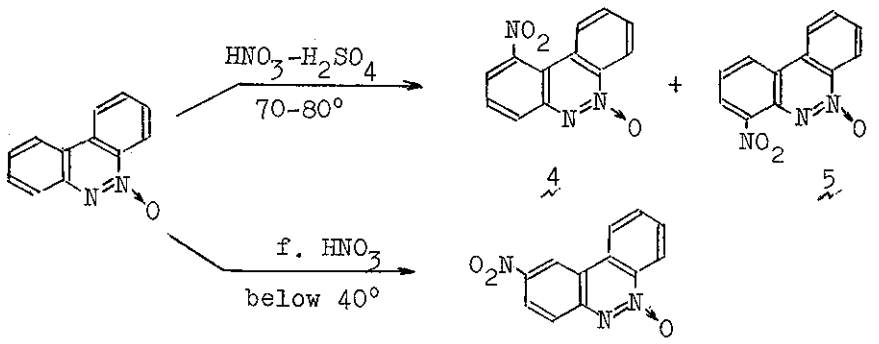
Concentration of H_2SO_4	Reaction temp.(°C)	time(hr)	Product, yield(%) 2	3	others	Recov. 1
98%	70	2	7.6	3.0	---	---
85%	70	2	---	12.8	a)	37.6
85%	70	10	---	7.9	---	35.4
85%	90	2	---	11.4	b)	11.6

a) 1-Cyanoisoquinoline, 0.5% b) 6-Nitroisoquinoline 2-oxide, 1.3%

The nitration in 98% sulufuric acid at 70° resulted in the formation of 5-nitro derivative (2), pale yellow crystalls, mp 227-228°, and 6-nitro derivative (3), colorless plates, mp 224° (decomp.), in 7.6 and 3.0% yields, respectively. On the other hand, the reaction using 85% sulfuric acid produced 3 in slightly better yields of 7.9-12.8%, no 2 being detected. Although these results are not satisfactory with respect to the yield of 3, the orienting effect of the N-oxide function is apparently operative

and affected by the concentration of sulfuric acid.

Barton et al.[6] have reported that the nitration of benzo[c]-cinnoline 5-oxide with nitric and sulfuric acids affords 10- and 7-nitro derivatives (4 and 5), which correspond to 5- and 8-nitro derivatives of isoquinoline 2-oxide, respectively, whereas the nitration with fuming nitric acid gives 9-nitro compound (6) corresponding to 6-nitroisoquinoline 2-oxide.

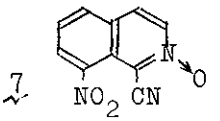


4 5 6

Therefore, the nitration of 1 with fuming nitric acid (d=1.50) was next tried, and the results shown in Table II were obtained.

Table II Nitration of 1-Cyanoisoquinoline 2-Oxide (1) with Fuming Nitric Acid (d=1.50)

Reaction temp.(°C)	time(hr)	Product, yield(%) 2	3	7	8
40	2	1.5	50.8	5.7	14.7
60	2	---	56.7	13.1	1.5
70	2	---	58.2	3.6	10.1
80	2	---	46.0	6.6	10.1



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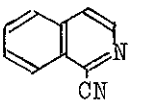

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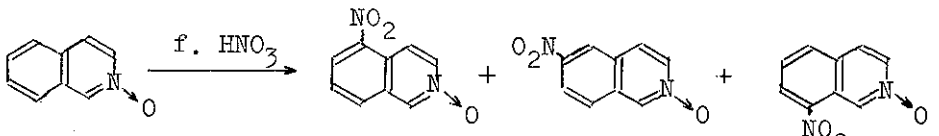
Thus, the formation of 6-nitro compound 3 in fairly good yields was performed. While 2 was isolated only in a minute amount in one example, 8-nitro derivative 7 was formed in all runs in a little better yields. This fact is interestingly in constrast to the nitration of isoquinoline 2-oxide with nitric and sulfuric acids[3], which gives overwhelmingly the 5-nitro derivative with only a small amount of the 8-nitro derivative, and demonstrates that the directive effect of the N-oxide group is transmitted not only to the 6-position but also to the 8-position though to a smaller extent. The oxidative deoxygenation of 1 by means of fuming nitric acid was also observed in all attempted reactions.

From these results, the nitration of isoquinoline 2-oxide (9) itself with fuming nitric acid was further examined, and the results shown in Table III were obtained.

The reaction with conc. nitric acid (d=1.38) at 60° for 2 hr gave no nitro compound, 9 being recovered almost quantitatively. Nitration took place by use of more concentrated acid (d=1.48, 1.50 and 1.52), and 5-, 6- and 8-nitro derivatives (10, 11 and 12) were formed always accompanied by considerable decomposition of 9. 6-Nitroisoquinoline 2-oxide 11 forms yellow sands of mp 241-242°. The results indicate that the orienting effect of the N-oxide function operates at the 6- and 8-positions, and the inherent reactivity of isoquinoline ring appears at the 5- and 8-positions. The former effect is apparently affected by the reaction temperature, and it is very significant that the 6-nitro derivative 11 was produced as a main product under the appropriate conditions although the yield is quite unsatisfactory.

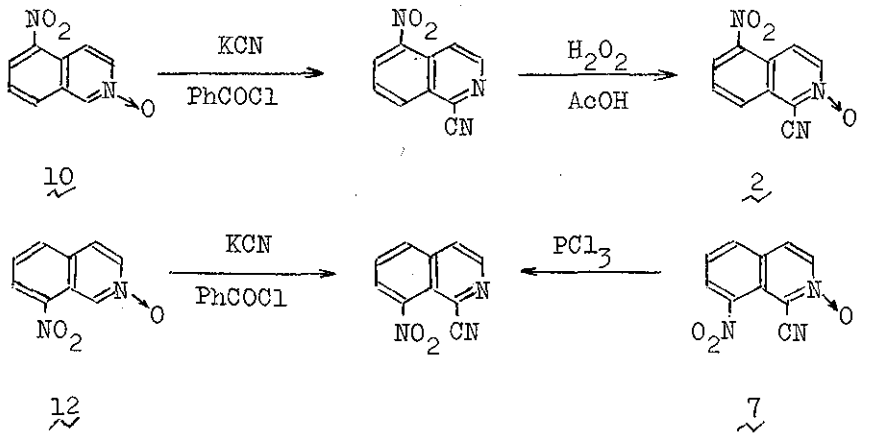
Table III Nitration of Isoquinoline 2-Oxide (9) with Fuming Nitric Acid



9 10 11 12

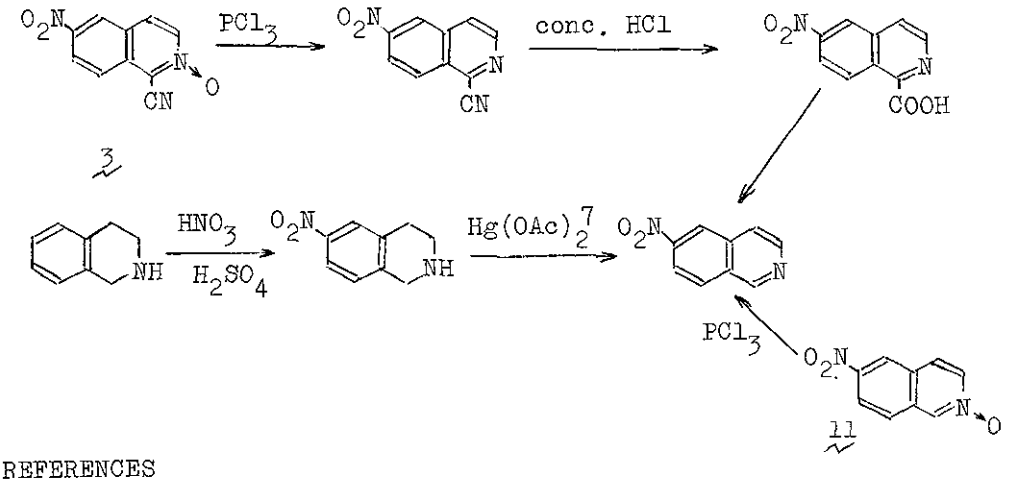
HNO_3(d)	Reaction temp.(°C)	Reaction time(hr)	Product, yield(%) 10	11	12	Recov. 9
1.38	60	2	---	---	---	90
1.48	70	2	---	1.1	---	20.1
1.50	R.T.	18	3.9	---	---	30.0
1.50	60	2	---	6.2	trace	35.8
1.50	70	2	---	4.1	2.5	7.0
1.52	40	2	3.5	1.2	2.3	9.0
1.52	60	0.5	3.1	7.2	2.3	10.0
1.52	80	0.5	---	1.8	1.4	---

The identity of the products isolated in the above reactions was established by elemental analyses, the IR, NMR and mass spectrometry, and further by some reactions illustrated below.



10 2

12 7



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5 1-Cyanoisoquinoline 2-oxide 1 was prepared from 1-cyanoisoquinoline on treatment with 30% H_2O_2-AcOH at 63° for 15 hr; pale yellow needles, mp 207-208° (EtOH-$CHCl_3$).

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