

REINVESTIGATION OF THE REACTION OF 3-BROMO-4-NITROQUINOLINE  
1-OXIDE WITH 1-MORPHOLINOCYCLOHEXENE

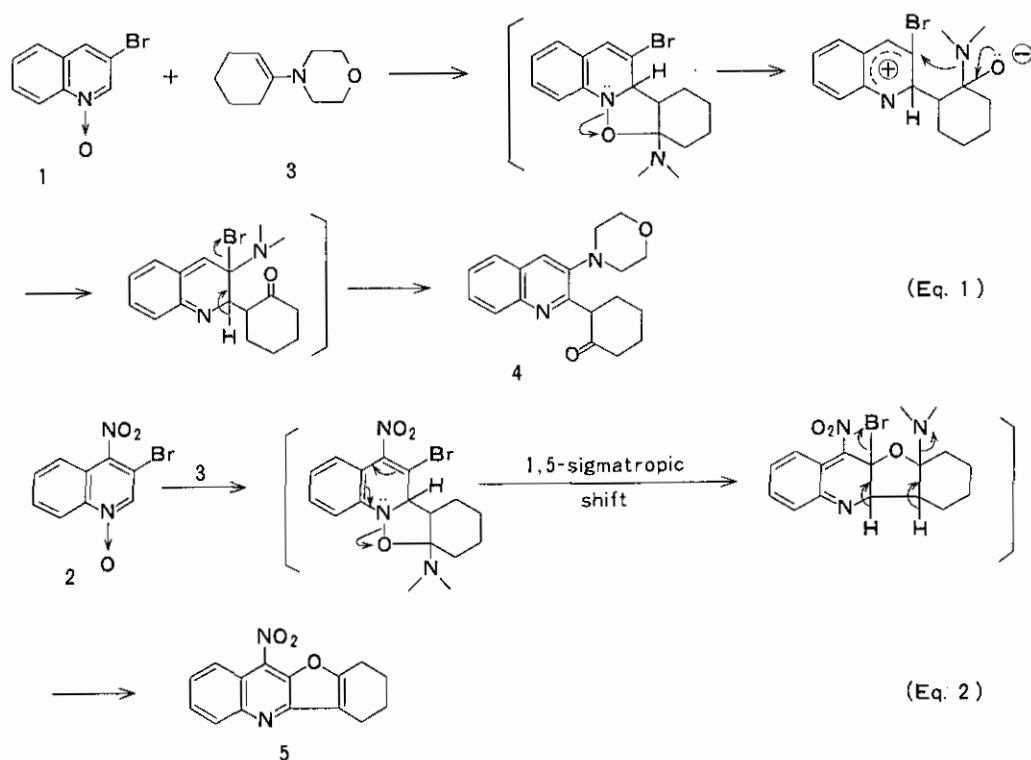
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Abstract — Reinvestigation of the reaction of 3-bromo-4-nitroquinoline 1-oxide (2) with 1-morpholinocyclohexene (3) has revealed that the reaction proceeds by a multistep ionic process involving the initial formation of 3-morpholino-4-nitro-2-(2-oxocyclohexyl)quinoline (6) and the subsequent transformation of 6 into 10-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-b]quinoline (5). Not only 2 reacts with various enamines in the same way, but also 3-bromo-4-nitropyridine N-oxide (7) undergoes the same type of reactions.

One of the authors (M.H.) and his co-workers have previously reported that, whereas quinoline 1-oxide itself does not react with enamines unless acylating agents are present,<sup>1</sup> some 3-substituted and 3,4-disubstituted quinoline 1-oxides undergo 1,3-dipolar cycloaddition upon treatment with enamines in the absence of acylating agents.<sup>2</sup> For example, reactions of 3-bromoquinoline 1-oxide (1) and 3-bromo-4-nitroquinoline 1-oxide (2) with 1-morpholinocyclohexene (3) at room temperature in chloroform afforded 3-morpholino-2-(2-oxocyclohexyl)quinoline (4) and 10-nitro-1,2,3,4-tetrahydrobenzofuro[3,2-b]quinoline (5), respectively, and the formation of 4 and 5 has been explained by the following two courses (Eq. 1 and 2 in Scheme 1). In connection with an investigation of the cyclization reaction of 3-substituted quinoline 1-oxides to 2,3-fused quinolines, we reinvestigated the reaction of 2 with 3 in some detail and obtained the interesting results.

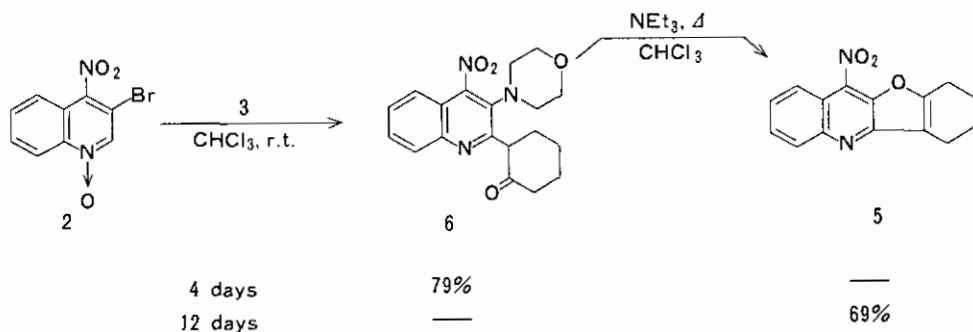
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We wish to dedicate this paper to the late Professor Dr. T. Kametani.



Scheme 1

A solution of 2 and an excess of 3 (5 equiv.) in chloroform was allowed to stand at room temperature and the reaction was monitored by means of thin layer chromatography. After confirmation of the disappearance of 2 (4 days), the reaction mixture was poured into water and the residue from the chloroform layer was chromatographed on silica gel with chloroform to give 3-morpholino-4-nitro-2-(2-oxocyclohexyl)quinoline (6) in 79% yield, the furoquinoline 5 being not formed at all. On



Scheme 2

the other hand, the prolonged reaction (12 days) at room temperature provided only the furoquinoline 5 in 69% yield (Scheme 2). These findings apparently demonstrate that the reaction proceeds stepwise and initially gives 6, corresponding to product 4 formed in the reaction of 1 with 3, which is subsequently converted to 5. This process was further confirmed by reactions carried out under some conditions in boiling chloroform as shown in Table.

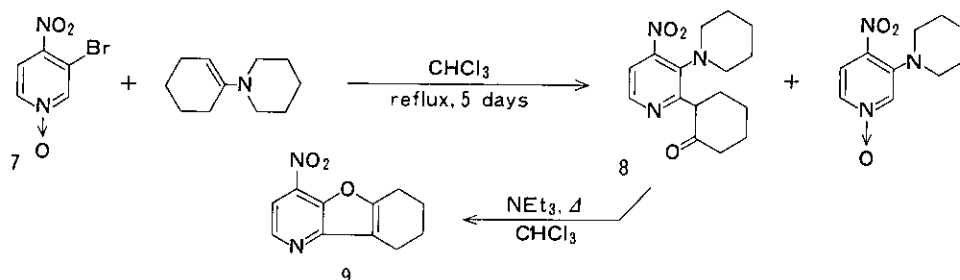
Table. Reactions of 3-Bromo-4-nitroquinoline 1-Oxide (2) with 1-Morpholinocyclohexene (3) in Boiling Chloroform

| Equiv. of 3 | Reaction Time<br>(h) | Products (yield:%) |       |
|-------------|----------------------|--------------------|-------|
|             |                      | 6                  | 5     |
| 2.5         | 6                    | 88                 | trace |
| 5.0         | 9                    | 41                 | 3.7   |
| 30.0        | 30                   | —                  | 57.0  |

The isolated product 6 was inert to heating in chloroform, but it was almost quantitatively transformed into 5 upon heating with triethylamine (2 equiv.) in chloroform for 30 h (Scheme 2).

As previously described,<sup>2</sup> 2 reacts with a variety of enamines to give the corresponding furoquinolines. We now succeeded in isolation of the respective 2,3-disubstituted 4-nitroquinolines corresponding to 6 from reactions of 2 with enamines, such as piperidine and dialkyl enamines of cyclohexanone, and enamines of hexanal and diethyl ketone.

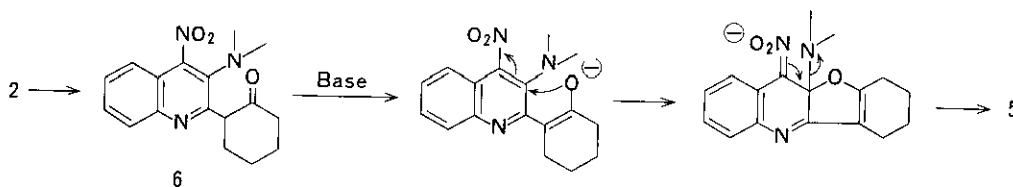
It was further found that 3-bromo-4-nitropyridine 1-oxide (7) also underwent the same type of reaction. Thus, treatment of 7 with 1-piperidinocyclohexene (2.5 equiv.) under reflux in chloroform for 1 day gave 4-nitro-2-(2-oxocyclohexyl)-3-



Scheme 3

piperidinopyridine (**8**) and 4-nitro-3-piperidinopyridine 1-oxide in 41 and 36% yields, respectively. Conversion of the isolated **8** into the corresponding furo-pyridine (**9**) was effected in 33% yield with 30% recovery of **8** by heating with triethylamine (2 equiv.) in chloroform for 3 days (Scheme 3).

Abramovitch and Shinkai have examined 1,3-dipolar cycloaddition of pyridine 1-oxides with various 1,3-dipolarophiles, and concluded that the primary cycloadducts, 1,2-dihydropyridines, are not stable enough to isolate and immediately undergo 1,5-sigmatropic rearrangement to 2,3-dihydropyridine intermediates, which are further transformed into the respective stable products.<sup>3</sup> As mentioned above, however, the reaction of **2** with **3** is evidently a multistep ionic process involving the initial formation of **6**, and the mechanism for the formation of **5** formulated in Eq. 2 should be ruled out. The initial formation of **6** should be considered to follow the same course as that illustrated in Eq. 1, since only one spot appeared on thin layer chromatogram at this step. Conversion of **6** to **5** may be rationalized by the following base-catalyzed nucleophilic reaction (Scheme 4). Apparently, the strong electron-withdrawing effect of the 4-nitro group is essential for the reaction to proceed; compound **4** and its analogues resist this type of conversion.



Scheme 4

#### REFERENCES

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