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

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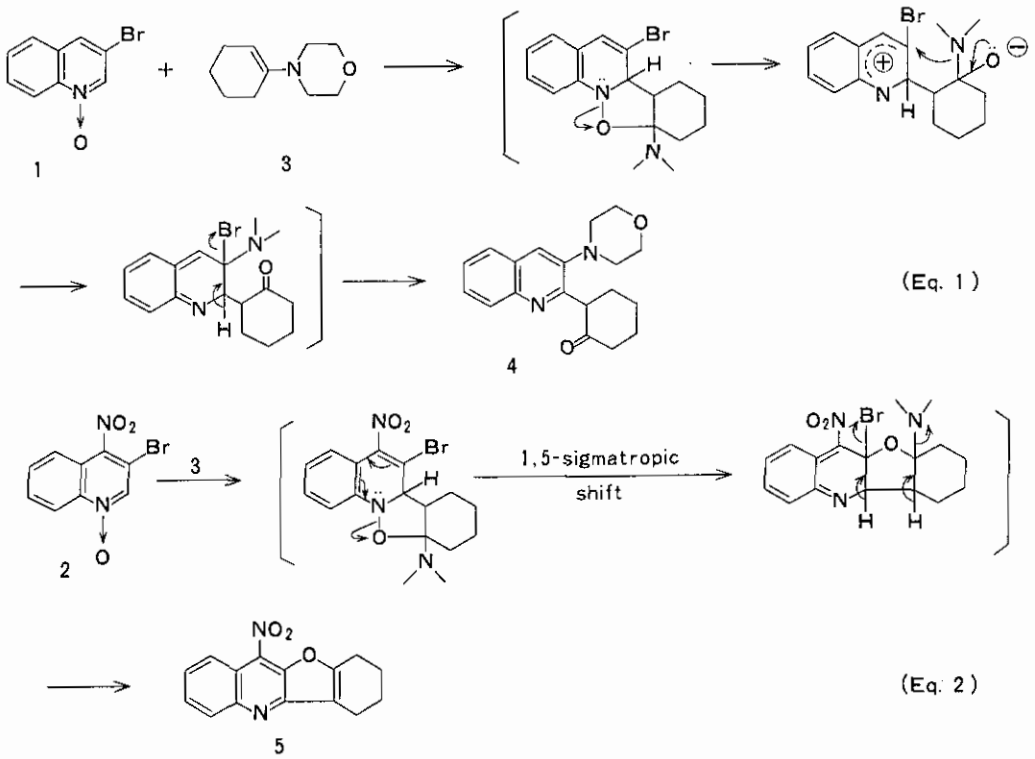
Abstract — Reinvestigation of the reaction of 3-bromo-4-nitroquinoline 1-oxide (**2**) with 1-morpholinocyclohexene (**3**) has revealed that the reaction proceeds by a multistep ionic process involving the initial formation of 3-morpholino-4-nitro-2-(2-oxocyclohexyl)quinoline (**6**) and the subsequent 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,[1] 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.[2] 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-tetrahydrobezofuro[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).

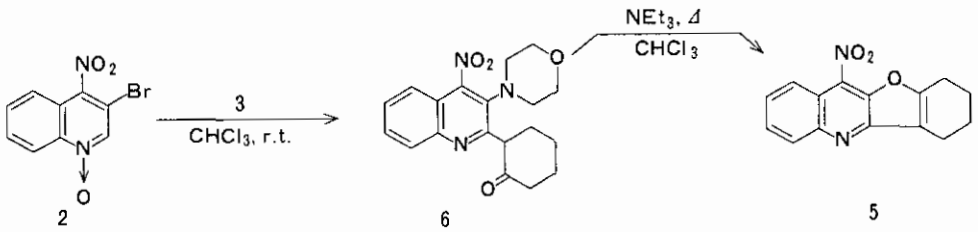
In connection with an investigation of the cyclization reaction of 3-substituted quinoline 1-oxides to 2,3-fused quinolines, we reinvestigated the reaction of **2** with **3** in some detail and obtained the interesting results.

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.

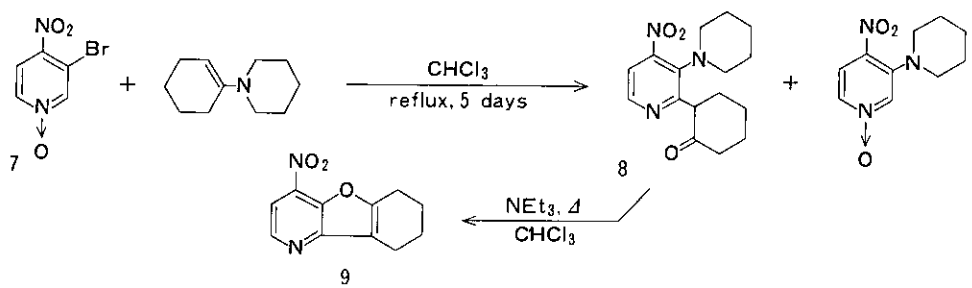
Table. Reactions of 3-Bromo-4-nitroquinoline 1-Oxide (**2**) with 1-Morpholinocyclohexene (**3**) in Boiling Chloroform

Equiv. of **3**	Reaction Time (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,[2] **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.

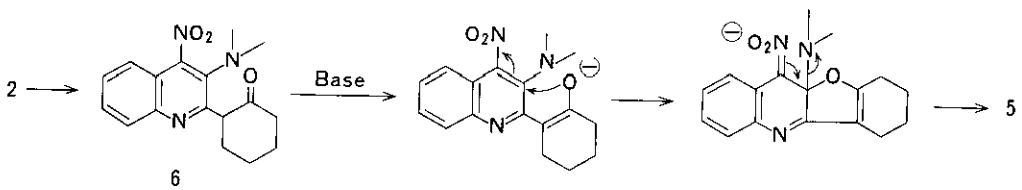
It was further found that 3-bromo-4-nitropyridine 1-oxide (**7**) also underwent the same type of reaction. Thus, treatment of **7** with 1-piperidinocyclohexene (2.5 equiv.) under reflux in chloroform for 1 day gave 4-nitro-2-(2-oxocyclohexyl)-3-



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 furopyridine (**9**) was effected in 33% yield with 30% recovery of **8** by heating with triethylamine (2 equiv.) in chlorofom 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.[3] 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

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