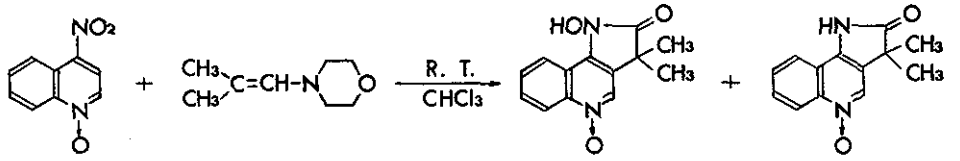
REACTION OF 3-BROMO-4-NITROQUINOLINE 1-OXIDE WITH ENAMINES. A NOVEL CYCLIZATION REACTION TO FURO[3,2-b]QUINOLINE SYSTEM[1]

Hiroshi Noda, Teruo Yamamori, Mitsutaka Yoshida
and Masatomo Hamana*
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi, Higashi-ku, Fukuoka, Japan

3-Bromo-4-nitroquinoline 1-oxide (1) reacts with 1-morpholinocyclohexene at room temperature in chloroform to give 10-nitrotetrahydrobenzofuro[3,2-b]quinoline (2) in high yield via the primary adduct of the 1,3-dipolar cycloaddition reaction. The scope of this type of reaction is widespread, but similar reactions of 3-bromo- and 3-bromo-4-methoxyquinoline 1-oxides afford 2-(2-oxocyclohexyl)-3-morpholinoquinoline (14a) and its 4-methoxy derivative (14b).

A previous paper has reported that treatment of 4-nitroquinoline 1-oxide with enamines of isobutyraldehyde at room temperature in chloroform results in a novel cyclization reaction producing pyrrolido[4,5-c]quinoline derivatives as exemplified below.[2]

In exploring the mechanism of this reaction we carried out the reaction of 3-bromo-4-nitroquinoline 1-oxide (1) with enamines and happened to come across another novel cyclization reaction



leading to furo[3,2-b]quinoline ring system.

A chloroform solution of 1 and 4.8 equivalents of 1-morpholinocyclohexene was kept at room temperature for 10 days. The reactants were purified by chromatography on silica gel with benzene followed by recrystallization from n-hexane to give 10-nitrotetrahydrobenzofuro[3,2-b]quinoline (2), yellow needles, mp 155-156°, in almost quantitative yield.

The structure assignment of 2 was based on the elemental analysis, the mass spectrum (M^+, m/e 268), IR absorptions at 1528 and 1351 cm^{-1} (NO_2) and the NMR spectrum which showed eight protons of 1,2-disubstituted cyclohexene as two multiplets at δ 1.7-2.2 (4H) and δ 2.7-3.1 (4H), and four aromatic protons of benzene moiety of quinoline ring as two multiplets at δ 7.53-7.84 (2H) and δ 8.03-8.37 (2H), but no signals due to C_2-H, C_3-H and C_4-H of quinoline ring.

Heating 2 with concentrated hydrochloric acid or phosphorus trichloride readily afforded the corresponding 10-chloro derivative (3, mp 133-134°), which was in turn converted smoothly into 10-alkoxy derivatives (4a, R=CH_3, mp 139-140°; 4b, R=C_2H_5, mp 148-149.5°). Whereas catalytic hydrogenation of 3 in the presence of palladium charcoal caused only dechlorination to give compound 5 (mp 135-136), compounds 5 and 4 were transformed into dihydrofuran derivatives (6, bp 170-180°/0.2 mm, and 7, mp 148-149°) by hydrogenation using platinum oxide as catalyst (Chart 1). Such a

behavior of furo[3,2-b]quinoline system in catalytic hydrogenation is fairly different from that of the naturally occurring furo[2,3-b]quinolines[3] such as dictamnine and skimmianine which are more susceptible to reduction or reductive cleavage of furan ring as illustrated in Chart 1.

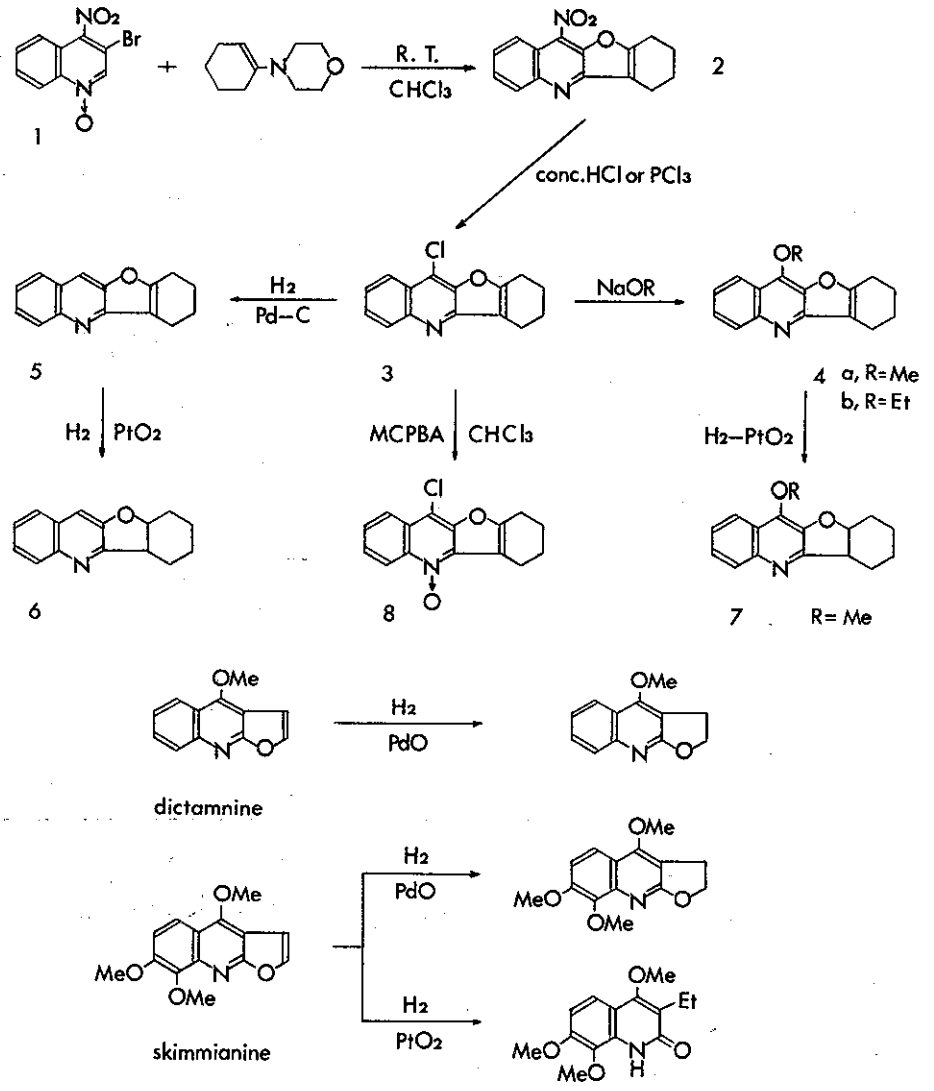
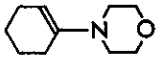
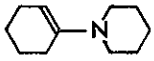
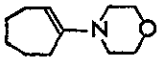
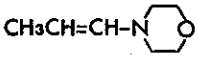
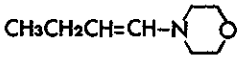
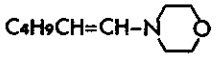
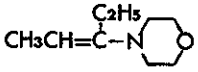
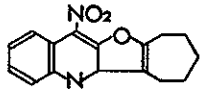


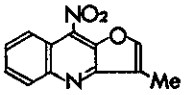
Chart 1

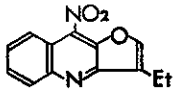
Treatment of 3 with m-chloroperbenzoic acid (MCPBA) in chloroform gave 5-oxide (8, mp 152-154°). Its NMR spectrum showed the lower-field signals at δ 2.76-2.96 (2H, m, C_4-H) and at δ 8.68-8.84 (1H, m, C_6-H) compared with those of 3 at δ 2.16-3.0 (4H, m, C_1-H and C_4-H) and at δ 8.02-8.35 (2H, m, C_6-H and C_9-H). These observations apparently indicate that positions C_4 and C_6 of 8 are spatially near to its N-oxide function.

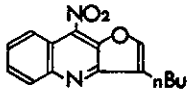
Table Reaction of 3-Bromo-4-nitroquinoline 1-Oxide with Enamines

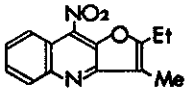
Enamine	Reaction Condition temp.	time (day)	Product No.	mp (C°)	yield (%)
	R.T.	10	2	155-156	quant.
	R.T.	20	2	〃	80
	40°	5	9	140-141	46
	R.T.	5	10	155-156	24
	R.T.	15	11	126-127	87
	R.T.	14	12	78-79	81
	R.T.	6	13	165-166	21

9 

10 

11 

12 

13 

The scope of this type of reaction is fairly widespread, and various enamines react with 1 producing the corresponding products in moderate to high yields. Some representative results are shown in Table.

The formation of 2 can be rationalized by the course similar to that advanced for the reaction of N-oxides of 3-substituted pyridine[4] and quinolines[5] with phenyl isocyanate as formulated in Chart 2.

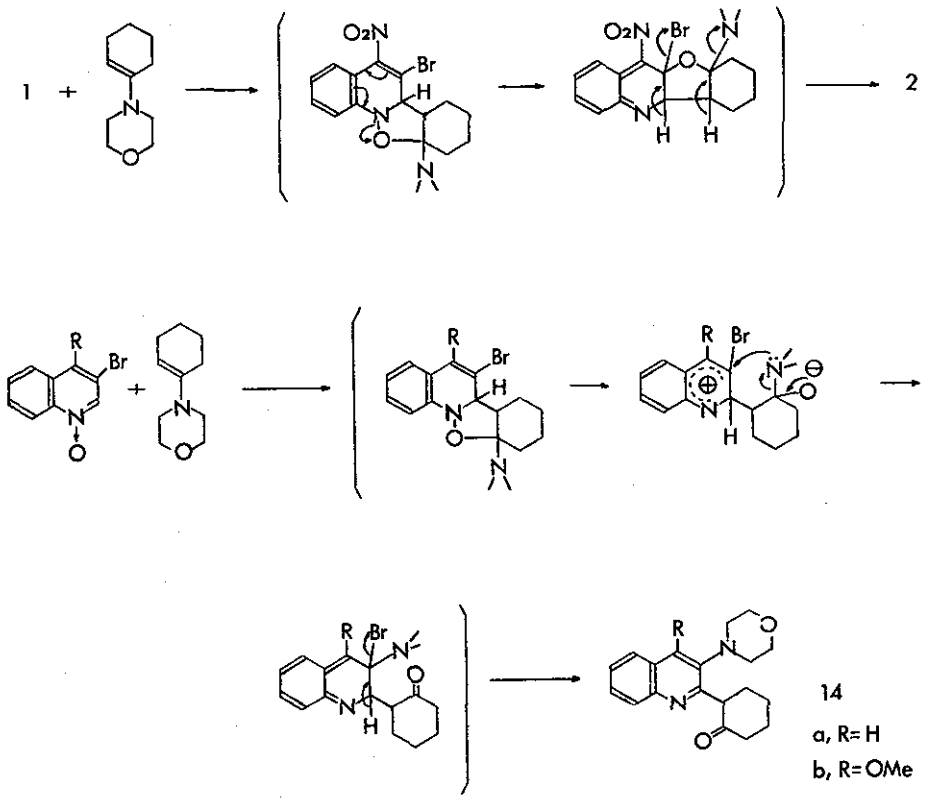


Chart 2

Recently Abramovitch and Shinkai have obtained pyrido[3,2-b]-benzofuran or -furan derivatives from the reaction of 3,5-dihalopyridine 1-oxide with benzyne or acetylene compounds, and proposed the 1,5-sigmatropic shift of the initially formed 1,3-dipolar cycloadduct as the reaction mechanism[6]. However, the reactions of 3-bromo- and 3-bromo-4-methoxyquinoline 1-oxide with 1-morpholinocyclohexene under similar conditions were found to give 2-(2-oxocyclohexyl)-3-morpholinoquinoline (14a, mp 153-154°) and its 4-methoxy derivative (14b, mp 130-131°) in 16 and 34% yields, respectively. Therefore, multistep process is apparently more reasonable at least in the reaction described here.

Of much more interesting is the ease with which 1 undergoes 1,3-dipolar cycloaddition. Taking into account the fact that quinoline 1-oxide resists the 1,3-dipolar cycloaddition even with a typical 1,3-dipolarophile, pheny isocyanate, in contrast to the high reactivity of pyridine 1-oxide[7] and does not react with enamine at all unless an acylating agent is present[8], 3-substituents apparently promote the 1,3-dipolar cycloaddition of quinoline 1-oxide[5]. Furthermore, the enhanced reactivity of 1 toward enamine should be explainable in term of multiplied effect of both 4-nitro and 3-bromo groups, the details of which remains to be explored

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