γ-BROMINATION OF QUINOLINE AND PYRIDINE N-OXIDES

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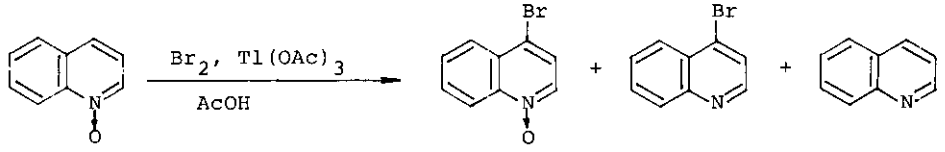
Abstract——Treatment of quinoline 1-oxide (1) with bromine (2 equiv.) and thallium triacetate (3 equiv.) in acetic acid at 50° for 29 hr produces 4-bromoquinoline 1-oxide (2) in 65.8 % yield. Similarly, quinaldine and 3-bromoquinoline 1-oxides (5 and 12) give the corresponding γ-bromo derivatives (6 and 13) in good yields. From the reaction of 2-cyanoquinoline 1-oxide (8), 2-cyano-4-bromoquinoline 1-oxide (9) and 2-carbamoyl-4-bromoquinoline 1-oxide (10) are obtained. The reactivity of N-oxides of pyridine series is somewhat lower and pyridine and 2-picoline 1-oxides resist bromination under similar conditions, but 2,6-lutidine, 3-picoline and 3,5-lutidine 1-oxides (14, 16 and 18) afford the corresponding γ-bromo derivatives (15, 17 and 19).

Contrary to the facile γ-nitration of pyridine and quinoline 1-oxides, the corresponding γ-halogenation has long been rather difficult[1,2]. For instance, H. den Hertog and his co-workers obtained 2-bromo- and 4-bromo-pyridine 1-oxides in a total yield of 10 % on heating pyridine 1-oxide with excess bromine in 90 % sulfuric acid at 200° in the presence of silver sulfate[3]. Ochiai and Okamoto[4] have reported that 4-bromoquinoline 1-oxide is formed in 32 % yield when the perbromide of quinoline 1-oxide ($C_9H_7ON \cdot 1/2HBr_3$) was shaken with bromine water in a sealed tube at room temperatures, however its reproducibility is rather poor for the synthetic procedure.

We now wish to report the successful γ-bromination of quinoline and pyridine 1-oxides under rather mild conditions by means of bromine and thallium triacetate. A solution of quinoline 1-oxide (1, 0.8 g), bromine (1 g, 1.1 equiv.) and thallium triacetate (2.3 g, 1.1 equiv.) in acetic acid (10 ml) was stirred at room tempera-

tures. While thallium triacetate dissolved in a little while, no reaction occurred and 1 was recovered almost quantitatively after 24 hr's reaction. However when the same reactants were warmed at 70° for 3 hr, 4-bromoquinoline 1-oxide (2), colorless needles, mp 127-128.5°, and quinoline (4) were obtained in 14.5 and 4.2 % yields, respectively, accompanied by recovery of 1 in 45 % (Exp. 3 in Table I). Representative results obtained under various conditions are given in Table I.

Table I. Bromination of Quinoline 1-oxide (1)



1 2 3 4

Exp. NO.	Br_2 (equiv.)	$Tl(OAc)_3$ (equiv.)	Reaction Temp.(°C)	Time(hr)	Product, Yield(%) 2	3	4	Recov.(%) 1
1	1.1	1.1	50	4	9.7	-	8.2	41.1
2	1.1	1.1	60	4	21.4	-	7.7	36.0
3	1.1	1.1	70	3	14.5	-	4.2	45.0
4	1.1	1.1	80	4	11.8	-	6.6	33.5
5	2.0	1.0	60	4	minute	4.8	4.4	
6	1.0	2.0	50	4	27.4	-	2.2	41.4
7	2.0	3.0	50	4	46.4	3.9	-	23.5
8	2.0	4.0	50	4	34.8	1.9	-	34.5
9	2.0	3.0	50	29	65.8	6.0	13.6	12.1

These results indicate that the reaction is fairly affected by the reaction temperature and the amount of reagents. While the reaction is very slow at room temperatures, warming at 50-60° substantially promotes the reaction to give 2 in 10-22 % yields even when molar equivalent amounts of bromine and thallium triacetate were used, but higher reaction temperatures (over 70°) conversely decrease the yield of 2. The use of two or three molar excess of the reagents was apparently favorable for the γ-bromination, and the best yield (65.8 %) was obtained from a run under the conditions of Exp. 9 shown in Table I. A small amount of 4-bromoquinoline (3) was also formed as a by-product in reactions using excess reagents. Subsequently, bromination of some derivatives of 1 was carride out (Chart 1). While lepidine 1-oxide gave no bromo derivative, quinaldine 1-oxide (5) underwent γ-bromination more readily than 1 to afford 4-bromoquinaldine 1-oxide (6), pale yellow needles, mp 141-143°, and 4-bromoquinaldine (7), bp 130°/4 mm. (picrate, mp

246-247°) in 63 and 0.9 % yields, respectively. In view of its high susceptibility to bromination, it is very noteworthy that the active 2-methyl group was inert to bromination under the above conditions. The structures of 6 and 7 were confirmed by their independent syntheses from 4-nitroquinaldine N-oxide[5].

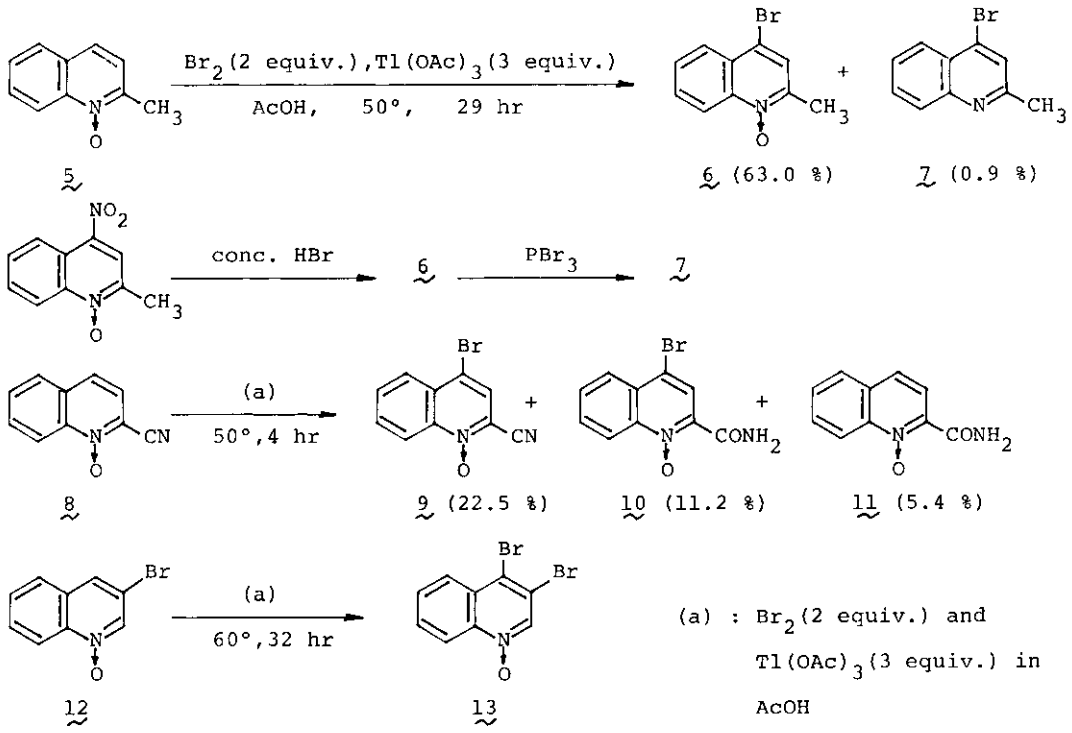


Chart 1.

The reaction of 2-cyanoquinoline 1-oxide (8) resulted in the formation of 2-cyano-4-bromoquinoline 1-oxide (9), pale yellow needles, mp 188-189°, 2-carbamoyl-4-bromoquinoline 1-oxide (10), colorless needles, mp 278-279°, and 2-carbamoylquinoline 1-oxide (11)[6], colorless plates, mp 223°, in the respective yields of 22.5, 11.2 and 5.4 %. It was clarified by separate reactions that 8 was convertible into 11 by the action of thallium triacetate in acetic acid, and 10 originated only from 9 but not from 11. Bromination of 3-bromoquinoline 1-oxide (12) produced 3,4-dibromoquinoline 1-oxide (13), colorless needles, mp 146-147°, in a high yield of 95.7 %.

The reactivity of N-oxides of pyridine series was found to be considerably lower compaerd to that of quinoline 1-oxides. Thus any brominated products could not be isolated from reactions of pyridine and 2-picoline 1-oxides in spite of many at-

tempts under various conditions, the N-oxide being recovered in each case. However, 2,6-lutidine 1-oxide (14) afforded 4-bromo-2,6-lutidine 1-oxide (15), colorless needles, mp 67-68°, under the conditions shown in Chart 2. 3-Picoline 1-oxide (16) and 3,5-lutidine 1-oxide (18) were more reactive as expected, and the corresponding 4-bromo derivatives 17[7], colorless pillars, mp 112-113° (59.2 %) and 18, colorless needles, mp 199° (72.8%), were obtained, respectively. The structures of 15, 17 and 19 were unambiguously established by elemental analyses, the mass and NMR spectrometry.

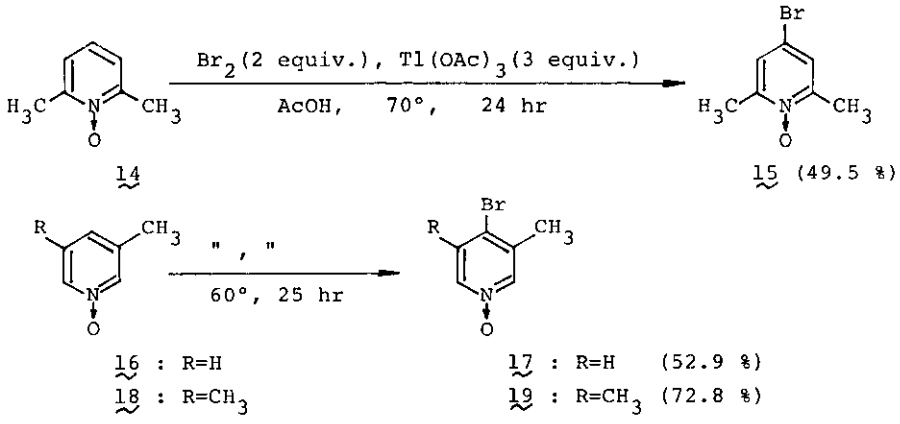


Chart 2.

The orienting effect of N-oxide function apparently operates not only in the formation of 15 but also in that of 17, because 3-picoline is known to give not 4-bromo derivative by the usual bromination procedure[8]. Although no information is available on bromination of 3,5-lutidine, it may be reasonably assumed that the directing effect of N-oxide function appears also in the formation of 19. Further studies are in progress to explore the scope of the reaction and elucidate the mechanism.

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