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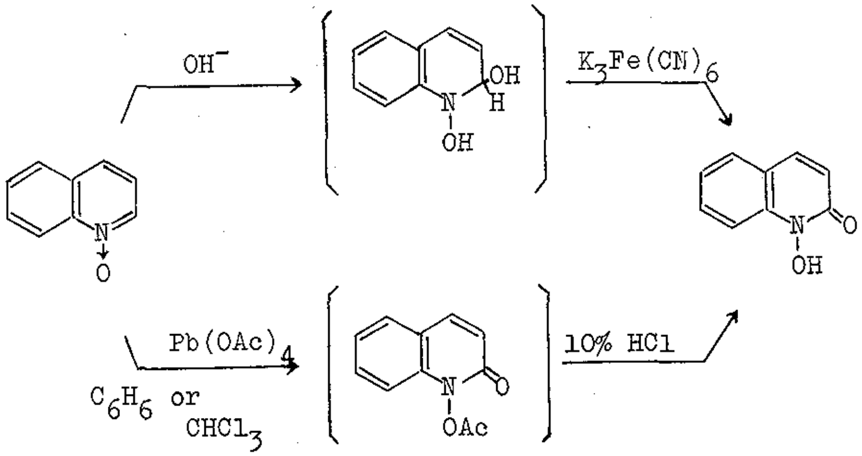
A NOVEL OXIDATION OF QUINALDINE N-OXIDE

Hirohisa Saito, Hideki Muro, Seitaro Saeki, and Masatomo Hamana*
Faculty of Pharmaceutical Sciences, Kyushu University
Maidashi, Higashi-ku, Fukuoka, Japan

Treatment of quinaldine N-oxide (1) with thallium triacetate or lead tetraacetate in acetic acid or/and acetic anhydride leads to the formation of 2-acetoxymethylquinoline N-oxide (2), diacetate of quinaldaldehyde (3), quinaldaldehyde (4) and quinaldaldehyde N-oxide (5). The selective preparation of 2, 3, 4 or 5 can be effected by adjusting the reaction conditions.

Quinoline N-oxides undergo oxidative hydroxylation on treatment with potassium ferricyanide in alkaline medium[1] or with lead tetraacetate in benzene or chloroform[2] as exemplified below, however direct oxidation of quinaldine N-oxide (1) into 2-quinolinemethanol N-oxide derivatives has not been reported.



In the course of the study on electrophilic reaction of aromatic N-oxide, we have found a novel oxidative hydroxylation of quinaldine N-oxide **1** by means of thallium triacetate or lead tetraacetate. The representative results are summarized in Table I.

A solution of **1** (94.6 mg) and thallium triacetate (**A**, 272 mg, 1.2 equiv.) in acetic acid (5 ml) including acetic anhydride (73 mg, 1.2 equiv.) was stirred at room temperatures for 48 h to give 2-acetoxymethylquinoline N-oxide[3] (**2**) as the main product in 70.2% yield accompanied by recovery of **1** in 8.5% yield (Exp. 2).

The reaction did not progress at room temperature unless acetic anhydride was present, and curiously the yield of **2** was decreased by the use of 2.4 molar excess of **A** in the similar way in the reaction using 0.6 equivalent **A** (Exp. 1 and 3).

When **1** was treated with **A** and acetic anhydride at room temperatures without acetic acid, the reaction proceeded to further step and diacetate of 2-quinaldaldehyde[4] (**3**) was produced in fairly good yields, formation of **2** being not noticed (Exp. 4 and 5).

Further it was found that heating **1** with **A** in acetic acid afforded 2-quinaldaldehyde[5] (**4**) and its N-oxide[6] (**5**) (Exp. 6, 7 and 8). The yield of **4** was not so much affected by the amount of **A** but that of **5** apparently increased with the amount of **A**.

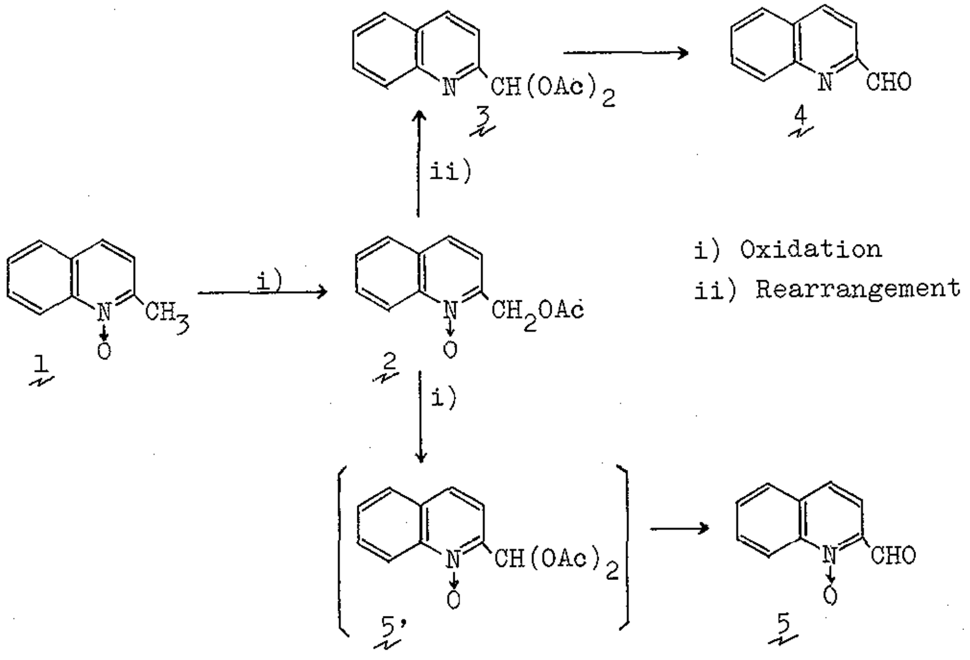
Subsequently, the reaction using lead tetraacetate (**B**) in place of **A**, was examined under the similar conditions.

Treatment of **1** with **B** and acetic anhydride in acetic acid always yielded not only **2** but also **3** in fair yields, respectively (Exp.9 and 10). In contrast to the reaction with **A**, the sole production of **2** was not successfully performed and the effect of the amount of **B** on this reaction was not so great.

The reaction omitting acetic acid led to the formation of **3** in much higher yields as compared with the reaction with **A** under the same conditions (Exp. 11 and 12).

On the other hand the reaction of **1** with **B** in hot acetic acid gave **2**, **3** and **4**, but no clear-cut correlation between the proportion of products and reaction conditions was obtained in spite of various attempts (Exp. 13).

The above-mentioned reactions apparently involves two types of reactions, that is, oxidation and rearrangement, and two reaction



Scheme 1

pathways through **2** may be conceivable as shown in Scheme 1.

The oxidation of **1** to **2** with **A** or **B** in the presence of acetic anhydride may be likely rationalized by the course *a* illustrated by the reaction with **A** as shown in Scheme 2. Betaine or anhydrobase (**7**) derived from the initially formed acetic anhydride-adduct of **1** (**6**) undergoes electrophilic attack by **A** to give **8** which is subsequently converted to acetic anhydride-adduct of **2** (**9**) and thallium acetate.

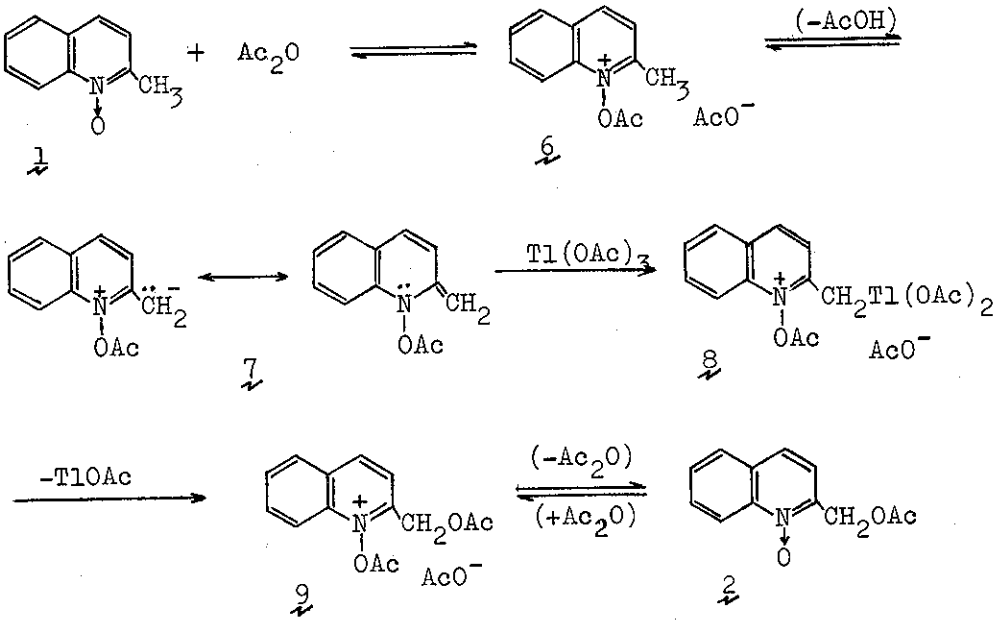
However from Exp. **6**, **7** and **8**, an alternative course *b* should be considered in which thallium triacetate-adduct of **1** (**6'**) is first formed instead of **6**; transformation of **6'** to **2** may be well visualized by the similar path through **7'**, **8'**, and **9'** (Scheme 2).

Of course the oxidation of **1** with lead tetraacetate **B** can be rationalized in the same way.

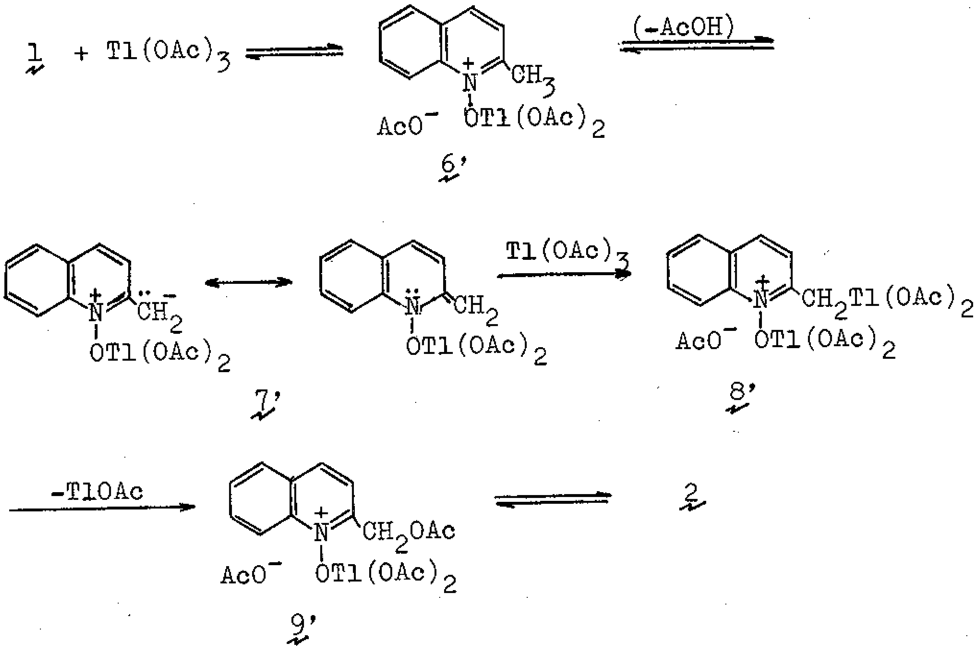
Subsequent rearrangement of **2** by means of acetic anhydride affords **3** or its hydrolysis product **4**. On the other hand, further oxidation of **2** gives **5** through its diacetate (**5'**); no isolation of 5' may be probably ascribed to its high instability.

As a consequence of the experiments described above it has now proved possible to prepare selectively **2**, **3** or **4**, and **5** from **1**. However, several problems, such as the correlation between courses *a* and *b*, the mechanism of the formation of **4** in the reaction with **A** or **B** in acetic acid and the effect of the amount of reagents and solvent on yields of the products, remain to be clarified. In order to explore these aspects as well as the scope of this type of reaction, further work is in progress in our laboratory.

Course a



Course b



Scheme 2

Table I. Oxidation of Quinaldine N-Oxide (1)a)

Exp. No.	Oxidizing agent (equiv.)	Ac_2O	AcOH (ml)	Reaction temp. (C°)	Reaction time (h)	Product, yield (%)b) 2	3	4	5	Recov. 1
1	A: 0.6	1.2 eq.	5	R.T.	48	33.4	---	---	---	33.6
2	A: 1.2	1.2 eq.	5	R.T.	48	70.2	---	---	---	8.5
3	A: 2.4	1.2 eq.	5	R.T.	48	34.2	---	---	---	59.3
4	A: 1.2	5 ml	---	R.T.	48	---	52.5	---	---	29.3
5	A: 1.2	10 ml	---	R.T.	48	---	55.1	---	---	31.4
6	A: 1.2	---	10	heat	21	---	---	20.2	trace	24.5
7	A: 2.4	---	10	heat	21	---	---	15.5	34.5	21.4
8	A: 3.2	---	10	heat	21	---	---	20.0	57.1	22.7
9	B: 1.2	1.2 eq.	5	R.T.	48	28.0	39.8	---	---	37.0
10	B: 2.4	1.2 eq.	5	R.T.	48	29.9	31.6	---	---	17.6
11	B: 1.2	5 ml	---	R.T.	48	---	99.4	---	---	---
12	B: 1.2	10 ml	---	R.T.	48	---	98.7	---	---	---
13	B: 1.2-3.6	---	5	heat	5	10-30	10-30	5.0-20	---	10-70

a) In all experiments, 94.6 mg of anhydrous quinaldine N-oxide (1) was used.

b) Values analyzed by glpc (Silicon OV-17)

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3 E. Ochiai, S. Suzuki, Y. Utsunomiya, T. Ohmoto, K. Nagatomo and M. Itoh, *Yakugaku Zasshi*, **80**, 339 (1960); **2** forms hight yellow cubes, mp 116-118° (AcOEt).

4 Prepared by heating **2** with acetic anhydride on a water bath; an oil, bp 180° (3 mmHg).

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