

THE REACTION OF 3-BROMO-4-METHOXYQUINOLINE 1-OXIDE WITH DIMETHYL  
ACETYLENEDICARBOXYLATE

Yasuhisa Ishiguro, Mitsutaka Yoshida,<sup>1</sup> Kazuhisa Funakoshi, Seitaro Saeki,  
and Masatomo Hamana<sup>1\*</sup>

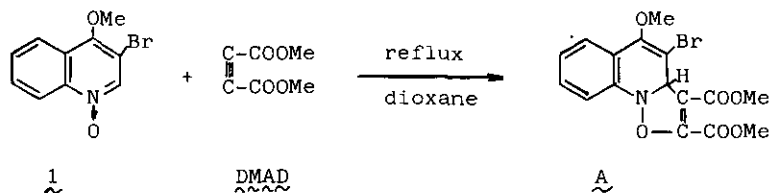
Faculty of Pharmaceutical Sciences, Kyushu University  
Maidashi 3-1-1, Higashi-ku, Fukuoka 812, Japan

Ikuhiko Ueda and Shigeaki Kawano

College of General Education, Kyushu University  
Ropponmatsu 4-2-1, Chuo-ku, Fukuoka 810, Japan

**Abstract** — 3-Bromo-4-methoxyquinoline 1-oxide (1) reacts with dimethyl acetylenedicarboxylate (DMAD) at room temperature in dioxane, CH<sub>2</sub>Cl<sub>2</sub>, MeCN or DMF to give α-[N-(3-bromo-4-methoxyquinolinium)]-α,β-bismethoxycarbonyl-β-oxo-ethylide (2) and methyl 2-(3-bromo-4-methoxyquinoline)-acetate (4). On the other hand, heating 1 with DMAD in dioxane or DMF affords dimethyl α-[N-(3-bromo-4-oxo-1,4-dihydroquinolyl)]-β-methoxyfumarate (3) as the predominant product, which is proved to be formed by thermal rearrangement of 2.

Previously, we isolated colorless prisms of mp 188-192°C from the reaction of 3-bromo-4-methoxyquinoline 1-oxide (1) with dimethyl acetylenedicarboxylate (DMAD) in boiling dioxane, and assigned a 1,2-dihydroquinoline structure (A) principally based on the elemental analyses and the MS and PMR spectroscopies.<sup>2,3</sup> However, it



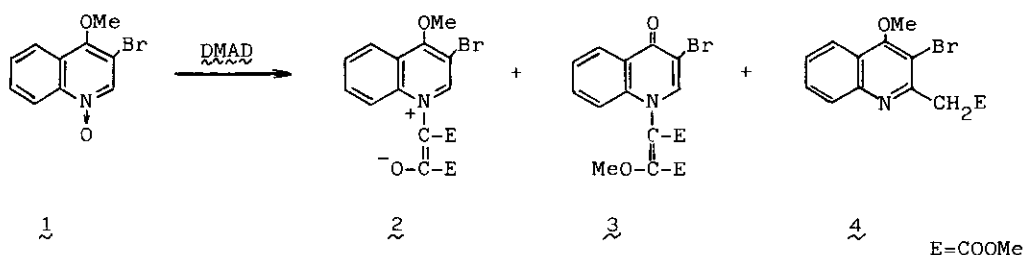
was recently found that its <sup>13</sup>C NMR spectrum does not show any signals due to methine-carbon. This finding prompted us to re-examine the reaction in some detail, and it was disclosed that the reaction of 1 with DMAD affords three products,

that is,  $\alpha$ -[N-(3-bromo-4-methoxyquinolinium)]- $\alpha,\beta$ -bismethoxycarbonyl- $\beta$ -oxo-ethylide (2: orange needles), dimethyl  $\alpha$ -[N-(3-bromo-4-oxo-1,4-dihydroquinolyl)]- $\beta$ -methoxy-fumalate (3: colorless prisms, mp 191-191.5°C) and methyl 2-(3-bromo-4-methoxyquinoline)acetate [4: colorless prisms, mp 276-278°C (decomp.)], and that the previously reported product is not the 1,2-dihydroquinoline A, i.e., the primary cycloadduct, but a novel rearrangement product 3.

According to the procedure reported previously, 1 was first treated with DMAD (1.2 equiv.) for 1 h in boiling dioxane, and the mixture of products was carefully chromatographed on silica gel to give 2, 3 and 4 in 19.3, 44.8 and 18.2% yields, respectively.

Subsequently, various conditions were examined and the results listed in Table were obtained.

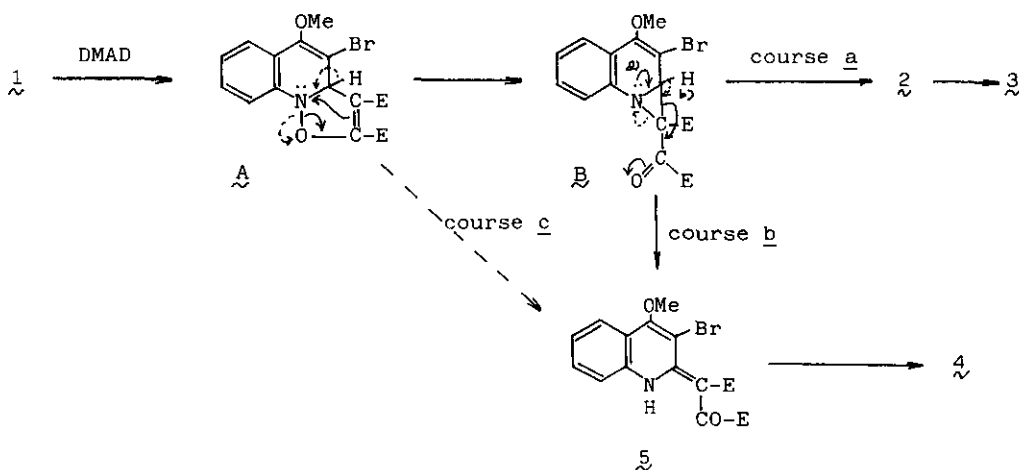
Table. The Reaction of 3-Bromo-4-methoxyquinoline 1-Oxide (1) with Dimethyl Acetylenedicarboxylate (DMAD)



Solvent	Reaction		Product, Yield (%)		
	temp.	time (h)	<u>2</u>	<u>3</u>	<u>4</u>
dioxane	r.t.	12	59.0	---	11.7
dioxane	101°	1	19.3	44.8	18.2
CH <sub>2</sub> Cl <sub>2</sub>	r.t.	12	51.3	---	8.2
MeCN	r.t.	12	71.8	---	13.1
MeCN	80°	1	46.2	---	16.4
DMF	r.t.	12	46.2	---	24.6
DMF	100°	1	---	50.0	16.4

Product 4 was formed as a minor one under all the conditions employed. In reactions conducted below 100°C, the main product was always 2, no formation of 3 being noticed at all. On the other hand, yield of 2 substantially decreased and 3 was predominantly yielded when the reaction temperature was raised to ca. 100°C;

nevertheless, **3** was curiously not formed at all in the reaction at 80°C in MeCN. Product **2** was rather unstable and could not be recrystallized from the usual solvent because of partial conversion to **3**. Furthermore, **2** was quantitatively transformed into **3** upon direct melting or heating at 100°C in DMF. These observations evidently demonstrate that **3** is produced by thermal rearrangement of **2**. The structure assignments of the products were based on elemental analyses, and the IR and PMR spectroscopies.<sup>4-6</sup> Further, the structure of **3** was unambiguously established by an X-ray diffraction study.<sup>7</sup> Apparently, the product previously reported as **A** should be corrected as **3**. An acceptable mechanistic interpretation of the reaction is formulated below. The primary cycloadduct **A** initially formed is not stable enough to be isolated and readily converts to an aziridine intermediate (**B**)<sup>8,9</sup> which isomerizes to **2**, and **2** undergoes thermal rearrangement to give **3** (course a). The concerted loss of the  $\alpha$ -proton with a C-N bond fission in **B** (course b) produces a 2-substituted quinoline (**5**) which loses a methoxalyl group to give **4**, although the details of the elimination process of methoxalyl group is not clear.



According to the recent observations on the 1,3-dipolar cycloaddition of aromatic N-oxides of pyridine series<sup>9,10</sup>, the direct transformation of the primary cycloadduct **A** to **5** (course c) appears unlikely. Taking account of the fact that N-substituted products, **2** or/and **3**, were produced predominantly in all the reactions, it seems most probable that the intermediate **B** is the common and key species in the above reactions.

Details of this work and further studies on the reaction of other 3,4-disubstituted quinoline 1-oxides will be published shortly.

#### ACKNOWLEDGEMENT

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#### REFERENCES and NOTES

1. Present address: Chugai Central Research Laboratories, Takada 3-41-8, Toshima-ku, Tokyo 171, Japan.
2. M. Yoshida, Y. Ishiguro, T. Yamamori, A. Aoyama, T. Endo, H. Noda, K. Funakoshi, S. Saeki and M. Hamana, Abstr. Papers, 11th Congress of Heterocyclic Chemistry, Kanazawa, 1978, 168; Idem, Heterocycles, 1979, 12, 167.
3. M. Hamana and S. Saeki, Kagaku no Ryoiki Zokan, Nankodo, 1979, No. 123, p. 219.
4. 2, orange needles. IR (Nujol)  $\text{cm}^{-1}$  : 1670, 1740 (C=O). PMR ( $\text{CDCl}_3$ )  $\delta$  : 3.63 (3H, s,  $\text{COOCH}_3$ ), 3.93 (3H, s,  $\text{COOCH}_3$ ), 4.52 (3H, s, 4-OCH<sub>3</sub>), 7.68-8.38 (4H, m, Ar-H), 8.90 (1H, s, C<sub>2</sub>-H).
5. 3, colorless prisms, mp 191-191.5°C. IR (Nujol)  $\text{cm}^{-1}$  : 1710, 1750 (C=O). PMR ( $\text{CDCl}_3$ )  $\delta$  : 3.68 (3H, s,  $\text{COOCH}_3$ ), 3.82 (3H, s,  $\text{COOCH}_3$ ), 4.06 (3H, s, 4-OCH<sub>3</sub>), 7.04-7.72 (3H, m, Ar-H), 7.80 (1H, s, C<sub>2</sub>-H), 8.45 (1H, dd,  $J_{5,6}=8$  Hz,  $J_{5,7}=2$  Hz, C<sub>5</sub>-H).
6. 4, colorless needles, mp 106-107°C (decomp.). IR (Nujol)  $\text{cm}^{-1}$  : 1735 (C=O). PMR ( $\text{CDCl}_3$ )  $\delta$  : 3.74 (3H, s,  $\text{COOCH}_3$ ), 4.08 (3H, s, 4-OCH<sub>3</sub>), 4.24 (2H, s, CH<sub>2</sub>), 7.40-8.12 (4H, m, Ar-H).
7. I. Ueda et al., Acta Cryst. B38, 1982, in press.
8. Y. Ishiguro, K. Funakoshi, S. Saeki, M. Hamana and I. Ueda, Heterocycles, 1980, 14, 179.
9. R. A. Abramovitch and I. Shinkai, Accts. Chem. Res., 1976, 9, 192.
10. T. Hisano, T. Matsuoka, M. Ichikawa and M. Hamana, Heterocycles, 1980, 14, 19.

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