

REACTION OF QUINOLINE N-OXIDES WITH BARBITURIC ACID IN THE
PRESENCE OF ACETIC ANHYDRIDE¹.

Mohammed M. YOUSIF², Seitaro SAEKI and Masatomo HAMANA^{*}

Faculty of Pharmaceutical Science, Kyushu University

Maidashi, Higashi-ku, Fukuoka 812, Japan

Abstract — Reactions of quinoline N-oxides (1) with barbituric acid in Ac₂O (1.2 eq)-DMF afford regioselectively 2-substituted quinolines (3) or quinolinium ylides (4), depending upon the nature of 1 and the reaction conditions. The reactions of quinoline and lepidine N-oxides (1a, 1b) at room temperature give the N-ylides (4a, 4b), and those at 90° yield 2-substituted quinolines (3a, 3b). The directive effect of the reaction temperature is the very reverse in reactions of 4-methoxy- and 4-chloro-quinoline N-oxides (1c, 1d); nevertheless, the reactions in Ac₂O at 90° afford 3c and 3d. While 3-cyanoquinoline N-oxide (1g) gives only 2-substituted product (3g), 4-morpholino-, 3-bromo- and 3-acetamido-quinoline N-oxides (1e, 1f, 1h) afford N-ylides (4e, 4f, 4h), independently of the reaction conditions.

In continuation of studies on the reaction of aromatic N-oxides with heterocyclic active methylenes in the presence of acetic anhydride³, we found that reactions of quinoline N-oxides (1) with barbituric acid (2) afforded 2-substituted quinolines (3) or quinolinium ylides (4), depending upon the nature of the N-oxides and the reaction conditions.

A solution of quinoline N-oxide (1a) and acetic anhydride (1.2 eq) in DMF was added to a solution of 2 in DMF at 90°. The reactants immediately turned orange, and orange precipitates began to separate. After heating was continued for 2 h until precipitation ceased, precipitates were recrystallized from acetic acid to give 5-(2-quinolyl)barbituric acid (3a) [orange granules, mp >300°] in 86% yield. The reaction using only acetic anhydride as the medium gave essentially the same

result. On the other hand, when 1a was treated with 2 in Ac_2O (1.2 eq)-DMF at room temperature, yellow crystals gradually separated out. After 3 h, precipitated crystals were recrystallized from 5% hydrochloric acid to afford quinolinium 5-barbituric acid ylide (4a) [yellow needles, $\text{mp} > 300^\circ$] in 93% yield (Chart 1). Identification of 3a and 4a was performed by elemental analyses, spectral examinations and some chemical reactions. While a signal due to $\text{C}_2\text{-H}$ of quinoline ring was not noticed in the NMR spectrum of 3a, it appeared at δ 9.20-9.32 as a multiplet in the spectrum of 4a. The UV spectrum of 3a was quite different from that of 4a, but rather similar to that of 2-(2-quinolyl)cyclohexan-1,3-dione⁶. Oxidation of 3a with 30% hydrogen peroxide in boiling acetic acid gave 5-(1-oxido-2-quinolyl)barbituric acid (5)⁷, contrary to the cases of other 2-substituted quinoline analogues in which quinaldic acid N-oxide was always produced³. Oxidation of 4a under the same conditions yielded 1a in the similar manner with the previously reported N-ylides⁸. It was further ascertained that 3a was not identical with

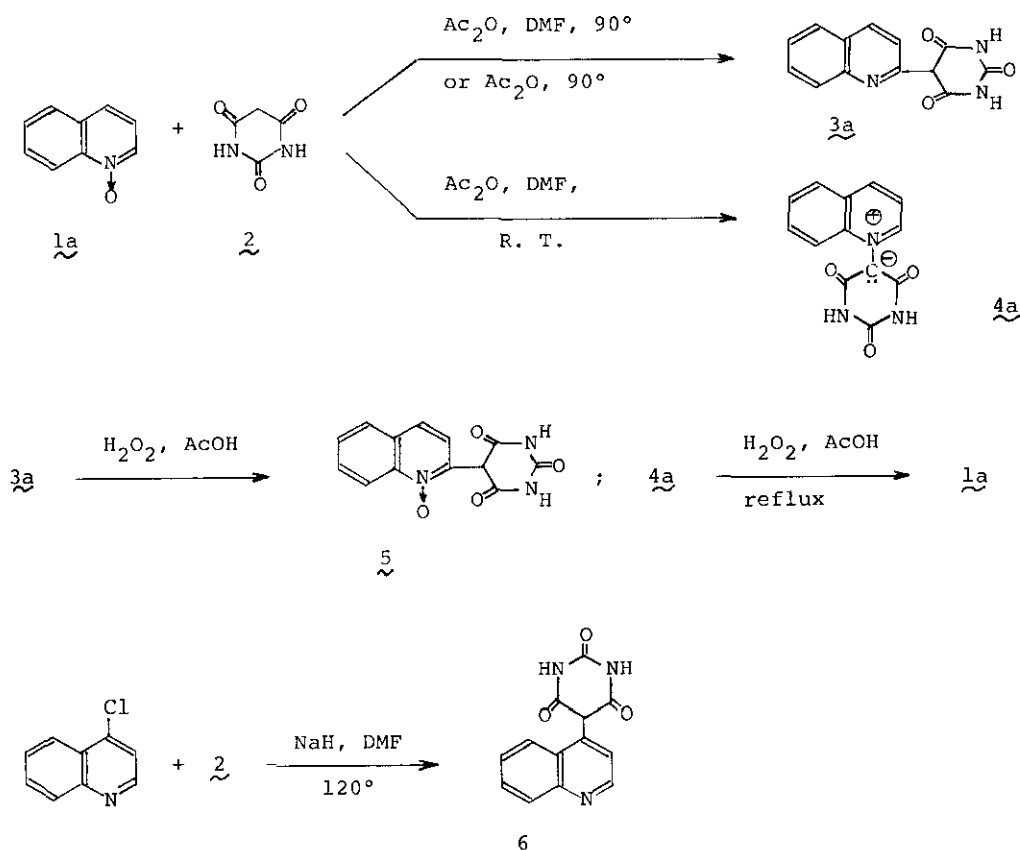
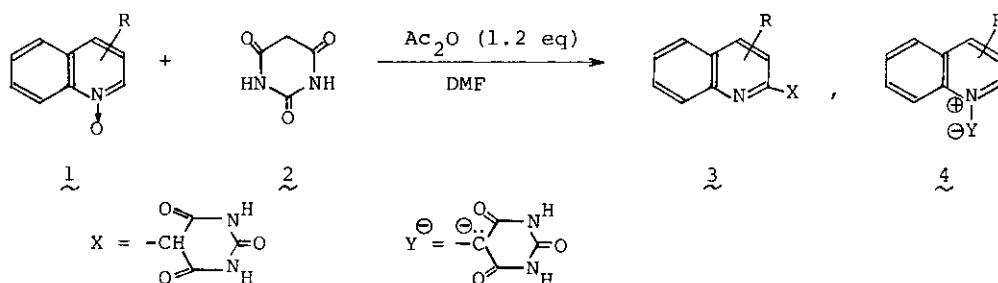


Chart 1

5-(4-quinolyl)barbituric acid (6)⁹ prepared by heating 4-chloroquinoline with sodium salt of 2 in DMF (Chart 1).

In order to explore the effects of substituents on the reaction course, reactions of some 4- and 3-substituted quinoline N-oxides (1b-1h) with 2 were carried out principally in Ac₂O (1.2 eq)-DMF at room temperature or at 90°. The results thus obtained are listed in Table.

Table Reactions of Quinoline N-Oxides (1a-1h) with Barbituric acid (2) in Ac₂O (1.2 eq)-DMF



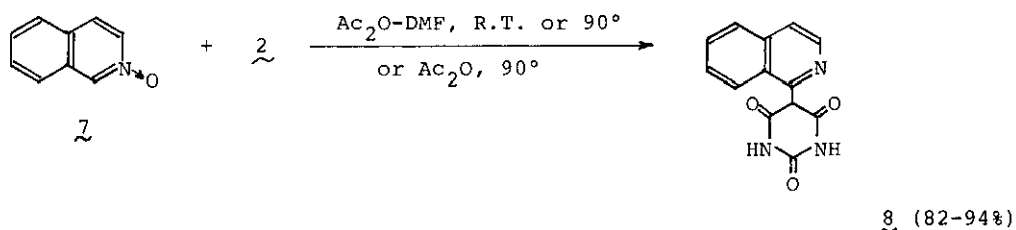
<u>1</u>	Reaction		Product, Yield (%)	
		Temp. Time (h)	<u>3</u>	<u>4</u>
<u>1a</u> R= H	R.T. 3 90° 2		<u>3a</u> : 86	<u>4a</u> : 93
<u>1b</u> R= 4-Me	R.T. 1 90° 2		<u>3b</u> : 85	<u>4b</u> : 96
<u>1c</u> R= 4-OMe	R.T. 4		<u>3c</u> : 85	
	90° 2 90° a) 2		<u>3c</u> : 92	<u>4c</u> : 99
<u>1d</u> R= 4-Cl	R.T. 4		<u>3d</u> : 93	
	90° 2			<u>4d</u> : 85
	90° a) 2		<u>3d</u> : 84	
<u>1e</u> R= 4-N ₂ O	R.T. 1			<u>4e</u> : 94
	90° 2			<u>4e</u> : 81
<u>1f</u> R= 3-Br	R.T. 2			<u>4f</u> : 82
	90° 1			<u>4f</u> : 95
<u>1g</u> R= 3-CN	R.T. 2		<u>3g</u> : 76	
	90° 1		<u>3g</u> : 87	
<u>1h</u> R= 3-NHAc	R.T. 3 90° 1			<u>4h</u> : 71 b)

a) The reaction was carried out in Ac₂O at 90°.

b) 5-Dimethylaminomethylidenebarbituric acid.

Reactions of lepidine, 4-methoxy- and 4-chloroquinoline N-oxides (1b, 1c and 1d) afforded both of 2-substituted quinolines (3b, 3c and 3d) and N-ylides (4b, 4c and 4d). The behavior of 1b was quite similar to that of 1a; the reaction at room temperature gave the N-ylide (4b) [yellow granules (AcOH-MeOH), mp>300°] as a sole product, and only the 2-substituted quinoline (3b) [red granules (AcOH), mp>300°] was isolated from the reaction at 90°. On the other hand, the effect of the temperature was the very reverse in the reactions of 1c and 1d; the reactions at room temperature gave 2-substituted quinolines, 3c [orange granules (AcOH-MeOH), mp>300°] and 3d [yellow granules (AcOH), mp>300°], and those at 90° afforded 4c [yellow granules (AcOH-MeOH), mp>300°] and 4d [yellow needles (5% HCl), mp>300°], exclusively in each case. Nevertheless, the reactions in acetic anhydride alone at 90° gave not the N-ylides, but instead 3c and 3d. This finding apparently indicates that the solvent effect is more efficient than the temperature effect in these cases.

4-Morpholino- and 3-bromo-quinoline N-oxides (1e and 1f) gave only the corresponding N-ylides, 4e [yellow needles (AcOH), mp>300°] and 4f [orange granules (AcOH), mp>300°], independently of the reaction conditions; no formation of 2-substituted quinolines being noticed. The reaction of 3-acetamidoquinoline N-oxide (1h) at room temperature produced also the N-ylide (4h) [orange granules (AcOH), mp>300°], but that at 90° followed an alternate path to give 5-dimethylaminomethylidenearbituric acid in 80% yield. On the contrary, 3-cyanoquinoline N-oxide (1g) gave only the 2-substituted quinoline (3g) [red powder (AcOH), mp>300°] under the both conditions. Further, isoquinoline N-oxide (7) was found to react also readily with 2 under various conditions to give always the 1-substituted isoquinoline (8) [yellowish orange prisms (AcOH), mp>300°]. Any satisfactory results were not obtained yet with pyridine N-oxides, only resinous substance being formed. The structure elucidation of the products was made by elemental analyses and spectral examinations in the same way as the case of 1a.



Although the high regioselectivity as well as high yield in each case is very remarkable, the directive effects of the nature of substituents and the reaction conditions cannot be uniformly explained at present. It is reasonably conceivable that a mixture of 3 and 4 might be formed in reactions of 1a-ld at the intermediate temperatures between 20-25° and 90°. In fact, reactions of 1d at 30° and at 50° gave 3d and 4d in the ratios of roughly 2:1 and 1:2, respectively, which could be rather easily estimated by the NMR spectral examinations. However, the separation of the products failed because of their highly sparing solubilities. When the reaction was carried out at 70°, 4d was obtained as a sole product. Similar studies on reactions of 1a-lc are now in progress in our laboratory.

The formation of 2-substituted quinolines, for example 3a from 1a, can be well explained by path a involving liberation of the acetic acid component from a 1,2-dihydroquinoline intermediate (A), in the usual way. According to the mechanism previously proposed for N-ylide formation from quinoline N-oxides and some active methylenes⁸, the formation of N-ylide 4a should be assumed to follow path b which proceeds through an aziridine intermediate (B). However, the intermediacy of B seems rather unlikely in this case because of its highly strained structure. This situation suggests the possibility of an alternative path c, which involves the N-OAc bond fission with the concerted 1,2-shift of the side chain in A.

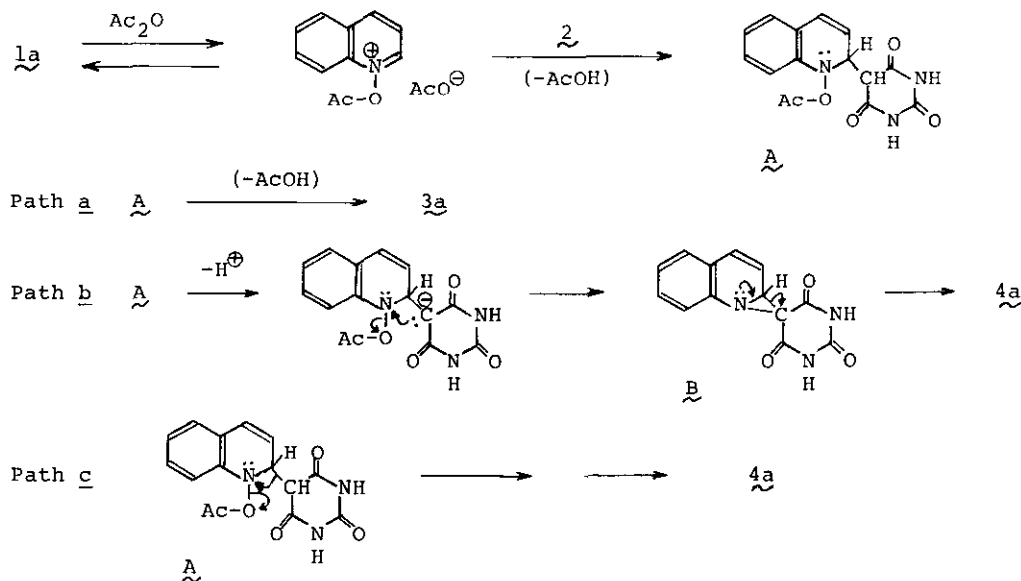


Chart 2

The detailed feature of the N-ylide formation remains to be further explored. In connection with the reaction mechanism, the interconversion between 3 and 4 was tried under various conditions but no fruitful result was obtained (Chart 2).

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REFERENCES and NOTES

1. We wish to dedicate this paper to Professor Tetsuji Kametani on the occasion of his retirement.
2. Foreign Student from Al-Mansoura-University, Faculty of Sciences, Chemistry Department, Egypt.
3. M.M. Yousif, S. Saeki and M. Hamana, *J. Heterocycl. Chem.*, 1980, 17, 305, 1029.
4. 3a. IR (Nujol) cm^{-1} : 1725 (CO), 3150 (NH). NMR (DMSO- d_6) δ : 9.15 (1H, d, $J=10.0$ Hz, $\text{C}_3\text{-H}$), 8.45 (1H, d, $J=10.0$ Hz, $\text{C}_4\text{-H}$), 7.50-8.20 (4.5H, m, Ar-H and >CH-), 10.95 (2H, bs, NH), 16.45 (0.5H, bs). UV (EtOH) nm (log ϵ): 234 (3.97), 282 (3.24), 386 (3.81), 400 (3.80). MS m/e : 255 (M^+).
5. 4a. IR (Nujol) cm^{-1} : 1720 (CO), 3200 (NH). NMR (DMSO- d_6) δ : 9.20-9.32 (2H, m, $\text{C}_2\text{-H}$ and $\text{C}_8\text{-H}$), 7.60-8.43 (5H, m, Ar-H), 10.15 (2H, bs, NH). UV (EtOH) nm (log ϵ): 209 (3.87), 236 (4.08), 318 (3.73). MS m/e : 255 (M^+).
6. M.M. Yousif's unpublished datum, which will appear in the near future.
7. 5. Colorless prisms (EtOH-MeOH), mp 295° (dec.). IR (Nujol) cm^{-1} : 1725, 1755 (CO), 3200 (NH). NMR (DMSO- d_6) δ : 7.65-7.96 (3H, m, Ar-H), 8.13 (1H, d, $J=9.0$ Hz, $\text{C}_3\text{-}$ or $\text{C}_4\text{-H}$), 8.17 (1H, d, $J=9.0$ Hz, $\text{C}_3\text{-}$ or $\text{C}_4\text{-H}$), 8.38 (1H, d, $J=8.5$ Hz, $\text{C}_8\text{-H}$), 8.37 (1H, s, >CH-), 11.60 (2H, s, NH).
8. K. Funakoshi, H. Sonoda, Y. Sonoda and M. Hamana, *Chem. Pharm. Bull.*, 1978, 26, 3504.
9. 6. Yellow powder (AcOH), mp $>300^\circ$. IR (Nujol) cm^{-1} : 1720 (CO), 3200 (NH). NMR (DMSO- d_6) δ : 8.72 (1H, d, $J=8.0$ Hz, $\text{C}_2\text{-H}$), 7.02 (1H, d, $J=8.0$ Hz, $\text{C}_3\text{-H}$), 7.55-8.02 (4H, m, Ar-H), 11.2 (2H, s, NH).

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