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73. **Masatomo Hamana and Motoyoshi Yamazaki**: Studies on Tertiary Amine Oxides. XV.[*1] Reaction of Quinoline 1-Oxide with Acetyl Cyanide.

(*Institute of Pharmaceutical Sciences, Faculty of Medicine, Kyushu University*[*2])

In the course of an investigation on the reaction of aromatic amine oxides with acylating agents, a novel reaction of quinoline 1-oxide with acetyl cyanide was happened to come across.

When quinoline 1-oxide (I) was treated with acetyl cyanide in chloroform or acetic acid otherwise without solvent, no reaction occurred and the starting material was recovered almost quantitatively. However, if acetyl cyanide was added to a solution of I in 1.2 equivalent amount of acetic anhydride, an exothermic reaction took place and reddish brown crystals were separated from the reaction mixture. After the reaction mixture was kept standing overnight in a refrigerator, the crystals (III) were filtered from the solution and the filtrate was treated with sodium carbonate solution and extracted with chloroform. Steam distillation of the extracted substances gave quinaldonitrile (II) in 8% yield from the distillate recovering 27% of I from the residue. II, m.p. 94°, was identified by elementary analysis and admixture with an authentic specimen prepared by the method of Henze.[1] Recrystallization of the separated crystals III from ethanol afforded brown needles, m.p. 176~178°, with an empirical formula, $C_{12}H_8ON_2$, in 25% yield which exhibited an infrared absorption band at 2250 cm^{-1}, characteristic to the nitrile, though weakly.

When III was heated in 10% sodium hydroxide solution, it gave quinaldine together with ammonia; oxidation with potassium permanganate yielded quinaldic acid.[1] 2-Tribromomethyl-[2] or 2-dibromomethyl-quinoline[3] was prepared, when III was subjected to bromination with bromine in chloroform or sodium hypobromite in alkali solution. Further, III was treated anhydrous ethanolic hydrogen chloride to afford ethyl 2-quinolinepyruvate which proved to be identical with an authentic specimen[4] prepared from quinaldine and diethyl oxalate under the catalytic circumstances of potassium ethoxide.

From these results, III is most probably assumed to be 2-quinolinepyruvonitrile and its reactions may be illustrated as shown in Chart 1.

It was subsequently examined how the course of reaction would be affected by the nature of reaction medium or the amount of the reagents employed, and the results will be shown in Table I.

[*1] Part XIV: This Bulletin, **10**, 969 (1962).
[*2] Katakasu, Fukuoka (浜名政和, 山崎企善).
[1] M. Henze: Ber., **69**, 1566 (1936).
[2] D.L. Hammick: J. Chem. Soc., **1923**, 2882.
[3] B.R. Brown, D.L. Hammick: *Ibid.*, **1950**, 628.
[4] N.J. Leonard, J.H. Boyer: J. Am. Chem. Soc., **72**, 2980 (1950).

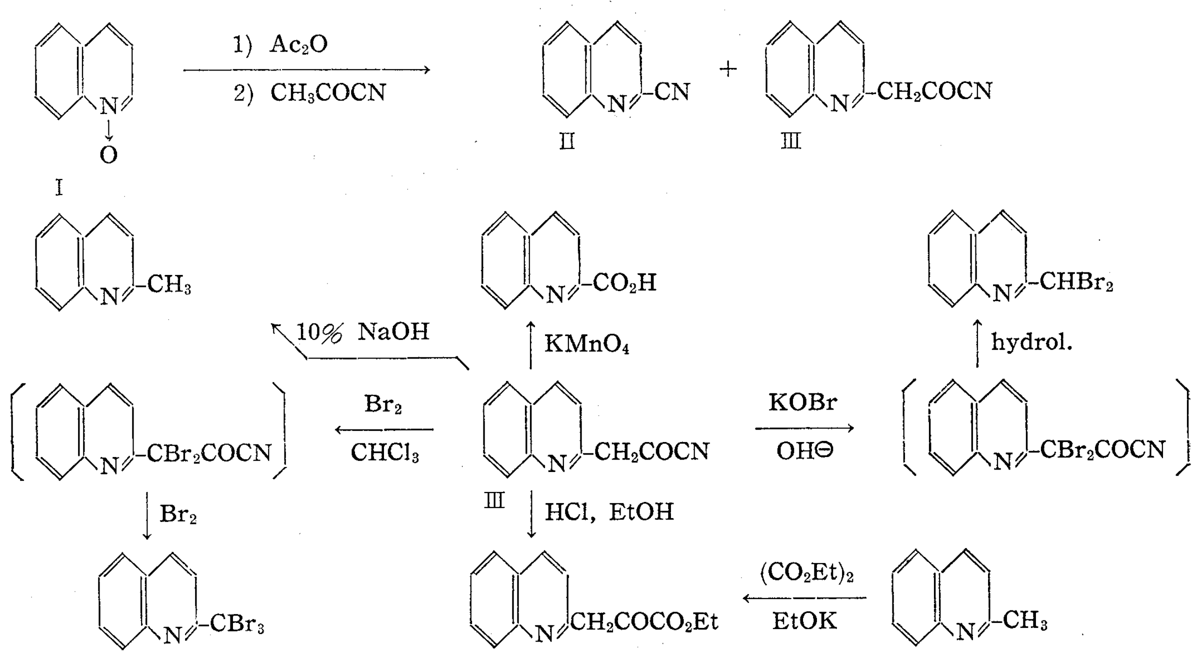

Chart 1.

Table I. The Reactions of Quinoline 1-Oxide with Acetyl Cyanide in the Presence of Acetic Anhydride

Ac_2O (mole)	Solvent	Yields of products (%)		Recovery of I (%)
		II	III	
1.2	—	8	25	27
2.5	—	trace	36	33
1.2	dioxane	55	—	23
1.2	$CHCl_3$	10	—	41

It was found that the course of reaction was affected to a large extent with or without solvent; II was the sole product in dioxane or chloroform solution, while III was the main product without solvent and its yield was increased by using an excess of acetic anhydride.

These results apparently demonstrate that quinoline 1-oxide itself is not capable to react with acetyl cyanide but its acetic anhydride adduct, 1-acetoxyquinolinium acetate (IV) is so reactive that it may be attacked by the reagent, in two different ways depending upon the reaction condition, giving either II or III. The formations of II and III will be illustrated by the following two courses (A) and (B). In the course (A), at first, IV reacted with acetyl cyanide to give V with a liberation of acetic anhydride; in the course (B), on the other hand, V′ is formed with an elimination of acetic acid instead of acetic anhydride. This difference in the first step would decide the following sequences of reactions. The conversion of both V and V′, through VI and VI′, into II and III may be rationalized by entirely analogous mechanisms to the Reissert's reaction of quinoline 1-oxide as shown in Chart 2.

Taking account of the equilibria in the first step of the reaction, it seems to be reasonable that an employment of an excess acetic anhydride is favorable to the course (B).

Kaneko[5] found that the application of benzoyl chloride and silver cyanide to quinoline 1-oxide in chloroform afforded quinaldonitrile and carbostyril. Since the latter

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[5] C. Kaneko: This Bulletin, 8, 286 (1960).

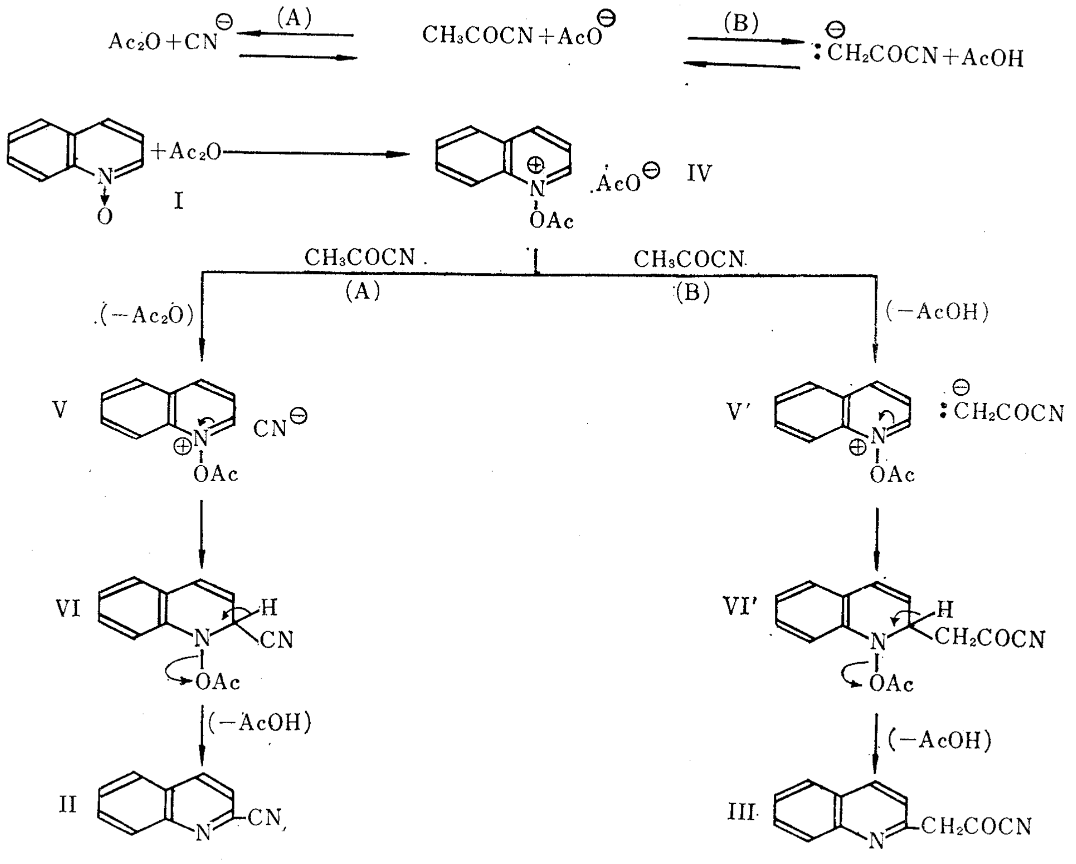
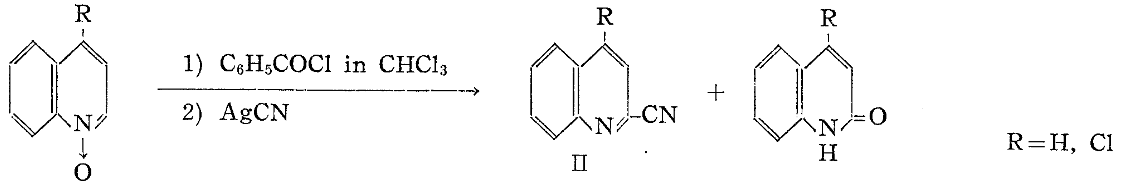


Chart 2.

compound has never been obtained in our experiments, these two reactions may be different in the detailed mechanism in spite of their apparent similarities.



Formation of II from I is regarded as a modification of the Reissert's reaction of quinoline 1-oxide in non-hydrous medium as likely as the reaction reported by Kaneko.⁵⁾ Of much more interest is the formation of III; this suggests a possibility of bringing about an introduction of a carbon-substituent into the quinoline ring, by the application of appropriate compounds containing reactive hydrogens to quinoline 1-oxide in the presence of acetic anhydride.

Experimental

Reaction of Quinoline 1-Oxide (I) with AcCN in the Presence of Ac_2O——(1) To a solution of I (1.5 g.) in Ac_2O (1.3 g.) was added dropwise AcCN (0.7 g.) with ice-cooling and stirring, the mixture was stirred further for 1 hr. and kept overnight in a refrigerator. The crystals (III) deposited were filtered and the filtrate treated with MeOH to decompose an excess of Ac_2O which was evaporated under reduced pressure. The residue was made alkaline with KOH solution and extracted with $CHCl_3$,*[3] which was evaporated *in vacuo* and steam distilled. Extraction of distillate with Et_2O followed by recrystallization from MeOH-H_2O gave 0.12 g. (8%) of quinaldonitrile (II), colorless plates, m.p. 194°, and no depression on admixture with an authentic sample.¹⁾ The residual solution from steam distil-

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*[3] No carbostyril could be isolated from the residual alkaline solution on adding NH_4Cl and extracting with $CHCl_3$.

lation was made alkaline with K_2CO_3 and extracted with $CHCl_3$ giving 0.4 g. of I, b.p.$_4$ 160∼180° (bath temp.). Picrate: m.p. 199∼200°.

2-Quinolinepyruvonitrile (Ⅲ), was recrystallized from EtOH as brown needles, m.p. 176∼178° (decomp.), yielding, 0.5 g. (25%). *Anal.* Calcd. for $C_{12}H_8ON_2$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.57; H, 3.85; N, 14.14. IR: $\nu_{C\equiv N}$ 2250 cm^{-1} (Nujol).

(2) From another run which 2.5 equivalent amount of Ac_2O was employed, Ⅲ was obtained in 36% yield together with a trace of Ⅱ, I being recovered in 33% yield.

(3) To a mixture of I (1.5 g.), dioxane (10 cc.) and Ac_2O (1.3 g.), was added dropwise a solution of AcCN (0.7 g.) in dioxane (5 cc.) with ice-cooling and stirring. After standing overnight at room temperature, the reaction mixture was treated with MeOH to decompose an excess of Ac_2O which was evaporated *in vacuo*. An addition of a small amount of H_2O to the residue precipitated a crystalline substance, which was filtered and taken up in Et_2O. The Et_2O solution was washed with 10% NaOH, dried over Na_2SO_4 and evaporated to give 0.85 g. (55%) of Ⅱ, m.p. 194°, after recrystallization from hyd. MeOH. When the above washings (10% NaOH solution) were acidified with HCl under ice-cooling, a trace of Ⅲ was obtained as a precipitate. The remaining aqueous solution from extraction of Ⅱ was made alkaline with K_2CO_3 and extracted with $CHCl_3$ to afford 0.5 g. of I.

(4) An entirely similar procedure using $CHCl_3$ in place of dioxane gave Ⅱ in 10% yield and a trace of Ⅲ, recovering 41% of I.

Reactions of 2-Quinolinepyruvonitrile (III): (1) Alkaline Hydrolysis——A mixture of Ⅲ (0.2 g.) and 10% NaOH (10 cc.) was heated under reflux for 2 hr. After cooling, the reaction mixture was extracted with Et_2O to give an oily substance, which afforded picrate, yellow plates, m.p. 193∼194°, undepressed on admixture with quinaldine picrate.

(2) **$KMnO_4$-Oxidation**——A mixture of Ⅲ (1.0 g.) and powdered $KMnO_4$ (3 g.) in Me_2CO was allowed to stand at room temperature for 2 days. After decomposing an excess of $KMnO_4$ with oxalic acid, precipitates were collected by filtration and extracted several times with hot H_2O. The combined filtrate and washings was concentrated under reduced pressure, acidified with H_2SO_4, and followed by adding saturated solution of $CuSO_4$ to deposit a cupric salt, which was filtered and washed with H_2O. This was suspended in MeOH and saturated with H_2S under reflux to separate CuS, which was filtered off. The filtrate was evaporated to dryness and the solidified residue was recrystallized from MeOH-benzene to give 0.3 g. of quinaldinic acid, m.p. 155∼156°, undepressed on admixture with an authentic specimen.

(3) **Reaction with Br_2**——To a solution of Ⅲ (0.2 g.) in $CHCl_3$ (10 cc.) was added dropwise elementary Br_2 until the color of Br_2 no longer disappeared, and the mixture was allowed to stand at room temperature for 5 hr. The reaction mixture was then shaken with 10% Na_2CO_3 and dried over Na_2SO_4. Evaporation of $CHCl_3$ gave 0.12 g. of 2-tribromomethylquinoline, which formed colorless scales, m.p. 130∼132°, from AcOH and identified with an authentic specimen$^{2)}$ by admixture. *Anal.* Calcd. for $C_{10}H_6NBr_3$: C, 31.58; H, 1.58; N, 3.68. Found: C, 31.40; H, 1.83; N, 4.07.

(4) **Reaction with KOBr**——To a solution of KOBr (6 g.), prepared from Br_2 (5 g.), H_2O (47.7 g.) and KOH (5.3 g.), was added Ⅲ (0.2 g.) with ice-cooling. After standing at room temperature for 5 hr., the reaction mixture was diluted with H_2O to dissolve the precipitate, neutralized with AcOH and extracted with Et_2O, which was evaporated. The residue was recrystallized from petr. benzin to 0.25 g. of colorless needles of 2-dibromomethylquinoline, m.p. 119∼120°, identified with an authentic specimen$^{3)}$ by admixture. *Anal.* Calcd. for $C_{10}H_7NBr_2$: C, 39.87; H, 2.33; N, 4.65. Found: C, 40.14; H, 2.58; N, 4.27.

(5) **Reaction with HCl-EtOH**——A solution of Ⅲ (0.2 g.) in anhyd. EtOH (50 cc.) was saturated with dry HCl under ice-cooling. After standing overnight at room temperature, the reaction mixture was refluxed for 1 hr. and the solvent was removed under reduced pressure. The residue was made weakly alkaline with $NaHCO_3$ solution and extracted with $CHCl_3$. Evaporation of $CHCl_3$ followed by recrystallization from petr. benzin gave 0.06 g. of yellow scales of ethyl 2-quinolinepyruvate, m.p. 132∼133, showing no depression on admixture with an authentic specimen.$^{4)}$ *Anal.* Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.31; H, 5.29; N, 5.66.

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Summary

While quinoline 1-oxide itself is not capable to react with acetyl cyanide, an exothermic reaction occurred in the presence of acetic anhydride, and quinaldonitrile and 2-quinolinepyruvonitrile were obtained. The former was a sole product from the reaction in dioxane or chloroform, whereas the latter was the main product without solvent.

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