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Summary

3,4-Dinitrophthalic acid gave a sensitive violet coloration with glucose when heated in aqueous sodium carbonate. In this color reaction, the acid was reduced to 3-nitro-4-hydroxylaminophthalic acid. 4,5-Dinitrophthalic acid behaved in the same way as the 3,4-isomer, and was reduced to 4-hydroxylamino-5-nitrophthalic acid. 3,5-Dinitrophthalic acid was less sensitive in the reaction, showing a yellow coloration by its reduced substances down to 3-amino-5-nitrophthalic acid.

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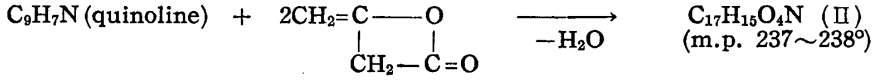
4. **Tetsuzo Kato and Hiroshi Yamanaka** : Studies on Ketene and its Derivatives. V.[1] Reaction of Diketene with Quinoline N-Oxide.

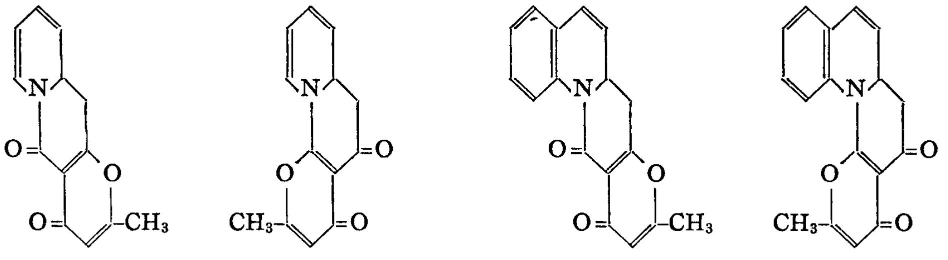
(*Pharmaceutical Institute, Tohoku University School of Medicine*[*1])

In a previous paper[2] of this series we have reported that diketene reacts with quinoline readily to give a yellow crystal of m.p. 237~238° (decomp.) which has a quite similar structure with one of socalled Wollenberg's compound[3,4] isolated from the reaction of ketene with pyridine, and that the compound thus obtained is represented as either II-a or II-b.

$$C_5H_5N\,(\text{pyridine}) + 4CH_2{=}C{=}O \xrightarrow[-H_2O]{} C_{13}H_{13}O_4N\ (\text{I})\ (\text{Wollenberg's compound})$$



$$C_9H_7N\,(\text{quinoline}) + 2\begin{array}{c}CH_2{=}C{-}O\\ |\quad\ \ |\\ CH_2{-}C{=}O\end{array} \xrightarrow[-H_2O]{} C_{17}H_{15}O_4N\ (\text{II})\ (\text{m.p. } 237{\sim}238^\circ)$$



I-a I-b II-a II-b

Chart I.

[*1] Kita-4, Sendai, Miyagi-Ken (加藤鉄三, 山中 宏).

[1] Part IV. T. Kato, H. Yamanaka, F. Hamaguchi : Yakugaku Zasshi, **83**. 741 (1963).

[2] T. Kato, T. Kitagawa, Y. Yamamoto : *Ibid.*, **83**, 267 (1963).

[3] O. Wollenberg : Ber., **67**, 1675 (1934).

[4] J. Berson, W. Jones : J. Am. Chem. Soc. **78**, 1625 (1956).

Although the reaction mechanism has not been completely dissolved yet, it will be clear that the endomethylene carbanion of diketene attacked on the α-carbon of quinoline ring and the carbonium ion of diketene reacted with the ring-nitrogen giving a new quinolizine ring system. As of particular interest is the influence of N-oxide function, we have extended this reaction to quinoline 1-oxide, which is described in this paper.

Reaction of excess diketene on quinoline 1-oxide in chloroform under reflux resulted in the formation of white needles of m.p. 126~127°, together with formation of quinaldine as a by-product. Elemental analyses of m.p. 126~127° established its empirical formula as $C_{16}H_{13}O_2N$ (III), and the infrared absorption spectrum of III contradicted the existence of N-oxide function in the range of 1200~1300 cm^{-1} and exhibited characteristic peaks at 1665, 1609 and 1588 cm^{-1} (4-pyrone). Hydrolysis of III with KOH in EtOH-H_2O resulted in the formation of quinaldine in a good yield, together with formations of acetone, carbon dioxide and acetic acid. On warming with liquid ammonia in a sealed tube, III was converted into white prisms of m.p. 310~315° (decomp.), $C_{16}H_{14}ON_2$ (IV). The infrared absorption spectrum of IV exhibited a peak at 1630 cm^{-1} (4-pyridone). Treatment of IV with phosphoryl chloride afforded white prisms of m.p. 119~120°, $C_{16}H_{13}N_2Cl$ (V). The infrared absorption spectrum of V contradicted the existence of C=O stretching in the range of 1600~1700 cm^{-1}. From these observations described above, we concluded that III is uniquely represented as 2-(2-quinolyl)methyl-6-methyl-4*H*-pyran-4-one. The ultraviolet absorption spectrum also leads to our conclusion as shown as in Fig. 1. In consequence, IV and V are represented as 2-(2-quinolyl)methyl-6-methyl-4(1*H*)-pyridone (IV) and 2-(2-quinolyl)methyl-4-chloro-6-methylpyridine (V) respectively.

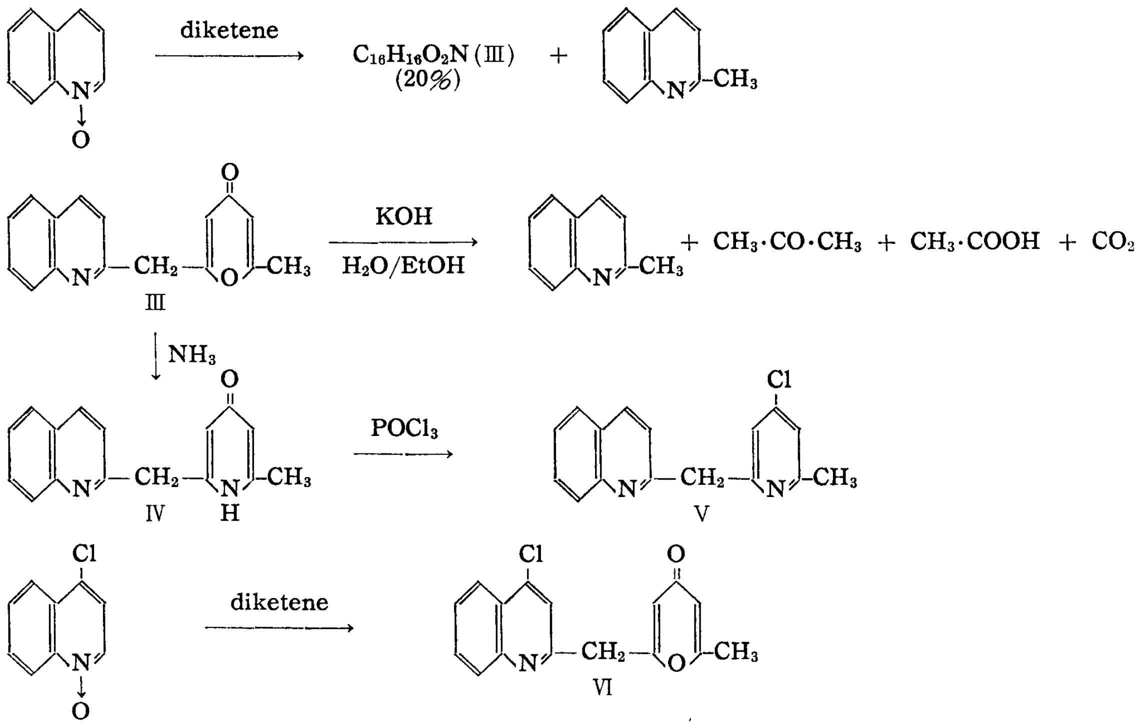


Chart 2.

Attempts were made to extend this reaction to other N-oxides, such as pyridine 1-oxide, 4-nitroquinoline 1-oxide and 4-chloroquinoline 1-oxide. Although reactions of pyridine 1-oxide and nitroquinoline 1-oxide on diketene resulted in the recovery of the starting N-oxide respectively, 4-chloroquinoline 1-oxide reacted with diketene giving white downy crystals of m.p. 171~173°, $C_{16}H_{12}O_2NCl$ (VI). The infrared absorption spectrum of

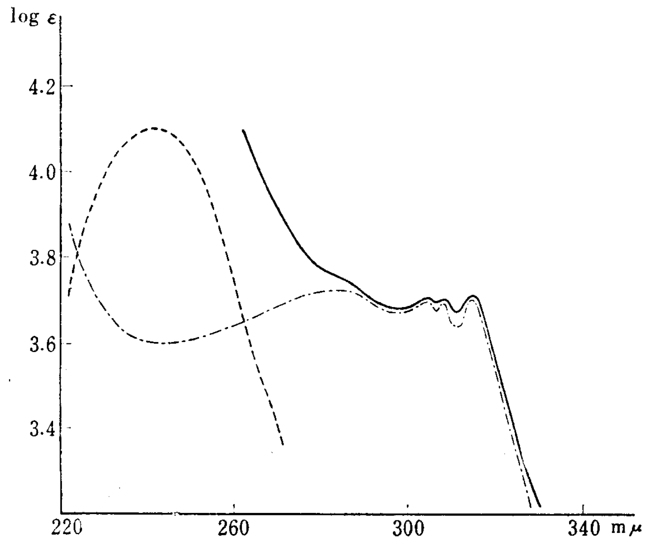


Fig. 1. Ultraviolet Absorption Spectra in Ethanol

—— III
-·-·- quinoline
-------- 2,6-dimethyl-4*H*-pyran-4-one

VI indicated the existence of 4-pyrone and the absence of N-oxide function. Thus, VI is presumably represented as 2-(4-chloro-2-quinolyl)methyl-6-methyl-4*H*-pyran-4-one. Although details of the mechanism of the formation of III or VI from the reaction of diketene with quinoline 1-oxide or its 4-chloro derivative remain not clear for the present, a probable mechanism is shown in Chart 3. None of compounds (VII~X) in parenthesis in Chart 3 could be isolated. However, a likely intermediate would be IX-a. The subsequent stage might well involve the fission of N-O linkage to give X, followed by decarboxylation giving III. This likely mechanism also suggests that a Wollenberg's compound and a quinoline-diketene adduct would be represented rather as I-a and II-a than as I-b and II-b respectively. That is, if IX-b, which is corresponding to I-b or II-b, is an intermediate in this reaction, the formation of III is impossible.

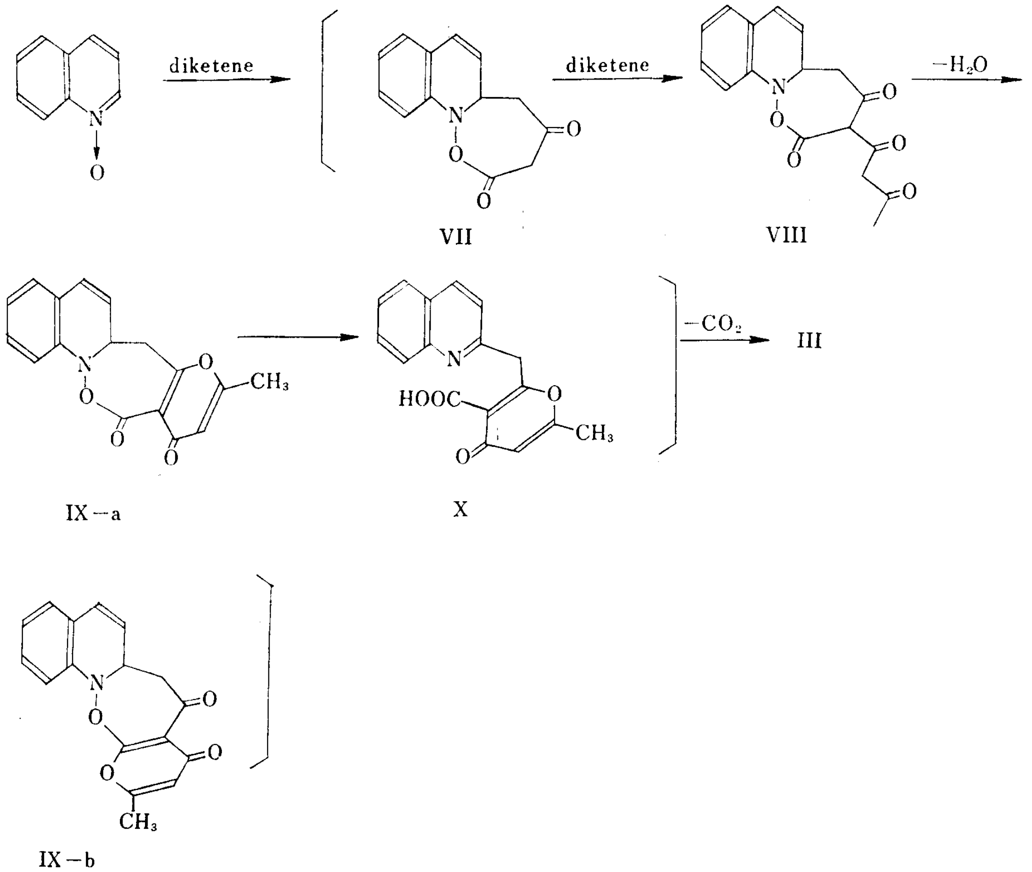


Chart 3.

Experimental

Reaction of Quinoline 1-Oxide with Diketene——To a solution of 2.9 g. (0.02 mole) of quinoline 1-oxide in 20 ml. of $CHCl_3$, was added 3.4 g. (0.04 mole) of diketene in 20 ml. of $CHCl_3$ dropwise over a period of 30 min. under reflux. After reflux for 1 additional hr., the reaction mixture was cooled, extracted with 10% of HCl. The HCl soluble layer was separated, neutralized with $NaHCO_3$, washed with Et_2O several times. The Et_2O washings were combined, dried (K_2CO_3), chromatographed over alumina to give 10 mg. of quinaldine (picrate, m.p. 194°, undepressed on admixture with an authentic sample), and 0.95 g. of white crystals of m.p. 120~124°. Recrystallization from petr. ether and Et_2O afforded white long needles of m.p. 126~128°. Yield, 20%. *Anal.* Calcd. for $C_{16}H_{13}O_2N$ (III) : C, 76.49; H, 5.46; N, 5.75. Found : C, 76.47; H, 5.22; N, 5.57. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1665 (CO), 1609, 1588 (C=C). The $NaHCO_3$ solution, after washing with Et_2O, was made basic with K_2CO_3, then extracted with $CHCl_3$. From the $CHCl_3$ extract 0.2 g. of the starting quinoline 1-oxide was recovered.

Reaction of 4-Chloroquinoline 1-Oxide with Diketene——To a solution of 1.8 g. (0.01 mole) of 4-chloroquinoline 1-oxide in 20 ml. of $CHCl_3$, was added 1.9 g. (0.022 mole) in 20 ml. of $CHCl_3$ by drops under reflux. After reflux for 2 hr., the reaction mixture was extracted with 10% of HCl. The HCl soluble layer was separated, neutralized with $NaHCO_3$ to yield a yellowish oil. It was extracted with $CHCl_3$, and the $CHCl_3$ layer was dried with Na_2SO_4, decolorized by passing an alumina column to give 0.6 g. of needles after removal of the solvent. Recrystallization from Et_2O gave white down crystals of m.p. 171~173°, 0.45 g. (16%). Beilstein test for chlorine was positive. *Anal.* Calcd. for $C_{16}H_{12}O_2NCl$ (VI) : C, 68.15; H, 4.32; N, 4.76. Found : C, 67.84; H, 4.55; N, 4.97. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1672, 1625, 1592 (4-pyrone).

Reaction of 4-Nitroquinoline 1-Oxide with Diketene——To a solution of 4-nitroquinoline 1-oxide (0.8 g.) in 10 ml. of $CHCl_3$ was added 2 g. of diketene by drops. After reflux for 14 hr., the mixture was condensed *in vacuo*. From the distillate starting diketene was recovered. The residue was recrystallized from MeOH to give 0.72 g. of pale yellowish needles (m.p. 152~154°), undepressed on admixture with the starting N-oxide. 90%.

Hydrolysis of 2-(2-Quinolyl)methyl-6-methyl-4*H*-pyran-4-one (III)——A mixture of 0.25 g. of III and 1.5 g. of KOH in 10 ml. of 50% EtOH was heated on a steam bath for 1 hr.,[*2] then distilled at atmospheric pressure, and a small amount of the fore-run was collected. To this distillate was added 2,4-dinitrophenylhydrazine (H_2SO_4-MeOH solution) to give orange yellow crystals of m.p. 128°, undepressed on admixture with an authentic acetone 2,4-dinitrophenylhydrazone. After removal of the fore-run the reaction mixture was condensed again under reduced pressure. To the resulted residual oil was added ca. 5 ml. of H_2O, and washed with Et_2O. The H_2O layer was devided into two portions. To one half of this layer was added 10% of HCl to give a gas which was absorbed into a $Ba(OH)_2$ solution giving a white precipitate of $BaCO_3$. To another half was added conc. H_2SO_4, and the specific odor of AcOH was identified. The Et_2O washing was dried, purified by alumina chromatography to give a colorless oil (0.12 g. 85%), which was identical with quinaldine by the admixture test of its picrate (m.p. 195°) with an authentic sample.

Reaction of 2-(2-Quinolyl)methyl-6-methyl-4*H*-pyran-4-one (III) with Ammonia——In a sealed pyrex glass tube was placed a solution of 1 g. of III in 10 ml. of EtOH and 20 ml. of liq. NH_3. After heating in a water bath at 50° for 24 hr., EtOH and NH_3 were evaporated to give white crystals. Recrystallization from EtOH gave 0.8 g. of white prisms of m.p. 315° (decomp.). *Anal.* Calcd. for $C_{16}H_{16}O_2N_2$ (IV-H_2O) : C, 72.00; H, 6.15; N, 10.86. Found : C, 71.62; H, 6.01; N, 10.44.

After drying at 200° under reduced pressure for 1 hr., Calcd. for $C_{16}H_{14}ON_2$ (IV) : C, 75.89; H, 5.71; N, 11.40. Found : C, 76.78; H, 5.64; N, 11.19. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1} : 1630 (4-pyrone).

Reaction of 2-(2-Quinolyl)methyl-6-methyl-4(1*H*)-pyridone (IV) with Phosphoryl Chloride——A mixture of 0.05 g. of IV and 10 ml. of $POCl_3$ was refluxed for 20 min. After evaporation of $POCl_3$ under reduced pressure, the residue was added to 10 ml. of ice H_2O, neutralized with K_2CO_3, extracted with Et_2O. The Et_2O layer was separated, dried (Na_2SO_4), condensed to give 40 mg. of crystalline solid. Recrystallization from petr. ether gave 0.03 g. of white prisms of m.p. 119~120°. Both of Beilstein test for chlorine and the fusion test with Na for N were positive. *Anal.* Calcd. for $C_{16}H_{13}N_2Cl$ (V) : C, 71.51; H, 4.84. Found : C, 71.85; H, 4.94.

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[*2] The opening of the condenser was protected from atmospheric CO_2 with a KOH tube.

Summary

Reaction of quinoline 1-oxide with diketene results in the formation of 2-(2-quinolyl)methyl-6-methyl-4*H*-pyran-4-one (Ⅲ) in 20% yield, together with formation of quinaldine as a by-product. Hydrolysis of Ⅲ gives quinaldine, acetone, carbondioxide and acetic acid. Reaction of Ⅲ with liquid ammonia affords 2-(2-quinolyl)methyl-6-methyl-4(1*H*)-pyridone (Ⅳ). Treatment of Ⅳ with phosphoryl chloride gives 2-(2-quinolyl)methyl-4-chloro-6-methylpyridine (Ⅴ). Similarly, 2-(4-chloro-2-quinolyl)methyl-6-methyl-4*H*-pyran-4-one (Ⅵ) is prepared from 4-chloroquinoline 1-oxide in 16% yield. The reaction mechanism is discussed in this report.

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