[Chem. Pharm. Bull. 22(5)1206—1208(1974)]

UDC 547.831.04 : 547.445.04

Studies on Ketene and Its Derivatives. LX.[1] Reaction of Diketene with Quinoline 1-Oxide (Supplement)[2]

Tetsuzo Kato, Hiroshi Yamanaka, Takao Sakamoto, and Takayuki Shiraishi

Pharmaceutical Institute, Tohoku University[3]

(Received September 25, 1973)

Previously, we reported that the reaction of diketene with quinoline 1-oxide gave a crystalline substance of $C_{16}H_{13}O_2N$, to which we proposed the structure 2-(2-quinolylmethyl)-6-methyl-4H-pyran-4-one (I′) based on the followings; (a) hydrolysis of I′ with aq. alkalis gave 2-methylquinoline, (b) treatment of I′ with ammonia afforded easily crystals of $C_{16}H_{14}ON_2$ (II′), which, on treatment with $POCl_3$, were easily converted to the chloropyridine derivative (III′), (c) infrared (IR) and ultraviolet (UV) spectra of both I′ and II′ were consistent with these structures, (d) as shown in Chart 1, the formation of I′ could be explained with analogy of the reaction, in which the Wollenberg's type compound was obtained from diketene and quinoline.[4,5]

During the course of the investigation on the synthesis of methylquinoline derivatives we have reinvestigated this reaction and found that the correct structure of the product from the reaction of diketene and quinoline 1-oxide is not 2-(2-quinolyl)methyl-6-methyl-4H-pyran-4-one (I′) but 2,6-dimethyl-3-(2-quinolyl)-4H-pyran-4-one (I), which is the subject of this paper.

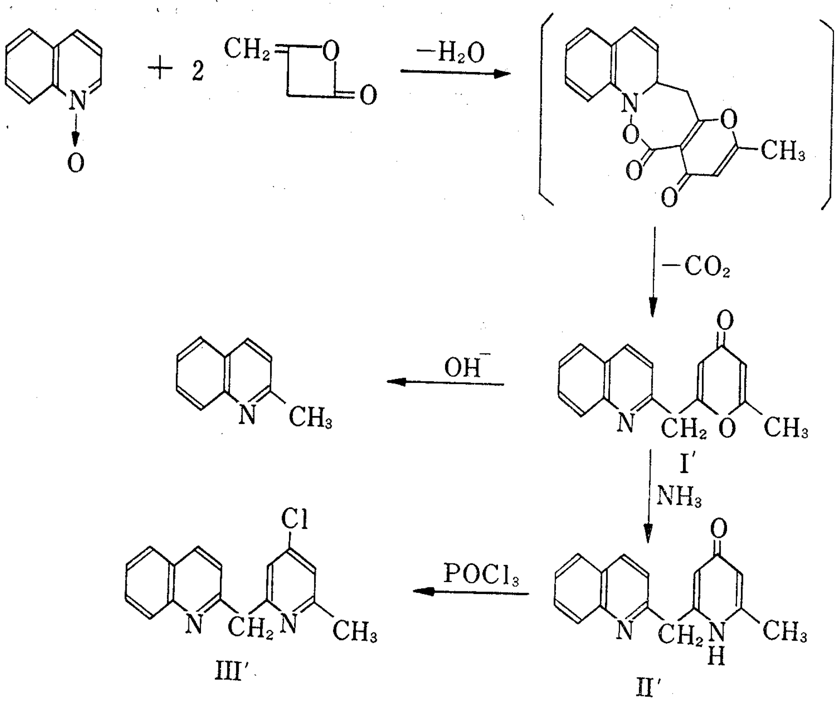

Chart 1

---

[1] Part LIX: T. Kato, Y. Yamamoto and M. Kondo, *Yakugaku Zasshi*, **93**, 1685 (1973).

[2] T. Kato and H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **12**, 18 (1964).

[3] Location: *Aobayama, Sendai 980, Japan.*

[4] T. Kato, T. Kitagawa and Y. Yamamoto, *Yakugaku Zasshi*, **83**, 267 (1963).

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

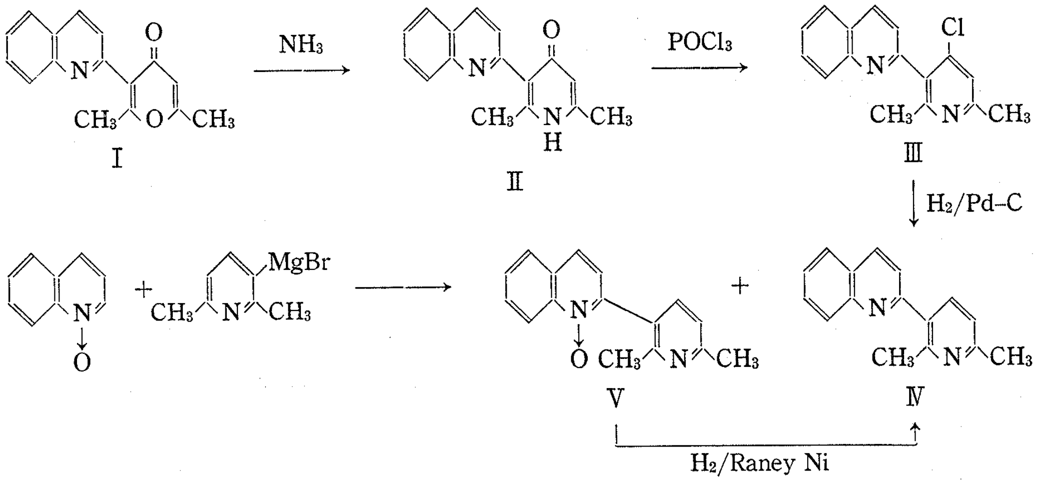

Chart 2

As reported previously, IR and UV spectral data and chemical behaviors were consistent with the existence of 4-pyrone in its structure, however, nuclear magnetic resonance spectrum ($CDCl_3$) shows signals at 2.30 ppm (3H, singlet), 2.39 ppm (3H, singlet), 6.16 ppm (1H, singlet), and 7.4—8.3 ppm (6H, multiplet), which suggests that the product has to have two methyl groups in its structure.

Similarly, the nuclear magnetic resonance (NMR) spectrum (CF_3COOH) of the ammonolysis product, $C_{16}H_{14}ON_2$, contradicts the structure of I′, because no signal due to methylene protons can be observed (2.75 ppm (3H, singlet), 2.86 ppm (3H, singlet), 7.40 ppm (1H, singlet), 8.0—8.7 ppm (5H, multiplet), 9.32 ppm (1H, doublet)).

Accordingly, the structure of the chloro-derivative prepared from ammonolysis product (II) and phosphorous oxychloride must have the structure 4-chloro-2,6-dimethyl-3-(2-quinolyl)-pyridine (III) but not III′ proposed before.

Upon catalytic reduction with a 10% paradium on carbon III was easily transformed to 2,6-dimethyl-3-(2-quinolyl)pyridine (IV).

On the other hand, we have reported the Grignard reactions of quinoline 1-oxide to give 2-substituted quinoline derivatives.[6]

Following the similar fashion given for phenylmagnesium bromide, quinoline 1-oxide was allowed to react with Grignard reagent prepared from 3-bromo-2,6-dimethylpyridine to give 2,6-dimethyl-3-(2-quinolyl)pyridine (IV) and 2,6-dimethyl-3-(1-oxido-2-quinolyl)-pyridine (V).

Compound V was reduced readily to IV, which was uniquely identical with the product derived from the reaction of diketene and quinoline 1-oxide described above. This observation is also well consistent with the structure I, but not with the isomeric I′ proposed previously.

Similary the NMR spectrum ($CDCl_3$) of the product (mp 171—173°) from the reaction of 4-chloroquinoline 1-oxide with diketene shows signals at 2.30 ppm (3H, singlet), 2.35 ppm (3H, singlet), 6.23 ppm (1H, singlet), 7.2—8.4 ppm (5H, multiplet), which suggests that the product must not have the structure 2-(4-chloro-2-quinolyl)methyl-6-methyl-4H-pyran-4-one, but 2,6-dimethyl-3-(4-chloro-2-quinolyl)-4H-pyran-4-one, reported in the previous paper.[2]

Although in the previous paper we presumed a mechanism of the formation of I′ applying the formation of Wollenberg's type compound, we would like to modify probable pathway for the formation of I as shown in Chart 3.

Namely, quinoline 1-oxide reacts with diketene to give a seven membered ring derivative (VI) as an intermediate, followed by decarboxylation to 2-acetonylquinoline (VII). VII

---

[6] T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965).

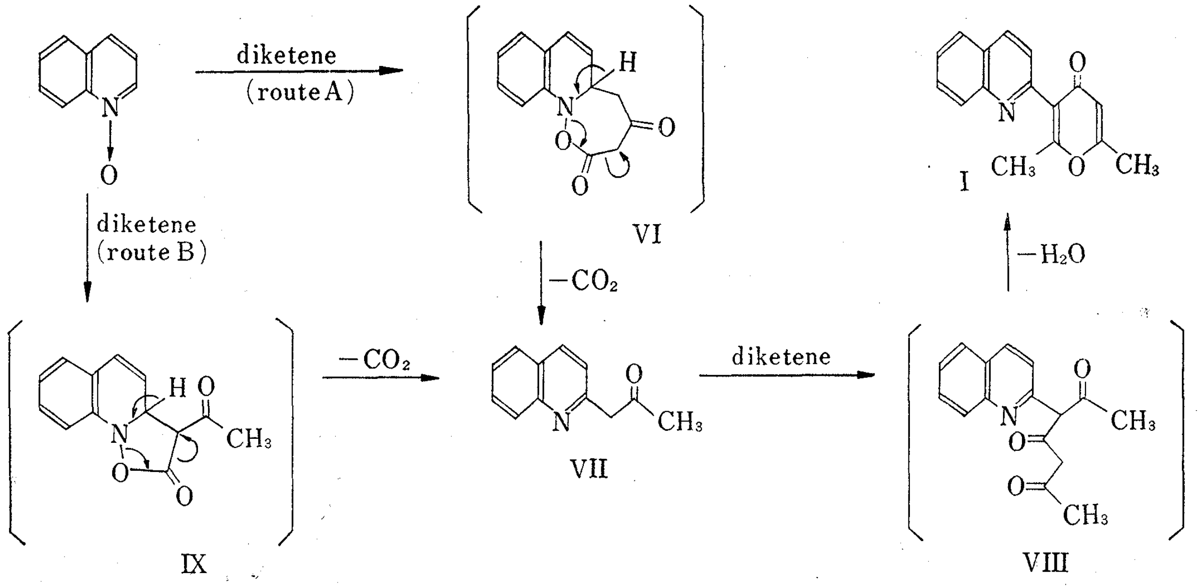

Chart 3

will easily reacts with diketene to give I *via* an intermediate such as compound VIII (A-route).

Another likely pathway may be explained by B-route, that is diketene adds to quinoline 1-oxide to form a five membered intermediate (IX), which is transformed to VIII, *via* VII.

Actually, the reaction of diketene with an excess of quinoline 1-oxide in acetic acid at room temperature afforded VII as a stable intermediate, which on treatment with diketene, was converted to I in good yield (79%).

Experimental

Reaction of Quinoline 1-Oxide with 2,6-Dimethyl-3-pyridylmagnesium Bromide——To a mixture of 0.8 g (0.033 mole) of Mg and a catalytic amount of I_2 in 10 ml of anhydrous tetrahydrofuran (THF) was dropwise added a solution of 5.6 g (0.03 mole) of 3-bromo-2,6-dimethylpyridine in 10 ml of THF under gentle refluxing. After the addition was completed, the reaction mixture was heated under reflux for additional 1 hr.

The resulting mixture was added to a solution of 2.2 g (0.015 mole) of quinoline 1-oxide in 40 ml of THF over a period of 1 hr, and the reaction mixture was refluxed for 4 hr, and cooled. After adding a small amount of H_2O, the reaction mixture was condensed under reduced pressure. The resulting residue was extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 10% HCl. The aqueous layer was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated to dryness to leave a residue, which was chromatographed on alumina. The elution with mixture of petroleum ether and ether gave colorless prisms (IV) (mp 93—95° from ether–petroleum ether, 1.28 g (36.5%)), and colorless needles (V) (mp 125—126° from ether, 0.84 g (22.5%)). *Anal.* Calcd. for $C_{16}H_{14}N_2$ (IV): C, 82.02; H, 6.02; N, 11.96. Found: C, 81.71; H, 5.95; N, 11.98. NMR (CCl_4, TMS, ppm): 2.52 (3H, singlet), 2.59 (3H, singlet), 6.9—8.1 (8H, multiplet). *Anal.* Calcd. for $C_{16}H_{14}ON_2$ (V): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.44; H, 5.55; N, 11.25. IR ν_{max}^{KBr} cm^{-1}: 1217. (N-oxide). NMR ($CDCl_3$, TMS, ppm): 2.46, 2.60 (each 3H, singlet), 7.0—8.0 (7H, multiplet), 8.82 (1H, multiplet).

Catalytic Reduction of 2,6-Dimethyl-3-(1-oxido-2-quinolyl)pyridine (V) with Raney Nickel——A solution of 0.75 g of 2,6-dimethyl-3-(1-oxido-2-quinolyl)pyridine (V) in 15 ml of MeOH was shaken in H_2 with Raney Ni prepared from 1 g of Ni-alloy. After 1 mole of H_2 was absorbed, the catalyst was removed by filtration. The filtrate was evaporated, and the resulting residual solid was purified by recrystallization from ether–petroleum ether to colorless prisms of mp 93—95°, undepressed on admixture with a sample of IV. Yield, 0.57 g (81.5%).

Catalytic Reduction of 4-Chloro-2,6-dimethyl-3-(2-quinolyl)pyridine (III)——A solution of 0.80 g (0.003 mole) of 4-chloro-2,6-dimethyl-3-(2-quinolyl)pyridine (III) in 15 ml of MeOH was shaken in H_2 with 0.3 g of 10% Pd-C and 0.12 g (0.003 mole) of NaOH. After absorption of H_2 was completed, the catalyst was removed by filtration. The filtrate was evaporated, and the residue was purified by recrystallization from ether–petroleum ether to colorless prisms of mp 93—95° undepressed on admixture with sample of IV. Yield, 0.46 g (65.5%).