BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 2590—2593 (1972)

Base-catalyzed Condensation of *o*-Nitroacetophenone. V. Hydrogenation of Compound A, a Condensation Product. Formation of a 4-Quinolone from an Indoline System

Toshio Miwa
Faculty of Science, Osaka City University Sumiyoshiku, Osaka

(Received January 24, 1972)

The catalytic hydrogenation of compound A, a base-catalyzed condensation product of *o*-nitroacetophenone, followed by treatment of the product with acid gave a 4-quinolone. The quinolone proved to be 2-[1-(*o*-aminophenyl)-1-hydroxyethyl]-4-quinolone by the oxidative degradation of the corresponding quinoline derivative.

In an attempt to isolate the basic fraction from the catalytic reduction mixture of compound A,[1] $C_{17}H_{14}O_5N_2$, a base-catalyzed condensation product of *o*-nitroacetophenone, there was obtained an amphoteric compound, $C_{17}H_{16}O_2N_2$, (I). Measurement of the *C*-methyl group of this compound gave a value of 0.71. Its ultraviolet spectrum shows an intensive maximum at 238 nm and characteristic twin maxima at 317 and 329 nm (Fig. 1). These absorption features are typical of 4-quinolones;[2] especially, the shape and location of the twin maxima and the disappearance of the bifurcation in acid solution suggest that a 2-substituted 4-quinolone structure is seemingly preferable to a 3-substituted one for this compound.[3]

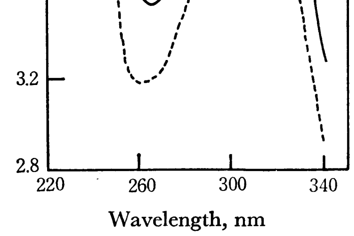


Fig. 1. UV spectra of the 4-quinolone I in ethanol (——) and in 0.1N hydrochloric acid (----).

Acetylation of the compound I with acetic anhydride in aqueous alkali gave a monoacetyl derivative II, $C_{19}H_{18}O_3N_2$. Its infrared spectrum ($\nu_{C=O}$ 1667 cm^{-1}) indicated the compound to be an *N*-acetyl derivative. The ultraviolet absorption was similar to that of the compound I.

On the other hand, treatment of the alkaline solution of compound I with benzoyl chloride gave a dibenzoyl derivative III, $C_{31}H_{24}O_4N_2$. Its infrared spectrum ($\nu_{C=O}$ 1748 and 1667 cm^{-1}) showed that, besides the amino group, a phenolic hydroxyl group had been acylated. From the ultraviolet spectrum (Fig. 2), which lacks the bifurcation near 320 nm and resembles

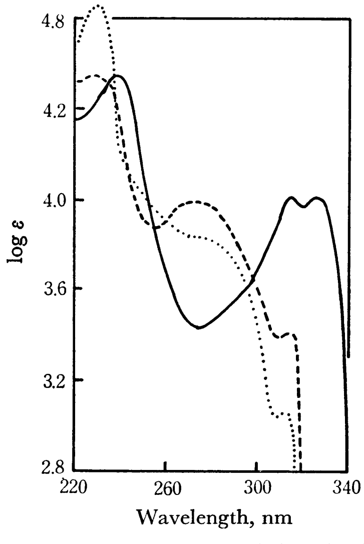


Fig. 2. UV spectra of the *N*-acetyl (——), *O,N*-dibenzoyl (----), and *N*-acetyl (····) derivatives.

---

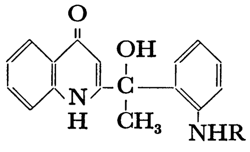
[1] T. Sakan, K. Kusuda, and T. Miwa, This Bulletin, **37**, 1678 (1964).

[2] R. S. Beer, L. McGroth, and A. Robertson, *J. Chem. Soc.*, **1950**, 3283. B. Witkop, J. B. Patrick, and M. Rosenblum, *J. Amer. Chem. Soc.*, **73**, 2641 (1951).

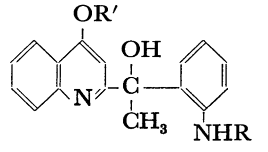
[3] G. W. Ewing and E. A. Steck, *ibid.*, **68**, 2181 (1946); E. A. Steck, G. W. Ewing, and F. C. Nachod, *ibid.*, **71**, 238 (1949).

those of quinolines,[4] apparently the 4-hydroxyl group of the 4-quinolone nucleus was acylated. Methylation of the *N*-acetyl derivative II with diazomethane yielded a methyl ether IV, $C_{20}H_{20}O_3N_2$,[5] having an ultraviolet spectrum similar to the compound III.

From these observations, structures I, II, III, and IV were assigned to the compound I, its *N*-acetyl, *O*,*N*-dibenzoyl, and *N*-acetyl-*O*-methyl derivatives, respectively, the remaining inert oxygen function being tentatively assumed to be a tertiary alcohol.



I: R=H
II: R=$COCH_3$



III: R, R′=COC_6H_5
IV: R=$COCH_3$, R″=CH_3

To confirm these structures, attempts were made to convert the 4-quinolone system to a quinoline nucleus, which was seemingly suitable to oxidative degradation. Transformation of 4-quinolones to the corresponding quinolines has been effected usually through the 4-chloro compounds.[6]

For replacement of the 4-hydroxyl group by chlorine, refluxing with phosphorus oxychloride is recommended as the best method.[7] Treatment of the *N*-acetyl derivative II with the reagent led to a chloride V, $C_{19}H_{15}ON_2Cl$, with evolution of hydrogen chloride. Ultraviolet absorption (Fig. 3) of the chloride supported the formation of a quinoline nucleus sufficiently. Simultaneous formation of an oxazine ring,[8] consequently the presence of an *o*-acylamidobenzylalcohol system in II, was proved by lack of the 3000-cm^{-1} band, disappearance of the amide I band and existence of a C=N stretching band (1631 cm^{-1}) in the infrared spectrum as well as by appearance of a new maximum at 268 nm in the ultraviolet absorption.[9]

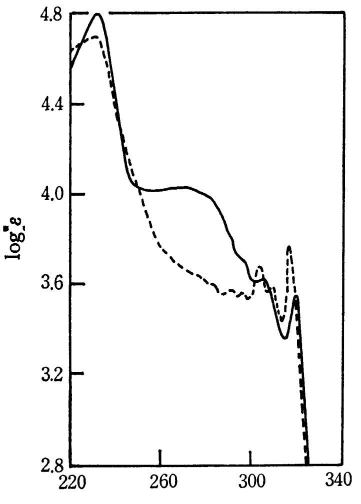
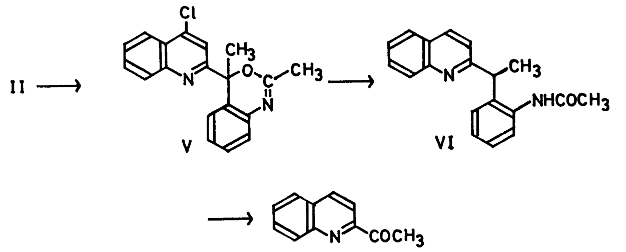


Fig. 3. UV spectra of the chloride V (——) and its hydrogenolysis product VI (----).

Hydrogenation of the chloride V over palladium-on-carbon in the presence of potassium acetate produced a chlorine-free compound VI, $C_{19}H_{18}ON_2$, infrared spectrum of which showed an amide I band at 1686 cm^{-1}, indicating re-formation of an amide function by hydrogenolysis of the oxazine ring.

The quinoline VI was hydrolyzed with dilute sulfuric acid and the resulting amine was immediately oxidized by addition of the Beckmann solution. From the basic volatile fraction, a methyl ketone was isolated as a semicarbazone, which decomposed at the same temperature as those of both 2- and 3-acetylquinolines; however, comparison of the infrared spectra established the semicarbazone from the oxidation product to be that of 2-acetylquinoline. Consequently, the compound I was confirmed to be 2-[1-(*o*-aminophenyl)-1-hydroxyethyl]-4-quinolone (I).



The acid catalysis in the rearrangement of the reduction product was verified by the spectral tracing of the reaction. The ultraviolet absorption of the crude reduction mixture showed a strong absorption at 380 nm reminiscent of compound A. Addition of one drop of dilute hydrochloric acid into the photometrical cell caused a momentary, striking change of the spectrum into one similar to that of the compound I in acid solution (see Experimental). The mechanism proposed in Chart 1 is obvious when the carbon skeleton of the 4-quinolone is compared with that of compound A.

This rearrangement provides a novel type of ring enlargement of a nitrogen heterocycle, different nitrogen atoms participating in the ring formation. Formation of the *β*-diaminoketone from the reduction product might be reversible; however, stabilization by the formation of the quinolone nucleus makes the last step

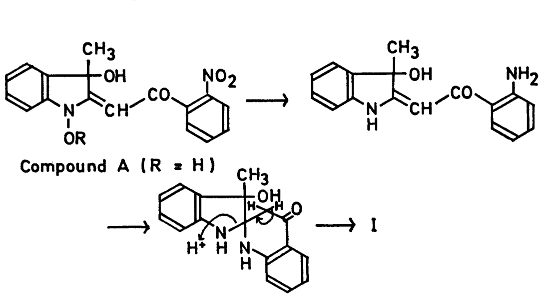


Chart 1.

---

[4] D. Sutherland and C. Compton, *J. Org. Chem.*, **17**, 1257 (1952).

[5] Methylation of 4-quinolone with diazomethane gives 4-methoxyquinoline: H. Meyer, *Monatsh. Chem.*, **27**, 987 (1906).

[6] E. g., E. Späth and J. Pikl, *Ber.*, **62**, 2244 (1929).

[7] A. Albert, "Heterocyclic Chemistry," Essential Books, London (1959), p. 80.

[8] J. B. Patrick and B. Witkop, *J. Org. Chem.*, **19**, 1824 (1954).

[9] 4-Chloromethyl-2,4-dimethyl-4*H*-3,1-benzoxazine has its absorption maximum at 259 nm (log ε 3.87). [C. W. Rees and C. E. Smithen, *J. Chem. Soc.*, **1964**, 928.

irreversible and the cleavage of the indoline ring is apparently the acid-catalyzed step.

Hydrogenation of compound A and its methyl ether in the presence of hydrochloric acid gave the compound I directly as expected.

Experimental

All melting points are not corrected. Unless otherwise noted, ultraviolet spectra were taken in ethanol and infrared spectra in Nujol mull; they are expressed in λ_{max} nm (log ε) and ν_{max} cm^{-1}, respectively.

Hydrogenation of the Compound A Methyl Ether. 2-[1-(2-aminophenyl)-1-hydroxyethyl]-4-quinolone (I). An ethanol solution of 340 mg (1 mmol) of compound A methyl ether was shaken in the presence of 5% palladium-on-carbon under atmospheric pressure of hydrogen for 4 hr, during which 115 m*l* (*ca.* 18°C) of hydrogen was absorbed. Ultraviolet absorption taken immediately after the reduction (unknown concentration): λ_{max} ($-\log T$): 236 (0.818), 305 (0.150), and 403 (0.663). After addition of one drop of N hydrochloric acid (the same concentration): λ_{max} ($-\log T$): 235 (3.85), 304 (0.520), and 389 (0.320). After removal of the catalyst, followed by evaporation of the solvent *in vacuo*, the resulting residue was taken in N sulfuric acid and washed with ether. The aqueous solution was treated with active carbon, filtered and made faintly alkaline with aqueous ammonia to separate amorphous precipitates, which were collected by filtration, washed with water and dried; yield 195 mg. This material was used without further purification for formation of derivatives.

In one run, the precipitates were dissolved in ether and the ethereal solution was re-extracted with N sodium hydroxide. Neutralization of the alkaline solution with 2N hydrochloric acid produced precipitates again. After filtration of the precipitates, the mother liquor containing some ether was left to evaporate to deposit crystals, decomposing at 122°C. λ_{max} 238 (4.66), 317 (4.14), and 329 (4.13). $\lambda_{max}^{0.1N\ HCl}$ 235 (4.75) and 306 (3.91).

Found: C, 66.29; H, 6.35; N, 8.77%; *C*-methyl group:[10] 0.71. Calcd for $C_{17}H_{16}O_2N_2\cdot 1.5H_2O$: C, 66.43; H, 6.23; N, 9.12%.

Hydrogenation of both compound A and its methyl ether over 5% palladium-on-carbon in the presence of equimolecular amount of hydrochloric acid gave similar results.

2-[1-(2-Acetamidophenyl)-1-hydroxyethyl]-4-quinolone (II). Crude compound I (159 mg) was dissolved in 4.2 m*l* of 2N sodium hydroxide. After removal of a little amount of insoluble material, the clear solution, chilled in an ice-bath, was treated with 0.2 m*l* of acetic anhydride. Trituration caused crystallization. Filtration, followed by washing with water and drying, yielded 128 mg of crystals, which, after recrystallization from aqueous ethanol, decomposed at 198—201°C. λ_{max} 239 (4.55), 315 (4.02), and 327 (4.03). ν_{max} 1664 and 1621 (C=O).

Found: C, 66.62; H, 5.58; N, 8.73%. Calcd for $C_{19}H_{18}O_3N_2\cdot H_2O$: C, 67.04; H, 5.92; N, 8.23%.

2-[1-(2-Benzamidophenyl)-1-hydroxyethyl]-4-benzoyloxyquinoline (III). A solution of 168 mg of the crude compound I in 1.5 m*l* of 0.2N sodium hydroxide, chilled in ice, was treated with 0.1 m*l* of benzoyl chloride and triturated to deposit crystals, which weighed 100 mg. Recrystallization from methanol gave crystals melting at 169—170°C. λ_{max} 229 (4.55), 276 (3.99), and 315 (3.42). ν_{max} 1751 and 1669 (C=O). This material was analyzed after drying at 80°C for 1 hr.

Found: C, 75.51; H, 4.96; N, 5.80%. Calcd for $C_{31}H_{24}O_4N_2$: C, 76.21; H, 4.95; N, 5.73%.

2-[1-(2-Acetamidophenyl)-1-hydroxyethyl]-4-methoxyquinoline (IV). A suspension of 300 mg of the *N*-acetyl derivative II in 10 m*l* of methanol was treated with an ethereal solution of diazomethane prepared from 1.0 g of nitrosomethylurea. Evaporation of the solvent left crystals, which were recrystallized from 50% methanol to give *ca.* 170 mg of crystals melting at 168°C. λ_{max} 230 (4.86) and 313 (3.07). ν_{max} 1684 (C=O).

Found: C, 71.75; H, 6.18; N, 8.31%. Calcd for $C_{20}H_{20}O_3N_2$: C, 71.41; H, 5.99; N, 8.33%.

*4-(4-Chloro-2-quinolyl)-2,4-dimethyl-4*H*-3,1-benzoxazine (V).* A mixture of 0.80 g of the *N*-acetyl derivative II (monohydrate) and about 5 m*l* of phosphorus oxychloride was heated on a water bath, yielding a yellow solution immediately with evolution of hydrogen chloride. After being heated for 15 min, the mixture was removed from phosphorus oxychloride under reduced pressure and the residue poured into a mixture of ice and aqueous ammonia to separate brown precipitates. The mixture was extracted with ether; the extract was washed with sodium bicarbonate solution, dried and evaporated. Trituration of the residue with petroleum benzine yielded crystals, which, after filtration and subsequent washing with petroleum benzine, weighed 0.36 g. The crystals, after recrystallization from methanol–petroleum ether, melted at 125°C. λ_{max} 232 (4.80), 268 (4.03), 307 (3.62), and 320 (3.56). ν_{max} 1631 (C=N).

Found: C, 70.79; H, 4.98; N, 8.48%. Calcd for $C_{19}H_{15}ON_2Cl$: C, 70.69; H, 4.68; N, 8.68%.

2-[1-(2-Acetamidophenyl)ethyl]quinoline (VI). A mixture of 0.36 g of the chloride V, 0.20 g of sodium acetate trihydrate and 0.40 g of 5% palladium-on-carbon in 20 m*l* of ethanol containing 10 drops of water was hydrogenated at atmospheric pressure, absorbing 73 m*l* of hydrogen. After removal of the catalyst, evaporation of the solvent left a residue, which was taken in ether and washed with water. Evaporation of the dried ethereal solution left crystals, which, after recrystallization from ether–petroleum ether, weighed 0.21 g and melted at 115.5—116.5°C. λ_{max} 232 (4.70), 291 (3.58), 297 (3.56), 304 (3.68), 310 (3.57), and 317 (3.77). ν_{max} 1686 (C=O).

Found: C, 78.73; H, 6.35; N, 9.79%. Calcd for $C_{19}H_{18}ON_2$: C, 78.59; H, 6.25; N, 9.65%.

Oxidative Degradation into 2-Acetylquinoline. A mixture of 140 mg of the amide VI, 5 m*l* of water and 15 m*l* of N sulfuric acid was heated on a water bath for 8 hr. Into the cooled mixture, 8 m*l* of the Beckmann solution (prepared by dissolving 2.94 g of potassium dichromate in a little amount of water, adding 2.5 m*l* of concentrated sulfuric acid, and diluting to 25 m*l*) was added and stirred at the room temperature for 8 hr. After decomposition of the excess dichromate with ethanol, the mixture was made alkaline and extracted with ether. Evaporation of the ethereal solution gave a residue, which was distilled under a 5 Torr-pressure to give a fraction boiling at a bath temperature below 100°C. The distillate (λ_{max} 243 and 290), which gave a positive iodoform test, was converted into a semicarbazone (10 mg), decomposing at 239°C after recrystallization from ethanol. The infrared spectrum of the semicarbazone was not identical with that of 3-acetylquinoline[11] semicarbazone [mp 245°C

---

[10] E. J. Eisenbraun, S. M. McElvain, and B. F. Aycock, *J. Amer. Chem. Soc.*, **76**, 607 (1954). The measurement was carried out by Dr. Shōji Hayashi, to whom the author is indebted.

[11] V. Boekelheide and J. Weinstock, *J. Amer. Chem. Soc.*, **74**, 660 (1952).

(decomp.); lit, 236—236.5°C[12]], but completely idendical with that of 2-acetylquinoline[13] (λ_{max} 244 (4.51) and 293 (3.75)] semicarbazone [mp 242°C (decomp.). Found: C, 63.34; H, 5.31; N, 23.64%. Calcd for $C_{12}H_{12}ON_4$: C, 63.14; H, 5.30; N, 24.55%].

The author wishes to express his thanks to Mr. Jun'ichi Gōda and his associates for their elementary analyses and to Mrs. Hiromi Aotani for her infrared determinations.

---

12) S. Yamada and I. Chibata, *Chem. Pharm. Bull.* (Tokyo), **3**, 21 (1955).

13) R. B. Woodward and E. C. Kornfeld, *J. Amer. Chem. Soc.*, **70**, 2508 (1948).