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164. Hiroshi Tanida : Quinoline and Related Compounds. II.[1] The Rearrangement of 2-Aminoquinoline 1-Oxide with Tosyl Chloride.

(*Research Laboratory, Shionogi & Co., Ltd.*[*1])

As a part of investigations to introduce a hydroxyl group into β-position of quinoline,[2] the reaction between 2-aminoquinoline 1-oxide (I)[1] and tosyl chloride was studied. There are several reports on formation of a phenolic product by the action of tosyl

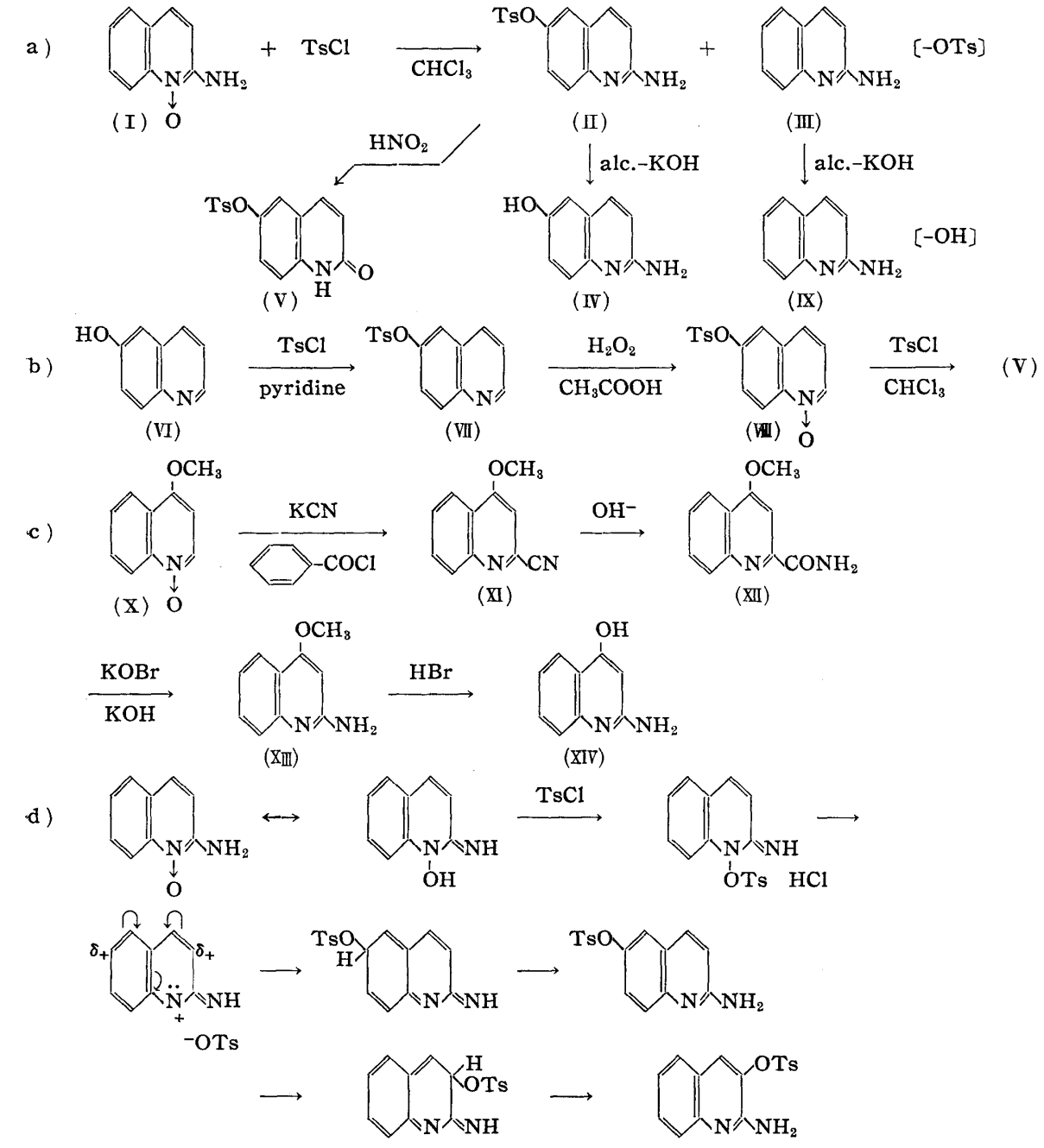

Chart 1.

*1 Imafuku, Amagasaki, Hyogo-ken (谷田 博).

1) Part I : Yakugaku Zasshi, **79**, 1063(1959).

chloride on quinoline 1-oxide and its homologs[2~4] but its reaction mechanism is not yet clear and the effect of polar substituents on the reaction was first examined.

Treatment of quinoline 1-oxide (I) with an equivalent amount of tosyl chloride in chloroform produced colorless cubic crystals (II), m.p. 201~203°, and colorless needles (III), m.p. 145~146°. Their analytical values agreed with the formula $C_{16}H_{14}O_3N_2S$. The former was the main product with 49% yield and the latter yield was only 7%.

As the ultraviolet absorption spectra of both compounds are almost analogous to

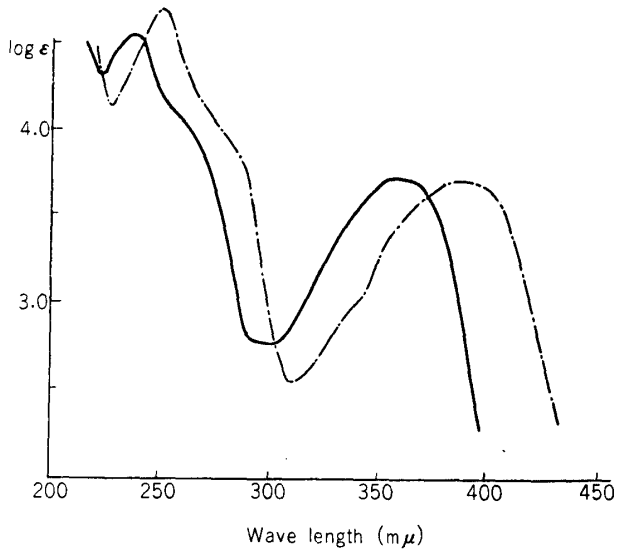

Fig. 1.
UV Spectra of 2-Amino-6-quinolinol
——— in 95% EtOH
——·—·— in KOH-EtOH

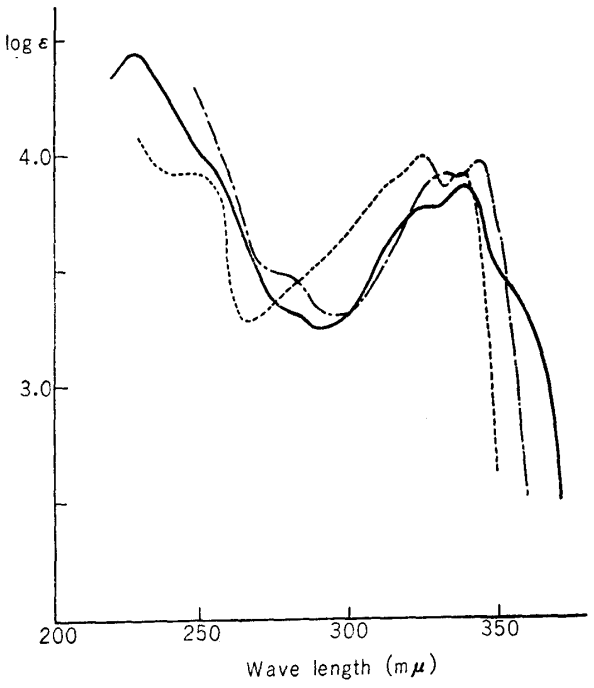

Fig. 2. UV Spectra of 2-Amino-x-quinolinol
——— in 95% EtOH ——— in 0.1*N* NaOH

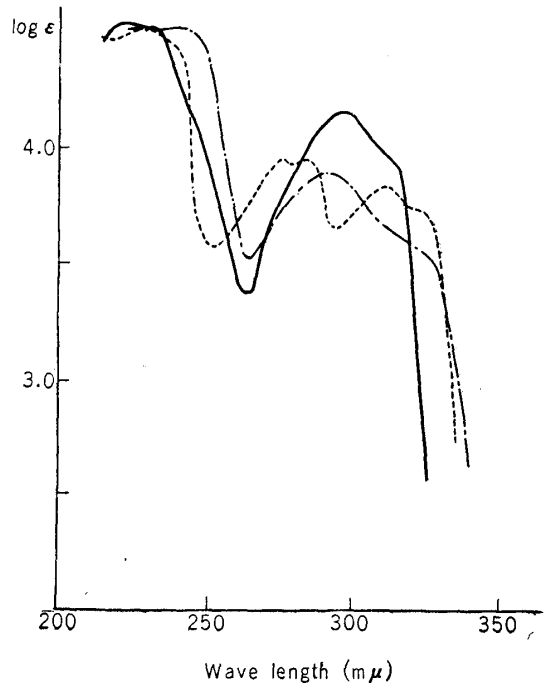

Fig. 3. UV Spectra of 2-Amino-4-quinolinol
-------- in 0.1*N* HCl

2) H. Tanida : Yakugaku Zasshi, **78**, 1083(1958).
3) E. Ochiai, T. Yokogawa : *Ibid.*, **75**, 213(1955).
4) E. Ochiai, M. Ikehara : This Bulletin, **3**, 454(1955).

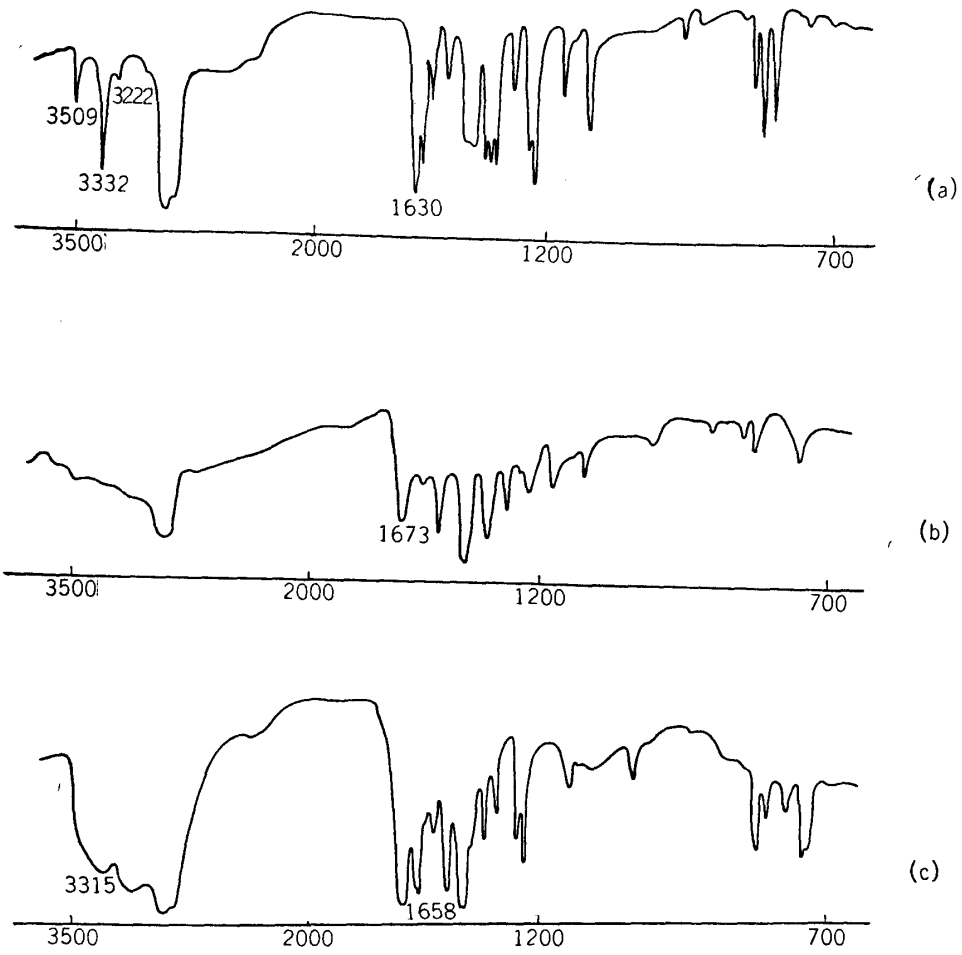

Fig. 4. IR Spectra (in Nujol)
(a) 2-Amino-6-quinolinol
(b) 2-Amino-x-quinolinol
(c) 2-Amino-4-quinolinol

that of 2-aminoquinoline,[5] it seemed most reasonable to assume that the tosyloxyl group was introduced into the ring and the infrared absorption curve was not inconsistent with the above deduction.

When (II) was hydrolysed with ethanolic potassium hydroxide, colorless needles (IV), m.p. 208.5~209.5°, $C_9H_8ON_2$, were obtained. This substance (IV) was found to be a typical phenol, being easily soluble in sodium hydroxide solution and showing a positive ferric chloride and diazo reactions. Moreover, when the shape of its ultraviolet absorption spectrum curve, as given in Fig. 1, and the character of bathochromic shift in caustic alkali solution were considered, (IV) must be assumed as 2-amino-3-quinolinol. Consideration of the reaction mechanism given in Chart 1(d) gave some support to the deduction that the position of the hydroxyl group should be 3 or 6. Although 3-hydroxyl group should be linked to the 2-amino group by intramolecular hydrogen bond, an attempt to determine the nature of hydrogen bond in (IV) by means of infrared absorption spectrum was not feasible, because (IV) is not soluble in any solvents like chloroform and carbon tetrachloride. The infrared curve in Nujol is shown in Fig. 4. By the action of nitrous acid, (II) was converted into β-tosyloxy-2-quinolinol (V), m.p. 260~261°. On the other hand 6-tosyloxy-2-quinolinol was prepared by the route shown

5) E. A. Steck, G. W. Ewing: J. Am. Chem. Soc., **70**, 3397(1948).

in Chart 1(b). This authentic sample had the same melting point as (V) and the melting point was not depressed by admixture with (V). Further, the infrared spectra of the two were identical. On the basis of these data, it was determined that (II) is 2-amino-6-tosyloxyquinoline.

According to the same hydrolysis as above, the by-product (III) was converted into 2-amino-x-quinolinol (IX), m.p. 128~130°, $C_9H_8ON_2$, which gave an intense violet-blue ferric chloride and red diazo reaction. It dissolved easily in alkali hydroxide solution, but did not show the bathochromic shift of ultraviolet absorption curve in alkali, as given in Fig. 2. The infrared spectrum of (IX), shown in Fig. 5, exhibited characteristic peaks at 1673 cm^{-1} (two peaks) which might be assigned to the overlapping absorption of carbonyl and amino groups, but it was impossible to learn the character of hydrogen bond by the same reason as in the case of (IV). A possibility evident from these data that (IX) might be 2-amino-4-quinolinol was excluded from the mode of its synthesis. 2-Amino-4-quinolinol was already described in the literature by Gabriel[6] and Hardman[7] who obtained it by ring-closure. They had however made no proof of its structure and moreover the metling points of the compound and its picrate were very different from those of (IX). Therefore, an authentic sample of (XIV) was synthesized through the new process shown in Chart 1(c), which utilized the Reissert and Hofmann reactions. The ultraviolet absorption curves of this sample are given in Fig. 3, and its infrared spectrum, in Fig. 6, exhibited characteristic peaks at 1645 cm^{-1} (two peaks) which were assigned to the overlapping absorption of carbonyl and amino groups. The constants of this sample did not agree with those of (IX) but did with those of Gabriel and Hartman's sample. Thus, although (IX) is most likely to be 3-hydroxyl derivative, the position of the tosyloxyl in (III) was not determined owing to the lack of sample and the difficulty of preparing authentic 2-amino-3-quinolinol.

This reaction is thought to be the first example of the oxygen atom of the N-oxide migrating to the ring not containing nitrogen. Its mechanism is proposed as the intramolecular nucleophilic rearrangement, as given in Chart 1(d).

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Experimental

Reaction of 2-Aminoquinoline 1-Oxide (I) with Tosyl Chloride—(I) (480 mg.) was dissolved in $CHCl_3$ (30 cc.) as much as possible. This solution was mixed with TsCl (630 mg.) and water (50 mg.), and refluxed for 45 min. The reaction mixture was then treated with K_2CO_3 solution and the $CHCl_3$ layer was evaporated after drying over K_2CO_3. The crystals (360 mg.) that separated when the residue (800 mg.) was treated with acetone were recrystallized from acetone-MeOH to colorless cubic crystals (II), m.p. 201~203°. This was insoluble in dil. HCl and alkali hydroxide. Halogen, negative. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2S$: C, 61.14; H, 4.49; N, 8.91. Found : C, 61.52; H, 4.54; N, 8.74. IR ν_{max}^{Nujol} cm^{-1} : 1192, 1360 (OSO_2); 3317, 3502^{-1}(NH); δ_{max}^{Nujol} 1650^{-1}(NH).

The residue (420 mg.) from the above acetone mother liquor was chromatographed on alumina (14 g.). Fraction 1 (from $CHCl_3$) : The crystals (65 mg.), after recrystallization from acetone-benzene mixture, gave colorless needles (III), m.p. 145~146°. This was easily soluble in 5% HCl and insoluble in 10% KOH. *Anal.* Calcd. for $C_{16}H_{14}O_3N_2S$: the same as the above. Found : C, 61.70; H, 4.45; N, 8.83. IR ν_{max}^{Nujol} cm^{-1} : 1198, 1368 (OSO_2); 3325, 3536^{-1}(NH); δ_{max}^{Nujol} 1655 (NH). Picrate : m.p. 250°.

Fraction 2 (from $CHCl_3$-acetone) : The crystals (100 mg.) were the same product as (II).

Hydrolysis of 2-Amino-6-tosyloxyquinoline (II)—A mixture of (II) (150 mg.) and 6% ethanolic KOH (3.5 cc.) was refluxed for 3 hr. EtOH was distilled off from the reaction mixture and the residue was treated with water and ether. The aqueous layer was made alkaline by saturation of

6) S. Gabriel : Ber., **51**, 1502(1918).
7) R. Hardman, M. W. Partridge : J. Chem. Soc., **1954**, 3878.

CO_2 gas and extracted with ether. The ether extract (50 mg.) was recrystallized from acetone-benzene to colorless needles, m.p. 208.5~209.5°. *Anal.* Calcd. for $C_9H_8ON_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.81; H, 5.04; N, 17.48. Picrate: Needles (from MeOH), m.p. 257~258°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot C_6H_3O_7N_3$: C, 46.28; H, 2.85. Found: C, 46.25; H, 3.42.

Hydrolysis of x-Tosyloxy-2-aminoquinoline (III)—A mixture of (III) (100 mg.) and 6% ethanolic KOH (2.5 cc.) was refluxed for 3 hr. EtOH was distilled off from the reaction mixture and the residue was treated with water and ether. When the separated aqueous layer was made alkaline with CO_2, crystals precipitated. The colorless prisms (IX), m.p. 128~130° (crude product), were purified by the preparation of hydrochloride as colorless needles, m.p. 280°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot HCl$: N, 14.25. Found: N, 13.79. Picrate: Needles (from MeOH), m.p. 236°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot C_6H_3O_7N_3$: N, 17.99. Found: N, 18.00.

Reaction of 2-Amino-6-tosyloxyquinoline (II) with Nitrous Acid—The solution of (II) (400 mg.) in glacial AcOH (1 cc.) was added to the mixture of $NaNO_2$ (480 mg.) and conc. H_2SO_4 (1.5 cc.) under ice-cooling. The reaction mixture was poured on ice (20 g.) after stirring for 0.5 hr. and the crystals (300 mg.) (75%) that separated were recrystallized from MeOH to colorless flaky crystals (V), m.p. 260~261°, undepressed by admixture with 6-tosyloxy-2-quinolinol which was prepared through authentic route. This product was insoluble in 10% HCl and 10% KOH. *Anal.* Calcd. for $C_{16}H_{13}O_4NS$: C, 60.95; H, 4.16. Found: C, 60.53; H, 4.23. IR ν_{max}^{Nujol} cm^{-1}: 1197, 1367 (OSO_2); 1668 (C=O); 3190 (OH).

6-Tosyloxyquinoline (VII)—The procedure was the same as for 3-tosyloxyquinoline described in the preceding paper.[1] Colorless prisms (from EtOH), m.p. 95~97°.

6-Tosyloxyquinoline 1-Oxide (VIII)—A mixture of (VII) (1.2 g.) and 30% H_2O_2 (0.9 cc.) in glacial AcOH (7 cc.) was heated at 80~90° for 6 hr. The reaction mixture was treated by the usual procedure. The crude product was recrystallized from 90% EtOH to colorless needles (850 mg.), m.p. 193~195°. *Anal.* Calcd. for $C_{16}H_{13}O_4NS$: C, 60.95; H, 4.16; N, 4.44. Found: C, 61.11; H, 4.16; N, 4.27. Contrary to (VII), 3-tosyloxyquinoline did not form an N-oxide.[8]

6-Tosyloxy-2-quinolinol (V)—A mixture of (VIII) (150 mg.), tosyl chloride (96 mg.), and water (100 mg.) in $CHCl_3$ (20 cc.) was refluxed for 0.5 hr. After crystals deposited, the chloroform layer was washed with Na_2CO_3 solution, and $CHCl_3$ was evaporated. The combined crystals and residue were recrystallized from MeOH to colorless flaky crystals, m.p. 260°. *Anal.* Cacld. for $C_{16}H_{13}O_4NS$: C, 60.95; H, 4.16. Found: C, 60.84; H, 4.20.

2-Cyano-4-methoxyquinoline (XI)—4-Methoxyquinoline 1-oxide (X) (2.7 g.) and KCN (2 g.) were dissolved in water (60 cc.) and BzCl (2.6 g) was added dropwise to the above solution under stirring at room temperature. After 1 hr.'s stirring, the reaction mixture was made alkaline and extracted with $CHCl_3$, $CHCl_3$ extract was dried with K_2CO_3, and evaporated. The crystalline residue (2.9 g.) was recrystallized from benzene to colorless needles, m.p. 119~121°. Yield, 2.6 g. (91.7%). *Anal.* Calcd. for $C_{11}H_8ON_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 72.13; H, 4.37; N, 14.94.

4-Methoxyquinoline-2-carbonamide (XII)—The nitrile (XI) (2.4 g.) suspended in a mixture of *N* NaOH solution (5.2 cc.) and EtOH (20 cc.), was treated with 30% H_2O_2 (3.25 cc.), by which (XI) dissolved in the solution and new crystals deposited gradually. After the mixture was allowed to stand overnight, the crystals were collected by filtration and washed with water. Recrystallization of the crude amide from MeOH gave 2.25 g. (85%) of colorless needles, m.p. 175~176°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.44; H, 5.17; N, 14.29.

2-Amino-4-methoxyquinoline (XIII)—Bromine (1.45 g.) was dissolved under ice-cooling in aqueous solution (18 cc.) of KOH (2.8 g.) and (XII) was added dropwise under cooling. When the mixture was gradually warmed on a water bath, the original material dissolved and new crystals separated. After warming for 1 hr., separated crystals were collected and recrystallized from MeOH to slightly yellow cubic crystals (770 mg.), m.p. 189~190.5°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.69; H, 5.87; N, 16.16.

2-Amino-4-quinolinol (XIV)—The solution of (XIII) (100 mg.) in 48% HBr (1 cc.) was refluxed for 1 hr. The excess HBr was distilled off from the reaction mixture under a reduced pressure. The residue was poured into water, made alkaline, and crystals that separated were recrystallized from EtOH to colorless needles, m.p. 302~304°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot \frac{1}{3}H_2O$: C, 65.04; H, 5.26; N, 16.86. Found: C, 65.49; H, 5.36; N, 17.17.

Picrate: Yellow needles, m.p. 259~260°. *Anal.* Calcd. for $C_9H_8ON_2 \cdot C_6H_3O_7N_3$: C, 46.28; H, 2.85; N, 17.99. Found: C, 46.74; H, 2.77; N, 17.87.

Summary

2-Aminoquinoline 1-oxide gave 6-tosyloxy-2-aminoquinoline by rearrangement with tosyl chloride in 49% yield. A small quantity of an isomeric by-product (7%), which was considered to be 3-tosyloxy-2-aminoquinoline, was not identified.

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8) H. Tanida: Unpublished data.