44. **Utako Mizoguchi**: Synthesis of 6-Methoxy-4-aminoquinoline.

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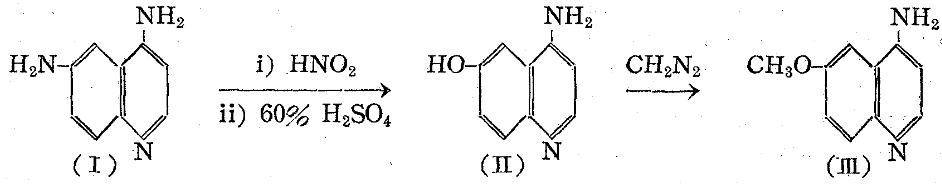
It has increasingly become evident that the presence of an unsubstituted 4-amino group in quinoline derivatives is a requisite in chemotherapeutics, as was first advocated by Jensch.[1] 6-Methoxy-4-aminoquinoline seemed to be an intermediate of great promise for the synthesis of chemotherapeutics in the quinoline series and its preparation from 4,6-diaminoquinoline was attempted, since Ishikawa[2] has shown that the nitration of 6-methoxyquinoline 1-oxide resulted in the formation of a 5-nitro derivative and not the 4-nitro compound. Ishikawa had previously found[3] that the nitration of 6-nitroquinoline 1-oxide did give 4,6-dinitroquinoline 1-oxide but the yield from derivation of 6-nitroquinoline to its 1-oxide was very poor, the fact having been later confirmed by Okamoto.

In 1925, Tschitschibabin reported[5] the formation of 6-nitro compound by the nitration of 4-aminoquinoline but later examination of this reaction by Simpson and Wright[6] and by Jensch[1] disclosed that the so-called 6-nitro compound of Tschitschibabin was a mixture of a mononitro compound (probably 3-nitro compound) and one kind of dinitro compound (probably 3,6-dinitro compound), making the final yield of 4-amino-6-nitroquinoline only 24~27%.

Nakayama[7] followed the method of Simpson and Wright[8] and found that the nitration of 3-bromo-4-aminoquinoline and reduction of the nitro compound thereby formed gave 4,6-diaminoquinoline in 52% yield. This has made it possible to obtain this diaminoquinoline in a comparatively facile manner.

4,6-Diaminoquinoline (I) prepared essentially by the method of Nakayama (*loc. cit.*) was diazotized with one mole of sodium nitrite and decomposed by boiling in dilute sulfuric acid, from which a sulfate was obtained as scaly crystals melting at 292~294° with decomposition. Its free base came as prismatic crystals of m.p. 254~256° and its analytical values agreed with the molecular formula of $C_9H_8ON_2$. Naito[9] had earlier shown that the amino group in the benzene portion of the quinoline ring was preferentially diazotized over that of the 4-amino group that it is quite certain that the above compound is the anticipated 6-hydroxy-4-aminoquinoline (II). Methylation of this compound with diazomethane gave colorless needle crystals of m.p. 83~85°(efferv.), which seemed to be the carbamate of the 6-methoxy compound (III).



(I) m.p. 218°(decomp.)

(II) m.p. 254~256°(decomp.)

(III) m.p. 83~85°(efferv.)

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1) H. Jensch: Z. angew. Chem., **50**, 891(1937).
2) M. Ishikawa: J. Pharm. Soc. Japan, **65**, B, 102(1945).
3) M. Ishikawa: Proc. Imp. Acad. (Tokyo), **20**, 599(1944).
4) E. Ochiai, T. Okamoto: J. Pharm. Soc. Japan, **70**, 384(1950).
5) Tschitschibabin: Ber., **58**, 803(1925).
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7) I. Nakayama: J. Pharm. Soc. Japan, **72**, 665(1952).
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Modification in the synthesis of 4,6-diaminoquinoline (I) was effected in the reduction of 4-nitroquinoline 1-oxide. It was found that the reduction could be effected more advantageously with iron powder in glacial acetic acid[10] at 60°, 4-nitroquinoline 1-oxide directly affording 4-aminoquinoline, generally in 66~75% yield. In this case, the base is obtained as a monohydrate directly from the alkalized solution or from methanol as colorless long needles of m.p. 67° and its recrystallization from chloroform, dried over potassium carbonate, affords the anhydrate base as slightly yellow, sandy crystals of m.p. 154~155°.

It was found during the course of the nitration of 3-bromo-4-aminoquinoline that the product thereby obtained is not a unity and that it contained differently nitrated products. The chief product, obtained generally in 70~75% yield, is the 6-nitro derivative, most sparingly soluble in hydrous acetone and coming as deep orange microprisms of m.p. 282~284° (beginning to brown from around 276°). The most usually obtained by-product in this nitration is a dinitro compound not containing bromine and coming as pale yellow, silky needles of m.p. 280~281°, which depresses to m.p. 260~265° on admixture with authentic 6-nitro compound. This substance is assumed to be 3,6-dinitro-4-aminoquinoline[6] from its analytical values. Dinitro-bromoaminoquinoline was also obtained but its characterization has not been carried out as yet.

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Experimental

1) **Reduction of 4-Nitroquinoline 1-Oxide**—A solution of 10 g. of 4-nitroquinoline 1-oxide dissolved in a mixture of 100 cc. of glacial AcOH and 20 cc. of water was warmed to 50°, 30 g. of iron powder was added slowly in small portions, maintaining the temperature below 60°, with efficient stirring, and the mixture was agitated for 6~7 hrs. thereafter, at around 60°. As the reaction progressed, sludgy precipitate of ferrous acetate separated out in abundance and the stirring became very difficult. The reaction mixture was then acidified with conc. HCl to dissolve the precipitate completely, Fe removed by filtration, and the greenish brown filtrate was evaporated under a diminished pressure. The hydrochloride of the iron complex separated out as greenish cubic crystals which were collected by filtration, dissolved in sat. NaOH solution, and this alkaline solution was filtered while hot from ferrous hydroxide. Cooling of the alkaline filtrate afforded the monohydrate of 4-aminoquinoline as colorless, long needles, m.p. 67°. The evaporation residue and ferrous hydroxide precipitate were extracted with MeOH and afforded further crops of the monohydrate. Combined yield, 76%. The monohydrate crystals were dissolved in $CHCl_3$, dried over K_2CO_3, and the solution concentrated from which 4-aminoquinoline was obtained as slightly yellow, sandy crystals of m.p. 154~155°.

2) **6-Nitro-3-bromo-4-aminoquinoline**—3-Bromo-4-aminoquinoline m.p. 201~203°, obtained by the bromination of 4-aminoquinoline in glacial AcOH with Br_2 in glacial AcOH, was dissolved in conc. H_2SO_4, chilled to 0° to 2°, and nitrated by the dropwise addition of conc. HNO_3(d=1.40). After stirring this mixture for 1 hr. at 1~3°, the reddish mixture was poured on cracked ice, basified with NaOH, and the orange precipitate thereby formed was collected by filtration. After washing with water and dried, the precipitate was recrystallized from a large amount of acetone to the first crop of deep orange microprisms, m.p. 282~284°. Yield, 87%.

Further concentration of the acetone mother liquor afforded some pale yellow needles, m.p. 280~281°. Mixed m.p. with the 6-nitro compound (m.p. 282~284°), 260~265°. Beilstein reaction, negative. *Anal.* Calcd. for $C_9H_6O_4N_4$ (4-Amino-3,6-dinitroquinoline): C, 46.2; H, 2.56; N, 24.35. Found: C, 45.85; H, 2.68; N, 24.32.

3) **4,6-Diaminoquinoline (I)**—Obtained by the reduction of (IV) as the dihydrochloride of pale greenish yellow microneedles, m.p. 317° (decomp.). Free base, pale brownish powder, m.p. 218° (decomp.). Sulfate, white scaly crystals, m.p. 267° (decomp.), insoluble in water and acids.

4) **6-Hydroxy-4-aminoquinoline (II)**—A solution of 0.5 g. of (I) in 20 cc. of water was added with 4 cc. conc. H_2SO_4, separating the white sulfate, chilled to 0° to −2°, and diazotized by the addition of 1 cc. of 0.2 *M* solution of $NaNO_2$. After standing for 10 mins., the yellow, diazotized solution was dropped into a boiling solution of 60% H_2SO_4, boiled for 10~30 mins. with efficient stirring, and al-

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[10] cf. H. J. den Hertog: Rec. trav. chim., **69**, 3 (1950).

lowed to cool. The pinkish precipitate that separated out was collected by filtration and recrystallized from hot water to whitish needles, m.p. 292~294°(decomp.)(sint. 288°). *Anal.* Calcd. for $C_9H_8ON_2 \cdot \frac{1}{2}H_2SO_4 \cdot H_2O$: C, 47.6; H, 4.75; N, 12.3. Found: C, 47.11; H, 4.75; N, 13.09.

Alkalization of the mother liquor with NaOH, passage of CO_2 through this pale brown solution, and extraction of the precipitate with AcOEt afforded the free base (II) as yellow powder, m.p. 254~256°(decomp.), sparingly soluble in AcOEt, somewhat soluble in $CHCl_3$, and soluble in MeOH.

5) **6-Methoxy-4-aminoquinoline (III)**—Ether solution of CH_2N_2 was added to the suspension of the free base of (II) in ether and the product was worked up in the usual manner. The pale yellow oily product thereby obtained was distilled *in vacuo* and gave a fraction of b.p$_{0.04}$ 23~28°, which crystallized to colorless needles (III), m.p. 83~85°(efferv.). The analytical values of this substance agreed with those of the carbamate of 6-methoxy-4-aminoquinoline. *Anal.* Calcd. for $C_{10}H_{10}ON_2 \cdot H_2CO_3 \cdot H_2O$: C, 51.6; H, 4.75. Found: C, 50.79; H, 4.40. A drop of dil. HCl applied to the crystals on a watch glass resulted in generation of CO_2 gas.

Summary

6-Methoxy-4-aminoquinoline was prepared from 4,6-diaminoquinoline through the 6-hydroxy compound.

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