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92. Morio Ikehara and Yuzuru Shimizu : Studies on the Nitration of 4-Isoquinolinol and its Derivatives.

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Some time ago, Ochiai and Ikehara[1] developed a relatively simple procedure for synthesis of 4-isoquinolinol by conversion of isoquinoline to its N-oxide, rearrangement to 4-tosyloxyisoquinoline by treatment with toluenesulfonyl chloride in alkaline solution, and hydrolysis of this ester to 4-isoquinolinol. Very few informations are available concerning this compound and examination of the chemical behavior of 4-isoquinolinol was undertaken.

First, electrophilic substitution in the isoquinoline ring was observed. On treating 4-isoquinolinol (I : R=H) with potassium nitrate in conc. sulfuric acid at 50~60° for 3 hours, a mononitro derivative (II) was obtained, which shows no coloration with ferric chloride. None of the other isomeric nitro compounds was obtained.

Oxidation of (II) with potassium permanganate in alkaline solution gave phthalic acid, which was confirmed by direct comparison with an authentic sample. From this fact, it was concluded that position of the nitro group in (II) should be at 1 or 3 of the pyridine portion of the isoquinolinol.

Catalytic reduction of (II) in ethanolic hydrochloric acid in the presence of palladized charcoal afforded an amino compound (IV) which was very unstable at room temperature, but its hydrochloride crystallized from ethanol and melted at 195~197°.

Treatment of (IV) with acetic anhydride or direct catalytic reduction of (II) in the same solvent gave a triacetate (V), as calculated from its elementary analytical data. This acetate melts at 115~116° and shows ultraviolet absorption spectrum very similar to that of isoquinoline or 4-tosyloxyisoquinoline in ethanol (Fig. 1). Furthermore, its maximum

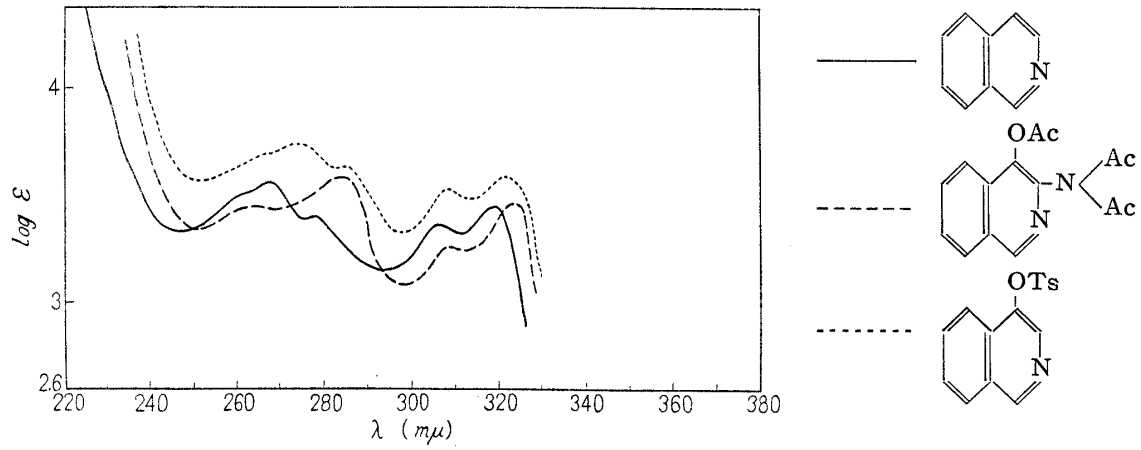

Fig. 1. Ultraviolet Spectra (in EtOH)

absorption shifted in dilute hydrochloric acid solution (pH 2.0), which was compared with the curve obtained from the ethanol solution of 4-chloro-3-aminoisoquinoline hydrochloride[2] (Fig. 2). According to this observation, the triacetate (V) should have a structure formulated as (VI) and not (VII).

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1) E. Ochiai, M. Ikehara : This Bulletin, **3**, 454(1955).
2) C. E. Teague, A. Roe : J. Am. Chem. Soc., **73**, 688(1951); F. H. Case : J. Org. Chem., **17**, 471(1952).

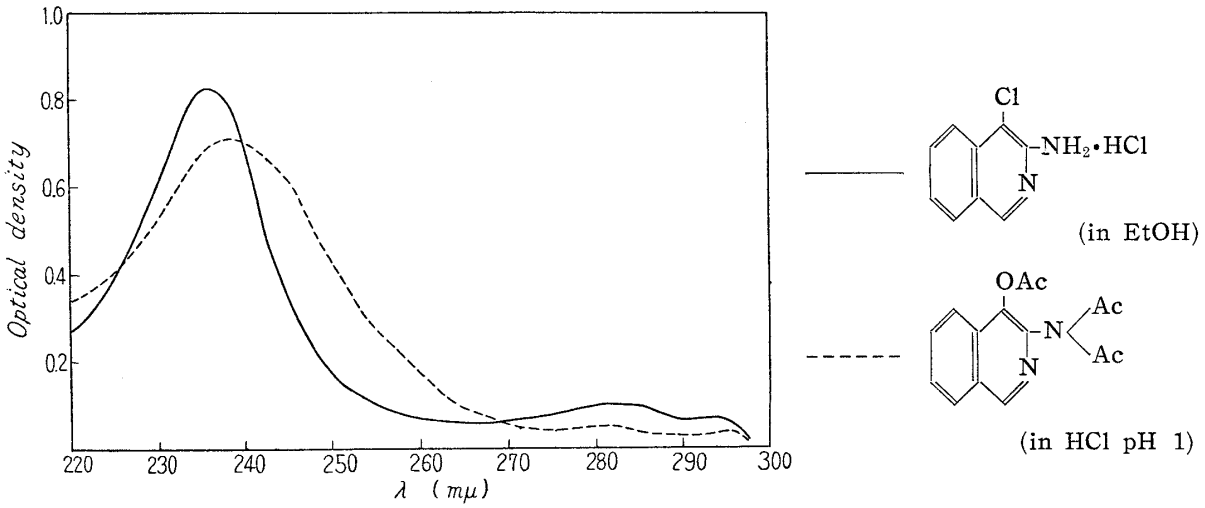
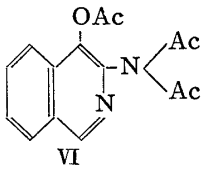
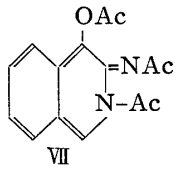


Fig. 2. Ultraviolet Spectra



VI



VII

In an attempt to effect 3–4 ring closure to an oxazole, the compound (IV) was boiled in acetic anhydride, in the presence of boric acid, and a crystalline compound containing boron, m.p. 199°, was obtained. In spite of various efforts, its definite structure has not been established as yet.

Contrary to expectations, the compound (II) was very easily chlorinated at the 4-position on heating with phosphoryl chloride and gave a chloro-nitro compound of m.p. 108~109°. This fact may suggest the presence of a nitro group vicinal to the hydroxyl, which overcame deactivating tendency of the nitrogen atom in the pyridine ring on the hydroxyl group at 4-position.

An attempt was made to obtain an aminoisoquinoline by catalytic hydrogenation of this activated chlorine atom in 4-position but the reaction failed and a chloro-amino com-

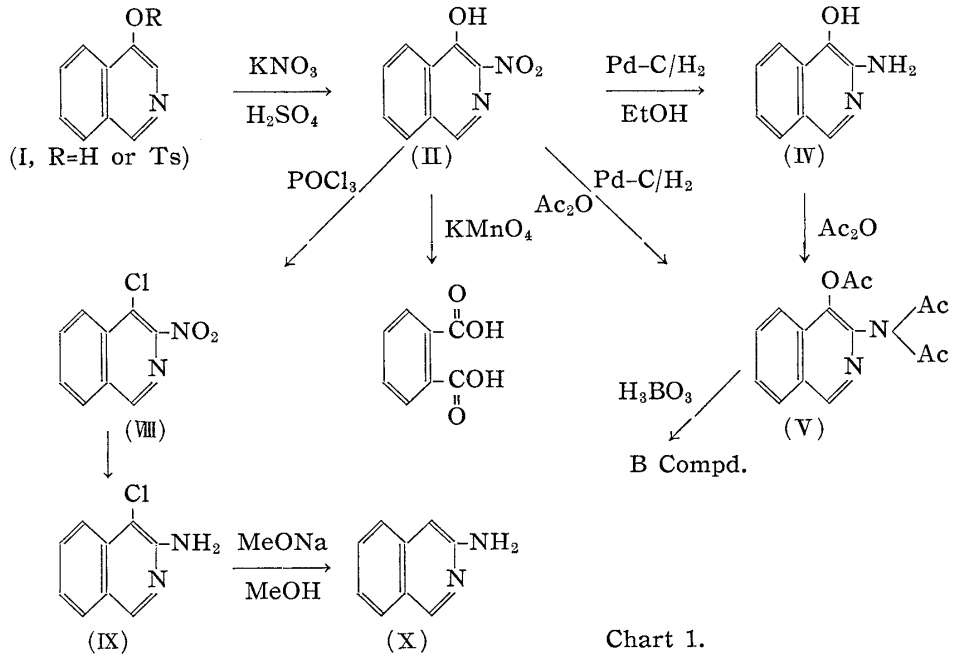


Chart 1.

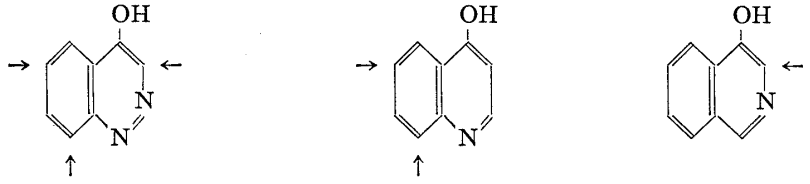
pound (IX) was obtained in a good yield. (IX) was identified as 3-amino-4-chloroisoquinoline from its ultraviolet absorption maxima (285 and 372 mμ) compared with those of 1-aminoisoquinoline (299 and 330 mμ).

The chlorine atom in (IX) was removed by boiling it with sodium methoxide in methanol at 200° in a sealed tube and 3-aminoisoquinoline (X), m.p. 176~178°, was obtained, characterized as its picrate and by comparison of its absorption maxima (231, 288, 353 mμ) with authentic data in the literature.[2,3]

The nitration of 4-tosyloxyisoquinoline (I : R=tosyl) with potassium nitrate in conc. sulfuric acid gave 3-nitro-4-hydroxyisoquinoline (II) alone and none of the tosyl esters was formed.

From these observations described above, it was concluded that the 3-position of 4-isoquinolinol is highly reactive to electrophilic displacement activated by the +tautomeric effect of the hydroxyl group in the 4-position.

Furthermore, this nature of 4-isoquinolinol gave a very strong support to the observation of Shofield and Simpson[4] who stated that, in the nitration of 4-hydroxycinnoline (XI), the 3-position was attacked overwhelmingly against 6- and 8-positions. As shown in the literature,[5] 4-hydroxyquinoline is nitrated at 6- and 8-positions. Together with this and foregoing facts, regarding the nature of 4-isoquinoline, it may be concluded that quinoline and isoquinoline have the same characteristics as the cinnoline ring.



(XI)

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Experimental*2

3-Nitro-4-isoquinolinol (II)—i) From 4-Isoquinolinol : To a solution of 3.0 g. of 4-isoquinolinol dissolved in 14 g. of conc. H_2SO_4, 2.4 g. of KNO_3 was added during 30 min., controlling the reaction temperature at 50~60° and the whole was maintained at this temperature for further 3 hr. The reaction mixture was poured onto crushed ice, the yellow precipitate was collected on a filter, and washed with cold water. Recrystallization from acetone gave yellow needles, m.p. 173°. Yield, 1.8 g. The mother liquor obtained after removal of these crystals showed a strong fluorescence but gave no crystalline substance. *Anal.* Calcd. for $C_9H_6O_3N_2$: C, 56.84; H, 3.18; N, 14.73. Found : C, 57.12; H, 3.07; N, 14.60. UV λ_{max}^{EtOH} mμ (log ε): 258 (4.60), 351 (3.88), 370 (3.89).

ii) From 4-Tosyloxyisoquinoline : To a solution of 3.0 g. of 4-tosyloxyisoquinoline dissolved in 14 g. of conc. H_2SO_4, 1.2 g. of KNO_3 was added and the whole was treated as in (i). One gram of 3-nitro-4-isoquinolinol was obtained and identified by admixture with the sample obtained in (i).

Oxidation of (II) with Potassium Permanganate—A solution of 0.6 g. of (II) in 40 cc. of water containing 4 g. of NaOH was heated on a water bath at 70° and 0.1*N* $KMnO_4$ solution was added dropwise until no decolorization was observed (ca. 110 cc.). Excess of $KMnO_4$ was decomposed with MeOH, MnO_2 was filtered off, yellow filtrate was made acid with AcOH, and evaporated to dryness *in vacuo*. The residue was extracted thoroughly with ether, the extract was dried over anhyd. Na_2SO_4, and ether was evaporated. Recrystallization from water gave white leaflets, m.p. 190°(decomp.). Direct comparison with authentic phthalic acid showed no depression. *Anal.* Calcd. for $C_8H_6O_4$: C, 57.83; H, 3.64. Found : C, 58.46; H 3.68.

*2 All m.p.s are uncorrected. Ultraviolet absorption spectra were measured with the Beckman DK-II spectrophotometer and infrared spectra by Koken Model DS-301 spectrophotometer.

3) A. R. Osborn, Shofield, Short : J. Chem. Soc., **1956**, 4186.
4) K. Shofield, J. C. E. Simpson : *Ibid.*, **1945**, 562.
5) K. Shofield, T. Swain : *Ibid.*, **1949**, 1367.

3-Amino-4-isoquinolinol (IV) Hydrochloride—A solution of 0.2 g. of (II) dissolved in 20 cc. of 98% EtOH and 10 cc. of 10% HCl added with Pd-C (prepared from 0.25 g. of activated charcoal and 25 cc. of 1% $PdCl_2$) was shaken in H_2 stream. After absorption of 80 cc. of H_2 (calcd., 70 cc.), the catalyst was removed by filtration, the yellow-green fluorescent solution thus obtained was evaporated to dryness *in vacuo*, and triturated with a small portion of acetone. Yellow needles, m.p. 195~197°, could not be recrystallized because of very rapid coloration. When treated with Na_2CO_3 solution, the liberated oil was rapidly decomposed to a black resin.

Triacetyl-3-amino-4-isoquinolinol (V)— 0.1 g. of crude hydrochloride of (IV) was dissolved in 10 cc. of Ac_2O and 0.1 g. of anhydr. AcONa was added. This solution was boiled for 1 hr., the reaction mixture was evaporated *in vacuo*, and the residue extracted with $CHCl_3$. Evaporation of the solvent after drying over Na_2SO_4 gave yellow syrup, which crystallized on trituration with MeOH. Recrystallization from MeOH gave pale yellow small prisms, m.p. 115~116° (0.4 g). *Anal.* calcd. for $C_{15}H_{14}O_4N_2$: C, 63.21; H, 4.90; N, 9.79. Found: C, 62.53; H, 4.59; N, 9.66. UV λ_{max}^{EtOH} mμ (log ε): 256 (3.46), 312 (3.37), 325 (3.45).

Attempted Ring-closure of (V)— The triacetate, prepared from 0.2 g. of (II) by the procedure described above, in 20 cc. of Ac_2O was added with 6 g. of H_3BO_3 and heated for 1 hr. at 150° in an oil bath. The reaction mixture was made alkaline with 10% NaOH solution, extracted with $CHCl_3$, dried over Na_2SO_4, and evaporated. The vitreous residue was triturated with acetone and recrystallized from the same solvent to yellow needles, m.p. 199°. *Anal.* Found: C, 55.30; H, 4.55; N, 7.51; Ash, 10.40. UV λ_{max}^{EtOH} mμ: 256, 312, 325, 385. IR cm^{-1}: 3330 (sharp) (NH), 1030 (broad) (B-O). This compound contains boron by qualitative test and forms a picrate of yellow needles (from EtOH), m.p. 183~185°.

3-Nitro-4-chloroisoquinoline (VIII)—0.5 g. of (II) was dissolved in 15 cc. of $POCl_3$ and heated at 100° in a fused tube for 3 hr. After cool, the reaction mixture was poured onto ice, white precipitate was collected on a filter. The filtrate was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. Precipitate and extracts were mixed and recrystallized from EtOH. Yellow needles, m.p. 108~109°. *Anal.* Calcd. for $C_9H_5O_2N_2Cl$: C, 54.22; H, 2.40; N, 13.40. Found: C, 54.63; H, 3.15; N 13.86. UV λ_{max}^{EtOH} mμ (log ε): 258 (4.12), 295 (3.58), 310 (3.50), 351 (3.48), 370 (3.89).

3-Amino-4-chloroisoquinoline(IX)—A solution of 2.0 g. of (VIII) dissolved in 50 cc. of EtOH and added with Pd-C (prepared from 5 cc. of 2% $PdCl_2$ and 500 mg. of activated charcoal) was shaken in H_2 stream and sbsorption of H_2 ceased after 650 cc. (theoretical, 645 cc. for 3 moles). The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. Residual hydrochloride was recrystallized from MeOH and acetone to 1.0 g. of fine yellow needles, m.p. 233~235°(decomp.). UV λ_{max}^{EtOH} mμ (log ε as monohydrochloride): 236 (4.73), 238 (3.81), 294 (3.69).

Free 3-amino-4-chloroisoquinoline was obtained by treatment of the hydrochloride with 10% NaOH and extraction with $CHCl_3$. After drying over Na_2SO_4 and evaporation of $CHCl_3$, the residue was recrystallized from benzene to pale yellow needles, m.p. 119~120°. *Anal.* Calcd. for $C_9H_7N_2Cl$: C, 60.55; H, 3.93; N, 15.68. Found: C, 61.55; H, 3.74; N, 15.80. UV λ_{max}^{EtOH}: 285, 372 mμ.

3-Aminoisoquinoline (X)—A solution of 0.19 g. of (IX) dissolved in MeONa solution prepared from 0.01 g. of metallic Na and 10 cc. of dehyd. MeOH was heated at 200° for 5 hr. in a sealed tube. When cool, the reaction mixture was evaporated *in vacuo* and the residual syrup was extracted with benzene. Recrystallization of residual oil from benzene after evaporation of the solvent gave yellow prisms, m.p. 168~170° *Anal.* Calcd. for $C_9H_8N_2$: C, 75.77; H, 5.56; N, 19.45. Found: C, 75.76; H, 5.56; N, 19.32. UV λ_{max}^{EtOH} mμ: 231, 288, 353.

Picrate: Yellow needles, m.p. 261°, formed from the above substance and picric acid in an ethereal solution.

Summary

4-Isoquinolinol was nitrated with potassium nitrate in conc. sulfuric acid to 3-nitro-4-isoquinolinol. Structure of the latter compound was established by conversion to 3-aminoisoquinoline via several steps. Structure of the triacetate of intermediate 3-amino-4-isoquinolinol was also discussed.

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