UDC 547.834.2.07

78. **Nobuo Ikekawa**: Studies on Naphthyridines. V.[1] Catalytic Reduction of Naphthyridines.

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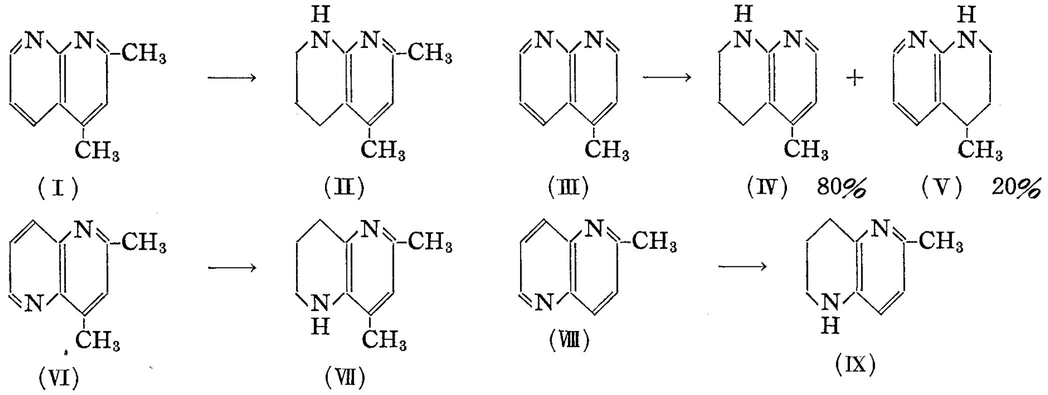
It is well known that catalytic hydrogenation of quinoline or isoquinoline gives 1,2,3,4-tetrahydro compound by the −E effect of nitrogen atom in the ring. In the case of naphthyridines possessing two nitrogen atoms in each ring, one of the two ring should easily be hydrogenated. Which ring is more reactive to hydrogenation is important in knowing the difference in the properties of various naphthyridines.

In order to compare the chemical properties and interaction of the two nitrogens in naphthyridine, catalytic reduction of 1,6-,[2] 2,7-[3] and 1,7-naphthyridines[4] over palladium in methanol was undertaken. Naphthyridine absorbs two moles of hydrogen more easily than quinoline, isoquinoline, or pyridine, due to the presence of a nitrogen atom in each ring.

1,8- and 1,5-Naphthyridine

Ochiai and Miyaki reported the catalytic hydrogenation of 1,8-[5] and 1,5-naphthyridine[6] and their methyl derivatives over platinum. By the +E effect of the methyl group, the ring possessing a methyl group resists hydrogenation and reduction of 2,4-dimethyl-1,8- (I) and 2,4-dimethyl-1,5-naphthyridine (VI) gives 5,6,7,8-tetrahydro compound (II or VII), that of 4-methyl-1,8-naphthyridine (III) gives 5,6,7,8-tetrahydro compound (IV) in 80% yield and 1,2,3,4-tetrahydro compound in 20% yield, and that of 2-methyl-1,5-naphthyridine (VIII) gives 5,6,7,8-tetrahydro compound (IX).



2,7-Naphthyridine

2,7-Naphthyridine (X), like 1,5- or 1,8-naphthyridine, has two nitrogen atoms in symmetrical position and accordingly hydrogenation leads only to one tetrahydro compound (XI). Hydrogenated product of 3-methyl-2,7-naphthyridine (XII) was presumed to be 5,6,7,8-tetrahydro compound (XIII) from the data of ultraviolet spectrum (λ_{max} 265.5mμ), which showed the same maximum position as that of 2,4,5-trimethylpyridine.[7] After recrystallization of the benzoate of the product, a compound of m.p. 84~85° was obtained.

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1) Part IV: This Bulletin, **6**, 404(1958).

2) N. Ikekawa: *Ibid.*, **6**, 263(1958).

3) *Idem.*: *Ibid.*, **6**, 269(1958).

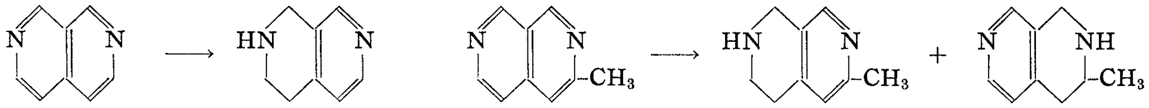
4) *Idem.*: *Ibid.*, **6**, 401(1958).

5) E. Ochiai, K. Miyaki: Ber., **74**, 1115(1941); K. Miyaki: Yakugaku Zasshi, **62**, 26(1942).

6) K. Miyaki: Yakugaku Zasshi, **62**, 257(1942).

7) N. Ikekawa, M. Maruyama, Y. Sato: This Bulletin, **2**, 209(1954).

Small amount of benzoate, m.p. 24~30°, was separated from the mother liquor by chromatography. The ultraviolet spectra of these benzoates showed maximum absorption at 265.5 mμ and 264 mμ, respectively. The infrared spectrum of the latter compound gave the band of 820 cm^{-1} associated with that of out-of-plane deformation vibration of two adjacent hydrogen atoms on the ring,[8] as shown in Fig. 1. From these results, it is assumed that the former of m.p. 84~85° is the benzoate of 5,6,7,8-tetrahydro compound (XIII), while the latter of m.p. 24~30° is that of 1,2,3,4-tetrahydro compound (XIV). From the amount of the benzoate, it was found that the hydrogenation of 3-methyl-2,7-naphthyridine produced 88% of (XIII) and 12% of (XIV).



(X) (XI) (XII) (XIII) 88% (XIV) 12%

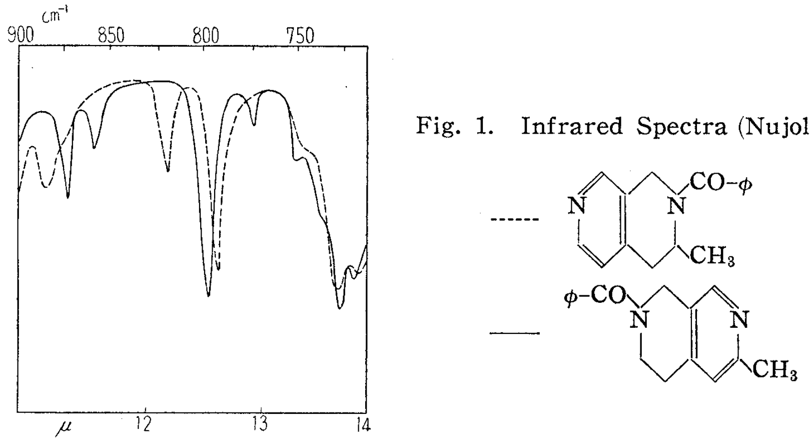
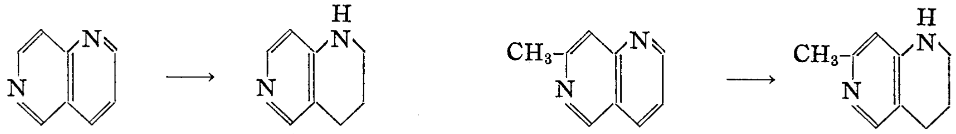


Fig. 1. Infrared Spectra (Nujol)

1,6-Naphthyridine

Hydrogenation of 1,6-naphthyridine (XV) gave only 1,2,3,4-tetrahydro-1,6-naphthyridine (XVI), m.p. 155~158°, and in the case of 7-methyl-1,6-naphthyridine (XVII) also, only the 1,2,3,4-tetrahydro compound (XVIII) was obtained. These tetrahydro compounds were identified with authentic samples reported in Part I of this series.[2]



(XV) (XVI) (XVII) (XVIII)

1,7-Naphthyridine

Ultraviolet spectra of hydrogenated product of 1,7-naphthyridine (XIX) showed almost the same absorption maximum as that of 3-dimethylaminopyridine[9] and the maximum shifted similarly in various pH. Therefore, the product obtained was considered to be 1,2,3,4-tetrahydro-1,7-naphthyridine (XX). The acetate, obtained by treatment with acetic anhydride under mild conditions, was passed through an alumina column and eluted with chloroform and ether mixture. Majority of the product was not eluted but a small amount (2%) of an acetate was obtained. It was presumed to be the acetate of 5,6,7,8-tetrahydro-1,7-naphthyridine (XXI) from its ultraviolet spectrum showing a maximum at 266 mμ and the infrared spectrum showing the bands at 778 and 704 cm^{-1} corresponding to out-of-plane deformation vibration of three adjacent hydrogen atoms remaining on the ring.[8]

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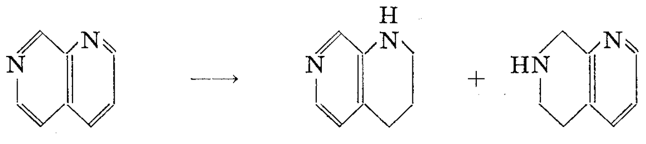
8) H. Shindo, N. Ikekawa : This Bulletin, **4**, 192(1956).

9) S. Okuda : *Ibid.*, **4**, 257(1956).

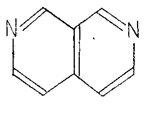


(XIX) (XX) 98% (XXI) 2%

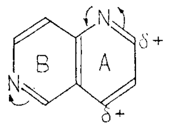
Discussions

In the case of compounds with nitrogen in symmetrical positions, such as 1,8-, 1,5-, and 2,7-naphthyridines, the product would be the same whichever ring is reduced. From the 2,4-dimethyl derivatives (I and VI) of these compounds, only the 5,6,7,8-tetrahydro compound is formed due to the +E effect of the methyl group but in the case of only one methyl group, its +E effect will be weak and a small amount of 1,2,3,4-tetrahydro compound is formed, as was seen in the case of (III) and (XII).

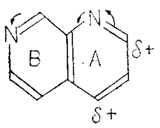
When the nitrogen is not in a symmetrical position, such as in 1,6- and 1,7-naphthyridines, the circumstance is entirely different and, in the case of alkyl derivatives, the reaction cannot be explained thoroughly by the effect of methyl group alone. The formation of only the 1,2,3,4-tetrahydro compound from 1,6-naphthyridine is thought to be due to the depletion of NA electrons, promoted by the −E effect of the nitrogen (NB) in the B ring, together with resonance of the nitrogen (NA) in the A ring with the B ring, with subsequent increase of −E effect of NA on the A ring, resulting in the reduction of A ring alone. The tendency is the same in 1,7-naphthyridine but in this case, NA is in a position *meta* to NB and their mutual action becomes smaller so that 5,6,7,8-tetrahydro compound (XXI) should be formed, even in an extremely small amount. Beside the interaction of two nitrogen atoms, the effect of the double bonds fixed to some extent in the form of (XV) or (XIX) should also be taken into the consideration. In short, the lone-pair electrons of NA are drawn toward NB and consequently, electron density of the A ring becomes much lower than that in the B ring.



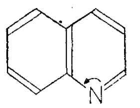
(X)

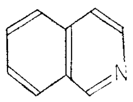


(XV)



(XIX)





Such an effect is also observed in quinoline and the smaller pKa value of quinoline than that of isoquinoline[10] is considered to be due to the resonance of the lone-pair electrons of nitrogen with the benzene ring in quinoline. As has already been reported,[2~4] the maximum absorption in the ultraviolet spectra is in the order of 2,7-, 1,7-, and 1,6-naphthyridines toward a longer wave length region and this indicates that the mutual interaction of nitrogen is the strongest in 1,6-naphthyridine, followed by 1,7-naphthyridine.[11]

The author expresses his deep gratitude to Prof. K. Tsuda for his continued and kind guidance throughout the course of this work. He is also grateful for many valuable advices from Prof. E. Ochiai, and is indebted to Mr. H. Shindo of Sankyo Co., Ltd. for infrared spectral measurements and to Miss H. Yamanouchi for elemental analyses.

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[10] pKa of quinoline, 4.85; that of isoquinoline, 5.14. cf. A. Albert, R. J. Goldacre, J. Phillips: J. Chem. Soc., **1948**, 2240.

[11] Measurement of pKa values of 1,6-, 1,7-, and 2,7-naphthyridines was attempted from titration curve but the values were so small and attempted samples were also small in amount that only rough results could be obtained. All these compounds gave values around 3.6～3.7 and there seemed to be no great difference.

Experimental

Catalytic Reduction—Naphthyridine (200～400 mg.) was hydrogenated in 4～8 cc. of MeOH over 100～200 mg. of Pd-$CaCO_3$ (Pd 15%). Absorption of hydrogen stopped after absorbing 2 moles of H_2 in 15～30 mins. Removal of the catalyst and solvent gave a crude product. The solution showed a green fluorescence, during the course of hydrogenation, by the formation of dihydronaphthyridine as an intermediate. Such a phenomenon is characteristic in hydrogenation of naphthyridine.

Hydrogenation of 2,7-Naphthyridine (X)—Hydrogenation of 200 mg. of (X) gave a thick liquid, b.p$_{10}$ 130～140°(bath temp.). U.V. λ_{max}^{MeOH} : 260 mμ(log ε 3.18). I.R. ν_{max} 837 cm^{-1}, 807 cm^{-1}(C-H out-of-plane deformation of free hydrogen).

Dipicrate : m.p. 230°(decomp.). *Anal.* Calcd. for $C_8H_{10}N_2 \cdot 2C_6H_3O_7N_3$: C, 40.49; H, 2.71; N, 18.93. Found : C, 40.65; H, 2.77; N, 18.80.

Hydrogenation of 3-Methyl-2,7-naphthyridine (XII)—Hydrogenation of 400 mg. of (XII) gave 390 mg. of crude product, U.V. λ_{max}^{MeOH} 265.5 mμ(log ε 3.43). BzCl (500 mg.) in 2 cc. of pyridine was added to a solution of 350 mg. of the reduction product in pyridine and the mixture was stood over night. Ice water was added to the resultant solution, which was made alkaline with Na_2CO_3 and extracted with $CHCl_3$. After drying over Na_2SO_4, $CHCl_3$ was evaporated, and the majority of pyridine was distilled off under a reduced pressure. After washing with a small portion of petr. ether, the residue was recrystallized from petr. ether and 310 mg. of product (A), m.p. 84～85°, was obtained. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.20; H, 6.35; N, 11.11. Found : C, 75.82; H, 6.43; N, 10.83.

Picrate : m.p. 180～181°. *Anal.* Calcd. for $C_{16}H_{16}ON_2 \cdot C_6H_3O_7N_3$: N, 14.55. Found : N, 14.10.

After removal of (A), the mother liquor was passed through alumina column. A small amount of pyridine was eluted by petr. ether and 30 mg. of benzoate (B), m.p. 24～30°, was obtained by elution with ether. *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.20; H, 6.35; N, 11.11. Found : C, 75.78; H, 6.10; N, 10.79.

Picrate : m.p. 80～90°(decomp.). *Anal.* Calcd. for $C_{16}H_{16}ON_2 \cdot C_6H_3O_7N_3$: N, 14.55. Found : N, 14.71.

After elution of (B), 40 mg. of liquid benzoate (C) was obtained. According to the infrared spectrum, (C) was a mixture of (A) and (B). U.V. λ_{max}^{MeOH} mμ(log ε) : (A), 265.3 (3.65), 273 (3.51) (shoulder). (B), 264 (3.15). I.R. spectrum of (B) showed the band at 820 cm^{-1} corresponding to C-H deformation vibration of the ring. From these data,' it was assumed that (A) is a benzoate of (XIII) and (B), a benzoate of (XIV). The ratio of the amount of the two benzoates was 88:12.

Hydrogenation of 1,6-Naphthyridine (XV)—Hydrogenation of 300 mg. of (XV) gave crystals of m.p. 150～156°. After recrystallization from benzene, 280 mg. of tetrahydro compound, m.p. 155～158°, was obtained, which did not depress the m.p. of a sample of 1,2,3,4-tetrahydro-1,6-naphthyridine. From the mother liquor, a compound corresponding to 5,6,7,8-tetrahydro derivative was not obtained.

Hydrogenation of 7-Methyl-1,6-naphthyridine (XVII)—Hydrogenation of 250 mg. of (XVII) gave 225 mg. of product, m.p. 144～146°(from benzene), which did not depress the m.p. of a sample of 1,2,3,5-tetrahydro-7-methyl-1,6-naphthyridine.

Hydrogenation of 1,7-Naphthyridine (XIX)—Yellow liquid (190 mg.) was obtained from 200 mg. of (XIX). U.V. λ_{max}^{MeOH} mμ(log ε) : 262 (3.57), 315.5 (3.15); $\lambda_{max}^{0.1N\ NaOH}$ 254 (3.60), 301.5 (3.13); $\lambda_{max}^{0.1N\ H_2SO_4}$ 267 (3.72), 314 (3.14).

3-Dimethylaminopyridine[9] : U.V. λ_{max}^{EtOH} mμ(log ε) : 257 (4.06), 312 (3.42); $\lambda_{max}^{0.1N\ NaOH}$ 250 (3.89), 299～300 (3.30); $\lambda_{max}^{0.1N\ H_2SO_4}$ 268 (4.03), 351～352 (3.41).

The product (150 mg.) was heated with 0.3 cc. of Ac_2O on a steamfor 1 hr. bath Ice water was added to the resulting solution, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. After drying and evaporating the solvent, the residue was chromatographed over alumina column using $CHCl_3$-ether (1:1) mixture. A compound (3 mg.) showing U.V. λ_{max}^{MeOH} 266 mμ(shoulder) and 273 mμ, and a compound (4 mg.) showing U.V. λ_{max}^{MeOH} 266 mμ were obtained. The latter compound was assumed to be the acetate of 5,6,7,8-tetrahydro compound (XXI) as its infrared spectra showed strong bands at 778 and 704 cm^{-1}. The yield of the acetate was 2%. Ultraviolet absorption maximum at 273 mμ in the former may be considered to arise from the acetate of (XX).

Summary

Catalytic hydrogenation over palladium of 3-methyl-2,7-naphthyridine gave 88% of 5,6,7,8-tetrahydro compound and 12% of 1,2,3,4-tetrahydro compound, that of 1,6-naphthyridine and 7-methyl-1,6-naphthyridine gave 1,2,3,4-tetrahydro compounds, and that of 1,7-naphthyridine gave 98% of 1,2,3,4-tetrahydro compound and 2% of 5,6,7,8-tetrahydro compound. The reaction mechanism of catalytic hydrogenation of naphthyridines was discussed.

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