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The Mechanism of the Formation of an Abnormal Product in the Chichibabin Reaction of Quinoline (Studies on the Syntheses of Heterocyclic Compounds. CCLIII[1])

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The Chichibabin reaction of quinoline (I) in dimethylaniline with sodium amide was carried out, to give a mixture of 2–aminoquinoline (II) and unexpected 2–amino–3,4–dihydroquinoline (III). Furthermore, the mechanism of the formation of III was revealed by comparison of the product obtained from 2–deuterioquinoline by the same method as above from the point of nuclear magnetic resonance and mass spectra.

In the previous short communication[3] one of the authors reported that the Chichibabin reaction[4–6] of quinoline (I) in dimethylaniline[4] with sodium amide gave a mixture of 2–aminoquinoline (II) and 2–amino–3,4–dihydroquinoline (III) unexpectedly. Furthermore, the Chichibabin reaction of 5–,6–,7–, and 8–methylquinoline[7–9] was investigated, by the result of which our objective 3,4–dihydroquinoline derivatives were obtained in a slight yield.

The purpose of the present investigation was to certify our proposed mechanism[3] on the formation of the abnormal product, namely, 2–amino–3,4–dihydroquinoline by deuterium labelling experiment.

Quinoline (I) was added dropwise to a stirred suspension of sodium amide in dimethylaniline at 120°. Then the mixture was heated at 120—130° for 3 hr. After cooling, the mixture was decomposed with water and extracted with ether. Removal of the solvent gave a crude oil, from which the excess of dimethylaniline was removed by distillation *in vacuo* to give a viscous substance. This residue afforded 2–amino–3,4–dihydroquinoline (III) as colorless prisms, mp 135—136°, whose nuclear magnetic resonance (NMR) spectrum (in $CDCl_3$) showed a $-CH_2CH_2-$ band at 7.0—7.8 τ as multiplet. The peak attributable to the amino hydrogens was also shown at 4.5 τ as broad singlet. On the other hand, the above filtrate, from which the crystals of III were filtered off, was concentrated and then distilled *in vacuo* to give a substance, which sublimed at 250° (0.5 mm). Recrystallization from water afforded 2–aminoquinoline (II)[10] as colorless scales, mp 128°, which

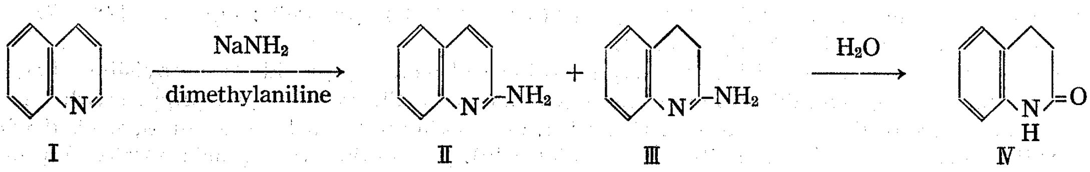

Chart 1

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[1] Part CCLII: *Tetrahedron Letters*, **1968**, 4251.

[2] Location: *No. 85, Kita–4–bancho, Sendai.*

[3] T. Kametani, K. Kigasawa, Y. Iwabuchi, and T. Hayasaka, *J. Heterocyclic Chem.*, **2**, 330 (1965).

[4] A.E. Chichibabin and M.P. Oparna, *J. Russ. Phys. Chem. Soc.*, **50**, 553 (1920); *Chem. Abstr.*, **18**, 1502 (1924).

[5] R.N. Shreve, E.H. Riechers, H. Rubenkoenig, and A.H. Goodman, *Ind. Eng. Chem.*, **32**, 173 (1940).

[6] German Patent 663891 [*Chem. Abstr.*, **33**, 175 (1939)].

[7] T. Kametani, H. Nemoto, and S. Takano, *Yakugaku Zasshi*, **88**, 453 (1968).

[8] T. Kametani and H. Nemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1910 (1967).

[9] T. Kametani, H. Nemoto, and S. Takano, *Chem. Pharm. Bull.* (Tokyo), **16**, 360 (1968).

[10] F.W. Bergstrom, *J. Am. Chem. Soc.*, **56**, 1748 (1934); *J. Org. Chem.*, **2**, 411 (1937).

was identified with authentic sample by mixed melting point test and infrared (IR) spectral comparison. Hydrolysis of the above compound (III) gave 3,4-dihydrocarbostyril (IV) as colorless prisms, mp 169°, whose IR spectrum showed a strong band for the C=O stretching vibration at 1680 cm^{-1}. This compound also showed no depression of melting point on admixture with the authentic sample.[11]

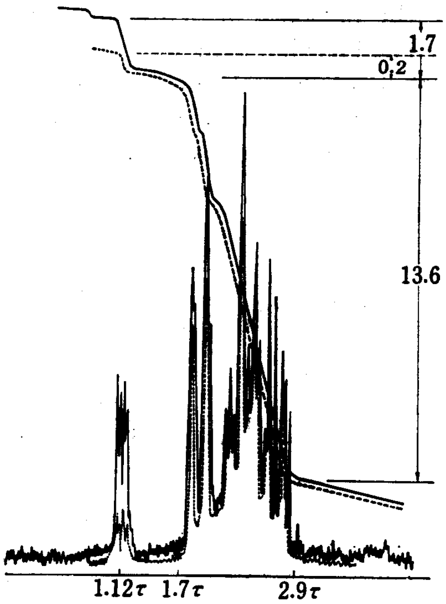
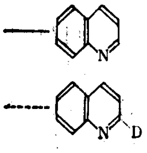


Fig. 1. NMR Spectra of Quinoline and 2-Deuterioquinoline (CCl_4, 60 Mc)



While the other solvents, for instance, benzene and toluene, were used instead of dimethylaniline, the Chichibabin reaction did not give the abnormal product (III), but only 2-aminoquinoline (II). This fact reveals that the role of dimethylaniline as reaction solvent would be very important.

Secondly, treatment of 2-deuterioquinoline N-oxide (IV), which was obtained from quinoline N-oxide (V) and 1% NaOD-D_2O according to Kawazoe and Ohnishi,[12] with phosphorous trichloride afforded 2-deuterioquinoline (VII), whose NMR spectrum revealed that the hydrogen at the C_2-position of quinoline was deuterated. Namely, one proton at the C_2-position, which was observed at 1.12τ (in CCl_4) in case of quinoline (I), disappeared almost completely (incorporation ratio was about 90%) in case of 2-deuterioquinoline (VII) as shown in Fig. 1. Moreover, the portion of the signal which remained was considerably sharpened because the coupling between C_2H-C_3H and C_2H-C_4H bonds was lessened on the introduction of deuterium at the C_2-position.

Furthermore, the mass spectrum of VII showed the hydrogen at the C_2-position was substituted with deuterium in the ratio of 91.99%.[13] In this case the molecular ion peak appeared at *m/e* 130.

The Chichibabin reaction of 2-deuterioquinoline (VII) was carried out according to the same procedure in case of I, and the reaction mixture was hydrolysed to give 3-hydro-4-

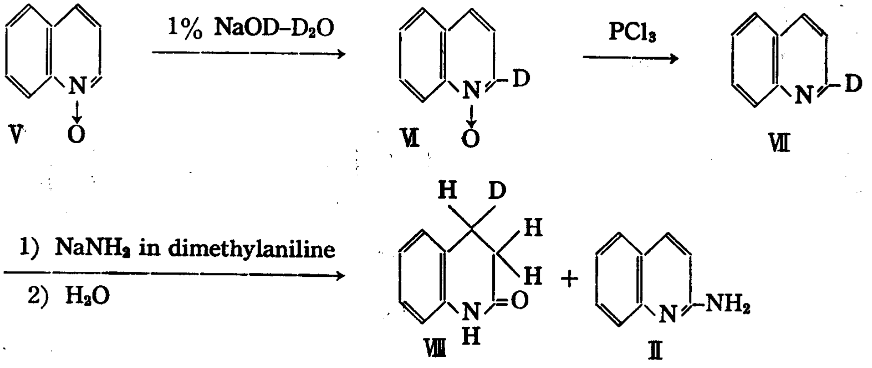


Chart 2

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11) E. Ochiai and C. Kaneko, *Chem. Pharm. Bull.* (Tokyo), **7**, 277 (1959).

12) Y. Kawazoe and M. Ohnishi, *Chem. Pharm. Bull.* (Tokyo), **15**, 826 (1967).

13) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. I, 1964, p. 34.

deuteriocarbostyril (VIII) and 2-aminoquinoline (II), the latter of which was identified by mixed melting point test and IR spectral comparison with an authentic sample. In this case the presence of deuterium was not observed in its mass spectrum of the compound (II).

The base ion peak in the mass spectrum of IVa (as an enol form) (molecular ion at *m/e* 147) which occurred at *m/e* 146 would be due to the loss of hydrogen. Further loss of carbon monoxide from ion a′ afforded ion b (*m/e* 118). Expulsion of hydrogen cyanide from ion b afforded the ion c (*m/e* 91).

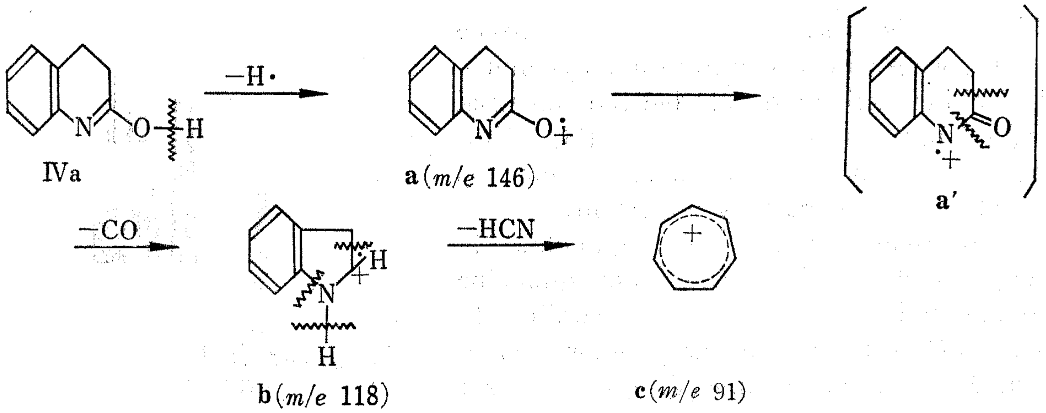

Chart 3

In the mass spectrum of the former compound (VIII) the presence of deuterium[13] was observed in the following fragments; the ion a (24.2%), the ion b (20.1%), and the ion c (14.5%), which were confirmed by one mass unit shift, respectively.

These facts showed that the hydrogen at the C_4-position was substituted partly with deuterium in case of VIII and that the mass fragmentation process of 3,4-dihydrocarbostyril has been explained reasonably and the hydrogen at the C_2-position might be moved in part to the C_4-position in case of the Chichibabin reaction.

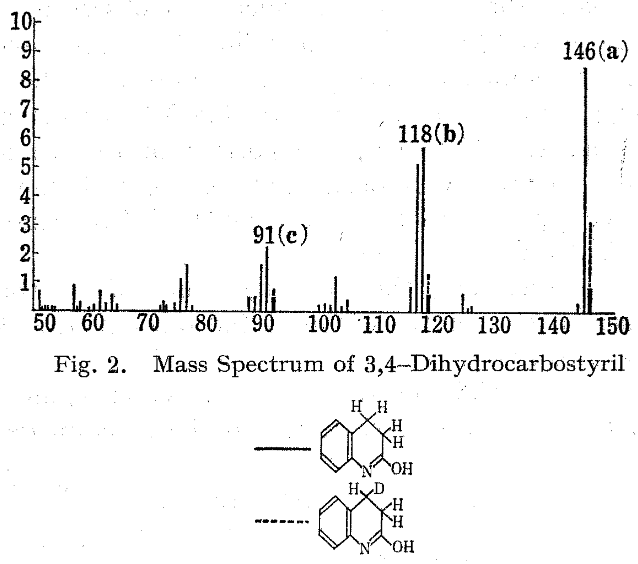

Fig. 2. Mass Spectrum of 3,4-Dihydrocarbostyril

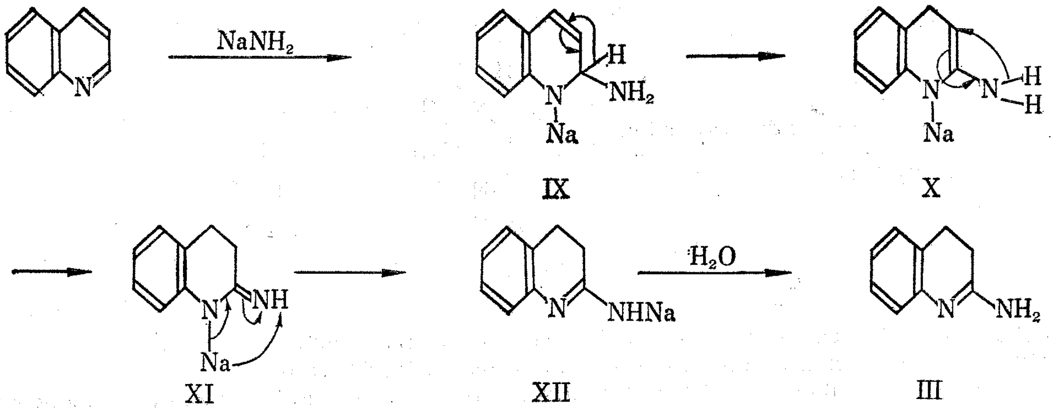

Chart 4

Therefore, the reasonable mechanism to explain the formation of III would involve addition of sodium amide (Na^+ and NH_2^-) to I with formation of IX and hydride shift from C_2–to C_4–position to yield an intermediate (X), which would be converted into XII through XI. Finally, hydrolysis of XII would afford the compound (III).

The attempted abnormal Chichibabin reaction of pyridine and isoquinoline in dimethylaniline failed, thus the expected 3,4–dihydroderivative was not obtained.

Experimental[14]

The mass spectrum was measured with a Hitachi RMU–6D mass spectrometer equipped with a direct inlet system; chamber voltage 70 V; total emission 80 μA; evaporation/source temp. 160/250°.

Chichibabin Reaction of Quinoline (I)—To a stirred suspension of 4.9 g of $NaNH_2$ in 29 g of dimethylaniline was added dropwise 12 g of quinoline at 120°. After the addition, the mixture was heated at 120—130° for 3 hr. After cooling, the reaction mixture was decomposed with water and extracted with ether. Removal of the solvent gave a crude oil, from which the excess of dimethylaniline was removed by distillation *in vacuo* to give a viscous substance. This residue afforded a colorless powder on being triturated with a small amount of ether. Recrystallisation from benzene afforded 3.3 g (24.3%) of III as colorless prisms, mp 135—136°, UV $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε): 252 (4.07), 267 (4.13). NMR (τ) ($CDCl_3$): 7.0—7.8 (4H, multiplet, $-C\underline{H}_2C\underline{H}_2-$) 4.5 (2H, broad singlet, $-N\underline{H}_2$). IR cm^{-1} (KBr): ν_{NH_2} 3450, 3350. *Anal.* Calcd. for $C_9H_{10}N_2$: C, 74.74; H, 6.90; N, 19.16. Found: C, 74.35; H, 6.49; N, 19.03.

The picrate formed yellow crystals (from EtOH), mp 247° (decomp.). *Anal.* Calcd. for $C_9H_{10}N_2\cdot C_6H_3O_7N_3$: C, 48.00; H, 3.49; N, 18.66. Found: C, 48.21; H, 3.44; N, 18.72.

The above filtrate, from which crystals of III were filtered off, was concentrated and then distilled *in vacuo* to give a substance, which sublimed at bp 250° (0.5 mm). Recrystallisation from water gave 1 g (7.5%) of 2–aminoquinoline (II) as colorless scales, mp 127—128°,[10] which were identical with the authentic sample from the point of IR spectrum and mixed melting point test. The picrate of II formed yellow crystals, mp255—256°.

2-Amino-3,4-dihydroquinoline (IV)——A mixture of 1 g of the above compound (III) with 15 ml of water was heated on a water–bath for a short time until all the crystals dissolved, and 0.988 mg (98.2%) of the crystals precipitated was collected by filtration after cooling. Recrystallisation from EtOH afforded colorless prisms, mp 162—163°. *Anal.* Calcd. for C_9H_9ON: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.92; H, 6.30; N, 9.74. IR cm^{-1} (KBr): $\nu_{C=O}$ 1680. This compound also showed no depression of melting point on admixture with the authentic sample.[11]

2-Deuterioquinoline (VII)——To a solution of 1.1 g of metallic Na in 10 ml of D_2O was added 14.5 g of quinoline N–oxide (V), and the resultant mixture was heated at 100° in a sealed tube for 1 hr. After cooling, the reaction mixture was extracted with $CHCl_3$. After the usual work up, the solvent was distilled to give 14 g (96%) of crystals (VI).

A mixture of 10 g of VI, 18.3 g of PCl_3, and 200 ml of $CHCl_3$ was heated on a water–bath for 1 hr. After cooling, the solvent was evaporated to give a syrup, whose distillation gave 7.5 g (84.5%) of an oil, bp 104° (10 mmHg). In case of NMR spectrum in CCl_4 the integration ratio of I between 1.7—2.9 τ and 1.12 τ was calculated as 1.7:13.6 and, on the contrary, the ratio between the above signals of VII was observed as 0.2:13.6. This increase in the ratio in case of VII shows that the C_2–position of quinoline is substituted with deuterium. Furthermore, the mass spectrum of VII showed the contents of deuterium to be 91.97% according to Djerassi.[13]

Chichibabin Reaction of 2-Deuterioquinoline (VII)——To a stirred suspension of 2.5 g of $NaNH_2$ and 15 g of dimethylaniline was added dropwise 6 g of VII at 120°. After the addition, the mixture was heated at 120—130° for 3 hr. After the reaction mixture had been decomposed with water, the resultant mixture was heated on a water–bath and, after cooling, extracted with ether. The usual work up afforded a syrup, which was chromatographed on silica gel. Removal of the solvent from the eluate using $CHCl_3$–hexane (1:2) gave 1.36 g (20.1%) of VIII as colorless needles, mp 161—162°. This compound was identical with the above compound (IV) by mixed melting point test. Removal of the solvent from the further $CHCl_3$ eluent gave 432 mg (6.5%) of II as colorless scales, mp 126—127°, which were identical with the compound (II) mentioned above on mixed melting points test and IR spectral comparison.

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[14] All melting points were not corrected.