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245. Tetsuji Kametani and Hideo Nemoto*1: Chichibabin Reaction. II.*2 Chichibabin Reaction of 8-Methylquinoline and Migration of the Methyl Group in the Synthesis of 3,4-Dihydro-8-methylcarbostyril by Friedel-Crafts Reaction. (Studies on the Syntheses of Heterocyclic Compounds. CCIII.*3)

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Chichibabin reaction of 8-methylquinoline (I) in dimethylaniline with sodium amide gave a mixture of 2-amino-8-methylquinoline (II) and 2-amino-3,4-dihydro-8-methylquinoline (III), the latter of which was characterized as its hydrolyzed product, namely, 3,4-dihydro-8-methylquinolone (IV). Furthermore, Friedel-Crafts reaction of N-(*o*-tolyl)-β-chloropropionamide (V) was examined in order to synthesize an authentic sample (IV) for comparison, but a mixture of 5-methyl- (VI) and 8-methyl-3,4-dihydrocarbostyril (IV) was obtained unexpectedly. This fact shows the migration of the methyl group was occurred in case of Friedel-Crafts reaction by aluminum chloride without solvent. On the other hand, catalytic hydrogenation of 8-methylcarbostyril (XI) in the presence of 40% palladium-charcoal afforded the above compound (IV), which was also identical with the sample obtained by Chichibabin reaction of I, followed by hydrolysis, and by Friedel-Crafts reaction of V.

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In a previous paper*2 one of the authors has reported that the Chichibabin reaction of quinoline in dimethylaniline with sodium amide gave a mixture of 2-aminoquinoline and unexpected 2-amino-3,4-dihydroquinoline as one of the by-products. The purpose of the present investigation was to study the Chichibabin reaction of 8-methylquinoline (I) in order to examine whether or not the same abnormal reaction as above would occur, by the result of which our expected 2-amino-3,4-dihydro-8-methylquinoline (III) seemed to be formed as by-product in a poor yield besides a normal product, namely, 2-amino-8-methylquinoline, (II). In this case the compound (III) as an intermediate could not be separated, but since the formation of 2-amino-3,4-dihydroquinoline had already been proved in case of quinoline,*2 we assumed the formation of III tentatively. Furthermore, the migration of the methyl group was recognized in case of the synthesis of an authentic sample by Friedel-Crafts reaction, unexpectedly.

8-Methylquinoline (I)[1] was added dropwise to a stirred suspension of sodium amide in dimethylaniline at 130°. After the addition, the mixture was heated under reflux for 3 hours. After cooling, the reaction mixture was decomposed with water and extracted with benzene. Chromatography under the various conditions was carried out in order to obtain our expected 2-amino-3,4-dihydro-8-methylquinoline (III), but resulted in failure. Therefore, after the reaction mixture had been hydrolyzed by heating with water for 3 hours, our expected two compounds, (II) and (IV), were obtained by extraction with hexane or alumina-chromatography. 2-Amino-8-methylquinoline (II) was first obtained by extraction with hot hexane as colorless needles, m.p. 89~89.5° in 33.46% yield, which were characterized by elementary analysis, infrared (IR), and nuclear magnetic resonance (NMR) spectra. Secondly, 8-methyl-3,4-dihydrocarbostyril (IV) was separated by alumina-chromatography in 1.04% yield as colorless needles, m.p. 131~132°, which were found

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*2 Part I. T. Kametani, K. Kigasawa, Y. Iwabuchi, T. Hayasaka: J. Heterocyclic Chem., 2, 330 (1965).
*3 Part CCII. Yakugaku Zasshi, 87, 1411 (1967).
1) Z. H. Skraup: Monatsch., 2, 153 (1881).

to be identical with an authentic sample[2] by admixed melting point test and infrared (IR) spectrum.

Furthermore, an alternative synthesis of Ⅳ according to Mayer's procedure[3] was examined in order to identify the above compound (Ⅳ). Friedel-Crafts reaction of N-(*o*-tolyl)-*β*-chloropropionamide (Ⅴ), which was obtained by condensation of *o*-toluidine with *β*-chloropropionyl chloride, afforded a mixture of the compound, m.p. 131~132°, and unexpected compound, m.p. 162~163°. Neither of both melting points was recorded in the literature[3] and Mayer showed m.p. 112° for the compound (Ⅳ), but the former compound of m.p. 131~132°, identical with the authentic sample described later, was

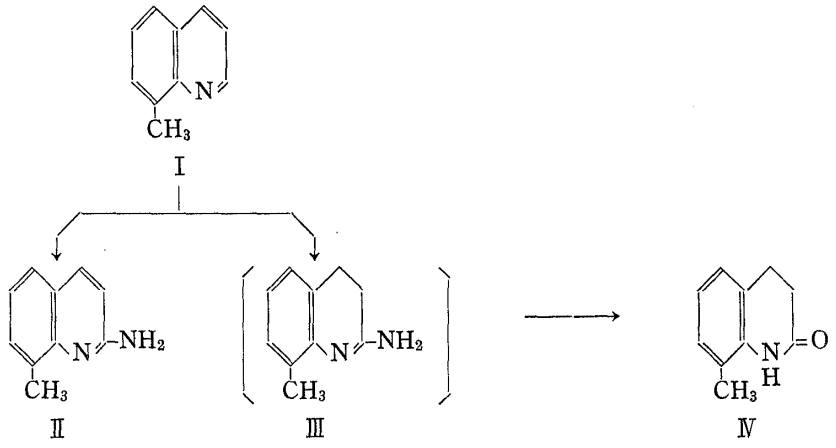

Chart 1.

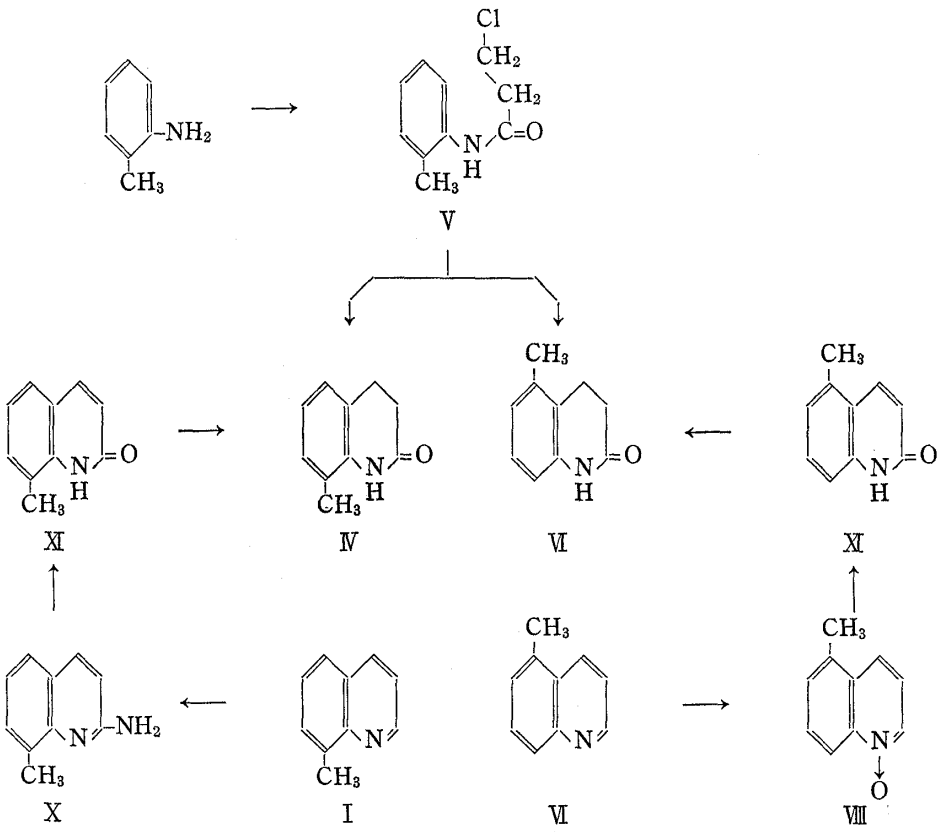

Chart 2.

2) F.H. Case, J.J. Lafferty : J. Org. Chem., **23**, 1375 (1958).
3) F. Mayer, L. van Zuetphen, H. Phillips : Ber., **60**, 858 (1927).

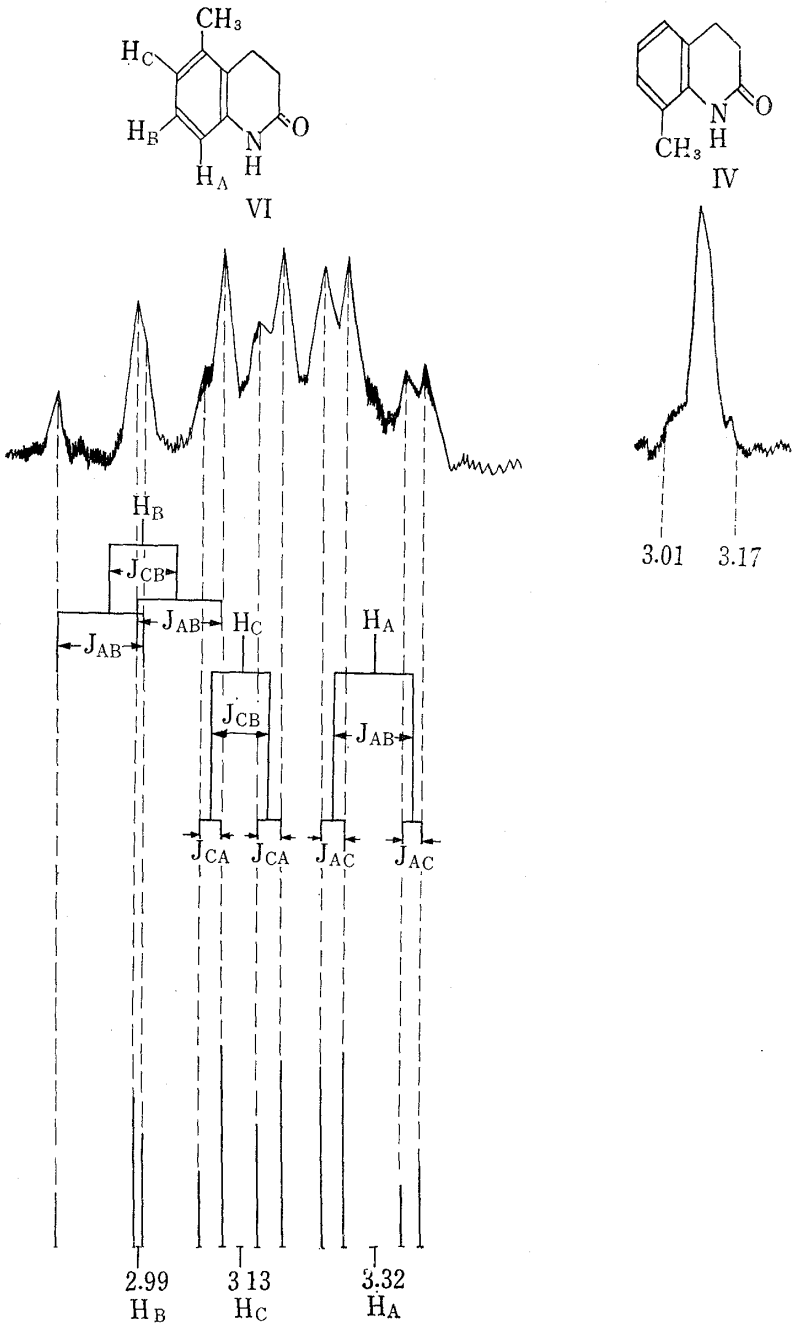

Fig. 1. The NMR Spectra of 3,4-Dihydro-5-methylcarbostyril (Ⅵ) and 3,4-Dihydro-8-methylcarbostyril (Ⅳ) in $CDCl_3$

also identical with the compound obtained as one of by-products in the Chichibabin reaction on admixed melting point test and spectral determination. Therefore, the compound[3] of m.p. 112° obtained by Mayer seems to be a mixture of both specimens as above. In fact, admixed melting point test of both specimens showed nearly m.p. 112°.

On the other hand, elementary analysis of the latter compound having m.p. 162~163°, gave a composition of $C_{10}H_{11}ON$, whose IR spectrum showed maxima at 3150 (NH) and 1675 cm^{-1} (lactam C=O). The NMR spectrum (in $CDCl_3$) of this compound showed the protons (4H) of two methylene groups at 7.17~7.36τ, the protons (3H) of methyl group at 7.75τ, and one aromatic proton (H_A) adjacent to 1-imino group at 3.32τ, the

4) cf. E. Ochiai, T. Yokogawa: Yakugaku Zasshi, **75**, 213 (1955).

latter of which is located in a higher field than that of the aromatic protons in case of Ⅳ presumably due to the anisotropy of an imino group at ortho-position. Furthermore, since three aromatic protons of the compound (Ⅳ) which exist between the methylene and methyl groups are almostly magnetically equivalent, the aromatic protons are observed as a broad singlet at 3.01~3.17τ but, the signals of one aromatic proton of the compound (Ⅵ) are shown as two doublets at 3.32τ because of ortho-coupling (J_{AB}=7.5 c.p.s.) and metha-coupling (J_{AC}=2.0 c.p.s.). Furthermore, the proton (H_C) at the C_6-position shows the signals of ortho- and metha-coupling at 3.13τ as two doublets with J_{CB}=6.5 c.p.s. and J_{CA}=2.0 c.p.s., respectively, and the proton (H_B) at C_7-position shows only the signals corresponding to ortho-coupling (J=7.5 c.p.s.) at 2.99τ as triplet with J_{BC}=6.5 c.p.s. and J_{BA}=7.5 c.p.s. These facts suggest the latter compound having m.p. 162~163° to be 3,4-dihydro-5-methylcarbostyril (Ⅵ).

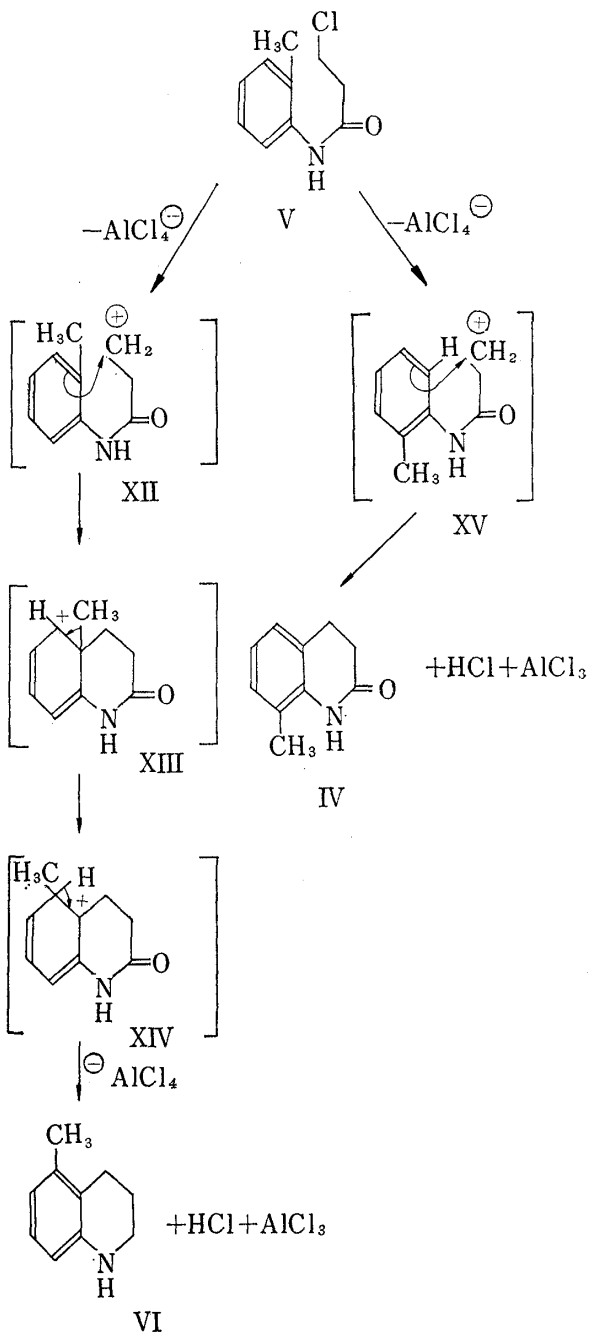

Chart 3.

Accordingly, an alternative synthesis of Ⅵ was investigated as follows. Rearrangement with tosyl chloride[4] of 5-methylquinoline 1-oxide (Ⅷ), which was obtained by oxidation of 5-methylquinoline[5] (Ⅶ) with 29% hydrogen peroxide in acetic acid, afforded 5-methylcarbostyril (Ⅸ). Catalytic hydrogenation of Ⅸ in ethanol in the presence of 40% palladium-charcoal[6] at atmospheric pressure gave the compound (Ⅵ) which was identical with our sample mentioned above.

Furthermore, diazotization of Ⅹ with nitrosylsulfuric acid, followed by hydrolysis of the resultant diazonium compound, gave 8-methylcarbostyril (Ⅺ).[2] Catalytic hydrogenation of Ⅺ in the presence of 40% palladium-charcoal afforded 3,4-dihydro-8-methylcarbostyril (Ⅳ), which was also identical with the sample obtained by Friedel-Crafts reaction of V.

It is as a matter of course that the compound (Ⅳ) was formed *via* an intermediate (XV) by normal Friedel-Crafts reaction, but the formation of the migrated compound (Ⅵ) seems to be very interesting. Perhaps the simplest mechanism to explain the formation of Ⅵ would initially involve ring-formation at the carbon having methyl

5) L. Brandford, T. J. Elliott, F. M. Rowe : J. Chem. Soc., **1947**, 437.
6) cf. C. J. Cavallito, T. H. Haskell : J. Am. Chem. Soc., **66**, 1166 (1944).

group as XIII *via* XII and migration of the methyl group to 5-position to give VI *via* XIV (Chart 3).

Experimental*4

8-Methylquinoline (I)——A mixture of 10.7 g. of *o*-toluidine, 25 g. of glycerine, 25 g. of sodium *m*-nitrobenzenesulfonate, and 136 g. of 65% H_2SO_4 was heated under reflux in an oil-bath for 3 hr. After cooling, the reaction mixture was made basic with 50% KOH aq. solution and extracted with benzene. The extract was washed with saturated NaCl aq. solution, dried on Na_2SO_4, and evaporated to give a syrup, whose distillation *in vacuo* afforded 9.0 g. (63%) of colorless oil, b.p_9 100～104°. Recrystallization of the picrate from acetone gave yellow needles, m.p. 201～202° (lit.,[1] m.p. 200°). *Anal.* Calcd. for $C_{10}H_9N \cdot C_6H_3O_7N_3$: C, 51.62; H, 3.25; N, 15.05. Found: C, 52.05; H, 3.34; N, 15.41.

The Chichibabin Reaction of 8-Methylquinoline (I)——To a heated suspension of 4.9 g. of $NaNH_2$ in 30 g. of dimethylaniline was added dropwise with shaking 13 g. of 8-methylquinoline at 130° within 20 min. After the addition, the heating and stirring were continued for 3 hr. The reaction mixture was admixed with water, then refluxed on a water-bath for 3 hr., and extracted with benzene after cooling. The extract was treated as usual and distilled to give a viscous syrup, which was extracted several times with hexane. The hexane extract was evaporated to a suitable amount until crystals began to separate. After cooling, collection by filtration gave 4.81 g. (33.5%) of colorless needles (II), m.p. 89～89.5° (lit.,[2] m.p. 84～85°). *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37. Found: C, 75.42; H, 6.14. IR ν_{max}^{KBr} cm^{-1}: 3280, 3400 (NH). NMR (τ) (in $CDCl_3$): 7.41 (3H, singlet, $-C\underline{H}_3$), 2.27, 3.44 (1H, 1H, doublet, $-C_3\underline{H}=C_4\underline{H}-$, J=8.5 c.p.s.), 2.56～3.16 (3H, multiplet, $C_6\underline{H}_3$).

The above filtrate in case of recrystallization of II was chromatographed on alumina. Removal of the EtOAc eluate and recrystallization from ether gave 155.7 mg. (1.04%) of 3,4-dihydro-8-methylcarbostyril (IV) as colorless needles, m.p. 131～132°. *Anal.* Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.56; H, 7.17; N, 8.69. IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1680 (amide C=O). NMR (τ) (in $CDCl_3$): 7.81 (3H, singlet, $-C\underline{H}_3$), 7.16～7.50 (4H, multiplet, $-C\underline{H}_2C\underline{H}_2-$), 3.01～3.17 (3H, broad singlet, $-C_6\underline{H}_4$).

This compound (IV) was identical with authentic sample described later.

N-(*o*-Tolyl)-β-chloropropionamide (V)——A solution of 7.2 g. of 3-chloropropionyl chloride in 15 ml. of acetone was added drop by drop to a refluxed solution of 12.1 g. of *o*-toluidine in acetone, and the mixture was refluxed on a water-bath for 1 hr. The reaction mixture was poured into water containing HCl, and the crystals were precipitated. After collection by filtration, recrystallization from dilute EtOH afforded 9.2 g. (82.14%) of V as colorless needles, m.p. 79～80° (lit.,[4] m.p. 78°). Thin-layer chromatography on silica-gel using $CHCl_3$–MeOH–hexane (1:0.5:1) as solvent showed one spot.

Friedel-Crafts Reaction of V——To 1.7 g. of the preceding amide (V) heated at 100° was added in small portions with stirring 3.5 g. of $AlCl_3$ within 5 min., and the mixture was stirred and heated at 100° for 1 hr. After cooling, the reaction mixture was decomposed with water and extracted with ether. Removal of the solvent gave a solid, which was recrystallized from ether to give 207.6 mg. (14.9%) of 3,4-dihydro-5-methylcarbostyril (VI) as colorless needles, m.p. 162～163°. *Anal.* Calcd. for $C_{10}H_{11}ON$: C, 74.51; H, 6.88; N, 8.59. Found: C, 74.53; H, 6.98; N, 8.92. IR ν_{max}^{KBr} cm^{-1}: 3150 (NH), 1675 (amide C=O). NMR (τ) (in $CDCl_3$): 7.75 (3H, singlet, $-C\underline{H}_3$), 7.17～7.36 (4H, multiplet, $-C\underline{H}_2C\underline{H}_2-$), 3.32 (1H, two doublets, J_{AC}=2.0 c.p.s., J_{AB}=7.5 c.p.s., C_8–H), 3.13 (1H, two doublets, J_{CA}=2.0 c.p.s., J_{CB}=6.5 c.p.s., C_6–$\underline{H}$), 2.99 (1H, triplet, J_{BA}=7.5 c.p.s., J_{BC}=6.5 c.p.s., C_7–$\underline{H}$).

Evaporation of the above filtrate in case of recrystallization gave the crystals, which were recrystallized from MeOH to give 170.8 mg. (12.4%) of IV as colorless needles, m.p. 131～132°. The IR spectrum of this substance was superimposable on that of the sample obtained by Chichibabin reaction, and both specimens showed no depression on admixed melting point test.

5-Methylcarbostyril (IX)——A mixture of 2 g. of 5-methylquinoline,[5] 1.26 ml. of 29% H_2O_2, and 4.2 ml. of AcOH was heated at 60～70° for 3 hr., and an additional 1.12 ml. of 29% H_2O_2 was then added and heated at 65～70° for further 6 hr. Most bulk of the solvent was evaporated *in vacuo*, made basic with hot saturated Na_2CO_3 aq. solution, and extracted with $CHCl_3$. The extract was distilled until an inorganic salt began to precipitate, and after removal of the salt by filtration, the resultant filtrate was evaporated to give the solid, which was washed with ether, dried, and used in the following reaction without purification.

To a solution of the preceding solid in 6.6 ml. of $CHCl_3$ was added in small portions with shaking 1.3 g. of tosyl chloride, and the mixture was refluxed on a water-bath for 10 min. After cooling the reaction mixture was made basic with 10% Na_2CO_3 aq. solution and extracted with $CHCl_3$. Evaporation of the solvent and recrystallization from MeOH afforded 403.1 mg. (18.1%) of 5-methylcarbostyril (IX), m.p. 228.5～229.5°. *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.43; H, 5.69; N, 8.79. Found: C, 75.64; H, 5.98; N, 8.64. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1680 (amide C=O).

*4 All melting points were not corrected.

3,4-Dihydro-5-methylcarbostyril (VI)——The preceding carbostyril (Ⅸ) (100 mg.) in 20 ml. of EtOH was hydrogenated at atmospheric pressure in the presence of 90 mg. of 40% Pd-C, and the mixture was shaken at 25° for 48 hr., a calculated amount of H_2 being absorbed. Filtration and removal of the solvent gave 99 mg. (98%) of Ⅵ. Recrystallization from ether gave colorless needles, m.p. 162~163°, which were identical with the sample obtained by Friedel-Crafts reaction by mixed melting point test and IR spectrum.

3,4-Dihydro-8-methylcarbostyril (IV)——A mixture of 43 mg. of 8-methylcarbostyril (Ⅺ),[2] 10 ml. of EtOH, and 40 mg. of 40% Pd-C was hydrogenated at room temperature and atmospheric pressure, and a calcurated amount of H_2 was thus almostly absorbed for 40 hr. Filtration and removal of the solvent gave a solid, whose recrystallization from ether afforded 40 mg. (91%) of Ⅳ as colorless needles, m.p. 131~132°. This compound was identical with the sample obtained by Chichibabin and Friedel-Crafts reaction on admixed point test and IR comparison.

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