[Chem. Pharm. Bull. 15(5) 704~707 (1967)] UDC 547.836.07

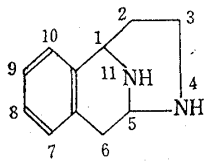
Azabenzomorphan and Related Compounds. X.[*1] A Synthesis of 1-Methyl-3-aminoisoquinoline. (Studies on the Syntheses of Heterocyclic Compounds. CLXXX.[*2])

Tetsuji Kametani,[*3] Kazuo Kigasawa,[*3] and Mineharu Hiiragi[*4]:

*(Pharmaceutical Institute, Tohoku University School of Medicine,[*3] and Research Laboratories, Grelan Pharmaceutical Co., Ltd.[*4])*

(Received February 15, 1966)

In the previous papers,[1,2] reductive cyclization of 1-methyl-4-(2-aminoethyl)-3,4-dihydrocarbostyril and 4-(2-methylaminoethyl)-derivative with metallic sodium in ethanol gave, respectively, the expected azabenzomorphan derivatives, 1-methyl and 1,3-dimethyl-2,6-methano-1,2,3,4,5,6-hexahydrobenzo[*d*][1,3]diazocine. In this paper will be described some results of synthetical experiments of 1,5-imino-1,2,3,4,5,6-hexahydrobenzo[*d*][4]azocine (I) which led eventually to reveal that a novel synthetic procedure of 1-methyl-3-aminoisoquinoline was established.



I

Chart 1.

Since only a few synthetic routes of 3-aminoisoquinoline derivatives[3~5] have been reported, methods for synthesis of Ⅺ seem to be very interesting.

Oxidation of indene with potassium bichromate and sulfuric acid gave homophthalic acid,[6] whose ammonium salt was heated to afford 1,3-dihydroxyisoquinoline (Ⅱ).[7] Halogenation of Ⅱ with phosphoryl chloride gave 1,3-dichloroisoquinoline (Ⅲ)[8] as a starting material.

Condensation of Ⅲ with diethyl malonate in the presence of sodium hydride in xylene gave diethyl 1-(3-chloroisoquinolyl)malonate (Ⅳ), b.$p_{1.5}$ 160°, which solidified on being allowed to stand in a refrigerator. Hydrolysis of Ⅳ with an aqueous potassium hydroxide solution, followed by acidification with dilute hydrochloric acid solution, afforded 2-(3-chloroisoquinolyl)acetic acid (Ⅴ), m.p. 90° (decomp.). In this case decarboxylation was recognized at 0~5° in acidic media. When the above alkaline solution was acidified at more than 30°, successive decarboxylation occurred to give 1-methyl-3-chloroisoquinoline (Ⅵ), m.p. 61°. Catalytic hydrogenation of Ⅵ in the presence of 30% palladium-charcoal gave 1-methylisoquinoline (Ⅶ)[9,10] which was characterized as its picrate[11] and sulfate. The picrate, m.p. 233~234°, was identical with an authentic sample.[*5,9,11] Furthermore, the infrared spectrum of Ⅶ was identical with that of an

*1 Part Ⅸ: This Bulletin, **14**, 566 (1966).
*2 Part CLXXIX: This Bulletin, **15**, 613 (1967).
*3 No. 85, Kita-4-bancho, Sendai (亀谷哲治, 気賀沢和雄).
*4 Shinmachi-3-chome, Setagaya-ku, Tokyo (柊木峯治).
*5 According to Galat,[9] the picrate of Ⅶ showed m.p. 208~210°, but further recrystallization of the picrate obtained by Galat's method gave crystals which melted at 232~233°. Therefore, the lower melting point reported by Galat seems to be due to its impurity.

1) T. Kametani, K. Kigasawa, M. Hiiragi: Yakugaku Zasshi, **85**, 871 (1965).
2) *Idem*: This Bulletin, **13**, 1220 (1965).
3) T. Kametani: Yakugaku Zasshi, **71**, 329 (1951).
4) C.E. Teague, A. Roe: J. Am. Chem. Soc., **73**, 688 (1951).
5) F. Johnson, W.A. Nasutavicus: J. Org. Chem., **27**, 3953 (1962).
6) O. Grumitt, R. Egan, A. Buck: Org. Synthesis, Coll. Vol., **III**, 449 (1955).
7) B.R. Hariman, R.S. Shelton, M.G. Van Campen, M.R. Warren: J. Am. Chem. Soc., **67**, 1481 (1945).
8) S. Gabriel: Chem. Ber., **19**, 2354 (1886).
9) A. Galat: J. Am. Chem. Soc., **75**, 1738 (1953).
10) H.R. Snyder, F.X. Werber: *Ibid.*, **72**, 2952 (1950).
11) E. Schlittler, J. Müller: Helv. Chim. Acta, **31**, 914 (1948).

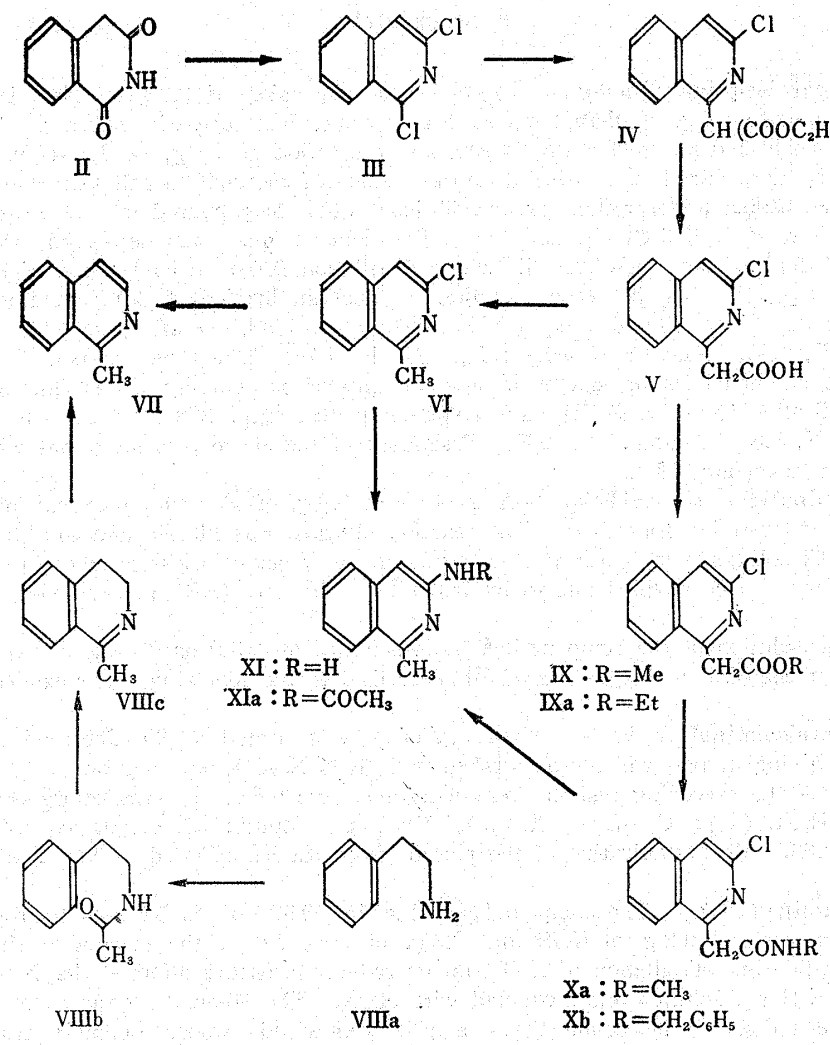


Chart 2.

authentic sample which was obtained from phenethylamine (Ⅷa) *via* Ⅷb and Ⅷc by the alternative synthetic methods.[9,10] These facts reveal that the chloro-atom at 1-position of Ⅲ reacted with diethyl malonate.

Secondly, esterification of Ⅴ with dry hydrogen chloride gas in ethanol did not give our expected ester (Ⅸa), but the above compound (Ⅵ) which formed by decarboxylation. Accordingly, methylation of potasssium salt of Ⅴ with dimethyl sulfate yielded methyl 2-(3-chloroisoquinolyl)acetate (Ⅸ), which was converted into N-methyl-2-(3-chloroisoquinolyl)acetamide (Xa) by heating with methylamine at 120° for 4 hr. in a sealed tube. Reflux of Ⅸ with an excess of benzylamine also gave N-benzyl-2-(3-chloroisoquinolyl)acetamide (Xb).

Finally, amination of Xa and Xb with 28% ammonium hydroxide solution in the presence of copper catalyst in an autoclave gave an unexpected 1-methyl-3-aminoisoquinoline (Ⅺ), which was also characterized as its picrate and acetyl derivative (Ⅺa). In the infrared spectrum of Ⅺ the deformation vibration of amino radical was observed strongly at 1642 cm^{-1} and its stretching vibrations were also observed at 3440 and 3340 cm^{-1}. Furthermore, amination of Ⅵ under the same conditions as above also gave the objective compound (Ⅺ) in 25% yield, which showed no depression of melting point on admixture with the substance obtained from Xa and Xb as above.

Nuclear magnetic resonance spectrum of the compound (Ⅺ) also shows the signal of the protons of methyl group at 1-position of isoquinoline nucleus at 7.20τ. This fact shows the presence of methyl group due to the decarboxylation of Xa and Xb.

Experimental

Diethyl 1-(3-Chloroisoquinolyl)malonate (IV)——To a suspension of 2.3 g. of NaH in 100 ml. of dry xylene was added dropwise 6.4 g. of diethyl malonate at room temperature with stirring. After the addition, the above mixture was heated at 70~80° for 0.5 hr., and a solution of 7.9 g. of 1,3-dichloroisoquinoline (III) in xylene was drop by drop added at 90~100° to a suspension of the sodium salt as above in xylene. The resultant mixture was heated under reflux for an additional 1 hr., then poured into an excess of H_2O after cooling, and acidified with 10% HCl aq. solution. The solvent layer was separated, washed with H_2O, dried on K_2CO_3, and distilled off to give an oil, whose distillation *in vacuo* gave 5.8 g. of the compound (IV) of a pale yellow oil, b.$p_{1.8}$ 160° as the second fraction.*6 Recrystallization of (IV) from ether gave colorless needles, m.p. 65~66°. IR cm^{-1} (liquid): $\nu_{C=O}$ 1740, 1760; $\nu_{C=N}$ 1632. *Anal.* Calcd. for $C_{16}H_{16}O_4NCl$ (IV): C, 59.72; H, 4.98; N, 4.35. Found: C, 59.91; H, 5.29; N, 4.28. When this compound was treated with conc. KOH aq. solution, its potassium salt of IV was precipitated as colorless plates due to its insolubility in water. Recrystallization from iso-PrOH gave colorless plates, m.p. 278~280° (decomp.). *Anal.* Calcd. for $C_{16}H_{15}O_4NClK$: N, 3.89. Found: N, 3.65. Treatment of the above potassium salt with 10% HCl aq. solution recovered the compound (IV).

2-(3-Chloroisoquinolyl)acetic Acid (V)——A mixture of 5.0 g. of IV and an excess of 20% aq. KOH solution was heated under reflux for 1.5 hr. The reaction mixture was filtered and the filtrate was neutralized with 10% aq. HCl solution very carefully, giving 2.1 g. of V as colorless needles, m.p. 90° (decomp.), which were very difficult to be purified due to its instability. IR cm^{-1} (KBr): ν_{OH} 3500; $\nu_{C=O}$ 1740; $\nu_{C=N}$ 1632.

When an alkaline solution of the compound (IV) was acidified at >30° or IV was allowed to stand in the air for a long time, it changed to the compound (VI) described in the following, accompanied by decarboxylation.

1-Methyl-3-chloroisoquinoline (VI)——When 1 g. of V was heated at 90~100°, an evolution of CO_2 gas was recognized, giving a solid which was washed with 10% Na_2CO_3 aq. solution.

Recrystallization of the preceding residue from *n*-hexane gave 0.5 g. of VI as colorless plates, m.p. 61°. *Anal.* Calcd. for $C_{10}H_8NCl$ (VI): C, 67.61; H, 4.51; N, 7.89. Found: C, 67.60; H, 4.72; N, 7.71. IR cm^{-1} (KBr): $\nu_{C=N}$ 1622. Recrystallization of the picrate from EtOH afforded yellow needles, m.p. 131~135°.

1-Methylisoquinoline (VII)——The compound (VI) (1 g.) in 50 ml. of EtOH was hydrogenated at room temperature in the presence of 0.2 g. of KOH and 0.3 g. of 30% Pd-C, the calculated H_2 being absorbed within 30 min. Filtration and distillation of EtOH under reduced pressure afforded the residue, which was basified with 10% NaOH aq. solution and extracted with ether. The ethereal extract was dried on K_2CO_3 and distilled to give 0.6 g. of the crude (VII) as a pale yellow oil, whose Beilstein test was negative. Recrystallization of the picrate from EtOH gave yellow needles, m.p. 234~235°. Recrystallization of H_2SO_4 salt of VII from EtOH afforded colorless prisms, m.p. 252~253°. Both specimens were, respectively, identical with an authentic sample[9,10] by mixed melting point test and infrared spectrum.

Methyl 2-(3-Chloroisoquinolyl)acetate (IX)——To a solution of 2.2 g. of V in 15 ml. of 5% KOH aq. solution was added 1.5 g of Me_2SO_4, and the above mixture was stirred for 15 min., crystals being gradually separated. After being allowed to stand at room temperature for an additional 30 min., the resultant reaction mixture was basified with 10% K_2CO_3 aq. solution and the crystals precipitated were collected by filtration. Recrystallization from iso-PrOH gave 1.5 g. of IX as colorless needles, m.p. 116~117.° *Anal.* Calcd. for $C_{12}H_{12}O_2NCl$ (IX): C, 61.15; H, 4.25; N, 5.94. Found: C, 61.22; H, 4.29; N, 5.92. IR cm^{-1} (KBr): $\nu_{C=O}$ 1725; $\nu_{C=N}$ 1622.

N-Methyl-2-(3-chloroisoquinolyl)acetamide (Xa)——A mixture of 2.35 g. of IX, 3.37 g. of $MeNH_2 \cdot HCl$, 2.8 g. of KOH and 70 ml. of EtOH was heated at 120° for 4 hr. in a sealed tube. After the reaction 1.8 g. of Xa was separated from the reaction mixture as colorless needles. Filtration and recrystallization from EtOH gave 1.8 g. of Xa as colorless needles,, m.p. 191~192°. *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl$ (Xa): N, 11.91. Found: N, 11.90. IR cm^{-1} (KBr): ν_{NH} 3200; $\nu_{C=O}$ 1641.

N-Benzyl-2-(3-chloroisoquinolyl)acetamide (Xb)——A mixture of 2.35 g. of IX and 7 g. of benzylamine was heated at 180~200° for 8 hr. The reaction mixture was acidified with 10% aq. HCl solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried on Na_2SO_4 and distilled to give the crude compound (Xb), whose recrystallization from EtOH gave 2.0 g. of Xb as colorless needles, m.p. 169~170°. *Anal.* Calcd. for $C_{18}H_{15}ON_2Cl$ (Xb): C, 69.57; H, 4.83; N, 9.02. Found: C, 69.65; H, 5.03; N, 8.90. IR cm^{-1} (KBr): ν_{NH} 3350; $\nu_{C=O}$ 1642; $\nu_{C=O}$ 1630 (shoulder).

1-Methyl-3-aminoisoquinoline (XI)——a) A mixture of 0.7 g. of Xa, 0.1 g. of CuO, 0.1 g. of $CuSO_4 \cdot 5H_2O$, and 50 ml. of 28% NH_4OH was heated at 200° for 8 hr. in an autoclave with stirring. After the reaction mixture had beed filtered, the resultant filtrate was extracted with $CHCl_3$. The solvent layer was separated and extracted with 10% aq. HCl solution. The acidic extract was basified with 10% aq. KOH

*6 As the first fraction 3 g. of the starting material (III) was recovered as an oil, b.p_{18} 120°.

solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried on K_2CO_3 and distilled *in vacuo* to give the crude compound (XI), whose recrystallization from EtOH gave 100 mg. of XI as colorless plates, m.p. 122~124°. Beilstein test of this compound was negative. IR cm^{-1} (KBr): ν_{NH} 3440, 3340; $\nu_{C=N}$ 1622; δ_{NH} 1642. NMR (τ) (in $CDCl_3$): 7.20 (3H, singlet, C_1-Me); 5.50~6.00 (2H, broad, NH_2); 3.47 (1H, singlet, C_4-H). *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.38; N, 17.71. Found: C, 75.72; H, 6.42; N, 17.96. Recrystallization of the picrate from EtOH gave yellow needles, m.p. 232~233°(decomp.). *Anal.* Calcd. for $C_{10}H_{10}N_2 \cdot C_6H_3O_7N_3$ (XI): C, 49.62; H, 3.38; N, 18.08. Found: C, 49.75; H, 3.64; N, 17.65.

b) Ammonolysis of 1.0 g. of Xb under the same conditions as the method a) gave 120 mg. of XI. Furthermore, ammonolysis of VI under the same conditions as the method a) also afforded 0.4 g. (25%) of XI. Both specimens were identical with the sample obtained by the procedure a) by mixed melting point test and infrared spectrum.

N-[3-(1-methylisoquinolyl)]acetamide (XIa)——A mixture of 100 mg. of XI with an excess of Ac_2O was heated on a water-bath for 1 hr. After the excess of Ac_2O was removed by distillation *in vacuo*, the residue was basified with 10% aq. NaOH solution and extracted with $CHCl_3$. The extract was washed with H_2O, dried on Na_2SO_4 and distilled. Recrystallization of the resultant residue from *iso*-PrOH gave 70 mg. of XIa as colorless plates, m.p. 202~203°. *Anal.* Calcd. for $C_{12}H_{12}ON_2$ (XIa): C, 71.84; H, 6.04; N, 13.99. Found: C, 72.02; H, 6.24; N, 13.35. IR cm^{-1} (KBr): ν_{NH} 3220; $\nu_{C=O}$ 1658; $\nu_{C=N}$ 1625 (shoulder).

We thank President A. Yanagisawa, Mr. O. Takagi, and Grelan Pharmaceutical Co., Ltd., for their grateful assistance. We also thank Mrs. F. Seto, Miss N. Nanjo, and Miss R. Kobayashi for microanalyses.

[Chem. Pharm. Bull. 15(5) 707~710 (1967)]

UDC 547.964.07

Kazumi Ogata and Satoru Ishii: Syntheses of Ophthalmic Acid and its Analogues.*1

(*Research Laboratory, Senju Pharmaceutical Co., Ltd.**2)

(Received March 18, 1966)

In 1956, Waley[1~3] isolated an acidic tripeptide, γ-L-glutamyl-L-α-amino-*n*-butyrylglycine, named ophthalmic acid, and an analogous tripeptide, γ-L-glutamyl-L-alanylglycine, named norophthalmic acid from calf lens. Afterward, he synthesized[4] ophthalmic acid by the reaction of N-benzyloxycarbonyl-L-γ-glutamyl azide with L-α-amino-*n*-butyrylglycine. Enzymatic synthesis of ophthalmic acid was reported by the same authors.[5]

At present, several syntheses of ophthalmic, norophthalmic acids and their analogue are reported. Kermack, *et al.*[6] synthesized DL-norophthalmic acid (γ-DL-glutamyl-DL-alanylglycine) from phthalylglutamic anhydride and alanylglycine. He obtained the optically active acid by the treatment of glutathione with Raney Nickel in poor yield. By using α-*tert* butyl N-benzyloxycarbonylglutamate and (α-amino-*n*-butyryl)glycine *tert* butyl ester, Taschner, *et al.*[7] synthesized ophthalmic acid. Shchukina, *et al.*[8]

---

*1 Presented at the 21th Meeting of the Pharmaceutical Society of Japan, at Tokushima, October, 1965 and the 4th Peptide Symposium, at Institute for Protein Research, University of Osaka, December, 1965.

*2 Iwazono-cho 416, Ashiya, Hyogo Pref. (緒方一美, 石井 覚).

1) S.G. Waley: Biochem. J., **64**, 715 (1956).
2) *Idem*: *Ibid.*, **67**, 172 (1957).
3) *Idem*: Proc. Chem. Soc., **1957**, 25.
4) S.G. Waley: Biochem. J., **68**, 189 (1958).
5) E.E. Cliffe, S.G. Waley: *Ibid.*, **79**, 669 (1961).
6) W.O. Kermack, N.A. Matheson: *Ibid.*, **65**, 45 (1957).
7) E. Taschner, T. Sokolowska, J.F. Biernat: Collection Czch. Chem. Communs., **27**, 2237 (1962).
8) L.A. Shchukina, A.L. Jouse: "Peptides," Ed. by G.T. Young, p. 189 (1963), Pergamon Press, London.