Tetsuji Kametani,* Kazuo Kigasawa,* and Mineharu Hiiragi†:
Azabenzomorphan and Related Compounds. X.* A Synthesis
of 1-Methyl-3-aminoisoquinoline. (Studies on the
Syntheses of Heterocyclic Compounds. CLXXX.*3)

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In the previous papers,1,5 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-hexahydro-
benzo[d][4]azocine (I) which led eventually to reveal that a novel synthetic procedure
of 1-methyl-3-aminoisoquinoline was established.

Since only a few synthetic routes of 3-aminoisoquinoline deriv-
atives2,5 have been reported, methods for synthesis of II seem
to be very interesting.

Oxidation of indene with potassium bichromate and sulfuric
acid gave homphalitic acid,6 whose ammonium salt was heated to
afford 1,3-dihydroxyisoquinoline (II).5 Halogenation of II with phos-
phoryl chloride gave 1,3-dichloroisoquinoline (III)6 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.,4 160°, 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-chloroisoquinoly)acetic acid (V), m.p. 90° (decomp.). In this case decarboxy-
lation 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-chloro-
isoquinoline (VI), m.p. 61°. Catalytic hydrogenation of VI in the presence of 30% palladium-charcoal gave 1-methy1isoquinoline (VII)6,16 which was characterized as its
picrate13 and sulfate. The picrate, m.p. 233~234°, was identical with an authentic sample,6,8,11) Furthermore, the infrared spectrum of VII was identical with that of an

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* According to Galat,10 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 222~232°. Therefore, the lower
melting point reported by Galat seems to be due to its impurity.

8) S. Gabriel : Chem. Ber., 19, 2354 (1886).
authentic sample which was obtained from phenethylamine (Ⅲa) via Ⅲb and Ⅲc by the alternative synthetic methods. 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 (Ⅵa), but the above compound (Ⅵ) which formed by decarboxylation. Accordingly, methylation of potassium salt of Ⅴ with dimethyl sulfate yielded methyl 2-(3-chloroisouquinolinyl)acetate (Ⅶ), which was converted into N-methyl-2-(3-chloroisouquinolinyl)acetamide (Ⅷa) by heating with methylamine at 120°C for 4 hr. in a sealed tube. Reflux of Ⅷ with an excess of benzylamine also gave N-benzyl-2-(3-chloroisouquinolinyl)acetamide (Ⅷb).

Finally, amination of Ⅷa and Ⅷb with 28% ammonium hydroxide solution in the presence of copper catalyst in an autoclave gave an unexpected 1-methyl-3-aminoisouquinoline (Ⅸa), which was also characterized as its picrate and acetyl derivative (Ⅸb). In the infrared spectrum of Ⅸ 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 Ⅷ under the same conditions as above also gave the objective compound (Ⅹ) in 25% yield, which showed no depression of melting point on admixture with the substance obtained from Ⅷa and Ⅷb as above.

Nuclear magnetic resonance spectrum of the compound (Ⅹ) also shows the signal of the protons of methyl group at 1-position of isoquinoline nucleus at 7.20r. This fact shows the presence of methyl group due to the decarboxylation of Ⅷa and Ⅷb.
Experimental

Diethyl 1-(3-Chloroisouquinolyl)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°C for 0.5 hr., and a solution of 7.9 g. of 1,3-dichloroisouquinoline (II) in xylene was drop by drop added at 90–100°C 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 H₂O after cooling, and acidified with 10% HCl aq. solution. The solvent layer was separated, washed with H₂O, dried on K₂CO₃, and distilled off to give an oil, whose distillation in vacuo gave 5.8 g. of the compound (V) of a pale yellow oil, b.p.18 163°C as the second fraction. Recrystallization of (V) from ether gave colorless needles, m.p. 65–66°C. IR cm⁻¹ (liquid): ν_C=O 1740, 1700; ν_C=N 1632. Anal. Calcd. for C₁₉H₁₉O₂NCl (V): 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 (V) was precipitated as colorless plates due to its insolubility in water. Recrystallization from iso-PrOH gave colorless plates, m.p. 278–280°C (decomp.). Anal. Calcd. for C₁₉H₁₅O₂NClK: N, 3.69. Found: N, 3.65. Treatment of the above potassium salt with 10% HCl aq. solution afforded the compound (VII).

2-(3-Chloroisouquinoly)acetic Acid (V)—A mixture of 5.0 g. of (V) 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°C (decomp.), which were very difficult to be purified due to its instability. IR cm⁻¹ (KBr): ν_H₂O 3500; ν_C=O 1740; ν_C=N 1632.

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

1-Methyl-3-chloroisouquinoline (VI)—When 1 g. of V was heated at 90–100°C, an evolution of CO₂ gas was recognized, giving a solid which was washed with 10% Na₂CO₃ aq. solution. Recrystallization of the preceding residue from n-hexane gave 0.5 g. of VI as colorless plates, m.p. 61°C. Anal. Calcd. for C₁₉H₁₄N₂ (VI): C, 76.61; H, 4.51; N, 7.89. Found: C, 76.50; H, 4.12; N, 7.71. IR cm⁻¹ (KBr): ν_C=N 1622. Recrystallization of the picrate from EtOH afforded yellow needles, m.p. 131–135°C.

Methyl-2-(3-Chloroisouquinoly)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 Me₂SO₄, 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% K₂CO₃ 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°C. Anal. Calcd. for C₁₉H₁₇O₂NCl (IX): C, 61.15; H, 4.25; N, 5.94. Found: C, 61.22; H, 4.29; N, 5.92. IR cm⁻¹ (KBr): ν_C=N 1622; ν_C=O 1755.

N-Methyl-2-(3-Chloroisouquinolyl)acetamide (Xa)—A mixture of 2.35 g. of IX, 3.37 g. of MeNH₂.HCl, 2.8 g. of KOH and 70 ml. of EtOH was heated at 120°C 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. 198–199°C. Anal. Calcd. for C₁₂H₁₇O₄NCl (Xa): N, 11.91. Found: N, 11.90. IR cm⁻¹ (KBr): ν_NH 3200; ν_C=O 1641.

N-Benzyl-2-(3-Chloroisouquinolyl)acetamide (Xb)—A mixture of 2.35 g. of IX and 7 g. of benzylamine was heated at 180–200°C for 8 hr. The reaction mixture was acidified with 10% aq. HCl solution and extracted with CHCl₃. The extract was washed with H₂O, dried on Na₂SO₄ 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°C. Anal. Calcd. for C₁₉H₁₄O₂NCl (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 3250; ν_C=O 1642; ν_C=Cl 1630 (shoul.)

1-Methyl-3-aminoisouquinoline (XI)—a A mixture of 0.7 g. of Xa, 0.1 g. of CuO, 0.1 g. of CuSO₄.5H₂O, and 50 ml. of 28% NH₄OH was heated at 200°C for 8 hr. in an autoclave with stirring. After the reaction mixture had been filtered, the resultant filtrate was extracted with CHCl₃. The solvent layer was separated and extracted with 10% aq. HCl solution. The acidic extract was basified with 10% aq. KOH

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As the first fraction 3 g. of the starting material (II) was recovered as an oil, b.p. 180°C.
solution and extracted with CHCl₃. The extract was washed with H₂O, dried on K₂CO₃ and distilled in vacuo to give the crude compound (X), whose recrystallization from EtOH gave 100 mg. of X as colorless plates, m.p. 122~124°C. Beilstein test of this compound was negative. IR cm⁻¹ (KBr): νₕ₂: 3440, 3340; νₒ₋₅ 1622; δₕ₂ 1642. NMR (δ) (in CDCl₃): 7.20 (3H, singlet, C₃-Me); 5.50~6.00 (2H, broad, NH₂); 3.47 (1H, singlet, C₆-H). Anal. Calcd. for C₁₅H₁₉N₂O₂: C, 75.92; H, 6.38; N, 17.71. Found: C, 75.72; H, 6.42; N, 17.96. Recrystallization of the picate from EtOH gave yellow needles, m.p. 232~233°C (decomp.). Anal. Calcd. for C₁₅H₁₉N₂O₂·C₂H₅OH (X): 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 X. Furthermore, ammonolysis of X under the same conditions as the method a) also afforded 0.4 g. (25%) of X. Both specimens were identical with the sample obtained by the procedure a) by mixed melting point test and infrared spectrum.

N-(3-[(1-methylisoquinolyl)acetamido (XIA)—A mixture of 100 mg. of X with an excess of Ac₂O was heated on a water-bath for 1 hr. After the excess of Ac₂O was removed by distillation in vacuo, the residue was basified with 10% aq. NaOH solution and extracted with CHCl₃. The extract was washed with H₂O, dried on Na₂SO₄ and distilled. Recrystallization of the resultant residue from iso-ProOH gave 70 mg. of XIA as colorless plates, m.p. 202~203°C. Anal. Calcd. for C₁₅H₁₅O₄ (XIA): C, 71.84; H, 6.04; N, 13.99. Found: C, 72.02; H, 6.24; N, 13.53. IR cm⁻¹ (KBr): νₕ₂ 3220; νₒ₋₅ 168; νₒ₋₅ 1625 (shoulder).

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

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In 1956, Waley,aa isolated an acidic tripeptide, γ-γ-glutamyl-γ-α-α-aminono-butyrylglycine, named ophthalmic acid, and an analogous tripeptide, γ-γ-glutamyl-γ-α-aminono-butyrylglycine, named norophthalmic acid from calf lens. Afterward, he synthesizedo ophthalmic acid by the reaction of N-benzoyloxycarbonyl γ-γ-glutamyl azide with γ-γ-aminono-butyrylglycine. Enzymatic synthesis of ophthalmic acid was reported by the same authors.b)

At present, several syntheses of ophthalmic, norophthalmic acids and their analogue are reported. Kermack, et al.o synthesized DL-norophthalmic acid (D-L-glutamyl-DL-α-aminono-butyrylglycine) from phthalyglutamic anhydride and alanylglycine. He obtained the optically active form of glutathione with Raney Nickel in poor yield. By using α-tert butyl N-benzoyloxycarbonylglutamate and (α-aminono-butyrylglycine tert butyl ester, Taschner, et al.o) synthesized ophthalmic acid. Shchukina, et al.o

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