Synthesis of Ibotenic Acid and 3-Deoxyibotenic Acid

In 1964 Takemoto, *et al.*^{1,2)} isolated ibotenic acid as a flycidal constituent from *Amanita strobiliformis* (PAUL) QUEL. and assumed its chemical structure as α -amino-3-hydroxy-5-isoxazoleacetic acid monohydrate (I). Besides the flycidal property, ibotenic acid has been known to have a very good taste.^{2,3)}

Recently Gagneux, *et al.*⁴⁾ reported the synthesis of this compound, which prompted the authors to present this communication on the synthesis of I and 3-deoxyibotenic acid (II).

Diethyl (3-chloropropionyl)malonate⁵⁾ (III) was allowed to react with sodium nitrite at 5~10° in the mixed solvent of dimethylsulfoxide and dimethylformamide to afford diethyl (3-nitropropionyl)malonate (IV), b.p._{0.25} 145~146° (NMR*¹ τ : 5.26 (3H unresolved multiplet), 6.68 (2H triplet) ($-\text{CH}_2\text{CH}_2\text{CO}-$), 5.67 (4H quartet) ($-\text{CH}_2\text{CH}_3$), 8.67 (6H triplet) ($-\text{CH}_2\text{CH}_3$), *Anal.* Calcd. for $\text{C}_{10}\text{H}_{15}\text{O}_7\text{N}$: C, 45.97; H, 5.79; N, 5.36. Found: C, 45.93; H, 5.87; N, 5.61. Cu-salt, m.p. 158.5° (decomp.), *Anal.* Calcd. for $(\text{C}_{10}\text{H}_{14}\text{O}_7\text{N})_2\text{Cu}$: C, 41.13; H, 4.83; N, 4.80; Cu, 10.92. Found: C, 41.10; H, 4.93; N, 4.67; Cu, 10.61) in 32% yield. IV was also prepared by the reaction of 3-nitropropionyl chloride⁶⁾ (V) with diethyl malonate.

After heating of IV at 70° for 4 hours in 30~32% hydrogen bromide in acetic acid containing a small amount of phosphorus tribromide, an oily substance was obtained by the distillation under reduced pressure from the reaction product. Although this oil was a mixture of several compounds and each component could not be isolated by fractional distillation, the presence of ethyl 3-bromo-5-isoxazoleacetate (VI) and diethyl 5-isoxazole malonate (VII) in the reaction mixture was assumed from the nuclear magnetic resonance spectrum. 3-Bromo-5-isoxazoleacetic acid (VIII) (yield: 10% from IV), m.p. 80~82° (NMR τ : -0.41 (1H, singlet) ($-\text{COOH}$), 3.53 (1H, singlet) ($=\text{CH}-$), 6.05 (2H, singlet) ($-\text{CH}_2\text{COOH}$), *Anal.* Calcd. for $\text{C}_5\text{H}_4\text{O}_3\text{NBr}$: C, 29.10; H, 1.96; N, 6.80. Found: C, 29.33; H, 1.95; N, 6.60) was obtained as potassium salt from the mixture by the hydrolysis with cold potassium hydroxide in ethanol. The fraction which was refractory toward the hydrolysis was separated, and treated with a dilute hydrogen chloride to yield 5-isoxazoleacetic acid (IX) (yield: 16.5% from IV), m.p. 104~104.5° (UV $\lambda_{\text{max}}^{\text{H}_2\text{O}}$ $m\mu$ (ϵ): 218 (6350). NMR τ (in D_2O): 1.61 (1H doublet, $J=2$ c.p.s.) ($-\text{N}=\text{CH}-$), 3.60 (1H doublet, $J=2$ c.p.s.) ($=\text{CH}-$), 6.04 (2H singlet) ($-\text{CH}_2\text{COOH}$). *Anal.* Calcd. for $\text{C}_5\text{H}_4\text{O}_3\text{N}$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.13; H, 3.97; N, 10.79).

The potassium salt of VIII was neutralized with hydrogen chloride to a free acid and the latter was converted to 3-methoxy-5-isoxazoleacetic acid (X) by refluxing with

*¹ NMR in CDCl_3 were obtained on a Varian A-60 instrument.

1) T. Takemoto, T. Nakajima: *J. Pharm. Soc. Japan*, **84**, 1186 (1964).

2) *Idem*: *Ibid.*, **84**, 1232 (1964).

3) T. Takemoto, *et al.*: *J. Japan Soc. Food & Nutrition*, **18**, 172 (1965).

4) A. R. Gagneux, *et al.*: *Tetrahedron Letters*, **1965**, 2081.

5) L. J. Haynes, A. H. Stanners: *J. Chem. Soc.*, **1956**, 4661.

6) G. Barger, F. Tutin: *Biochem. J.*, **12**, 405 (1918).

potassium hydroxide in 90% aqueous methanol for 8 hours. X was treated with hydrogen chloride in methanol to afford the methyl ester (XI) (yield: 27% from VIII), b.p._{0.4~0.55} 79~83° (NMR τ : 4.14 (1H singlet) (=CH-), 6.08 (3H singlet) (-OCH₃), 6.28 (5H) (-CH₂- and -COO-CH₃). *Anal.* Calcd. for C₇H₉ON: C, 49.12; H, 5.30; N, 8.12. Found: C, 48.39; H, 5.15; N, 7.66). A solution of XI in ethylene chloride was treated with N-bromosuccinimide and a small amount of benzoyl peroxide and the solution was heated under irradiation of ultraviolet ray. From the reaction product was isolated methyl α -bromo-3-methoxy-5-isoxazole acetate (XII) (yield: 50% from XI), b.p._{0.4~0.45} 92~94° (NMR τ : 3.81 (1H singlet) (=CH-), 4.70 (1H singlet) (-CHBr-), 6.03 (3H singlet) (-OCH₃), 6.13 (3H singlet) (-COOCH₃)).

XII was submitted to the hydrolysis with 48% hydrogen bromide-acetic acid (2:3) at 80° for 3 hours and the concentration of the reaction product afforded α -bromo-3-hydroxy-5-isoxazoleacetic acid (XIII), which was, without isolation, treated with conc. aqueous ammonia at room temperature to yield I. After purification as copper salt, I was recrystallized from water, m.p. 149~151° (decomp.) (yield: 1.4% from XII). The synthetic I was established to be identical with an authentic sample from the data of mixed melting point determination, infrared spectrum, paper chromatography, amino acid analysis and mass spectrum.

K was treated with hydrogen chloride in methanol to give the methyl ester (XIV) (yield: 80%), b.p.₂ 90~90.5° (NMR τ : 1.79 (1H doublet, J=2 c.p.s.) (-N=CH-), 3.71 (1H doublet, J=2 c.p.s.) (=CH-), 6.12 (2H singlet) (-CH₂-), 6.25 (3H singlet) (-OCH₃). *Anal.* Calcd. for C₆H₇O₃N: C, 51.06; H, 5.00; N, 9.93. Found: C, 51.18; H, 5.30; N, 9.91) and XIV was brominated to the α -bromo ester (XV), b.p._{0.25~0.3} 72~78° (yield: 65%) (NMR τ : 1.72 (1H doublet, J=2 c.p.s.) (-N=CH-), 3.40 (1H doublet, J=2 c.p.s.) (=CH-), 4.43 (1H singlet) (-CHBr-), 6.12 (3H singlet) (-OCH₃)), by the same procedure as in the synthesis of XII described above.

The bromo compound (XV) was then converted to α -bromo-5-isoxazoleacetic acid (XVI) (yield: 70%), m.p. 102.5° (NMR τ : 0.68 (1H broad) (-COOH), 1.64 (1H doublet, $J=2$ c.p.s.) (-N=CH-), 3.31 (1H doublet, $J=2$ c.p.s.) (=CH-), 4.42 (1H singlet) (-CHBr-). *Anal.* Calcd. for $C_5H_4O_3NBr$: C, 29.15; H, 1.95. Found: C, 29.12; H, 1.80) by the hydrolysis. XVI was also prepared directly from K by bromination. Treatment of XVI with conc. aqueous ammonia at room temperature afforded 3-deoxyibotenic acid (II) in 80% yield.

II gave colorless prisms, m.p. 178° (decomp.) (UV $\lambda_{max}^{H_2O}$ m μ (ϵ): 217 (5280). NMR τ (in D_2O): 1.49 (1H doublet, $J=2$ c.p.s.) (-N=CH-), 3.33 (1H doublet, $J=2$ c.p.s.) (=CH-), 4.77 (1H singlet) (-CHNH₂-). *Anal.* Calcd. for $C_5H_6O_3N_2$: C, 42.21; H, 4.45; N, 19.71. Found: C, 42.25; H, 4.26; N, 19.70) by recrystallization from water. On treatment of II with ninhydrin reagent on a filter paper, the initially appearing yellow color gradually turned purple as can be observed with I. On contrary to that I was a good taste substance, II was tasteless.

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