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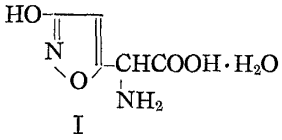
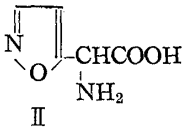
Synthesis of Ibotenic Acid and 3-Deoxyibotenic Acid

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).



I



II

Diethyl (3-chloropropionyl)malonate[5] (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) (-CH_2-CH_2CO-), 5.67 (4H quartet) (-CH_2-CH_3), 8.67 (6H triplet) (-CH_2-CH_3), *Anal.* Calcd. for $C_{10}H_{15}O_7N$: 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 $(C_{10}H_{14}O_7N)_2Cu$: 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 chloride[6] (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) (-COOH), 3.53 (1H, singlet) (=CH-), 6.05 (2H, singlet) (-CH_2COOH). *Anal.* Calcd. for $C_5H_4O_3NBr$: 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 $\lambda_{max}^{H_2O}$ mμ (ε) : 218 (6350). NMR τ (in D_2O) : 1.61 (1H doublet, J=2 c.p.s.) (-N=CH-), 3.60 (1H doublet, J=2 c.p.s.) (=CH-), 6.04 (2H singlet) (-CH_2COOH). *Anal.* Calcd. for $C_5H_4O_3N$: C, 47.25; H, 3.97; N, 11.02. Found : C, 47.13; H, 3.97; N, 10.79).

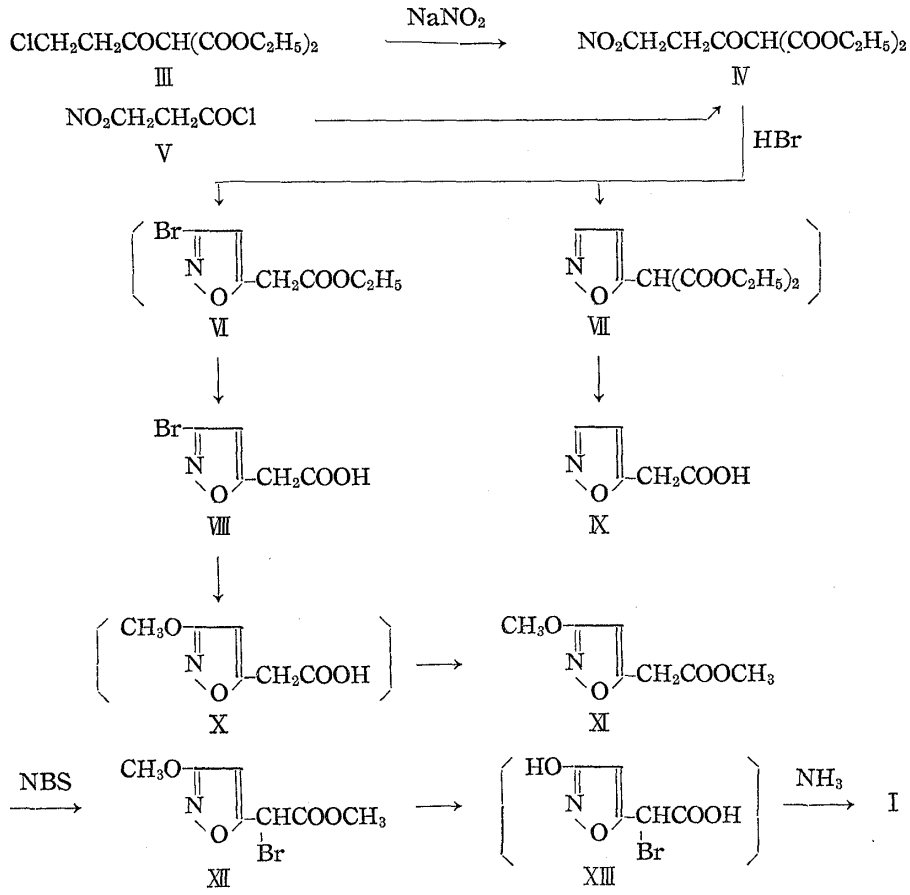
The potassium salt of VIII was neutralized with hydrogen chloride to a free acid and the latter was converted to 3-methoxy-5-isoxazoleacetic acid (X) by refluxing with

*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.$p_{0.4\sim0.55}$ 79～83° (NMR τ : 4.14 (1H singlet) (=CH-), 6.08 (3H singlet) (-OCH_3), 6.28 (5H) (-CH_2- and -$COOCH_3$). *Anal.* Calcd. for C_7H_9ON : 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.$p_{0.4\sim0.45}$ 92～94° (NMR τ : 3.81 (1H singlet) (=CH-), 4.70 (1H singlet) (-CHBr-), 6.03 (3H singlet) (-OCH_3), 6.13 (3H singlet) (-$COOCH_3$)).

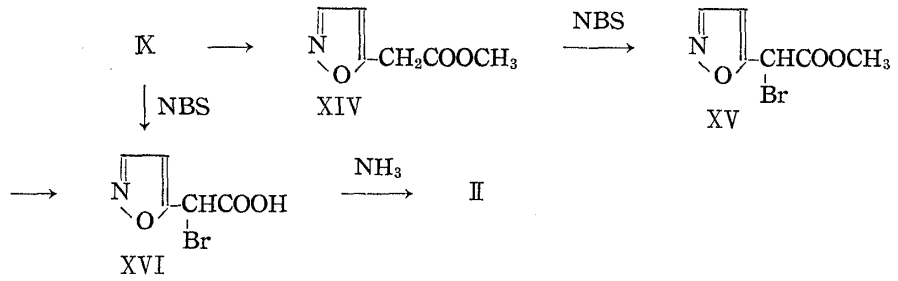
XII was submitted to the hydrolysis with 48% hydrogen bromide-acetic acid (2:3) at 80° for 3 hours and the concentration of the reaction product afforded α-bromo-3-hydroxy-5-isoxazoleacetic acid (XIII), which was, without isolation, treated with conc. aqueous ammonia at room temperature to yield I. After 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 chromatopgrahy, amino acid analysis and mass spectrum.



IX 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) (-CH_2-), 6.25 (3H singlet) (-OCH_3). *Anal.* Calcd. for $C_6H_7O_3N$: 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.$p_{0.25\sim0.3}$ 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) (-OCH_3)), 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 IX 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 $\lambda_{max}^{H_2O}$ mμ (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) (-CHNH$_2$-). *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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Chemical Research Laboratories,
Research & Development Division,
Takeda Chemical Industries, Ltd.,
Juso, Higashiyodogawa-ku, Osaka, Japan

Kenzo Sirakawa (白川研蔵)
Osami Aki (安芸修躬)
Susumu Tsushima (津島 進)
Kazuo Konishi (小西和雄)

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