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128. Yukichi Kishida, Tetsuo Hiraoka, Junya Ide, Atsusuke Terada, and Norio Nakamura: Studies on Acetylenic Compounds. XLIII.*1 Synthesis of Ibotenic Acid.*2

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Ibotenic acid (α-amino-3-hydroxy-5-isoxazoleacetic acid monohydrate) (I), a flycidal amino acid isolated from *Amanitae* fungi, was synthesized. The reaction of ethyl 4,4-diethoxytetrolate (V) with hydroxylamine in the presence of alkali gave 3-hydroxy-5-isoxazolecarboxaldehyde diethyl acetal (VI), which was hydrolyzed with 50% AcOH to the corresponding 3-hydroxy-5-isoxazolecarboxaldehyde (II). Strecker or Bucherer reaction of II followed by alkaline hydrolysis afforded I, which was identical with the natural ibotenic acid.

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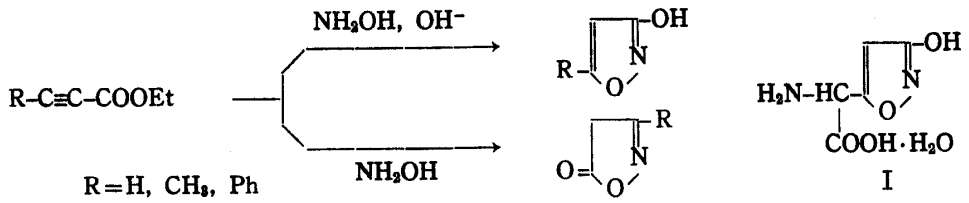
Recently our group reported that the derivatives of propiolic acid ester reacted with hydroxylamine in the presence of base to give 3-hydroxyisoxazoles, whereas the same reagents afforded 5-isoxazolones under neutral conditions.[1] In this paper we report an application of this cyclization reaction to the synthesis of ibotenic acid, a natural amino acid which has 3-hydroxyisoxazole structure.



Ibotenic acid was isolated by Takemoto, *et al.* from *Amanita strobiliformis* (Paul) Quel. (Japanese name: Ibotengutake),[2] *A. muscaria* (Fr.) S.F. Gray (Benitengutake) and *A. pantherina* (Dc.) Fr. (Tengutake),[3] as the flycidal constituent of these fungi. The structure of this new amino acid with a good taste was elucidated by them to be α-amino-3-oxo-4-isoxazoline-5-acetic acid monohydrate,[4] *i.e.* α-amino-3-hydroxy-5-isoxazoleacetic acid monohydyrate (I). Eugster, *et al.* also isolated ibotenic acid from *A. muscaria*.[5]

On the synthesis of ibotenic acid, three short communications*2,6,7 have been published. Gagneux, *et al.* have described a nine step route from 3-bromo-5-isoxazolecarboxylic acid *via* 3-benzyloxy-5-isoxazolecarboxaldehyde and its cyanohydrin.[6] Sirakawa, *et al.* have synthesized ibotenic acid by eight step reactions from diethyl (3-chloropropionyl)malonate *via* 3-bromoisoxazoleacetic acid.[7]

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*1 Part XLII, T. Hiraoka, I. Iwai: This Bulletin, **14**, 262 (1966).
*2 Short communication of this paper appeared in This Bulletin, **14**, 92 (1966).
*3 Hiromachi, Shinagawa-ku, Tokyo (岸田有吉, 平岡哲夫, 井手純也, 寺田敦祐, 中村紀雄).

1) I. Iwai, N. Nakamura: This Bulletin, **14**, 1277 (1966).
2) T. Takemoto, T. Yokobe, T. Nakajima: Yakugaku Zasshi, **84**, 1186 (1964).
3) T. Takemoto, T. Nakajima, R. Sakuma: *Ibid.*, **84**, 1233 (1964).
4) T. Takemoto, T. Nakajima, T. Yokobe: *Ibid.*, **84**, 1232 (1964).
5) C.H. Eugster, C.F.R. Müller, R. Good: Tetrahedron Letters, **1965**, 1813.
6) A.R. Gagneux, F. Häfliger, R. Meier, C.H. Eugster: *Ibid.*, **1965**, 2081.
7) K. Sirakawa, O. Aki, S. Tsushima, K. Konishi: This Bulletin, **14**, 89 (1966).

We synthesized ibotenic acid (I) by Strecker or Bucherer reaction of 3-hydroxy-5-isoxazolecarboxaldehyde (II), which was prepared by the cyclization reaction mentioned above.

The Grignard reagent prepared from propargyl aldehyde diethyl acetal (III) and ethyl magnesium bromide in tetrahydrofuran was treated with solid carbon dioxide in an autoclave to afford 4,4-diethoxytetrolic acid (IV). This acid was immediately esterified with ethanol and *p*-toluenesulfonic acid without purification, because it decomposed on distillation. Thus ethyl 4,4-diethoxytetrolate (V) of b.p_5 103~105° was obtained in 60% yield. The infrared spectrum of V showed an acetylenic band at 2250 cm^{-1} and ester absorptions at 1720 and 1245 $cm.^{-1}$ The nuclear magnetic resonance spectrum of V in carbon tetrachloride was also reasonable, showing 2H quartet at 4.22 and 3H triplet at 1.33 p.p.m. (J=7 c.p.s.) due to the carbethoxy group. The methylene protons of the acetal group were unequivalent and exhibited AB part multiplet of ABX_3 pattern at 3.67 p.p.m. (4H, center). The corresponding methyl groups exhibited 6H triplet (J=7 c.p.s.) at 1.22 p.p.m. Another 1H singlet at 5.28 p.p.m. was assigned to the diethoxymethine proton.

According to our method recently reported,[1] 3-hydroxy-5-isoxazolecarboxaldehyde diethyl acetal (VI) of m.p. 86~87° was obtained in 87% yield by the reaction of V with hydroxylamine at 30° in the presence of sodium hydroxide. As in the case of other 3-hydroxyisoxazoles,[1,9] infrared spectrum of VI in carbon tetrachloride showed broad absorption bands at 2646~2900 cm^{-1} due to the strong hydrogen bonding of the hydroxy group and isoxazole ring bands at 1628, 1526 and 1315 cm^{-1}. In the nuclear magnetic resonance spectrum of VI in carbon tetrachloride, a sharp singlet peak due to the 3-hydroxy proton was found at 11.12 p.p.m. and a 1H singlet due to the C_4-H of the ring at 5.96 p.p.m. These chemical shifts are similar to those observed for other 3-hydroxyisoxazoles.[1,8,9] In contrast with the case of V, the methylene protons of the ethoxy groups were apparently equivalent and exhibited 4H quartet (J=7 c.p.s.) at 3.60 p.p.m. The corresponding 6H triplet due to the two methyl groups was found at 1.20 p.p.m. Another 1H singlet peak was found at 5.44 p.p.m. and assigned to the diethoxymethine proton.

The structure of VI was further confirmed by the isolation of 4,4-diethoxytetrolohydroxamic acid (VII) as the intermediate of the cyclization reaction. When the temperature was kept at 10~15° throughout the reaction, only VII of m.p. 73~74° was

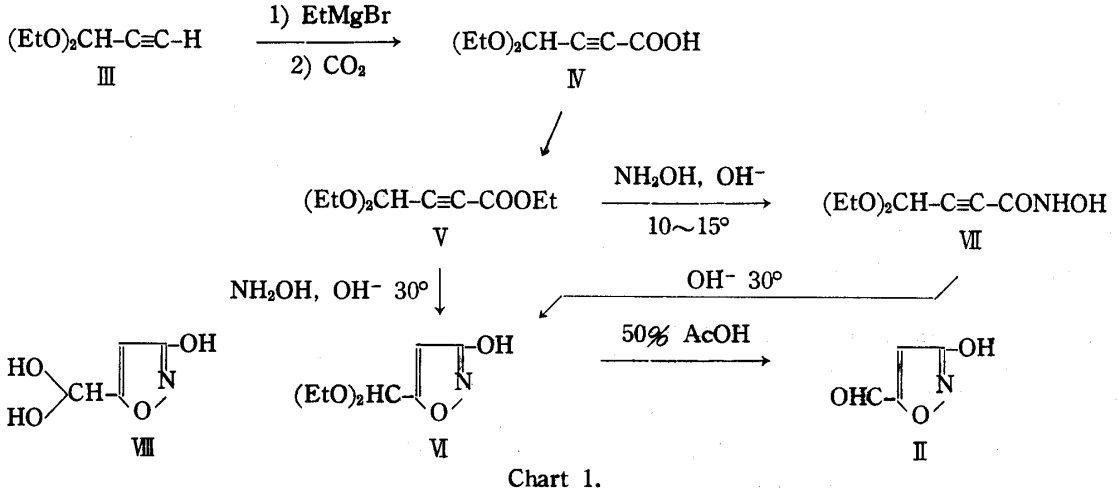

Chart 1.

8) A. J. Boulton, A. R. Katritzky, A. Mazid Hamid, S. ϕksne : Tetrahedron, **20**, 2835 (1964).
9) P. Bravo, G. Gaudiano, A. Quilico, A. Ricca : Gazz. chim. ital., **92**, 501 (1962).

obtained in 65% yield. The infrared spectrum of Ⅶ in chloroform showed broad bands due to the associated -OH or -NH-group at 2900, 3247, 3440, an acetylenic band at 2267 and a carbonyl band at 1666 cm^{-1}. When treated with 50% ethanol containing 5% sodium hydroxide at 30°, Ⅶ afforded Ⅵ in 77% yield. Therefore, the structure of Ⅵ was determined to be a 3-hydroxyisoxazole.

Hydrolysis of Ⅵ with 50% acetic acid at 70° quantitatively formed the corresponding 3-hydroxy-5-isoxazolecarboxaldehyde (Ⅱ) of m.p. 141~142°. Infrared spectrum of Ⅱ in KBr pellet showed a strong carbonyl absorption at 1713 cm^{-1}, which diappeared in deuterium oxide. It suggested that the aldehyde (Ⅱ) formed the hydrate (Ⅷ) in water. This interpretation was also supported by nuclear magnetic resonance spectroscopy. In deuterium oxide, two doublet peaks (J=0.7 c.p.s.) were found at 6.18 and 6.08 p.p.m. These signals were reasonably assigned to the C_4-H of the ring and dihydroxymethine proton of the hydrate (Ⅷ). In hexadeuterodimethyl sulfoxide, however, two singlet peaks due to the aldehyde proton and the C_4-H of Ⅱ appeared at 9.84 and 6.92 p.p.m.,[*4] respectivey. A broadened absorption due to the hydroxyl proton was also found at 10.3~12.5 p.p.m., as in the case of other 3-hydroxyisoxazoles in this solvent.[1,8] When the equal volume of deuterium oxide was added to the hexadeuterodimethyl sulfoxide solution, the two peaks at 9.84 and 6.92 p.p.m. greatly decreased in intensity and two singlet peaks corresponding to the hydrate structure (Ⅷ) appeared at 6.10 and 5.93 p.p.m. besides the water peak (Fig. 1).

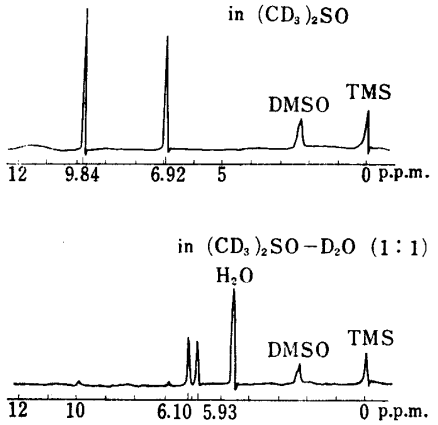

Fig. 1. Nuclear Magnetic Resonance Spectra of 3-Hydroxy-5-isoxazole-carboxaldehyde (Ⅱ)

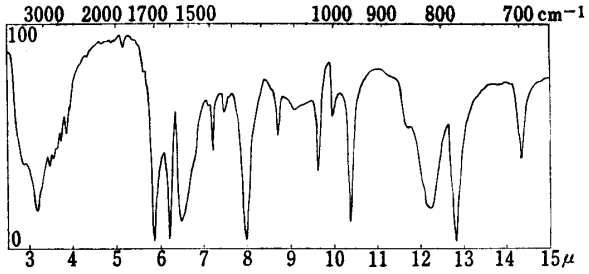

Fig. 2. Infrared Absorption Spectrum of 3-Hydroxy-5-carboxaldehyde (Ⅱ) (in KBr)

According to Bucherer's method,[10,11] an aqueous solution of Ⅱ, sodium cyanide and ammonium carbonate was heated at 80° for 2 hours, and then treated with alkali. From the alkaline solution, ibotenic acid (I) was isolated in 3.3% yield by successive column chromatography on Amberite IRC-50 (H^+ form) and Amberite IR-45 (OH^- form). Recrystallization from water gave colorless prisms of m.p. 151~152° (decomp.). The synthetic I was identical with the natural ibotenic acid in infrared spectroscopy, paper and thin-layer chromatography. Strecker reaction[12] of Ⅱ followed by hydrolysis also gave I in 0.26% yield. In the reactions mentioned above, any attempt to isolate the intermediate hydantoin (Ⅸ) or aminonitrile (Ⅹ) was unsuccessful.

*4 We correct the chemical shift values reported in our preliminary communication,[*2] 9.01 and 6.45 p.p.m. for these protons.

10) H. T. Bucherer, V. A. Lieb: J. pract. Chem., **141**, 5 (1934).
11) H. R. Henze, R. J. Speer: J. Am. Chem. Soc., **64**, 522 (1942).
12) N. Zelinsky, G. Stadnikoff: Chem. Ber., **41**, 2061 (1908).

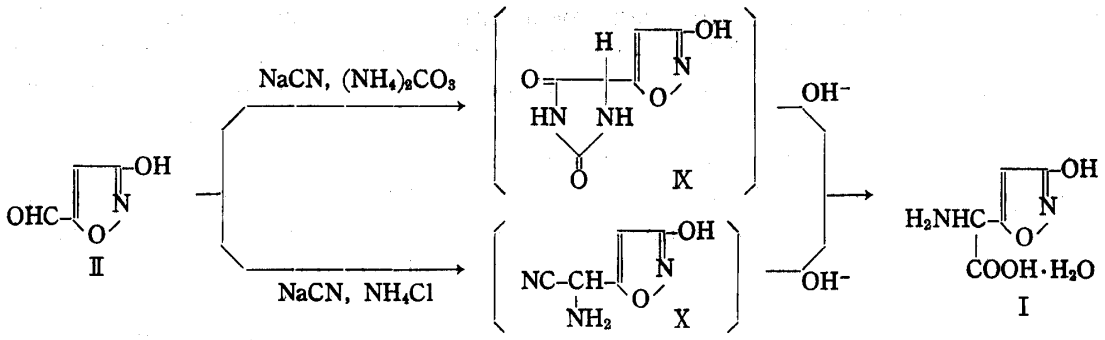

Chart 2.

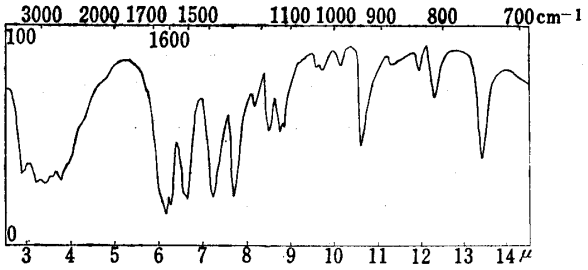

Fig. 3. Infrared Absorption Spectrum of Synthetic Ibotenic Acid (I) (in KBr)

To improve the poor yield of I, similar reactions on 3-benzyloxy-(XI) and 3-methoxy-5-isoxazolecarboxaldehyde (XII) were tried.

Benzylation of VI with benzyl chloride and potassium carbonate afforded a mixture of 3-benzyloxy-5-isoxazolecarboxaldehyde diethyl acetal (XIII) and 3-oxo-N-benzyl-5-isoxazolinecarboxaldehyde diethyl acetal (XIV). These isomers were separated by alumina column chromatography and easily distinguished from each other by infrared spectroscopy: the spectrum of the latter (film) showed strong carbonyl absorption at 1690 cm^{-1}, while the former lacked the carbonyl band. Similarly, 3-methoxy-5-isoxazolecarboxaldehyde diethyl acetal (XV) and 3-oxo-N-methyl-5-isoxazolinecarboxaldehyde diethyl acetal (XVI) were obtained by methylation of VI with dimethyl sulfate, diazomethane or methyl iodide. Methylation of some 3-hydroxyisoxazoles with these reagents has been reported by Cabiddu, *et al.* and afforded also a mixture of O-methyl and N-methyl products.[13] Infrared spectrum of XVI showed a carbonyl band at 1680 cm^{-1}. The acetals XIII and XV were hydrolyzed with 50% acetic acid to corresponding aldehydes XI and XII, respectively. The nuclear magnetic resonance spectrum of XI was essentially identical with that of an authentic sample.*[5,6]

All attempts to obtain O-benzyl or O-methylibotenic acid by Bucherer or Strecker reaction of XI or XVI ended in failure.

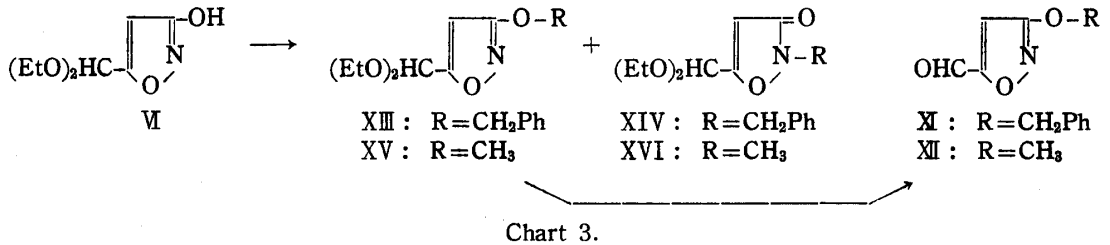

Chart 3.

*5 For this aldehyde, Gagneux, *et al.* reported the data in $CDCl_3$ with Varian A-60 spectrometer, 9.78 (1H, doublet, J=0.5 c.p.s.), 7.38 (5H, singlet), 6.57 (1H, doublet, J=0.5 c.p.s.) and 5.32 p.p.m. (2H, singlet).[6] With the same solvent and instrument, we found signals at 9.80 (1H, singlet), 7.40 (5H, singlet), 6.57 (1H, singlet) and 5.33 p.p.m. (2H, singlet). Even with 100 MC spectrometer (Varian HA-100), any coupling was not observed between the two peaks at 9.80 and 6.57 p.p.m.

13) S. Cabiddu, G. Gaudiano, A. Quilico: Gazz. chim. ital., **92**, 501 (1962).

Experimental*6

Ethyl 4,4-diethoxytetrolate (V)——To a mixture of magnesium (19.0 g.) and tetrahydrofuran (100 ml.) was added ethyl bromide (86.0 g.) dissolved in 300 ml. of tetrahydrofuran. After 2 hr. stirring, propargyl aldehyde diethyl acetal (III) (100 g.) in 400 ml. of tetrahydrofuran was added dropwise to the Grignard reagent at 0~5° over a period of 1 hr. Stirring was continued for 2 hr. at 25°, and the mixture was cooled to −30° by adding solid carbon dioxide. At first the inner temperature rose to 35°. The cooled mixture was packed in a 3-L autoclave with excess of solid carbon dioxide to show 15 atm. at the gauge after 12 hr. After shaken for 20 hr., the reaction mixture was poured into 250 ml. of cold 10% HCl solution and extracted twice with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue, crude 4,4-diethoxytetrolic acid (IV), was mixed with abs. EtOH (1200 ml.), dried benzene (1000 ml.) and *p*-toluenesulfonic acid (12 g.). The mixture was refluxed for 30 hr., poured into water and extracted three times with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. Distillation of the residue gave 94 g. of ethyl 4,4-diethoxytetrolate, b.p_5 103~105°. Yield, 60.2% based on III. *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.81; H, 8.34.

3-Hydroxy-5-isoxazolecarboxaldehyde Diethyl Acetal (VI)——To a mixture of hydroxylamine hydrochloride (16.68 g., 0.24 mole), H_2O (200 ml.), NaOH (25.6 g., 0.64 mole) and MeOH (200 ml.) was added a solution of V (40 g., 0.20 mole) in 50 ml. of MeOH at 15° over a period of 1 hr. After allowed to stand at 30° for a night, the mixture was acidified with AcOH to pH 5.5, saturated with Na_2SO_4 and extracted with ether. The extract was combined and dried over Na_2SO_4. After evaporation of the solvent, 32.7 g. of crude 3-hydroxy-5-isoxazolecarboxaldehyde diethyl acetal (VI) was obtained. Yield, 87.4%. Recrystallization from hexane gave white prisms of m.p. 86~87°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2600~3000 (associated-OH), 1628, 1526, 1315 (isoxazole ring). *Anal.* Calcd. for $C_8H_{13}O_4N$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.52; H, 6.96; N, 7.52.

4,4-Diethoxytetrolohydroxamic Acid (VII)——To a mixture of hydroxylamine hydrochloride (4.3 g., 0.062 mole) and 10% NaOH solution (70 ml.) was added a solution of V (8.2 g., 0.041 mole) in 70 ml. of MeOH, while the inner temperature was kept at 10~15° under ice cooling. After standing overnight at the temperature, the mixture was acidified with AcOH to pH 6.0 and extracted four times with ether. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue, crude 4,4-diethoxytetrolohydroxamic acid (VII) (5.0 g., 65.2%), was recrystallized from benzene-hexane to give fine needles of m.p. 73~74°. NMR δ p.p.m. in $CDCl_3$: 10.07 (2H, broad peak, -NH-OH), 5.38 (1H, singlet, -CH(OEt)$_2$), 3.70 (center, 4H, multiplet, -O-CH_2-CH_3), 1.23 (6H, triplet, J=7 c.p.s., -O-CH_2-CH_3). *Anal.* Calcd for $C_8H_{13}O_4N$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.10; H, 7.03; N, 7.33.

Conversion of VII to VI——A solution of VII (3.5 g.) in EtOH (15 ml.) was mixed with 15 ml. of 10% NaOH solution. After allowed to stand at 30° for a night, the mixture was acidified with AcOH to pH 6.0 and extracted three times with ether. The extract was dried over Na_2SO_4, and the solvent was evaporated. The residue was recrystallized from hexane to give prisms of VI, m.p. 86~87°. Yield, 2.7 g. (77%).

3-Hydroxy-5-isoxazolecarboxaldehyde (II)——A mixture of VI (10.503 g.) and 50% AcOH (200 ml.) was heated on a water bath (70°) for 3 hr. The solution was evaporated to dryness under reduced pressure. To remove remaining water, addition and evaporation of benzene was repeated four times. The crystalline residue (6.5 g.) was recrystallized from benzene to give prisms of 3-hydroxy-5-isoxazolecarboxaldehyde (II), m.p. 141~142° (3.825 g.). Concentration of the mother liquor gave further crystals of m.p. 140~141° (1.427 g.) and of m.p. 137~139° (0.668 g.). Total yield, 6.02 g. (95%). *Anal.* Calcd. for $C_4H_3O_3N$: C, 42.49; H, 2.67; N, 12.39. Found: C, 42.50; H, 2.73; N, 12.61.

***α*-Amino-3-hydroxy-5-isoxazoleacetic Acid Monohydrate (Ibotenic Acid) (I)**——i)[10,11] To a mixture of II (5.65 g., 0.05 mole) and 150 ml. of H_2O were added sodium cyanide (4.9 g., 0.10 mole) and ammonium carbonate (24.0 g., 0.25 mole). The mixture was heated on a water bath (80~85°) for 2 hr. After cooling, NaOH (30 g.) was added. The reaction mixture was again heated on a water bath (90°) for 2 hr. and diluted with 600 ml. of H_2O. The aqueous solution was passed through a column of Amberite IRC-50 (H^+ form, 900 ml.). The column was washed with 900 ml. of H_2O. The effluent and the washing was combined and chromatographed on a column of Amberite IR-45 (OH^- form, 100 ml.). The column was washed with 1000 ml. of H_2O and eluted with 0.1*N* AcOH. The first 1000 ml. of acidic eluate was collected and evaporated under reduced pressure, keeping the inner temperature below 40°. The residue was recrystallized from H_2O to give colorless prisms of ibotenic acid (I), melting at 141~142° (decomp.) (0.294 g., 3.3%). Further recrystallizations from H_2O (three times) afforded an analytical sample of m.p. 151~152° (decomp.) whose IR spectra in KBr pellet and nujol mull were superimposable on those of natural ibotenic acid. Paper and thin-layer chromatograms of I described below were also identical with those of the natural amino acid. Paper chromatography: Toyo No. 50, Rf=0.19 (solvent; BuOH : AcOH : H_2O=4:1:1). Thin-layer chromatography: cellulose powder (Seikagaku Kogyo), Rf=0.32 (solvent; BuOH : AcOH : pyridine : H_2O=15:

*6 All melting points were uncorrected. NMR spectra were taken on Varian A-60 spectrometer with Me_4Si or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as the internal standard.

3:10:12), Rf=0.48 (solvent; pyridine : MeOH : H_2O=9:160:40). *Anal.* Calcd. for $C_5H_8O_5N_2$: C, 34.09; H, 4.58; N, 15.91. Found : C, 33.89; H, 4.59; N, 15.92.

ii)[12] To a solution of ammonium chloride (0.52 g., 0.00972 mole) and sodium cyanide (0.477 g., 0.00972 mole) in 5 ml. of conc. aqueous ammonia solution was added portionwise II (0.50 g., 0.00442 mole) under ice-water cooling. Stirring was continued for 30 min. at room temperature and the reaction mixture was allowed to stand for a night. After KOH (1.2 g.) was added, the mixture was heated on a water bath (90°) for 6.5 hr. The solution was cooled, diluted with 10 ml. of H_2O and passed through a column containing 90 ml. of Amberite IR-120 (H^+ form). The column was eluted with H_2O. The first 500 ml. of the eluate was collected and evaporated under reduced pressure on a water bath (35°). An oily substance remained and partly crystallized on standing. Recrystallization from H_2O afforded I of m.p. 131~132°(decomp.) (0.004 g., 0.26%), whose IR spectrum (Nujol) was identical with that of natural ibotenic acid.

Benzylation of VI——To a mixture of VI (16.8 g., 0.09 mole), K_2CO_3 (12.4 g., 0.09 mole) and acetone (80 ml.) was added dropwise a solution of benzyl chloride (11.4 g., 0.09 mole) in acetone at room temperature. The reaction mixture was refluxed for 6 hr., filtered and the solvent was evaporated. The residue was dissolved in benzene, washed with H_2O and dried over Na_2SO_4. After the evaporation of the solvent, the residue (20.2 g.) was chromatographed on Al_2O_3 (Woelm, grade II, 400 g.). Elution with hexane-benzene (4:1) afforded 10.49 g. (42%) of 3-benzyloxy-5-isoxazolecarboxaldehyde diethyl acetal (XIII), $b.p_{0.03}$ 131~135°(bath temp.). NMR δ p.p.m. in $CDCl_3$: 7.43 (5H, singlet, C_6H_5-CH_2-), 6.03 (1H, doublet, J=0.8 c.p.s., C_4-H), 5.53 (1H, doublet, J=0.8 c.p.s., -CH$(OEt)_2$), 5.30 (2H, singlet, -O-CH_2-Ph), 3.66 (4H, quartet, J=7 c.p.s, -O-CH_2-CH_3), 1.23 (6H, triplet, J=7 c.p.s., -O-CH_2-CH_3). *Anal.* Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05. Found : C, 64.71; H, 6.80; N, 5.14. After the elution of XIII, 6.35 g. (25.6%) of 3-oxo-N-benzyl-5-isoxazolecarboxaldehyde diethyl acetal (XIV), $b.p_{0.02}$ 149~151°(bath temp.), was eluted by $CHCl_3$. IR ν_{max}^{film} cm^{-1} : 1690 (-CO-). NMR δ p.p.m. in $CDCl_3$: 7.23 (5H, singlet, C_6H_5-CH_2-), 5.73 (1H, doublet, J=0.8 c.p.s., C_4-H), 5.20 (1H, doublet, J=0.8 c.p.s., -CH$(OEt)_2$), 4.95 (2H, singlet, N-CH_2-Ph), 3.47 (4H, quartet, J=0.8 c.p.s., -O-CH_2-CH_3), 1.13 (6H, triplet, J=7 c.p.s., -O-CH_2-CH_3). *Anal.* Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05. Found : C, 64.86; H, 6.88; N, 4.84.

3-Benzyloxy-5-isoxazolecarboxaldehyde (XI)——A mixture of XIII (6.690 g.) and 50% AcOH (300 ml.) was heated on a water bath (80°) for 10 hr. The solvent was evaporated under reduced pressure. Distillation of the residue gave 4.783 g. (97.5%) of 3-benzyloxy-5-isoxazolecarboxaldehyde (XI), $b.p_1$ 114~116°(bath temp.), which crystallized on standing. Recrystallization from a small amount of EtOH gave prisms of m.p. 42.5~43.5°. IR ν_{max}^{film} cm^{-1} : 2860, 1710 (-CHO). NMR δ p.p.m. in $CDCl_3$[6] : 9.80 (1H, singlet, -CHO), 7.40 (5H, singlet, C_6H_5-CH_2-), 6.57 (1H, singlet, C_4-H), 5.33 (2H, singlet, -O-CH_2-Ph). *Anal.* Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.46; N, 6.89. Found : C, 64.95; H, 4.41; N, 6.67.

Methylation of VI with Dimethyl Sulfate——To a stirred solution of VI (2.87 g., 0.0157 mole) in 2*N* NaOH (10 ml.) was added dropwise dimethyl sulfate (2.6 g., 0.02 mole) at 9~10° under ice-cooling. The reaction mixture was stirred for 2 hr. at room temperature. An oily substance separated. The water layer was extracted three times with ether. The oil and the extract were combined, washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on Al_2O_3 (Woelm, grade III, 60 g.) Elution with benzene-hexane (1:4) afforded 3-methoxy-5-isoxazolecarboxaldehyde diethyl acetal (XV) of $b.p_1$ 90~90.5°. Yield, 0.619 g. (19.6%). NMR δ p.p.m. in $CDCl_3$: 5.99 (1H, doublet, J=0.8 c.p.s., C_4-H), 5.52 (1H, doublet, J=0.8 c.p.s., -CH$(OEt)_2$), 3.99 (3H, singlet, -O-CH_3), 3.66 (4H, quartet, J=7 c.p.s., -O-CH_2-CH_3), 1.23 (6H, triplet, J=7 c.p.s., -O-CH_2-CH_3). *Anal.* Calcd. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found : C, 53.63; H, 7.60; N, 6.74.

After elution of XV, 3-oxo-N-methyl-5-isoxazolinecarboxaldehyde diethyl acetal (XVI) (1.291 g., 40.9%) of $b.p_2$ 120~121°, which crystallized on cooling (m.p. 35~37°), was eluted by benzene. IR ν_{max}^{Nujol} cm^{-1} : 1680 (-CO-). NMR δ p.p.m. in $CDCl_3$: 5.78 (1H, doublet, J=0.8 c.p.s., C_4-H), 5.33 (1H, doublet, J=0.8 c.p.s., -CH$(OEt)_2$), 3.51 (3H, singlet, N-CH_3), 3.64 (4H, quartet, J=7 c.p.s., -O-CH_2-CH_3), 1.24 (6H, triplet, J=7 c.p.s., -O-CH_2-CH_3). *Anal.* Calcd. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found : C, 53.55; H, 7.78; N, 6.67.

Methylation of VI with Diazomethane——To a stirred solution of VI (10.8 g., 0.058 mole) in anhydrous ether was added dropwise a solution of diazomethane (2.606 g., 0.0638 mole) in ether (160 ml.) at 0~5. Stirring was continued for additional 2 hr. and AcOH (0.7 ml.) was added to the reaction mixture. After evaporation of the solvent, the colorless residue was chromatographed on Al_2O_3 (Woelm, grade III, 300 g.). The same solvents as described above afforded XV (6.3 g., 54%) of $b.p_1$ 90~90.5° and XVI (4.4 g., 37.7%) of $b.p_2$ 120~121°.

Methylation of VI with Methyl Iodide——To a solution of sodium (0.230 g., 0.01 mole) in abs. EtOH (20 ml.) was added VI (1.87 g., 0.01 mole). After stirred for 1 hr. at room temperature, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in acetonitrile (15 ml.) containing methyl iodide (7 g.) and refluxed for 21 hr. on a water bath. After evaporation of the solvent, the residue was mixed with H_2O and extracted three times with ether. The combined extract was washed

with H_2O, dried over Na_2SO_4 and the solvent was evaporated. Column chromatography of the residue on Al_2O_3 (Woelm, grade III, 30 g.) as described above afforded XV (0.364 g., 18.2%) and XVI (0.680 g., 34.0%).

3-Methoxy-5-isoxazolecarboxaldehyde (XII)——A mixture of XV (6.0 g., 0.03 mole) and 50% AcOH (250 ml.) was heated on an oil bath (75~80°) for 20 hr. The solvent was carefully distilled off under reduced pressure (2~5 mm. Hg), avoiding any loss of the wanted product. Distillation of the residue gave 1.801 g. (58.4%) of 3-methoxy-5-isoxazolecarboxaldehyde (XII), b.p_{10} 100~105°(bath temp.). IR ν_{max}^{film} cm^{-1}: 2860, 1700 (-CHO). NMR δ p.p.m. in $(CD_3)_2SO$: 9.82 (1H, singlet, -CHO), 7.10 (1H, singlet, C_4-H), 3.98 (3H, singlet, -O-CH_3). *Anal.* Calcd. for $C_5H_5O_3N$: C, 47.25; H, 3.97; N, 11.02. Found: C, 47.15; H, 3.91; N, 10.93.

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