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# The Improved Syntheses of *dl*-Ibotenic Acid and Muscimol

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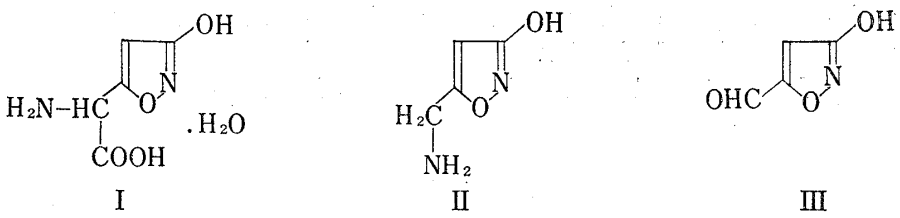
*dl*-Ibotenic acid (I) was synthesized in a better yield than the known methods, starting from diethyl 3-chloroglutaconate (VII). Reaction of VII with hydroxylamine in the presence of sodium hydroxide followed by esterification afforded ethyl 3-hydroxy-5-isoxazoleacetate (IV), which was, after benzenesulfonylation, brominated with NBS to ethyl α-bromo-3-benzenesulfonyloxy-5-isoxazoleacetate (X). Hydrolysis and treatment with ammonia of X gave I. Synthesis of muscimol (II) from IV was also described.

Ibotenic acid, α-amino-3-hydroxy-5-isoxazoleacetic acid monohydrate (I), is the flycidal constituent of a fungus *Amanita strobiliformis* isolated as the racemate by Takemoto, *et al.* in 1964.[2] The decarboxylation product of I, 3-hydroxy-5-aminomethylisoxazole (II), is identical with muscimol[2] (pantherine), which has been isolated from *Amanita pantherina* by Onda, *et al.*[3] Eugster, *et al.* have also reported the isolation of I and II from *Amanita muscaria*.[4] It has been shown that both I and II are active on the central nervous system.[4,5]




I II III

Chart 1

Gagneux, *et al.*[6] and Sirakawa, *et al.*[7] have reported the synthesis of I. They have introduced the 3-hydroxyisoxazole moiety by the known conversion[8] of the corresponding 3-bromoisoxazole derivatives *via* 3-alkoxyisoxazoles. We reported the synthesis of I from 3-hydroxyisoxazole-5-carboxaldehyde (III),[9] which was obtained by our new 3-hydroxyisoxazole synthesis starting from propiolic esters.[10] Because of the many steps or low yields involved in these procedures, a more efficient route is desirable for the preparation of this biologically interesting substance. In this paper the author wishes to report improved syntheses of I and II by the chemical modification of ethyl 3-hydroxy-5-isoxazoleacetate (IV).

1) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
2) *a*) T. Takemoto, T. Yokobe and T. Nakajima, *Yakugaku Zasshi*, **84**, 1186 (1964); *b*) *Idem, ibid.*, **84**, 1232 (1964); *c*) Nomenclature; C.H. Eugster and T. Takemoto, *Helv. Chim. Acta*, **50**, 126 (1967).
3) M. Onda, H. Fukushima and M. Akagawa, *Chem. Pharm. Bull.* (Tokyo), **12**, 751 (1964).
4) C.H. Eugster, G.F.R. Müller and R. Good, *Tetrahedron Letters*, **1965**, 1813; *idem, Helv. Chim. Acta*, **48**, 910, 927 (1965).
5) W. Theobald, O. Büch, G.A. Kunz, P. Krupp, E.G. Stengerand and H. Heiman, *Arzneim. Forschung*, **18**, 311 (1968); R.G. Benedict, V.E. Tyler Jr., and L.R. Brady, *Lloydia*, **29**, 333 (1966) (*C.A.*, **66**, 73248j (1967)).
6) A.R. Gagneux, F. Häfliger, R. Meier and C.H. Eugster, *Tetrahedron Letters*, **1965**, 2081.
7) K. Sirakawa, O. Aki, S. Tsushima and K. Konishi, *Chem. Pharm. Bull.* (Tokyo), **14**, 89 (1966).
8) P. Bravo, G. Gaudiano, A. Quilico and A. Ricca, *Gazz. Chim. Ital.*, **91**, 47 (1961); *b*) S. Cabiddu, G. Gaudiano and A. Quilico, *ibid.*, **92**, 501 (1962).
9) Y. Kishida, T. Hiraoka, J. Ide, A. Terada and N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **14**, 92 (1966); *idem, ibid.*, **15**, 1025 (1967).
10) I. Iwai and N. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **14**, 1277 (1966).

The first aim was to synthesize IV from esters of glutinic acid(V) according to our method.[10] Glutinic acid (V) exists in the allenic form (VI) and has been prepared from 3-chloroglutaconic acid.[11] It has been shown that in the reaction with hydroxylamine $\beta$-haloacrylic esters or nitriles are equivalent to the corresponding propiolic derivatives.[10,12] Therefore, diethyl 3-chloroglutaconate (VII) was chosen as the starting material. The chlorination of diethyl acetonedicarboxylate (VIII) with phosphorous pentachloride according to Ingold's method[13] gave a *cis–trans* mixture of VII and the two isomers were separated by fractional distillation. The low boiling main fraction (VIIa) (42.7% from VIII) of bp 108—112° (6 mmHg) showed nuclear magnetic resonance (NMR) absorption peaks in carbon tetrachloride at 6.15 (1H, singlet, olefinic proton), 4.13 (4H, quartet, $J$=7 cps, carbethoxy methylene protons), 4.00 (2H, singlet, allylic methylene protons) and 1.27 ppm (6H, triplet, $J$=7 cps, methyl groups). The NMR spectrum of highboiling minor fraction (VIIb) (4.3% from VIII) of bp 125—127° (5 mmHg) showed the olefinic peak at 6.13 (1H, triplet, $J$=1 cps) and the methylene signals at 3.37 (2H, doublet, $J$=1 cps) besides the peaks due to carbethoxy groups at 4.17 (4H, quartet, $J$=7 cps) and 1.28 ppm (6H, triplet, $J$=7 cps). The much lower field chemical shift value for the allylic methylene protons of VIIa than of VIIb shows that the carbethoxy methyl group and the other carbethoxy group of VIIa are *cis*.[14] Thus, VIIa was assigned as diethyl 3-chloro-*cis*-glutaconate and VIIb the *trans* isomer.

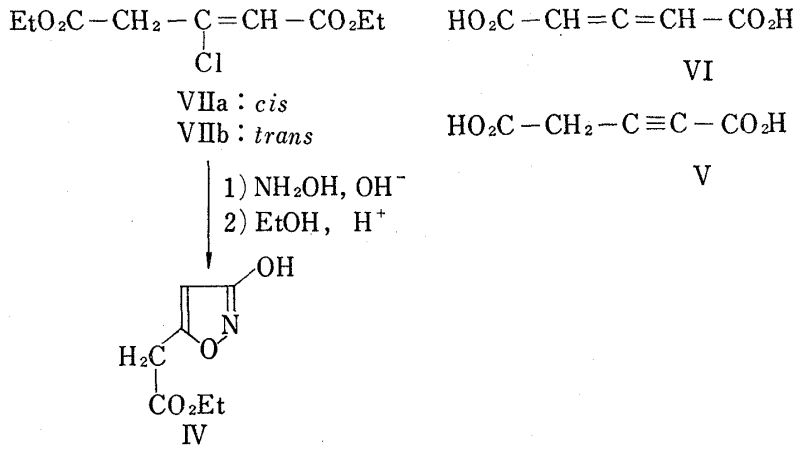



Chart 2

The reaction of VIIa and VIIb with hydroxylamine in the presence of excess sodium hydroxide followed by esterification furnished the ester (IV) of mp 78—79° in 60.1 and 53.4% yield, respectively. The structure of IV was evidenced by the NMR spectrum in deuteriochloroform showing a hydroxy singlet at 11.03 (1H), a singlet due to the ring $C_4$-hydrogen at 5.98 (1H) and an allylic methylene signal at 3.72 (2H, singlet) in addition to the carbethoxy signals at 4.23 (2H, quartet, $J$=7 cps) and 1.28 ppm (3H, triplet, $J$=7 cps).

Masking the hydroxy group of 3-hydroxyisoxazoles with diazomethane,[8b,9] dimethyl sulfate,[15] methyl iodide[9] or benzyl chloride[9] has been reported but such methods are plagued by the formation of N-alkylated products. We found that benzenesulfonylation of IV and other 3-hydroxyisoxazoles gave only O-substituted products. Treatment of IV with benzenesulfonyl chloride in the presence of triethylamine quantitatively afforded ethyl 3-benzenesulfonyloxy-5-isoxazoleacetate (IX), whose infrared (IR) spectrum in the $\nu_{C=O}$ region showed only one

11) J.M. Van der Zanden, *Rec. Trav. Chim.*, **54**, 289 (1935).
12) K. Tomita, M. Nagano and H. Oka, Japan Patent 43-14704 (1968).
13) C.K. Ingold and L.C. Nickolls, *J. Chem. Soc.*, **121**, 1638 (1922).
14) E.J. Corey and J.A. Katzenellenbogen, *J. Am. Chem. Soc.*, **91**, 1851 (1969).
15) K. Bowden, G. Crank and W.J. Ross, *J. Chem. Soc.*, **1968**, 172.

band due to the ester group at 1742 $cm^{-1}$. The characteristic band of N-substituted 4-isoxazolin-3-ones (1660—1690 $cm^{-1}$ [8,16]) was not noticeable. Vacuum distillation of IX was possible, bp 164—168° (0.01 mmHg), but about half the material resinified. Bromination of crude IX with N-bromosuccinimide and benzoyl peroxide under ultraviolet (UV) irradiation was slow but successful. After silica gel column chromatography, ethyl α-bromo-3-benzenesulfonyloxy-5-isoxazoleacetate (X) was isolated as a colorless oil in 54.6% yield. The NMR spectrum of X in deutriochloroform showed an aromatic multiplet (5H) at 7.2—8.1, a singlet due to the ring $C_4$-hydrogen (1H) at 6.57, another singlet due to the bromomethine proton (1H) at 5.30 and carbethoxy signals at 4.27 (2H, quartet, $J$=7 cps) and 1.30 ppm (3H, triplet, $J$=7 cps).

The bromo-ester (X) was hydrolyzed at 28° in a conc. hydrochloric acid–acetic acid mixture (1:2) and then treated with aqueous ammonia at room temperature. Benzenesulfonamide, mp 146—148° (63.7% yield), and a white solid (XIII), mp 121—123° (d), were isolated. The latter was assumed to be ammonium salt of ibotenic acid (I), based on its melting point (reported mp 120° (d)[6]) and the NMR absorption peaks in deuterium oxide at 5.90 (1H, singlet, ring $C_4$-hydrogen) and 4.92 ppm (singlet, 1H, aminomethine proton). Racemic ibotenic acid (monohydrate) (I) was isolated in 50.0% yield (from X) by treating the salt (XIII) with ion exchange resin, Amberite IR-120 ($H^+$ form).[6] Recrystallization from water afforded color-

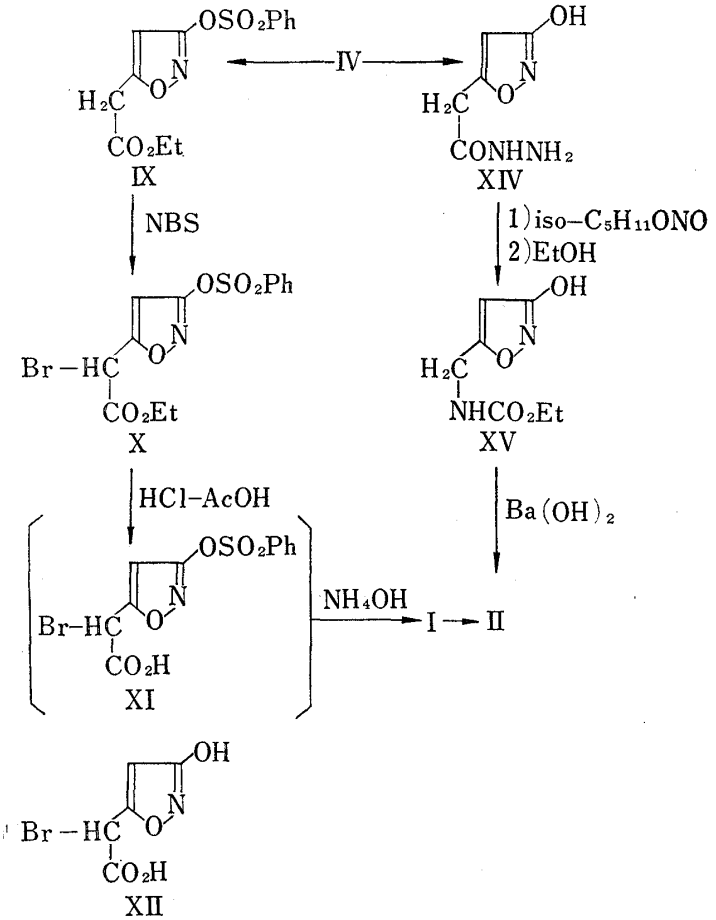



Chart 3

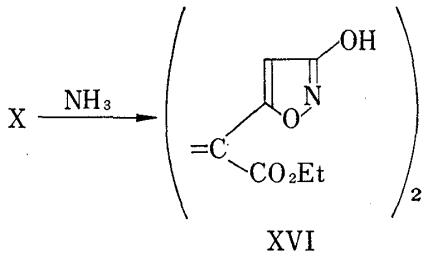



Chart 4

less prisms of mp 144—146° (d) (reported mp 151—152° (d),[2] 145° (d)[4]), which was identical with a natural monohydrate sample in the IR spectrum and by paper and thin-layer chromatography.[9] The isolation of benzenesulfonamide suggests that α-bromo-3-benzenesulfonyloxy-5-acetic acid (XI) was an intermediate. If the further hydrolyzed α-bromo-3-hydroxy-5-isoxazoleacetic acid (XII) was the intermediate, ammonium benzenesulfonate should be obtained. An anhydrous sample of *dl*-ibotenic acid of mp 151—152° (d) with the formula $C_5H_6O_4N_2$ and a different IR spectrum was obtained by grinding the monohydrate in methanol and removing the solvent. Recrystallization of the anhydrous sample from water regenerated the monohydrate of mp 144—146° (d).

16) A.J. Boulton, A.R. Katritzky, A. Majid Hamid and S. φksne, *Tetrahedron*, **20**, 2835 (1964).

An attempt to obtain ibotenic acid ethyl ester by the reaction of X with liquid ammonia was not successful and instead a halogen-free, dimerized product with the formula $C_{14}H_{14}O_8N_2$ (XVI) of mp 192—195° (d) (19.7%) was isolated in addition to benzenesulfonamide (51.8%). The mass spectrum of XVI showing the molecular ion peak at *m/e* 338 suggested a dimerized structure. The NMR spectrum of XVI in hexadeuterioacetone showed a singlet at 6.11 due to $C_4$-hydrogen of the isoxazole ring and ethoxy signals at 4.36 (quartet, $J=7$ cps) and 1.32 ppm (triplet, $J=7$ cps) (relative ratio, 1:2:3). The IR spectrum showed associated hydroxyl bands characteristic of 3-hydroxyisoxazoles at 2400—3200 and an ester band at 1740 $cm^{-1}$. The UV absorption at 290 m$\mu$ ($\varepsilon=10810$) suggested an extented conjugation system. From these spectral data, the author assigned XVI as being 1,2-dicarbethoxy-1,2-bis(3-hydroxy-5-isoxazolyl)ethylene. The geometrical configuration was not determined.

Three successful routes for the synthesis of muscimol (pantherine) (II) have been reported.[15,17,18] The author also succeeded in the synthesis of II from 3-hydroxyisoxazole-5-acetic acid hydrazide (XIV), mp 174—175° (d), which was obtained by the reactiton of IV with hydrazine in good yield. Anhydrous Curtius rearrangement[15] of XIV followed by treatment with ethanol gave 3-hydroxy-5-(ethoxycarbonylamino)methylisoxazole (XV) of mp 126—128°. Hydrolysis of XV with 20% aqueous barium hydroxide afforded II of mp 172—174° (d), whose IR[3], NMR[2] and mass spectra[15,19] were identical with those of the natural product and a sample obtained by the decarboxylation of ibotenic acid.

## Experimental[20]

**Diethyl 3-Chloroglutaconates, (VIIa) and (VIIb)**——A mixture of isomeric diethyl 3-chloroglutaconates (113 g, 52.6%) was prepared by the treatment of diethyl acetonedicarboxylate (197 g) with phosphorous pentachloride (208 g) followed by esterification according to Ingold's method.[13] The isomers were separated by fractional distillation.

Diethyl 3-Chloro-*cis*-glutaconate (VIIa): bp 108—112° (6 mmHg), yield 92 g (42.7%). NMR ($CCl_4$) $\delta$: 6.15 (1H, s, olefinic H), 4.13 (4H, q, $J=7$ cps, $-O-CH_2-$), 4.00 (2H, s, allylic $-CH_2-$), 1.27 (6H, *t*, $J=7$ cps, $-CH_3$). *Anal.* Calcd. for $C_9H_{13}O_4Cl$: C, 48.99; H, 5.94; Cl, 16.07. Found: C, 48.91; H, 5.94; Cl, 15.91.

Diethyl 3-Chloro-*trans*-glutaconate (VIIb): bp 125—127° (5 mmHg), yield 9.2 g (4.3%). NMR ($CCl_4$) $\delta$: 6.13 (1H, t, $J=1$ cps, olefinic H), 4.17 (4H, q, $J=7$ cps, $O-CH_2-$), 3.37 (2H, d, $J=1$ cps, allylic $-CH_2-$), 1.28 (6H, t, $J=7$ cps, $CH_3$). *Anal.* Calcd. for $C_9H_{13}O_4Cl$: C, 48.99; H, 5.94; Cl, 16.07. Found: C, 49.01; H, 6.01; Cl, 16.13.

**Ethyl 3-Hydroxy-5-isoxazoleacetate (IV)**——A mixture of sodium hydroxide (28 g, 0.7 mole), water (140 ml), hydroxylamine hydrochloride (10.43 g, 0.15 mole) and EtOH (280 ml) was cooled to −35° in an acetone–dry ice bath. To the stirred mixture was added a solution of diethyl 3-chloro-*cis*-glutaconate (VIIa) (30.28 g, 0.1373 mole) in EtOH (50 ml) during 2 min. The reaction temperature rose to −23°. After 1 hr's stirring the reaction mixture was allowed to stand at room temperature (18—20°) for a night. The red-brown mixture was neutralized with conc. HCl (60 ml) under ice-cooling and evaporated to dryness under reduced pressure. To the residue was added anhydrous EtOH (62 ml), benzene (130 ml) and conc. $H_2SO_4$ (0.5 ml). The mixture was refluxed for 24hr to remove 80 ml of the azeotrope, cooled and poured into 60 ml of ice-water. The organic layer was separated and the aqueous layer was extracted with 30 ml of benzene. The combined organic solution was washed with 2% $NaHCO_3$ (15 ml × 2) to remove dark colored resinous materials, water (30 ml × 2) and dried over $Na_2SO_4$. Evaporation of the solvent gave 14.10 g (60.1%) of white solid of IV. Recrystallization from a small amount of $(C_2H_5)_2O$ gave colorless needles of mp 78—79°. IR $\nu_{max}$ $cm^{-1}$ ($CHCl_3$)$\delta$: 3500—2300 (associated OH), 1742 ($-CO_2Et$), 1628, 1528 (ring modes). UV (Cary Model 14) $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 206 (7,080). NMR ($CDCl_3$) $\delta$: 11.03 (1H, s, −OH), 5.98 (1H, s, $C_4$-H), 4.23 (2H, q, $J=7$ cps, $-O-CH_2-$), 3.72 (2H, s, $-CH_2-CO_2Et$), 1.28 (3H, t, $J=7$ cps, $CH_3$). *Anal.* Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18. Found: C, 48.92; H, 5.26; N, 8.35.

The similar reaction of diethyl 3-chloro-*trans*-glutaconate (VIIb) (3.04 g, 13.7 mmoles) as described above gave IV (1.25 g, 53.4%).

17) A.R. Gagneux, F. Häfliger, C.H. Eugster and R. Good, *Tetrahedron Letters*, **1965**, 2077.
18) Geigy A.G., Dutch Patent 66,07677 and 66,07413.
19) T. Yokobe and T. Takemoto, *Yakugaku Zasshi*, **89**, 1236 (1969).
20) All melting points were not corrected. In NMR spectra tetramethylsilane was used as the internal standard.

**Ethyl 3-Benzenesulfonyloxy-5-isoxazoleacetate (IX)**——To a mixture of IV (3.42 g, 20 mmoles), triethyl amine (2.22 g, 22 mmoles) and anhydrous benzene (15 ml) was added dropwise benzensulfonyl chloride (3.53 g, 20 mmoles). An exothermic reaction occurred and triethylamine hydrochloride precipitated. After the reaction mixture was refluxed for 1 hr, 20 ml of water was added. The organic layer was washed with water (20ml) and dried over $Na_2SO_4$. Evaporation of the solvent left 6.18 g (99%) of oily ethyl 3-benzenesulfonyloxy-5-isoxazoleacetate (IX), which was used for further reactions. NMR ($CDCl_3$) $\delta$: 7.25—8.05 (5H, aromatic multiplet), 6.30 (1H, broad s, $C_4$-H), 4.16 (2H, q, $J=7$ cps, $-O-CH_2$), 3.73 (2H, broad s, allylic $-CH_2-$), 1.25 (3H, t, $J=7$ cps, $-CH_3$). IR $\nu_{max}$ $cm^{-1}$ (liq.): 1742 ($CO_2Et$), 1613, 1484 (ring modes), 1392, 1199 ($-OSO_2-$). Vacuum distillation afforded an analytical sample of bp 164—168° (0.01 mmHg, bath temp.), but about half of the crude IX resinified during the distillation. *Anal.* Calcd. for $C_{13}H_{13}O_6NS$: C, 50.16; H, 4.21; N, 4.50; S, 10.28. Found: C, 50.03; H, 4.29; N, 4.55; S, 10.30.

**Ethyl α-Bromo-3-benzenesulfonyloxy-5-isoxazoleacetate (X)**——A mixture of IX (33.0 g, 0.1061 mole), finely divided NBS (29.6 g, 0.159 mole), benzoyl peroxide (2.0 g) and carbon tetrachloride (320 ml) was refluxed for 34 hr under irradiation of an UV lamp (Ishii). Another portion of NBS (17.9 g, 0.1061 mole) and benzoyl peroxide (1.0 g) was added and the whole mixture was refluxed under irradiation for further 36 hr. After cooling, the carbon tetrachloride solution was filtered and evaporated to dryness under reduced pressure. The oily residue (45.4 g) was chromatographed on a column of $SiO_2$ (Kanto Kagaku Co., 400 g). Elution was with 1.6 liters of 50% benzene–hexane, 3.0 liters of 66% benzene–hexane and 8.0 liters of benzene with 250 ml fractions being collected. Fractions No. 20—44 gave colorless oil of X (23.61 g, 54.6%), which decomposed on high-vacuum distillation ($10^{-3}$ mmHg). NMR ($CDCl_3$) $\delta$: 7.2—8.1 (5H, aromatic multiplet), 6.57 (1H, s, $C_4$-H), 5.30 (1H, s, α-hydrogen), 4.27 (2H, q, $J=7$ cps, $-OCH_2Me$), 1.30 (3H, t, $J=7$ cps, $-CH_3$). *Anal.* Calcd. for $C_{13}H_{12}O_6NSBr$: C, 40.01; H, 3.10; N, 3.59; Br, 20.48. Found: C, 39.94; H, 3.08; N, 3.49; Br, 20.87. Further elution with 600 ml of 16% methanol–chloroform gave 10.68 g (32.3%) of the starting ester (IX).

***dl*-Ibotenic Acid (I)**——A mixture of X (7.80 g, 20 mmoles), conc. HCl (30 ml) and AcOH (60 ml) was kept at 28° for 15 hr, and concentrated to dryness under reduced pressure on a water bath at 40°. The oily residue was dissolved in conc. $NH_4OH$ (100 ml) under ice water cooling. After allowed to stand for 15 hr, the mixture was evaporated to dryness under reduced pressure. Water (20 ml) was added to the residue and insoluble benzenesulfonamide (2.00 g, 63.7%) was collected by filtration, washed with water (5 ml × 2), dried and recrystallized from water to afford colorless leaflets of mp 146—148°, which was identical with an authentic specimen of benzene sulfonamide. *Anal.* Calcd. for $C_6H_7O_2NS$: C, 45.86; H, 4.49; N, 8.92; S, 20.36. Found: C, 45.73; H, 4.48; N, 8.74; S, 20.10. The aqueous filtrate and the washings were combined and evaporated to dryness under reduced pressure. The residue was slurried in MeOH (50 ml) and stirred magnetically for 2 hr. The precipitated ammonium salt of I (XIII) (2.24 g, mp 121—123° (d)) was filtered and washed with MeOH (5 ml × 2). NMR ($D_2O$) $\delta$: 5.90 (1H, s) 4.92 (1H, s). A solution of the ammonium salt (XIII) (2.00 g) in water (30 ml) was passed through a column containing Amberlite IR-120 ($H^+$ form, 50 ml). Elution with water gave the fraction (1280 ml) containing I after rejection of the dark brown first effluent (220 ml). Evaporation of water under reduced pressure on a water bath at 30° afforded white solid of ibotenic acid monohydrate (I) (1.57 g, 50.0% from X) of mp 139—142° (d). Recrystallization from water gave colorless prisms of mp 144—146° (d) (0.766 g), which was identical with a natural sample in IR, paper- and thin-layer chromatography.[9] The mother liquor was treated with a small amount of charcoal, evaporated to dryness and the residue was recrystallized from water to give further prisms of I (0.493 g, mp 144—146° (d)). *Anal.* Calcd. for $C_5H_8O_5N_2$: C, 34.09; H, 4.58; N, 15.91. Found: C, 33.82; H, 4.64; N, 15.87.

The monohydrate (I) (73 mg) was slurried in MeOH (2 ml) and the solvent was removed by decantation. This operation was repeated twice and finally the precipitate was dried to afford anhydrous ibotenic acid (64 mg) of 151—152° (d). *Anal.* Calcd. for $C_5H_6O_4N_2$: C, 37.98; H, 3.83; N, 17.72. Found: C, 37.83; H, 4.04; N, 17.47. Recrystallization from water gave the monohydrate of mp 144—146° (d).

**The Reaction of X with Liquid Ammonia**——A solution of X (3.635 g, 9.3 mmoles) in $(C_2H_5)_2O$ (15 ml) was added dropwise to liquid ammonia (50 ml) at −53——−49° during 20 min. After stirring for 17 hr at that temperature, the cooling bath was removed and the solvent was allowed to evaporate at room temperature. To the residue was added anhydrous EtOH (16 ml). The insoluble material was filtered off and washed with EtOH (2 ml × 4). The alcoholic filtrate and washings were combined and evaporated to dryness under reduced pressure. The residual solid substance (2.868 g) was extracted with boiling chloroform (30 ml × 2). The extracts were combined and evaporated to give benzenesulfonamide (0.759 g, 51.8%), whose IR spectrum was identical with that of an authentic sample. The chloroform insoluble matter was dissolved in EtOH (2 ml), filtered and the solvent was evaporated to dryness. The residue was washed with water (2 ml × 2) and dried, leaving crude 1,2-dicarbethoxy-1,2-bis-(3-hydroxy-5-isoxazolyl)ethylene (XVI) (0.311 g, 19.7%). Recrystallization from aq. MeOH gave white needles of mp 192—195° (d). IR $\nu_{max}$ $cm^{-1}$ (Nujol): 2300—3200 (associated OH), 1730 ($CO_2Et$), 1613, 1602, 1527, 949 (isoxazole ring). NMR ($(CD_3)_2CO$) $\delta$: 6.11 (2H, s, $C_4$-H of the isoxazole ring), 4.36 (4H, q, $J=7$ cps, $-O-CH_2-Me$), 1.32 (6H, t, $J=7$ cps, $-CH_3$). Mass Spectrum *m/e*: 338 ($M^+$), 293 ($M^+ -45$), 265 ($M^+ -73$). *Anal.* Calcd. for $C_{14}H_{14}O_8N_2$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.81; H, 4.16; N, 8.41.

**3-Hydroxy-5-isoxazoleacetic Acid Hydrazide (XIV)**——The ester (IV) (4.46 g, 26.1 mmoles) was added portionwise to 100% hydrazine hydrate (1.35 g, 27 mmoles), which had been heated on a water bath at 94°. The mixture was heated for 3 hr on the water bath. After cooling, the mixture crystallized and was recrystallized from MeOH to afford white small needles of 3-hydroxy-5-isoxazoleacetic acid hydrazide, mp 170—173°. Yield, 2.64 g. Concentration of the mother liquor gave further crystals of mp 168—171° (1.18 g). Total yield, 3.82 g (93.1%). Analytical sample of mp 174—175° was obtained by further recrystallization from MeOH. IR $\nu_{max}$ $cm^{-1}$ (KBr): 3289, 3164 (NH), 2200—3500 (associated OH and NH), 1656 (C=O). *Anal.* Calcd. for $C_5H_7O_3N_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.23; H, 4.77; N, 26.82.

**3-Hydroxy-5-(carbethoxyamino)methylisoxazole (XV)**——A solution of (XIV) (3.41 g, 21.7 mmoles) in THF (30 ml) was mixed with a solution of dry hydrogen chloride in THF (6.55 ml, 9.94N). To this mixture cooled to −50° in a dry ice–acetone bath was added dropwise a solution of iso-amyl nitrite (2.81 g, 23 mmoles) in THF (10 ml) in 5 min. The cooling bath was removed and the mixture was allowed to stand for 15 min, and then stirred for additional 15 min at 15°. The insoluble material was filtered off and the solution was evaporated *in vacuo* to dryness. The residue was dissolved in ethyl acetate (80 ml), washed with a mixture of satd. aqueous $NaHCO_3$ and satd. aqueous NaCl solution (1:9, 20 ml×2), satd. aqueous NaCl solution (20 ml×2) and dried over $MgSO_4$. After the evaporation of the solvent, the oily residue was dissolved in anhydrous EtOH (40 ml) and heated on an oil bath to reflux for 45 min. After cooling, the solvent was evaporated *in vacuo*, leaving semi-crystallized material. The crystalline substance was separated by suction filtration and washed with benzene. Thus obtained urethane (XV) was recrystallized from benzene to afford white feathers of mp 126—128°. Yield, 1.21 g (30.0%). IR $\nu_{max}$ $cm^{-1}$ (KBr): 3333 (NH), 2300—3200 (associated NH or OH), 1700, 1524 (amide bands), 1634, 958 (isoxazole ring). NMR ($(CD_3)_2CO$)$\delta$: 6.65 (2H, broad m, –NH– and –OH), 5.83 (1H, broad s, $C_4$-H), 4.28 (2H, m, center, $-CH_2-$), 4.06 (2H, q, $J$=7 cps, $-O-CH_2-$), 1.18 (3H, t, $J$=7 cps, $-CH_3$). Mass Spectrum *m/e*: 186 ($M^+$), 157, 141, 130, 117, 113, 102, 98. *Anal.* Calcd. for $C_7H_{10}O_4N_2$: C, 45.16; H, 5.41; N, 15.05. Found: C, 44.95; H, 5.30; N, 15.04.

**3-Hydroxy-5-aminomethylisoxazole (Muscimol) (II)**——A mixture of XV (0.383 g, 2.05 mmoles) and 20% $Ba(OH)_2$ (8 ml) was refluxed for 15 hr. After cooling, the mixture was acidified with 10% $H_2SO_4$ to precipitate $BaSO_4$. The aqueous solution was filtered, diluted to a volume of 100 ml and introduced into a column containing Amberite IR-45 ($OH^-$ form, 20 ml). The resin was washed with water (20 ml) and transferred into a beaker with water (30 ml). The pH of the mixture was brought to 2.99 by adding AcOH. After 40 min stirring, the resin was filtered and washed with water (10 ml). The aqueous filtrate and washing were combined and evaporated *in vacuo*, leaving 0.110 g (47.0%) of muscimol (II). Recrystallization from MeOH gave colorless prisms of mp 172—174° (d), whose IR, NMR and mass spectra were identical with those of an authentic sample prepared by decarboxylation of ibotenic acid (I). *Anal.* Calcd. for $C_4H_6O_2N_2$: C, 42.10 H, 5.30; N, 24.55. Found: C, 42.34; H, 5.08; N, 24.79.