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SYNTHESIS OF IBOTENIC ACID

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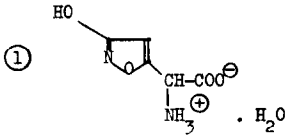
We wish to report the synthesis of ibotenic acid(1), a flykilling and narcosis potentiating dibasic amino acid, recently isolated from Amanita muscaria (L.) Fr. [1], Amanita strobiliformis (Paul) Quel. [2] and Amanita pantherina (DC.) Fr. [3]



① Heating 3-bromo-isoxazole-5-carboxylic acid② [4] in KOH/benzyl alcohol 1:20 (w/v) to 140° for 2 hours gave the corresponding benzyloxy-acid ③ a), m.p. 120-122° (7 b) : -0.54, 1H-singlet disappearing on addition of D_2O; 2.60, 5H-singlet; 3.30, 1H-singlet; 4.66, 2H-singlet) in 45% yield.

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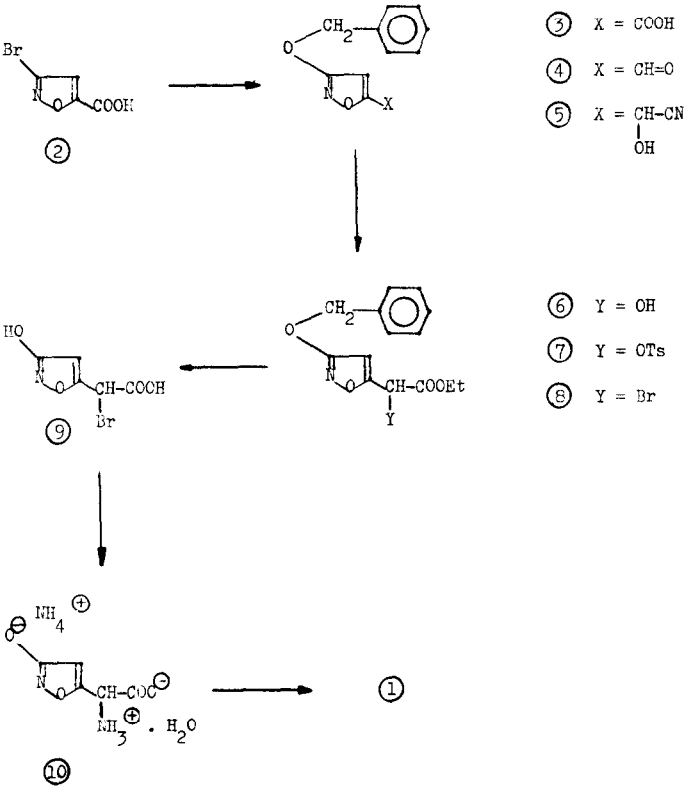
a) Satisfactory elemental analyses were obtained for all compounds except ⑨, which was not analyzed.

b) NMR-spectra in $CDCl_3$ were obtained with a Varian A-60 instrument using tetramethylsilane as an internal standard.

An essentially quantitative transformation to the aldehyde (4), (τ: 0.22, 1H-doublet, J~0.5 cps; 2.62, 5H-s.; 3.43, 1H-d. J~0.5 cps; 4.68, 2H-s.) was achieved by $LiAlH_4$-reduction of the ethylene-imide of (3).



Treatment of (4) with liquid HCN in the presense of NaCN at 20° gave rise to the cyanohydrin (5), m.p. 102-103° (τ: 2.60, 5H-s.; 3.80, 1H-d. J~0.5 cps; 4.45, 1H-d. J~0.5 cps; 4.76, 2H-s.; 5.25, 1H-s. disapp. D_2O), in 95% yield. When (5) was dissolved in ethanol of 20° saturated with dry HCl, the iminoester hydrochloride precipitated within 2 hours.

After hydrolysis at 20° ethyl 3-benzyloxy-5-isoxazolyl-glycolate (6), m.p. 50-55° ($\tilde{\nu}$: 2.62, 5H-s.; 4.00, 1H-d. J~0.5 cps; 4.76, 2H-s. 4.79 1H-δ. J~0.5 cps; 5.72; 2H-q. J = 7.2 cps; 6.05, 1H-s. disapp. D_2O; 8.76 3H-t. J = 7.2 cps) was isolated in 90% yield. Preparation of the corresponding p-toluene-sulfonate (7), m.p. 80-82°, yield 60% after chromatography on silicagel, followed by displacement of the tosylate group with NaBr in dimethylsulfoxide led to ethyl 3-benzyloxy-4-isoxazolyl-α-bromo-acetate (8), n_D^{21} 1.5458, yield 80%, ($\tilde{\nu}$: 2.62, 5H-s.; 3.74, 1H-d. J~0.5 cps; 4.68, 1H-d. J~0.5 cps; 4.73, 2H-s.; 5.70, 2H-q. J = 7.2 cps; 8.70, 2H-t. J = 7.2 cps).

Simultaneous hydrolysis of the ester- as well as the ether-function of (8) occured in 48% HBr/AcOH 2:3, within 15 hours at 30°. The resulting labile 5-hydroxy-5-isoxazolyl-α-bromo-acetic acid (9) was isolated as a viscous oil and dissolved in conc. aqueous ammonia without further purification. After 5 hours at 20°, excess reagent was evaporated at 30°, the residue stirred with methanol and tetrahydrofuran, filtered and dried in vacuo at 30° to yield 40% of the ammonia salt (10), m.p. 120° dec. Finally, chromatography of the latter on an Amberlite IR 120 ($H^{\oplus}$) ion exchanger using H_2O as an eluant, evaporation in vacuo at 30°, and drying over P_2O_5 for 12 hours, afforded the zwitterion hydrate (1), m.p. 150-152° dec. yield 90%. Its identity with natural ibotenic acid [1] was demonstrated by the easy decarboxylation [c] to pantherine [3,5], IR- and NMR-spectroscopy, thin layer chromatography als well as narcosis potentiation tests [d].

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c) Occuring upon dissolving in dimethylsulfoxide or refluxing in H_2O.

d) Carried out by Dr. W. Theobald, J.R. Geigy S.A., Basle, Switzerland.

REFERENCES

(1) C.H. Eugster, G.F.R. Müller and R. Good,
Tetrahedron Letters 23, 1813 (1965)

(2) T. Takemoto, T. Yokobe and T. Nakajima,
J. Pharm. Soc. Japan 84, 1186, 1232 (1964)

(3) T. Takemoto, T. Nakajima and R. Sakuma,
J. Pharm. Soc. Japan 84, 1233 (1964).

(4) R. Fusco and S. Rossi, Rend. Ist. Lombardo Sci. Pt. I. Classe
Sci. Mat. e Nat. 94A, 729 (1960, Chem. Abstr. 57, 16583 (1962).

(5) A.R. Gagneux, F. Häfliger, C.H. Eugster and R. Good,
Tetrahedron Letters 25, 2077 (1965)