

SYNTHESIS OF IBOTENIC ACID

A.R. Gagneux, F. Häfliger & R. Meier

J.R. Geigy S.A., Basle

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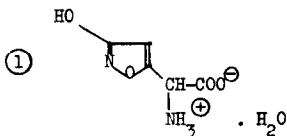
C.H. Eugster

Department of Organic Chemistry

University of Zurich, Switzerland.

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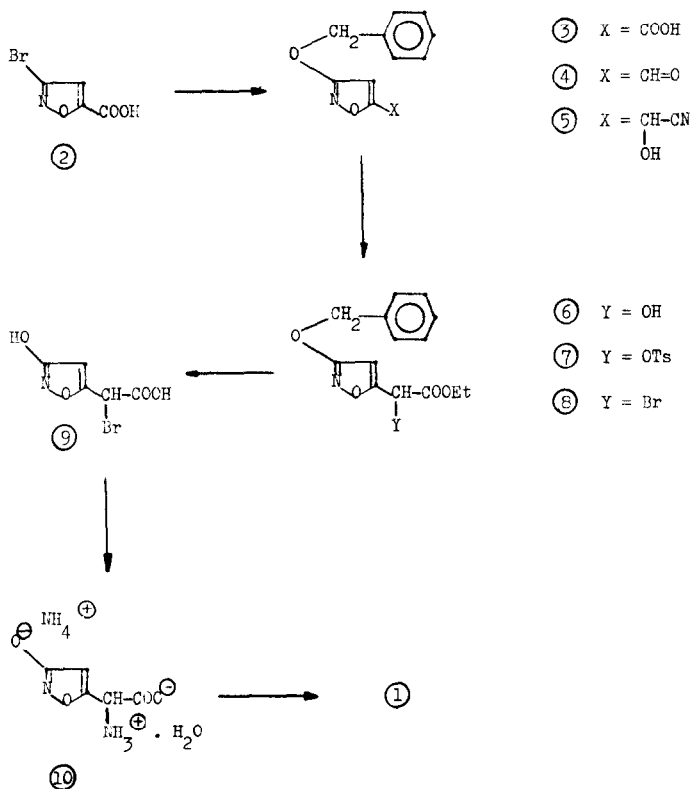
We wish to report the synthesis of ibotenic acid<sup>(1)</sup>, a flykilling and narcosis potentiating dibasic amino acid, recently isolated from Amanita muscaria (L.) Fr.<sup>(1)</sup>, Amanita strobiliformis (Paul) Quel.<sup>(2)</sup> and Amanita pantherina (DC.) Fr.<sup>(3)</sup>



Heating 3-bromo-isoxazole-5-carboxylic acid<sup>(2)</sup><sup>(4)</sup> in KOH/benzyl alcohol 1:20 (w/v) to 140° for 2 hours gave the corresponding benzyloxy-acid<sup>(3)</sup> a), m.p. 120-122° ( $\eta^b$ ): -0.54, 1H-singlet disappearing on addition of D<sub>2</sub>O; 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 <sup>(3)</sup>, which was not analyzed.  
b) NMR-spectra in CDCl<sub>3</sub> were obtained with a Varian A-60 instrument using tetramethylsilane as an internal standard.

An essentially quantitative transformation to the aldehyde (4), ( $\tau$ : 0.22, 1H-doublet,  $J \sim 0.5$  cps; 2.62, 5H-s.; 3.43, 1H-d.  $J \sim 0.5$  cps; 4.68, 2H-s.) was achieved by  $\text{LiAlH}_4$ -reduction of the ethylene-imide of (3).



Treatment of (4) with liquid HCN in the presence of NaCN at  $20^\circ$  gave rise to the cyanohydrin (5), m.p.  $10^\circ-103^\circ$  ( $\tau$ : 2.60, 5H-s.; 3.80, 1H-d.  $J \sim 0.5$  cps; 4.45, 1H-d.  $J \sim 0.5$  cps; 4.76, 2H-s.; 5.25, 1H-s. disapp.  $\text{D}_2\text{O}$ ), in 95% yield. When (5) was dissolved in ethanol of  $20^\circ$  saturated with dry HCl, the iminester 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.; 4.06, 1H-d.  $J \sim 0.5$  cps; 4.76, 2H-s. 4.79 1H- $\zeta$ .  $J \sim 0.5$  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- $\alpha$ -bromo-acetate (8),  $n_D^{21}$  1.5458, yield 80%, ( $\tilde{\nu}$ : 2.62, 5H-s.; 3.74, 1H-d.  $J \sim 0.5$  cps; 4.68, 1H-d.  $J \sim 0.5$  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) occurred in 48% HBr/AcOH 2:3, within 15 hours at 30°. The resulting labile 5-hydroxy-5-isoxazolyl- $\alpha$ -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 ( $H^+$ ) 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 <sup>c)</sup> to pantherine (3,5), IR- and NMR-spectroscopy, thin layer chromatography als well as narcosis potentiation tests <sup>d)</sup>.

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. Gagnoux, E. Häfliger, C.H. Eugster and R. Good,  
Tetrahedron Letters 25, 2077 (1965)