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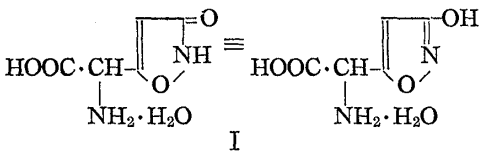
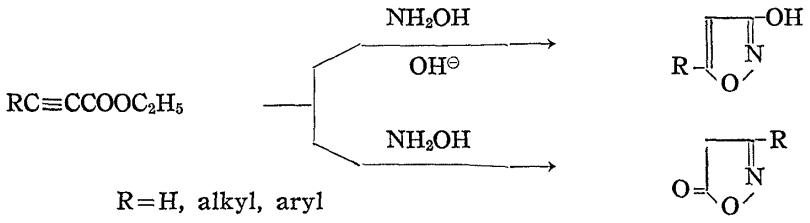
Studies on Acetylenic Compounds. XLIII.*1 Synthesis of Ibotenic Acid.

In 1964 a flycidal constituent "ibotenic acid" was isolated by Takemoto, *et al.* from *Amanita strobiliformis* (PAUL.) QUEL. (Japanese name : Ibotengutake),[1] *A. muscaria* (FR.) S. F. GRAY (Benitengutake) and *A. pantherina* (DC.) FR. (Tengutake).[2] The structure of this new amino acid having good taste was elucidated by them to be α-amino-3-oxo-4-isoxazoline-5-acetic acid, *e.g.* α-amino-3-hydroxy-5-isoxazoleacetic acid (I).[3]



I

The authors have found that the derivatives of propiolic acid ester react with hydroxylamine in the presence of base to afford 3-hydroxyisoxazoles, whereas the same reagents form 5-isoxazolones under neutral conditions.*2 We wish to report an application of this cyclization reaction to the synthesis of ibotenic acid.*3



The reaction of the Grignard reagent prepared from propargyl aldehyde diethyl acetal (Ⅱ) and ethyl magnesium bromide with solid carbon dioxide in an autoclave followed by esterification gave ethyl 4,4-diethoxytetrolate (Ⅳ) of b.p_5 103~105°*4 in 60% yield. Ⅳ reacted with hydroxylamine in 50% ethanol in the presence of sodium hydroxide at 30° to afford 3-hydroxy-5-isoxazolecarboxaldehyde diethyl acetal (Ⅵ) in 87% yield, m.p. 86~87°, IR $\nu_{max}^{CCl_4}$ cm^{-1} : 2646~2900 (associated OH), 1628, 1526, 1315 (isoxazole ring), NMR (δ, p.p.m. from TMS in CCl_4) : 11.12 (1H, singlet, -OH), 5.96 (1H, singlet, C_4-H), 5.44 (1H, singlet, C<u>H</u>$(OEt)_2$), 3.60 (4H, quartet), 1.20 (6H, triplet). When the temperature was kept at 10~15° throughout this reaction, only 4,4-diethoxytetrolohydroxamic acid (Ⅴ), m.p. 73~74°, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3247 (associated OH), 2267 (-C≡C-), 1666 (>C=O), was obtained in 65% yield. Ⅴ afforded Ⅵ in 77% yield, when treated with a mixture of ethanol and 10% sodium hydroxide (1:1) at 30°. Therefore, it was confirmed that Ⅵ was a 3-hydroxyisoxazole. Hydrolysis of Ⅵ with 50% acetic acid quantitatively formed the corresponding 3-hydroxy-5-isoxazolecarboxaldehyde (Ⅶ), m.p. 141~142°. IR spectrum of Ⅶ (KBr pellet) showed a strong aldehyde absorption band

*1 Part XLⅡ. T. Hiraoka, I. Iwai : This Bulletin, in press.

*2 The paper on this reaction will be published in the near future.

*3 i) Y. Kishida, T. Hiraoka, N. Nakamura : Patent application (12th, June, 1965). ii) This work is to be presented on 29th, October, 1965, at the 85st Annual Meeting of Pharmaceutical Society of Japan, in Tokushima. iii) Professor T. Takemoto briefly referred to this work in his lecture at Kanden Hall in Osaka, on the 12th of October, 1965. iv) After all of this work was completed, we have been aware of the appearance of an independent achievement of the synthesis of ibotenic acid by Swiss workers : A. R. Gagneux, F. Häfliger, R. Meier, C. H. Eugster : Tetrahedron Letters, **1965**, 2081.

*4 All melting points are uncorrected and satisfactory elemental analyses were obtained for all compounds reported here. NMR spectra were taken on Varian A-60 spectrometer with Me_4Si and 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as an internal standard.

1) T. Tak emoto, T. Yokobe, T. Nakajima : Yakugaku Zasshi, 84, 1186 (1964).
2) T. Takemoto, T. Nakajima, R. Sakuma : *Ibid.*, 84, 1233 (1964).
3) T. Takemoto, T. Nakajima, T. Yokobe : *Ibid.*, 84, 1232 (1964).

at 1713 cm^{-1}, which disappeared in deuterium oxide. It suggests that the aldehyde (Ⅶ) forms the hydrate (Ⅷ) in water. This interpretation was further supported by the NMR spectra : in deuterium oxide, two peaks at 6.05 and 6.18 p.p.m. (J=0.7 c.p.s.); in hexadeuterodimethyl sulfoxide, at 6.45 and 9.01 p.p.m.

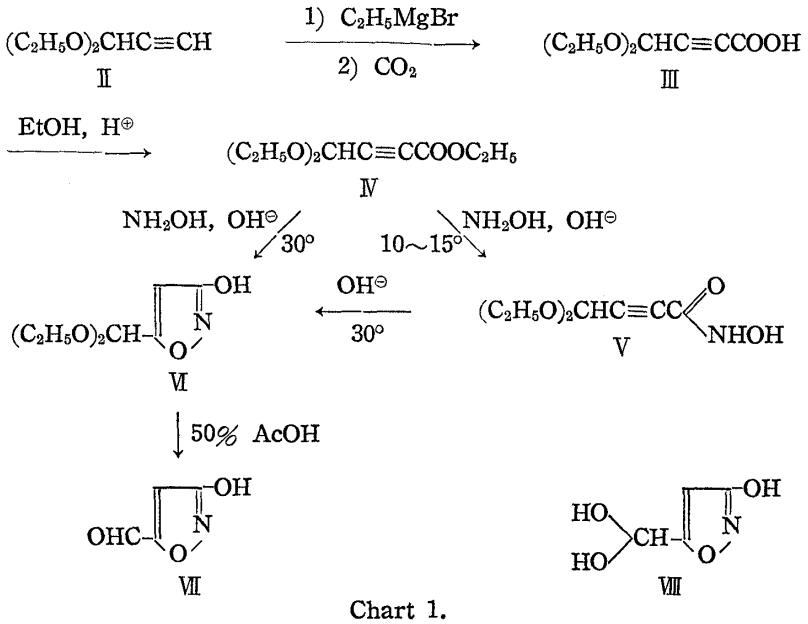


Chart 1.

The authors succeeded in the synthesis of ibotenic acid by Strecker reaction or Bücherer reaction of the aldehyde (Ⅶ) as is indicated in Chart 2. Any attempt to isolate the intermediate aminonitrile or hydantoin was unsuccessful and the reaction mixture was immediately hydrolysed by 10% potassium hydroxide or sodium hydroxide : i) Zelinsky's method[4] (Strecker reaction); To an aqueous ammonia solution of sodium cyanide and ammonium chloride was added the aldehyde (Ⅶ) under cooling and after standing overnight at room temperature, alkali was added and heated at 90° for 6 hours. ii) Bücherer's method;[5,6] Ⅶ, sodium cyanide and ammonium carbonate were dissolved in water and warmed at 80° for 2 hours, then alkali was added and heated at 90° for 2 hours.

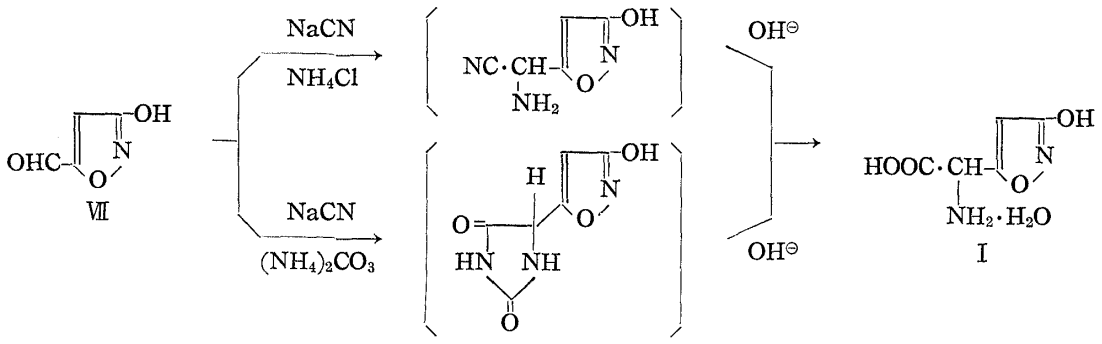


Chart 2.

The isolation of ibotenic acid from the reaction mixture was carefully done by the successive column chromatography using Amberlite IR-120, IRC-50 and finally IR-45

4) N. Zelinsky, G. Stadnikoff : Ber., **41**, 2061 (1908).
5) H. T. Bücherer, V. A. Lieb : J. prakt. Chem., **141**, 5 (1934).
6) H. R. Henze, R. J. Speer : J. Am. Chem. Soc., **64**, 522 (1942).

with 0.1*N* acetic acid. Recrystallization from water gave colorless prisms of I, m.p. 151~152° (decomp.).

Infrared spectrum in Nujol mull of the synthesized ibotenic acid (I) was completely superimposable on that of the natural ibotenic acid. Paper chromatography (solvent; butanol-acetic acid-water=4:1:1), thin-layer chromatography on cellulose powder (solvent; butanol-acetic acid-pyridine-water=15:3:10:12) also proved the complete identity.

This work was especially accelerated by the encouragement of Dr. Iwai of this laboratory whom the authors deeply appreciate. The authors are also very grateful to Professor T. Takemoto, Tohoku University, for supplying us with a sample of natural ibotenic acid.

Central Research Laboratories,
Sankyo Co., Ltd.,
Shinagawa-ku, Tokyo

Yukichi Kishida (岸田有吉)
Tetsuo Hiraoka (平岡哲夫)
Junya Ide (井手純也)
Atsusuke Terada (寺田敦祐)
Norio Nakamura (中村紀雄)

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The Constitution of Anomalin, a New Coumarin Isolated from the Root of *Angelica anomala* Lall. (Umbelliferae)

Angelica anomala Lall. is a stout herb widely distributed in northeastern Asia, and it has been regarded as one of the original plants of "Pai-chi," Chinese Angelica root.

In the previous paper,[1] it was reported that two known coumarins, umbelliferone and bergapten, were isolated from the ether extract of dried root of this species collected from Aomori Prefecture. Recently, a new blue-fluorescent compound, $C_{24}H_{26}O_7$, m.p. 173~174°, $[\alpha]_D^{27}$ −78.4° (EtOH), named anomalin (I), was isolated by silica gel column chromatography from the ether extract. The present communication concerns the structure elucidation of the compound.

Anomalin is freely soluble in ethyl acetate, benzene and chloroform, and sparingly soluble in ethanol, ether and hexane. It crystallizes from ethanol in colorless needles and it gives no reaction towards phenol and carbonyl reagents.

Its ultraviolet spectrum, maxima at 323 mμ and minima at 265 μ, is very similar to those reported for a number of 7-oxygenated coumarins.[2,3]

The infrared spectrum of anomalin reveals the presence of a conjugated lactone, an ester and an aromatic group. These spectra and blue-fluorescence indicate its coumarin structure which has been subsequently confirmed from chemical evidence discussed in the sequel.

The NMR spectrum of anomalin shows two pairs of doublet with intensities corresponding to one proton each, one pair appearing at τ 2.38 and 3. 80 (J=9.5 c.p.s.) can be assigned to protons at the 4- and 3-position respectively, and the other at τ 2.60 and 3.18 (J=8.5 c.p.s.) for the *ortho*-protons in the benzene ring. Further signals are observed at τ 3.30 and 4.56 (each 1H, doublet, J=5 c.p.s.), at τ 3.92 (2H, multiplet) and

1) K. Hata, M. Kozawa, K. Yen, Y. Kimura: Yakugaku Zasshi, **83**, 611 (1963).
2) R.E. Willette, T.O. Soine: Journal of Pharmaceutical Sciences, **51**, 149 (1962).
3) E. Smith, N. Hosansky, W.G. Bywater, E.E. van Tamelen: J. Am. Chem. Soc., **79**, 3534 (1957).