evaporated to dryness *in vacuo*. The residue was extracted with two 80 ml. portions of hot EtOH. The filtered EtOH extract was saturated with dry HCl and then evaporated *in vacuo* to about 3 ml. The residue was chilled by addition of ether to yield, 0.35 g. of corresponding hydroxymethyl compound hydrochloride (Ⅸ), m.p. 160~165°. This material was recrystallized from EtOH-ether to colorless needles, m.p. 169~170°. A mixed melting point of this substance with authentic Ⅸ undepressed.

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Summary

Condensation of I with several dienophiles caused three types of reaction, *i.e.* reaction A, B, and C; reaction B and C afforded 3-pyridinol derivatives. A likely mechanism of these reactions are considered as Diels-Alder's condensation of I with dienophiles and subsequent aromatization to pyridine nuclei.

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〔Added in Proof〕 After this work was completed, a patent which claims the preparation of dimethyl analogue of Ⅶ by condensation of I with dimethyl fumarate in nitrobenzene was seen. (Hoffman La-Roche & Co. A.G.: Fr. Pat.. 1,343,270 (1963), C.A., **60**, 11991 (1964)).

〔Chem. Pharm. Bull. 13(7) 878~881 (1965)〕 *UDC 547.823.07*

115. Toru Yoshikawa, Fumiyoshi Ishikawa, and Takeo Naito: Synthesis of 3-Pyridinols. III.*1 Synthesis of Pyridoxine Skeletons from 4-Methyloxazole.*2

(*Central Research Laboratory, Daiichi Seiyaku Co., Ltd.**3)

The preceding paper*1 has reported that condensation of 4-methyloxazole (I) with several dienophiles in acetic acid caused three types of reactions, *i.e.* reaction A, B, and C, in which reaction B and C afforded 2-methyl-3-pyridinol derivatives, and that a compound having pyridoxine-like structure, diethyl 5-hydroxy-6-methyl-3,4-pyridinedicarboxylate, was obtained by the reaction of I with diethyl fumarate or maleate. In the present paper, emphasis has been placed on synthesis of pyridoxine skeletons from I.

For purpose of application of reaction B to synthesis of a pyridoxine skeleton, I was allowed to react with 2-methoxymethyl-4-methoxycrotononitrile and a compound (Ⅱ) of syrupy oil (hydrochloride, m.p. 144°, picrate, m.p. 168°.) was obtained in poor yield. The mixed melting point of the picrate of Ⅱ with that of 2-methyl-4,5-bis-(methoxymethyl)-3-pyridinol prepared by Pfister's method[1] did not show depression.

*1 Part Ⅱ: This Bulletin, **13**, 873 (1965).
*2 A Part of this paper was presented at the Kanto Branch Meeting of the Pharmaceutical Society of Japan, Tokyo, September 19, 1964.
*3 Minamifunabori-cho, Edogawa-ku, Tokyo (吉川 徹, 石川文義, 内藤武男).
1) K. Pfister, 3rd, E.E. Harris, R.A. Firestone: Belg. Pat., 617,500 (1962). (C.A., **59**, 581 (1963)).

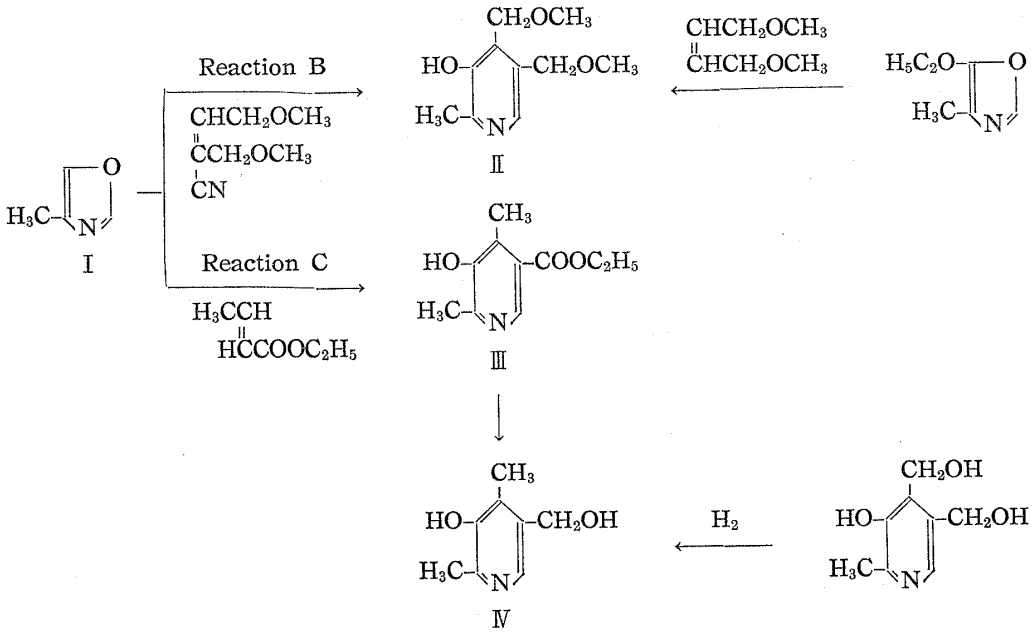

Chart 1.

Moreover, reaction C was applied to synthesis of such skeletons as follows. Since ethyl acrylate has predominantly given rise to reaction C,*1 in the present work, a homologue of ethyl acrylate, namely ethyl crotonate, was employed as a reaction agent. Condensation of this agent with I afforded in poor yield a product (Ⅲ) of m.p. 146~148°, $C_{10}H_{13}O_3N$, which exhibited a carbonyl group band in the infrared spectrum and gave positive Gibbs' test. Ⅲ was reduced with lithium alminum hydride to the corresponding hydroxymethyl compound hydrochloride (Ⅳ), m.p. 255°, which was identical with 4-deoxypyridoxine hydrochloride obtained by Heyl's method.[2] Thus, Ⅲ was established to be ethyl 5-hydroxy-4,6-dimethylnicotinate.

Recently, it has been reported by Okamoto, *et al.*[3] and Feely, *et al.*[4] that picolino- or isonicotino-nitriles were obtained by the reaction of cyanide anion with 1-alkoxy-pyridinium salts. In order to prepare pyridoxine skeletons, Okamoto's method was applied to 5-hydroxy-6-methylnicotinonitrile (Ⅴ), which has been obtained in 71% yield by the reaction of I with fumaronitrile as described previously.*1

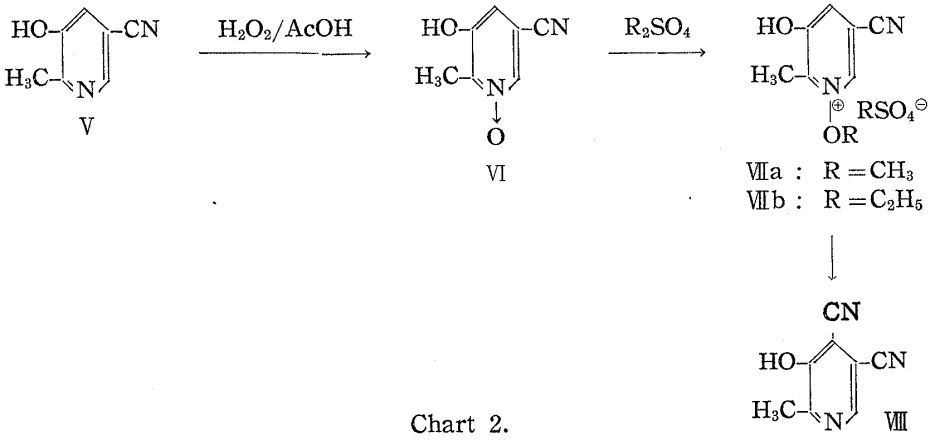

Chart 2.

2) D. Heyl, S. A. Harris, K. Folkers : J. Am. Chem. Soc., **75**, 653 (1953).
3) T. Okamoto, H. Tani : This Bulletin, **7**, 130 (1959).
4) W. E. Feely, E. M. Beavers : J. Am. Chem. Soc., **81**, 4004 (1959).

N-Oxidation of V with hydrogen peroxide in hot acetic acid gave 5-hydroxy-6-methylnicotinonitrile 1-oxide (VI), m.p. 278~280°, in 73% yield. Reaction of VI with dimethyl or diethyl sulfate yielded oily 1-methoxy-2-methyl-3-hydroxy-5-cyanopyridinium methosulfate (VIIa) or 1-ethoxy ethosulfate analogue (VIIb), m.p. 129~130°, respectively. From VIIa with pottasium cyanide in aqueous solution 5-hydroxy-6-methyl-3,4-pyridinedicarbonitrile (VIII), m.p. 188~189°, (79% yield from VI), was obtained and was identical with an authentic sample prepared by Harris' method.[5] VIII was derived to pyridoxine in good yield according to the procedure described in literature.[5]

By the reaction of 1-alkoxypyridinium salt (VIIa) with cyanide anion, 3,4-pyridinedicarbonitrile derivative (VIII) was exclusively afforded and no 2,3-dicarbonitrile derivative was isolated. This result seems not only interesting in view of the reaction mechanism but also fortunate for the synthesis of pyridoxine. Moreover, this method may provide a simple route to isotopically labelled pyridoxine.

Experimental*4

2-Methoxymethyl-4-methoxycrotononitrile——To a solution of 1.23 g. of KOH in 12 ml. of MeOH was added 5.5 g. of 2,3-dibromo-1,4-dimethoxybutane, and this mixture was refluxed for 1 hr. After addition of H_2O, the resulting mixture was extracted by $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4 and distilled. 2-Brom-1,4-dimethoxy-2-butene was obtained as colorless oil, $b.p_{12}$ 75~78°. 2.2 g. (56%). *Anal.* Calcd. for $C_6H_{11}O_2Br$: C, 36.93; H, 5.68. Found: C, 36.63; H, 5.66.

A mixture of 5.5 g. of 2-bromo-1,4-dimethoxy-2-butene, 3.5 g. of CuCN was heated in autoclave at 150° for 7 hr. The mixture was evaporated and to the residue $CHCl_3$ was added. Insoluble substance was filtered off, and filtrate was washed by H_2O, dried over Na_2SO_4 and distilled. 2-Methoxymethyl-4-methoxycrotononitrile was obtained as colorless oil, $b.p._8$ 84~86°, 2.9 g. (73%). IR cm^{-1}: $\nu_{C\equiv N}$ 2230. *Anal.* Calcd. for $C_7H_{11}O_2N$: N, 9.92. Found: N, 10.03.

2-Methyl-4,5-bis(methoxymethyl)-3-pyridinol (II)——A mixture of 0.8 g. of 4-methyloxazole, 2.1 g. of 2-methoxymethyl-4-methoxycrotononitrile, 0.2 ml. of H_2O and 4 ml. of glac. AcOH was heated in sealed tube at 95° for 40 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed in $CHCl_3$ over Al_2O_3, and from EtOH-$CHCl_3$ (5:95) elute crude syrupy product was obtained. To a solution of this material in dry iso-PrOH-HCl, dry ether was added. Precipitated 2-methyl-4,5-bis(methoxymethyl)-3-pyridinol hydrochloribe was recrystallized from iso-PrOH to yield pure substance, m.p. 143~144° (lit.[1] m.p. 144°).

To a solution of crude syrupy product in EtOH, picric acid-EtOH was added, and precipitated picrate, m.p. 168°, was identified by admixture and by the IR spectrum with authentic sample prepared by Pfister's method.

Ethyl 5-Hydroxy-4,6-dimethylnicotinate (III)——A mixture of 0.80 g. of 4-methyloxazole, 2.3 g. of ethyl crotonate, 0.18 ml. of H_2O and 3 ml. of glac. AcOH was heated in sealed tube at 90° for 20 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed in $CHCl_3$ over Al_2O_3, and from EtOH-$CHCl_3$ (5:95) elute 0.2 g. of crude product was obtained. Recrystallization from acetone afforded pure ethyl 5-hydroxy-4,6-dimethylnicotinate as colorless needles, m.p. 146~148°. IR cm^{-1}: $\nu_{C=O}$ 1730. *Anal.* Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N. 7.18. Found: C, 61.18; H, 6.65; N, 7.37.

5-Hydroxymethyl-2,4-dimethyl-3-pyridinol (4-deoxypyridoxine) (IV)——To a mixture of 50 mg. of $LiAlH_4$ in 15 ml. of dry tetrahydrofuran was added a solution of 80 mg. of II in 15 ml. of dry tetrahydrofuran, and the mixture was allowed to stand for 72 hr. at room temperature. AcOEt and then H_2O were added to the reaction mixture and resulting insoluble material was removed by filtration. After addition of dil. HCl to pH 2, the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH to yield 4-deoxypyridoxine hydrochloride as colorless plate, m.p. 255~257° (decomp.), which was identified by admixture and by IR spectrum with authentic sample prepared by Heyl's method.[2]

5-Hydroxy-6-methylnicotinonitrile 1-Oxide (VI)——To a hot solution of 4.0 g. of V in 90 ml. of glac. AcOH was added 6 ml. of 30% H_2O_2. The resulting mixture was heated at 100° for 1 hr., and with additional 6 ml. of 30% H_2O_2 for more 1 hr.; and after this procedure was repeated once more, heating was continued for 4 hr. The mixture was evaporated *in vacuo* to a half volume yielding 3.3 g. (73.4%) of

*4 All melting points are uncorrected.

5) E. E. Harris, R. A. Firestone, K. Pfister, 3rd, R. R. Boettcher, F. J. Cross, R. B. Currie, M. Monaco, E. R. Peterson, W. Reuter: J. Org. Chem., 27, 2705 (1962).

V, m.p. 278～280° (decomp.). IR cm^{-1}: $\nu_{C\equiv N}$ 2240. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.68; H, 4.08; N, 18.10.

1-Ethoxy-2-methyl-3-hydroxy-5-cyanopyridinium Ethosulfate (VIIb)——A mixture of 0.7 g. of VI and 0.7 g. of diethyl sulfate was heated at 100～110° for 2 hr. After cooling, solidified material was triturated with acetone, and filtered. VIIb was obtained as crysrals, 0.31 g. (82.1%), m.p. 129～130°. *Anal.* Calcd. for $C_{11}H_{16}O_6N_2S$: C, 43.41; H, 5.31; N, 9.22. Found: C, 43.75; H, 5.56; N, 9.06.

5-Hydroxy-6-methyl-3,4-pyridinedicarbonitrile (VIII)——A mixture of 0.6 g. of VI and 0.55 g. of dimethyl sulfate was heated at 100～110° for 2 hr. The resulting red brown syrup was dissolved in 5 ml. of H_2O. The solution was added to a solution of 0.65 g. of KCN dissolved in 8 ml. of H_2O dropwise with shaking at 5～7°, and allowed to stand for 1.5 hr. at room temperature. The reaction mixture was neutralized by dil. HCl to afford 0.55 g. of crystals, m.p. 189～190°, which was identified by admixture with VIII prepared by another route.[5]

The authors express their deep gratitude to Dr. J. Shinoda, Chairman of the Board of Direction, Dr. T. Ishiguro, President of this Company, and Dr. M. Shimizu, Director of this Laboratory, for their unfailing encouragement. Thanks are also due to Messrs. B. Kurihara and I. Ito and Miss K. Hanawa for elemental analysis.

Summary

Pyridoxine dimethyl ether (II) and 4-deoxypyridoxine (IV) were synthesized from I by reaction B and C, respectively. V was also derived to pyridoxine *via* VIII by application of Okamoto's method.

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