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114. Toru Yoshikawa, Fumiyoshi Ishikawa, Yoshiaki Omura, and Takeo Naito: Synthesis of 3-Pyridinols. II.[*1] Reaction of 4-Methyloxazole with Dienophiles.[*2]

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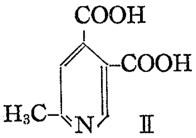
In the preceding paper,[*1] it was reported that 3-pyridinols were formed as main products by the reaction of 5-unsubstituted oxazoles with acrylonitrile and that a conceivable mechanism of this reaction is considered as Diels-Alder's condensation of those oxazoles with acrylonitrile followed by aromatization to 3-pyridinols under elimination of hydrogen cyanide. The present investigation was carried out to extend scope of this reaction and to elucidate the reaction mechanism.

For this purpose, 4-methyloxazole (I) was treated with twenty dienophiles, *i.e.* eighteen ethylenic and two acetylenic compounds, of which eight compounds, *i.e.* maleic anhydride, maleimide, fumaronitrile, acrylonitrile, diethyl fumarate, diethyl maleate, ethyl acrylate and ethyl *trans* 3-cyanoacrylate, afforded crystalline products as shown in table. In almost cases, the reactions were carried out in sealed tube by heating at 90~150° for several hours in acetic acid.

Table I. Dienophiles and Products

Dienophiles	Products (Yields)		
	A	B	C
Maleic anhydride	II (40%)	—	—
Maleimide	III (23%)	—	—
Fumaronitrile	—	IV (71%)	—
Acrylonitrile	—	V (28%)	IV (PPC)
Diethyl fumarate	—	VI (2%)	VII[a)] (PPC)
Diethyl maleate	—	VI (6%)	VII (PPC)
Ethyl acrylate	—	V (PPC)	VI (9%)
Ethyl *trans*-3-cyanoacrylate	—	VI (34%) IV (PPC)	—

a) By addition of hydrogen peroxide the yield of VI was increased to 27%.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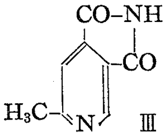
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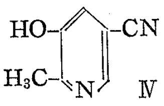
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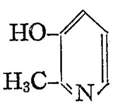
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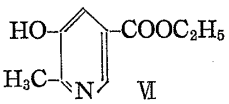
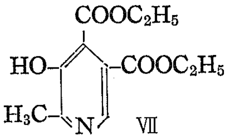

VI


VII

The condensation of I with maleic anhydride gave 6-methyl-3,4-pyridinedicarboxylic acid (II), and similarly the reaction with maleimide afforded the imide (III) of II. In these cases 3-pyridinol derivatives were not recognized in the reaction mixture even by paper partition chromatography (PPC). Then these reactions proceeded also in benzene instead of acetic acid.

[*1] Part I: This Bulletin, 13, 869 (1965).

[*2] A part of this paper was presented at the Kanto Branch Meeting of the Pharmaceutical Society of Japan, Tokyo, September 19, 1964.

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The reaction of I with funaronitrile was carried out, and a product of m.p. 246~247° (IV), $C_7H_6ON_2$, was obtained in 71% yield, when this yield was the highest one among the products synthesized herein. IV was considered to be a 4- or 5-cyano-2-methyl-3-pyridinol because of its infrared absorption band at $2220\,cm^{-1}$ ($C\equiv N$ group) and its positive Gibbs' test. Structure of IV was determined as indicated in Chart 1: hydrogenation of IV gave the corresponding aminomethyl derivative dihydrochloride (VIII), $C_7H_{10}ON_2 \cdot 2HCl$, m.p. 275~277°, which was converted with nitrous acid to the corresponding hydroxymethyl derivative hydrochloride (IX), $C_7H_9O_2N \cdot HCl$, m.p. 169~170°. IX was identified as 2-methyl-5-hydroxymethyl-3-pyridinol hydrochloride by mixed fusion and by comparison of infrared spectrum with the authentic sample.[1] Thus, IV was established to be 5-hydroxy-6-methylnicotinonitrile.

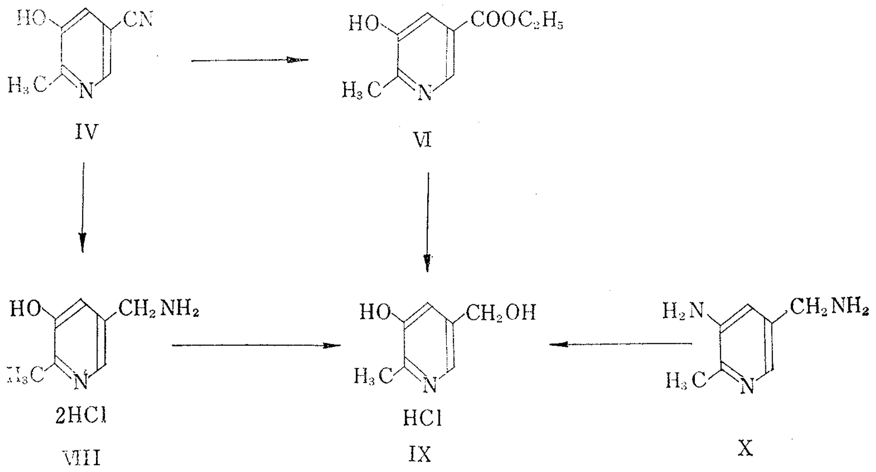

Chart 1.

As described previously,*[1] 2-methyl-3-pyridinol (V) has been obtained by the condensation of I with acrylonitrile, and, this time, IV was also detected by PPC as a by-product in the reaction mixture.

In the case of the condensation of I with diethyl fumarate, a compound of m.p. 200~201° (VI), $C_9H_{11}O_3N$, was obtained besides diethyl 5-hydroxy-6-methyl-3,4-pyridinedicarboxylate (VII) recognized only by PPC in the reaction mixture. The former compound (VI) showed an absorption due to a carbonyl group of ester at $1724\,cm^{-1}$ in its infrared spectrum, and gave a blue Gibbs' test. Therefore, it was considered that VI might be a 4- or 5-ethoxycarbonyl-2-methyl-3-pyridinol. The corresponding hydroxymethyl compound formed by reduction of VI with lithium alminum hydride was identical with IX, and VI was also obtained by heating of IV with ethanolic sulfuric acid. Thus, VI was established to be ethyl 5-hydroxy-6-methylnicotinate. In this reaction, yield of VII increased to 27% in presence of hydrogen peroxide, whereas that of VI decreased to a small amount only detectable by PPC.

Similarly, by the reaction of I with diethyl maleate (VI) was obtained as crystalline product, and in the mother liquor VII was detected by PPC.

Moreover, reaction between ethyl acrylate and I afforded VI and V, the later (V) of which compounds was proved by PPC. Ethyl *trans* 3-cyanoacrylate gave also VI as main product, when IV was recognized by PPC as by-product.

These results are summarized in table. It seems reasonable to classify the products in three types: products A are 3-unsubstituted pyridine derivatives formed by

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[1] L.A. Perez-Medina, R.P. Mariella, S.M. McElvain: J. Am. Chem. Soc., **69**, 2574 (1947).

Kondrat'eva's reaction[2] (reaction A), whereas products B and C are 3-pyridinol derivatives formed by new reactions (reaction B and C). In products C, two functional groups of dienophiles were both kept in 3-pyridinols formed, on the other hand, in products B, one of those was retained in 3-pyridinols formed but another was eliminated in the course of the reaction. This elimination always occured at position C-4 in 3-pyridinols.

3-Pyridinol derivatives were formed, as shown in table, from six dienophiles, in which four reagents gave rise to both reaction B and reaction C, and two compounds caused only reaction B. In comparison of the yields between products B and C, reaction B is observed to proceed more easily than reaction C. In reaction B, as the table indicates, it is clear that elimination takes place more readily in the cace of cyano group than in that of ethoxycarbonyl group, and more so in the case of fumaric acid derivatives than in that of acrylic acid derivatives. Thus, the tendency giving rise to reaction B decreases in the following order :

fumaronitrile>acrylonitrile>diethyl maleate, diethyl fumarate
>ethyl acrylate.

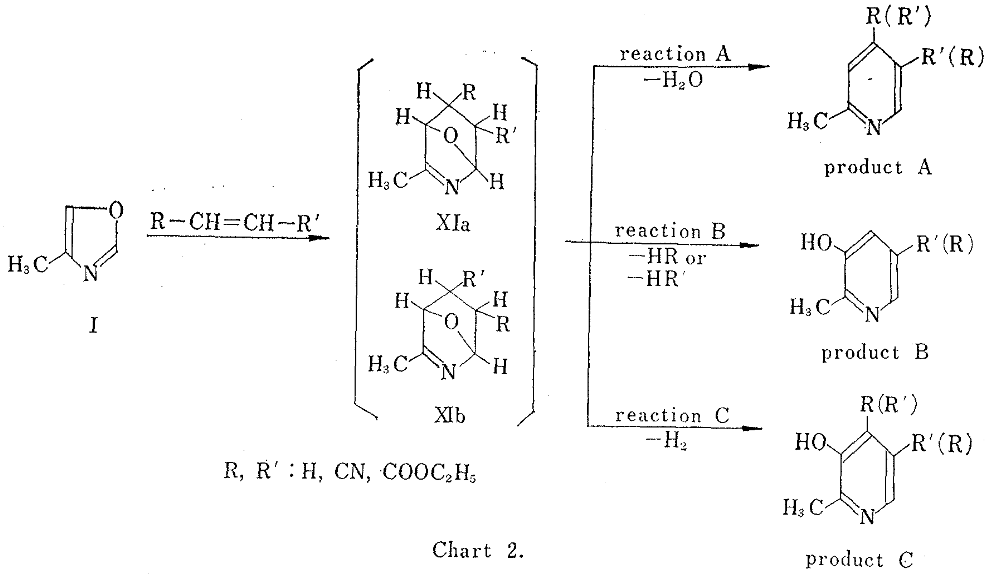

Chart 2.

Though the details of the mechanism of these reactions remain obscure for the present, a possible one is shown in Chart 2. In the first step of the reaction, Diels-Alder's condensation of I with dienophiles formes endo-oxo intermediates (XIa and XIb), 3-methyl-7-oxa-2-azabicyclco[2.2.1]hept-2-ene derivatives, which have not been isolated as yet. In the second step, under cleavage of oxygen bridge, the intermediates are aromatized into pyridine derivatives : products A are yielded with dehydration, products B are afforded with elimination of a hydrogen atom and a functional group at C-5 of XI and similarly products C are furnished with dehydrogenation. Increased yield of VII in presence of hydrogen peroxide gives ground for that reaction C involved a dehydrogenation.

These reactions of I may be applicable to other oxazoles.

Experimental*4

Method——Paper chromatography was carried out wish Toyo Filter Paper No. 50. The solvent systems employed were : (1) BuOH-conc. NH_3-H_2O=40:9:1 (Solvent A), (2) H_2O saturated MeCOEt (Solvent

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*4 All melting points are uncorrected.

2) G. Ya. Kondrat'eva, Ch. Huang : Doklady Akad. Nauk S. S. S. R., **141**, 628, 861 (1961).

B). Spots are located on paper chromatograms by their UV-absorption and by spray on the chromatograms with Gibbs' reagent. The Rf's of various compounds are in following : IV, A, 0.58, B, 0.95; V, A, 0.88, B, 0.75; VI, A, 0.90, B, 0.95; VII, A, 0.70, B, 0.80.

General Procedure of the Reaction between I and Dienophiles——A mixture of equimolar I and dienophiles in glac. AcOH was allowed to react in sealed tube at 60~90° for 20~48 hr. The reaction of I with acrolein, acrylic acid, maleic acid or fumaric acid gave brown resine, with acryl amide, maleamide, fumaramide, 2-butene-1,4-diol, or 1,4-dimethoxy-2-butyne did not proceed and recover starting materials, with 1,4-dimethoxy-2-butene or 2-butene-1,4-diol diacetate gave syrupy oil; with positive Gibbs' test and with diethyl acetylenedicarboxylate gave syrupy oil without Gibbs' test.

Reaction of I with Maleic Anhydride——i) In glac. AcOH : A mixture of 0.84 g. of I and 2.0 g. of maleic anhydride in 8 ml. of glac. AcOH was heated in sealed tube at 90° for 20 hr. Crystalline materials isolated from brown reaction mixture. The solvent was evaporated to dryness *in vacuo* and 5 ml. of H_2O was added to residue. The mixture was heated on boiling H_2O for 20 min. After cooling, crystals isolated as prisms of 6-methyl-3,4-pyridine dicarbexylic acid (II), m.p. 252~254° (decomp.), 0.73 g. (40.3%). A speciman was recrystallized from H_2O and was analyzed. *Anal.* Calcd. for $C_8H_7O_4N$: C, 52.71; H, 3.87; N, 7.74. Found : C, 53.30; H, 4.50; N, 7.40.

ii) In benzene : A mixture of 0.42 g. of I and 1.00 g. of maleic anhydride in 4 ml. of benzene was heated in sealed tube at 90° for 20 hr. After a few hours crystals began to isolate from brown reaction mixture. Work-up in the same manner as described above afforded I, m.p. 252~254° (decomp.), 0.59 g. (65.5%), identical with that obtained above.

Reaction of I with Maleimide——i) In glac. AcOH : A mixture of 0.80 g. of I and 1.00 g. of maleimide in 4 ml. of glac. AcOH was heated in sealed tube at 90° for 5 hr. After one hour crystals began to yield from reaction mixture. The yellow crystals were filtered and the fiiltrate was evaporated *in vacuo*. Crystals and residue was combined (1.22 g.), and purified by sublimation. 6-Methyl-3,4-pyridinedicarboximide (IV) was obtained as yellow needles in yield 0.35 g. (22.6%), m.p. 266~268°. *Anal.* Calcd. for $C_8H_6O_2N_2$: C, 59.25; H, 3.73; N, 17.28. Found : C, 58.61; H, 3.55; N, 16.94.

ii) In benzene : A mixture of 0.80 g. of I and 1.00 g. of maleimide in 5 ml. of benzene was refluxed on boiling water bath for 3 hr. The brown crystals separated in reaction mixture. The crystalline product was filtered and washed with acetone. Crude yellow powder (1.40 g.) was purified by sublimation under reduced pressure and by recrystallization from H_2O. Pure pale yellow needles, 0.15 g. (9.7%), m.p. 268~270° (decomp.), were identical with that obtained above.

Reaction of I with Fumaronitrile——A solution of 1.60 g. of I and 1.70 g. of fumaronitrile in 8 ml. of glac. AcOH was heated in sealed tube at 90° for 20 hr. After cooling, brown crystals separated from reaction mixture. They were collected by filtration, washed with acetone, and dried to give 1.72 g. of a fine crystals. The mother liquor was concentrated, a further amount (0.18 g.) of pure material was obtained, m.p. 246~247°. The structure of this compound (IV) was confirmed to be 5-hydroxy-6-methylnicotinonitrile as described below. IV could be recrystallized from acetone with negligible loss, yield 1.90 g. (71%). IR cm^{-1} : $\nu_{C\equiv N}$ 2220. *Anal.* Calcd. for $C_7H_6ON_2$: C, 62.67; H, 4.50; N, 20.88. Found : C, 62.89; H, 4.15; N, 20.82.

Paper chromatography of the mother liquor in solvent system A and B showed an absence of 5-hydroxy-6-methyl-3,4-pyridinedicarbonitrile, which could not be find by addition of H_2O_2 in reaction mixture.

H_2S gas was introduced to a mixture of IV (1.3 g.), Et_3N (1.1 g.) and EtOH (50 ml.) yielding corresponding thioamide, m.p. 259~260° (decomp.), as yellow needles. *Anal.* Calcd. for $C_7H_8ON_2S$: C, 50.00; H, 4.79; N, 16.13; S, 19.05. Found : C, 50.46; H, 5.14; N, 17.11; S, 18.68.

Reaction of I with Acryronitrile——2-Methyl-3-pyridinol (V) was obtained in 28% yield as described previously.[1] A speciman of the reaction mixture was chromatographed over filter paper, and the chromatogram gave 2 spots correspondlng to IV and V, respectively.

Reaction of I with Diethyl Fumarate——i) In glac. AcOH : A solution of 1.60 g. of I and 3.40 g. of diethyl fumarate in 8 ml. of glac. AcOH was heated in sealed tube at 120° for 20 hr. The reaction mixture was concentrated to dryness *in vacuo*, and re-concentrated to remove trace AcOH by co-distillation with toluene. The residual oil was dissolved in $CHCl_3$, and chromatographed over Al_2O_3 column. The column was eluted with $CHCl_3$, acetone and EtOH-$CHCl_3$ (1:9), successively. From $CHCl_3$ elute a large amount of diethyl fumarate was recovered. EtOH-$CHCl_3$ elute was evaporated to dryness *in vacuo* and a little crystalline solid (VI) separated from residual oil. VI was filtered, washed with acetone and dried, 0.07 g. (2.1%). Recrystallization from acotone afforded pure VI as colorless prisms, m.p. 201~202°. The structure of VI was confirmed to be ethyl 5-hydroxy-6-methylnicotinate as described below. IR cm^{-1} : $\nu_{C=O}$ 1724. *Anal.* Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.12; N, 7.73. Found : C, 59.16; H, 6.14; N, 7.79.

Paper chromatography of the reaction mixture in solvent system A and B showed the presence of two spots corresponding to VI and VII.

VI gave corresponding amide, colorless prisms, m.p. 305° (decomp.) and hydrazide, colorless scales, m.p. >330°, by the usual method.

ii) In glac. AcOH at the presence of H_2O_2: To a solution of 1.60 g. of I and 3.40 g. of diethyl fumarate in 4 ml. of glac. AcOH was added 4 ml. of 30% H_2O_2 in portions. The mixture was heated at 90~95° for 10 hr. After adding 3 ml. of H_2O, the solution was concentrated to dryness *in vacuo* and the residue was dissolved in 30 ml. of $CHCl_3$.

The solution was washed with $NaHCO_3$-sol. and H_2O, dried over Na_2SO_4, and concentrated to dryness *in vacuo*. To the residual oil was added EtOH–HCl (5 ml.) and evaporated to about 2 ml., the residue was treated with ether to precipitate a white solid of diethyl 5-hydroxy-6-methyl-3,4-pyridinedicarboxylate (VII) hydrochloride. This material was recrystallized from EtOH–ether to give colorless needles, 1.50 g. (27.5%), m.p. 143~144°. The melting point of this compound was undepressed by admixture with sample prepared by Cohen's method[3] and IR spectra of both compounds were also identical.

Paper chromatography of the reaction mixture in solvent system A and B showed the presence of two spots corresponding to VI and VII.

Reaction of I with Diethyl Maleate——The reaction employed diethyl maleate instead of diethyl fumarate in glac. AcOH was carried out in virtually same procedure with that described above. Yield of VI was 0.20 g. (5.8%), m.p. 199~200°. Similarly, VII was detected by paper chromatography.

Reaction of I with Ethyl Acrylate——A solution of 1.30 g. of I and 3.0 g. of ethyl acrylate in 3 ml. of glac. AcOH was heated in sealed tube at 90~100° for 20 hr. The solution was concentrated to dryness *in vacuo* and re-concentrated to remove trace of AcOH by co-distillation with toluene. The residue was dissolved in $CHCl_3$ and chromatographed over Al_2O_3 column as described above. From EtOH–$CHCl_3$ elute VI was obtained as colorless prisms, 0.25 g. (8.8%), m.p. 200~201°, which was identical with that obtained above.

Paper chromatography of the reaction mixture in solvent system A and B showed the presence of two spots, one corresponing to V and the other corresponding to VI.

Ethyl *trans*-3-Cyanoacrylate——Prepared by Korshnov's method.[4] b.p$_{16}$ 78~79°. IR cm^{-1}: δ_{C-H} 960.

Reaction of I with Ethyl *trans*-3-Cyanoacrylate——A mixture of 1.30 g. of I, 2.0 g. of ethyl *trans*-3-cyanoacrylate and 5 ml. of glac. AcOH was heated in sealed tube at 90° for 20 hr. The mixture was dissolved in EtOH and was evaporated to dryness *in vacuo*. The residue was triturated with EtOH, and the crude product crystallized. Recrystallization of the substance from EtOH afforded pure VI as colorless needles, m.p. 199~200°, 1.0 g. (34%), which was identical with that obtaind above.

Paper chromatography of the reaction mixture in solvent system A and B showed the presence of two spots, one corresponding to IV and the other corresponding to VI.

2-Methyl-5-hydroxymethyl-3-pyridinol Hydrochloride (IX)——i) To a 1.42 g. of IV in 120 ml. of EtOH were added: (a) 15 ml. of 1% $PdCl_2$ solution, (b) 3 ml. of conc. HCl and 80 ml. of EtOH, (c) 1.5 g. of Norit. This mixture was shaken with H_2 at room temperature. After 30 min., the absorption of H_2 had practically stopped. The catalyst were filtered and filtrate was concentrated to 5 ml. Addition of 50 ml. of ether caused the precipitation of 1.41 g. (63%) of corresponding aminomethyl compound dihydrochloride, VIII, m.p. 275~277° (decomp.), as white needles. *Anal.* Calcd. for $C_7H_{12}ON_2Cl_2$: C, 39.82; H, 5.73; N, 13.27. Found: C, 39.80; H, 5.73; N, 12.90.

To a hot solution of 0.42 g. of VIII in 30 ml. of *N* HCl was added a solution of 0.20 g. of $NaNO_2$ in 4 ml. of H_2O with portionwise. The solution was kept at 85° until the evolution of gas ceased (ca. 30 min.). Then the H_2O was removed *in vacuo* and the remaining crystalline solid was extracted three times with 20 ml. portions of boiling EtOH. The EtOH solution, after filtration, was concentrated to about 2 ml. and treated with ether to precipitate a white solid of corresponding hydroxymethyl compound hydrochloride, IX, 0.20 g. (62.7%). This material was recrystallized from EtOH–ether to give white needles, m.p. 169~170°. *Anal.* Calcd. for $C_7H_{10}O_2NCl$: C, 47.87; H, 5.74; N, 7.98. Found: C, 47.30; H, 5.80; N, 8.28.

A mixed melting point of IX with authentic sample prepared by Perez-Medina's method[1] undepressed and IR spectrum was also identical.

ii) A mixture of 0.40 g. of IV, 0.45 g. of conc. H_2SO_4 and 1.40 g. of EtOH was heated in sealed tube at 130~140° for 3 hr. The excess EtOH was evaporated to remove *in vacuo* and residue was dissolved in 5 ml. of H_2O. The solution was neutralized with solid $NaHCO_3$, white precipitate was filtered, washed with H_2O, and dried, 0.43 g. (79.2%), m.p. 197~199°, of VI was obtained. The material was recrystallized from acetone to give colorless prisms, m.p. 200~201°. A mixed melting point of this substance with a sample obtained above undepressed.

0.50 g. of VI was added *via* Soxlet extractor over a period of 8 hr. to a solution of 1.00 g. of $LiAlH_4$ in 150 ml. of ether. The reaction mixture was treated with 70 ml. of H_2O, adding dropwise at first. The mixture was filtered with aid of filter-cell, and the aqueous filtrate, after saturation with CO_2, was

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3) A. Cohen, J. W. Haworth, E. G. Hughes: J. Chem. Soc., **1952**, 4374.

4) I. A. Korshnov, Yu. V. Vodzinskiĭ, N. S. Vyazankin, A. I. Kalinin: Zhur. Obshcheĭ Khim., **29**, 1364 (1959).

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.

The authors express their deep gratitude to Dr. J. Shinoda, Chairman of the Board of Directions, 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

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.

(Received April 8, 1965)

[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)).

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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)).