

the anesthetized rat. Their absorption was considerably affected by the pH of solution. The unionized form was in general readily absorbed, while the ionized form was more slowly absorbed. Sulfonamides which are highly lipid-soluble were more readily absorbed than those which are poorly lipid-soluble. And there is a slightly acidic zone at the rectum-blood barrier, like the intestinal-blood barrier. The results suggest that sulfonamides are absorbed from the rectum by a passive transport, and that the patterns of absorption in the rectum are similar as a gastro-intestinal absorption of drugs. When the permeability constants were plotted against the absorption velocity constants, the good agreement was obtained among the spots. The diffusion constant as well as lipid-solubility is an important factor for rectal absorption.

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113. Takeo Naito, Toru Yoshikawa, Fumiyoshi Ishikawa,
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Synthesis of 3-Pyridinols. I. Reaction of 5-Un-
substituted Oxazoles with Acrylonitrile.*¹

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Recently, diene-synthesis of oxazoles was investigated by Kondrat'eva, *et al.*, and they described that 5-unsubstituted-3,4-pyridinedicarboxylic acids are obtained from 5-unsubstituted oxazoles with maleic anhydride¹⁾ and 5-hydroxy-3,4-pyridinedicarboxylic acids are formed by the same reaction from 5-alkoxyoxazoles.²⁾ This method was applied to 4-methyl-5-ethoxyoxazole with some dienophiles by Harris, *et al.* to synthesize several 3-pyridinols having pyridoxine-like structure.³⁾ The present paper deals with a new synthetic method of 3-pyridinols by condensation of 5-unsubstituted oxazoles with acrylonitrile.

4-Methyloxazole was treated with acrylonitrile in toluene (method A) or in acetic acid (method B). Reaction by method A gave three crystalline products, *i.e.* compounds (I), (II), and (III), under intensive evolution of ammonia, and that by method B

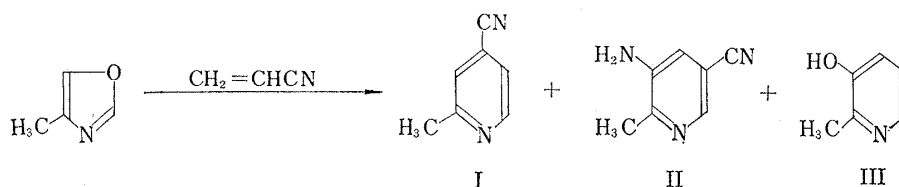


Chart 1.

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1) G. Ya. Kondrat'eva: *Khim. Nauk i Prom.*, **2**, 666 (1957). *Idem*: *Izv. Akad. Nauk, Otd. Khim. Nauk*, **1959**, 484.

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

3) 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).

gave only compound III accompanied by hydrogen cyanide. Structures of these compounds were established as follows.

Compound (I), m.p. 44°, gave a picrate of m.p. 163~164° and showed the absorption characteristic of cyano group at 2320 cm⁻¹ in its infrared spectrum, and its properties resembled those reported for 2-methylisonicotinonitrile. The mixed melting point of the picrate of I with that of authentic 2-methylisonicotinonitrile prepared by Okamoto's method⁴⁾ did not show depression.

The second product (II) of m.p. 174° analysed for C₇H₇N₃, exhibited a cyano group band at 2250 cm⁻¹ in the infrared spectrum and gave positive diazo test; II, therefore, was assumed a 3- or 5-aminopicoline with a cyano group. Catalytic reduction of II gave the corresponding aminomethyl derivative dihydrochloride, C₇H₁₁N₃·2HCl, m.p. 295~297°(decomp.), which was clarified to be identical with 2-methyl-3-amino-5-amino-methylpyridine dihydrochloride obtained by Perez-Medina's method.⁵⁾ Thus, II was determined to be 5-amino-6-methylnicotinonitrile.

The third compound (III), C₆H₇ON, m.p. 166~168°, was considered to be a 6-unsubstituted 3-pyridinol derivative because of its positive Gibbs' reaction, and was identified by infrared spectrum and by mixed fusion with the authentic 2-methyl-3-pyridinol synthesized by Okuda's method.⁶⁾

TABLE I. Reaction Products of 4-Methyloxazole with Acrylonitrile

Products	Yields (%)	
	Method A	Method B
2-Methylisonicotinonitrile	5	—
5-Amino-6-methylnicotinonitrile	1	—
2-Methyl-3-pyridinol	12	28

I is a normal product afforded by Kondrat'eva's reaction, and II and III are unexpected ones. In the course of the reaction by method A, ammonia evolved may participate in the formation of II, of which the mechanism remains obscure for the present. The results summarized in table suggest that III is the main product both in method A and in method B, and method B is more favorable to obtain III. Some attempts for preparation of III such as addition of copper acetate or boric acid as catalyst, hydroquinone or trichloroacetic acid as polymerization inhibitor were fruitless. In basic medium, *e.g.* in dioxane as solvent in presence of triethylamine, pyridine or Amberlite IR 400 (OH form), yield of III decreased.

It is an interesting fact that one of 3-pyridinol derivatives was formed from a 5-unsubstituted oxazole derivative and acrylonitrile, and, therefore, in order to elucidate the mechanism of this reaction the following experiments were undertaken by method B.

Reaction of 4-phenyl- or 2,4-dimethyl-oxazole with acrylonitrile afforded 2-phenyl- or 2,6-dimethyl-3-pyridinol, respectively, of which properties coincided with those in literature.^{7,8)} 4-Methyloxazole was allowed to react with acrylonitrile (cyano-¹⁴C)⁹⁾ to yield III which had practically no radio-activity. These results led to the following consideration: four atoms, *i.e.* N-1, C-2, C-3, and C-6, of 3-pyridinols were derived

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

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8) G. Kobayashi, S. Furukawa, Y. Kawada: Yakugaku Zasshi, 74, 790 (1954).

9) A. Murrey, D. L. Williams: Org. Synth. with Isotopes, 259 (1958).

from N-3, C-4, C-5, and C-2 of oxazoles, respectively, and C-4 and C-5 of 3-pyridinols were originated from the ethylenic two carbon atoms of acrylonitrile, whereas cyano group of acrylonitrile was eliminated in the course of the reaction.

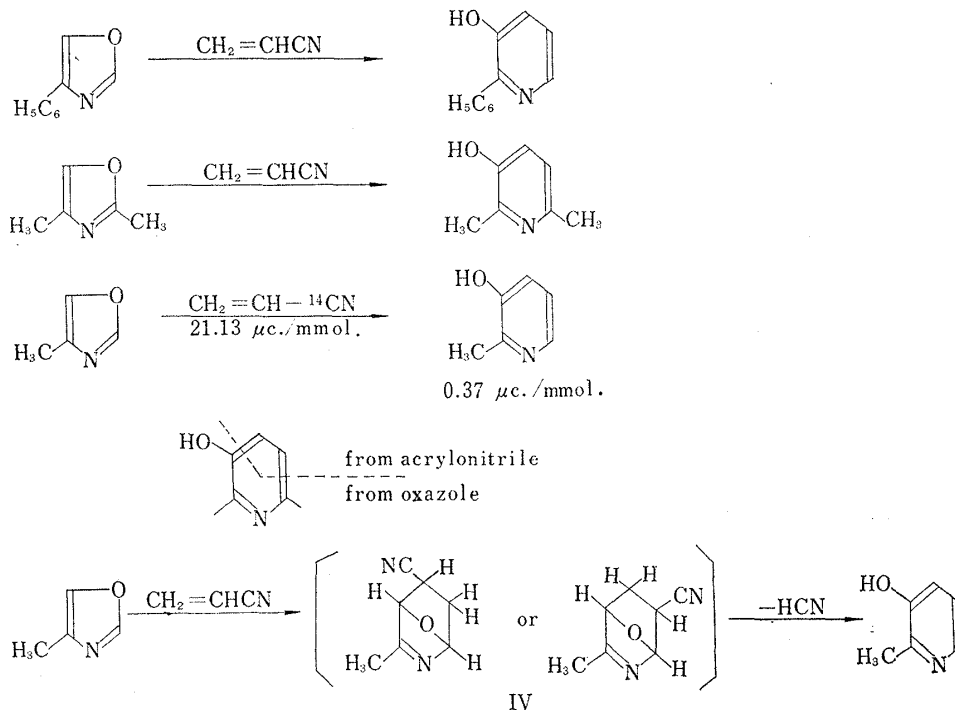


Chart 2.

On the basis of these evidences, it seemed reasonable to assume that Diels-Alder's condensation of 5-unsubstituted oxazoles with acrylonitrile, as shown in Chart 2, gave endooxo intermediates (IV), which was aromatized to 3-pyridinols under cleavage of oxygen bridge and elimination of hydrogen cyanide.

This reaction of acrylonitrile may be applicable to other dienophiles.

Experimental*3

Method—Specific activities of ^{14}C labeled compounds were determined by infinite thickness method¹⁰⁾ and Kobe Kogyo Geiger-Müller counter was employed.

Reaction of 4-Methyloxazole with Acrylonitrile—i) In toluene (Method A): A mixture of 2.4 g. of 4-methyloxazole, 2.7 g. of acrylonitrile and 5.0 ml. of toluene was heated in sealed tube at 150° for 4 hr. The mixture, which evolved NH_3 gas (positive Nessler test), was evaporated to dryness *in vacuo*. The residue was dissolved in CHCl_3 , and the CHCl_3 solution was submitted to Al_2O_3 column chromatography. Compound I, needles, m.p. $40\sim 44^\circ$, was obtained from a negative diazo test fraction of CHCl_3 elute. Distillation, b.p.₂₀ $90\sim 95^\circ$, gave 0.15 g. of pure I, m.p. $43\sim 44^\circ$. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$: 280. IR cm^{-1} : $\nu_{\text{C}\equiv\text{N}}$ 2320. Picrate, yellow needles, m.p. $163\sim 164^\circ$, was undepressed on admixture with 2-methylisonicotinonitrile picrate (m.p. $162\sim 163^\circ$) prepared by Okamoto's method.⁴⁾

From a positive diazo test fraction of CHCl_3 elute, 0.04 g. of crystals were obtained. Recrystallization from EtOH gave compound II as colorless prisms, m.p. 174° . *Anal.* Calcd. for $\text{C}_7\text{H}_7\text{N}_3$: C, 63.13; H, 5.30; N, 31.15. Found: C, 63.45; H, 5.24; N, 30.99. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$: 260, 320. IR cm^{-1} : $\nu_{\text{C}\equiv\text{N}}$ 2250.

Crude compound III was obtained from a part of EtOH- CHCl_3 (5:95) elute. Recrystallization from acetone gave 0.40 g. of colorless prisms, which showed positive ferric and Gibbs' test. UV $\lambda_{\text{max}}^{\text{EtOH}}$ $m\mu$: 282. *Anal.* Calcd. for $\text{C}_6\text{H}_7\text{ON}$: C, 66.05; H, 6.46; N, 12.84. Found: C, 66.48; H, 6.66; N, 12.78.

This compound showed no melting point depression on admixture with 2-methyl-3-pyridinol (m.p. $166\sim 168^\circ$) prepared by Okuda's method.⁶⁾

*3 All melting points are uncorrected.

10) K. Miyatake, M. Hasegawa, H. Ogawa, H. Kamuro: *Yakugaku Kenkyu*, **29**, 26 (1957).

ii) In AcOH (Method B): A mixture of 0.80 g. of 4-methyloxazole, 1.1 g. of acrylonitrile, 0.18 ml. of H₂O and 4 ml. of AcOH was heated in sealed tube at 95° for 20 hr. The mixture, which evolved HCN gas (positive copper acetate-benzidine acetate test), was dissolved in EtOH and was evaporated to dryness *in vacuo*. The residue was dissolved in CHCl₃, and the CHCl₃ solution was submitted to Al₂O₃ column chromatography as described above. From a part of EtOH-CHCl₃ (5:95) elute III was obtained after recrystallization from acetone. Yield, 0.30 g. (27.5%).

No increased yield was obtained by addition of hydroquinone, trichloroacetic acid, boric acid or copper acetate in AcOH.

iii) In basic medium: A mixture of 0.80 g. of 4-methyloxazole, 1.1 g. of acrylonitrile, 1 ml. of pyridine and 3 ml. of dioxane was heated in sealed tube at 130° for 20 hr. The mixture was treated as mentioned above and 0.13 g. of III was obtained.

Instead of pyridine, addition of Et₃N, or Amberlite IR-400 (OH⁻) did not give any crystalline substances.

Catalytic Reduction of II—A mixture of II (0.1 g.), 10% Pd-C (0.1 g.), 10% HCl (1.0 ml.) and MeOH (5.0 ml.) was subjected to hydrogenation under atmospheric pressure at a room temperature. Hydrogenation was stopped after 2 molar equivalents of H₂ had been absorbed (about 0.5 hr.). After removal of the catalyst and the solvent, the crystalline residue was collected and washed with EtOH. Recrystallization of this compound from conc. HCl-iso-PrOH afforded a colorless needles, m.p. 295~297° (decomp.), which was identified by admixture and by the IR spectrum with 2-methyl-3-amino-5-aminomethylpyridine dihydrochloride, m.p. 295~297° (decomp.), prepared by Perez-Medina's method.⁵⁾

2-Phenyl-3-pyridinol—A mixture of 1.5 g. of 4-phenyloxazole, 0.6 g. of acrylonitrile and 4 ml. of AcOH was heated in sealed tube at 150° for 30 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed in CHCl₃ over Al₂O₃, and from EtOH-CHCl₃ (5:95) elute crude product was obtained. Recrystallization from acetone afforded pure 2-phenyl-3-pyridinol as colorless prisms, m.p. 205~206° (lit.⁷⁾: m.p. 205°). A specimen of the product gave positive ferric and Gibbs' test.

2,6-Dimethyl-3-pyridinol—A mixture of 2.0 g. of 2,4-dimethyloxazole, 2.0 g. of acrylonitrile and 5 ml. of AcOH was heated in sealed tube at 100° for 20 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed in CHCl₃ over Al₂O₃, and from EtOH-CHCl₃ (5:95) elute crude product was obtained. Recrystallization from acetone afforded pure 2,6-dimethyl-3-pyridinol as colorless prisms, m.p. 209~210° (lit.⁸⁾: m.p. 210~212°). A specimen of the compound gave positive ferric test.

Acrylonitrile(cyano-¹⁴C)⁹⁾—A solution of 2.6072 g. of K¹⁴CN (ca. 2 mc.) and 10 ml. of H₂O was added to a solution of 8.0534 g. of 2-chloroethanol and 10 ml. of MeOH. The mixture was refluxed for 3 hr. The precipitated KCl was removed by filtration and the solution was evaporated to leave colorless oil, which on distillation gave 1.9716 g. (69.3%) of 3-hydroxypropionitrile (cyano-¹⁴C), b.p.₁₆ 110°.

A mixture of 1.9716 g. of 3-hydroxypropionitrile(cyano-¹⁴C), 0.3405 g. of basic MgCO₃ and 0.3485 g. of diethyleneglycol was heated for 6 hr. under a dry N₂ atmosphere at 230°. Reaction product was dried over CaCl₂, and distillation of the product afforded 1.152 g. (78.5%) of acrylonitrile(cyano-¹⁴C) as colorless oil, b.p. 78°. (Specific activity: 34.43 μc./mmol.).

Reaction of 4-Methyloxazole with Acrylonitrile(cyano-¹⁴C)—In 0.3308 g. of acrylonitrile(cyano-¹⁴C), 0.2082 g. of inactive acrylonitrile was mixed. (specific activity: 21.13 μc./mmol.). To the mixture, 0.8365 g. of 4-methyloxazole, 0.18 ml. of H₂O and 3 ml. of glac. AcOH were added, the solution was heated in sealed tube at 90° for 20 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed in CHCl₃ over Al₂O₃, and from EtOH-CHCl₃ (5:95) elute crude 2-methyl-3-pyridinol was obtained. Repeated chromatography and recrystallization from acetone afforded 2-methyl-3-pyridinol as colorless prisms, m.p. 166~168° (specific activity: 0.37 μc./mmol, isotopic yield: 1.75%).

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Summary

5-Unsubstituted oxazoles were allowed to react with acrylonitrile and structures of the products were determined. 3-Pyridinol derivatives were unexpectedly the main products in these reactions. A possible mechanism forming 3-pyridinols was discussed.

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