# Synthesis of Pyridoxine. I. Synthesis of 4-Methyl-5-ethoxycarbonyloxyoxazole

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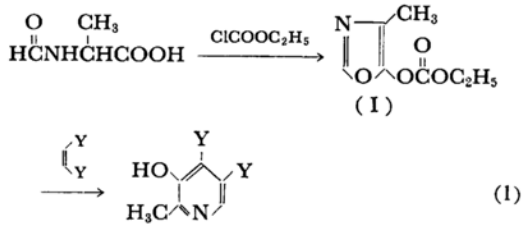
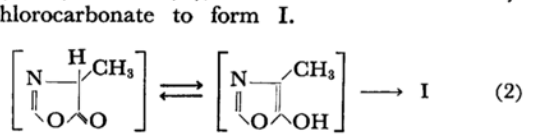
Recently, Firestone *et al.*[1] reported the synthesis of pyridoxine by the Diels-Alder reaction of 4-methyl-5-alkyoxyoxazole with various dienophiles followed by acid treatment and reduction. They prepared the oxazoles from alanine through three steps, but the yield of the last step was very low.[2] In the present paper, We describe an efficient synthetic method of 4-methyl-5-ethoxycarbonyloxyoxazole (I) as well as its Diels-Alder reaction.



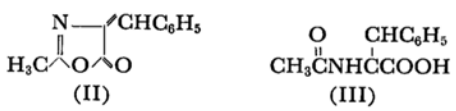
(1)

Compound I was obtained in 80% yield by treatment of *N*-formylalanine (1 mol) with ethyl chlorocarbonate (2 mol) in the presence of triethylamine at −10——20°C. The structure of I was confirmed by the elemental analysis and the spectral data.

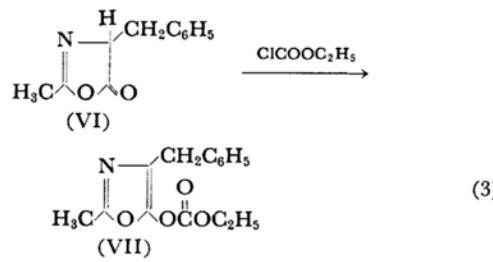
A synthetic method of oxazole by the reaction of acylamino acid with ethyl chlorocarbonate has never been reported, except the report on the synthesis of 2-methyl-4-benzal-5-oxazolone (II) by the reaction of $\alpha$-acetoaminocinnamic acid (III) with ethyl chlorocarbonate.[3] This result suggests that 4-methyl-5-oxazolone (IV) was intermediately formed and its enolized form, 4-methyl-5-hydroxyoxazole (V), further reacted with ethyl chlorocarbonate to form I.



(2)



Although, IV could not be isolated, this mechanism may be supported by the following fact: 2-methyl-4-benzyl-5-oxazolone (VI)[4] was converted into 2-methyl-4-benzyl-5-ethoxycarbonyloxyoxazole (VII) by treatment with ethyl chlorocarbonate under the same conditions.



(3)

As 4-methyl-5-alkoxyoxazole, I underwent the Diels-Alder reaction with various dienophiles. The resulting adducts were converted into pyridine derivatives on acid treatment: *e. g.*, by reaction with diethyl maleate, dimethyl thiofumarate or maleimide, I gave 2-methyl-3-hydroxy-4, 5-disubstituted pyridines. These pyridines were converted into pyridoxine by reduction. The reaction of I with maleic anhydride gave ethyl 2-methyl-3-hydroxypyridine-5-carboxylate accompanying with decarboxylation. But that of I with fumaronitrile in acetic acid produced 2-methyl-3-hydroxy-4, 5-dicyanopyridine, which was converted into pyridoxine by reduction.

## Experimental

**4-Methyl-5-ethoxycarbonyloxyoxazole (I).** To a suspention of 10 g of formylalanine in 50 m*l* of chloroform, 18 g of triethylamine was added. The solution was cooled at −10——20°C. To the solution, 18.8 g of ethyl chlorocarbonate was added drop by drop at −10——20°C under stirring. After being kept for 2 hr at the same temperature, the reaction mixture was washed succesively with water, 1% hydrochloric acid and water, and dried over anhydrous magnesium sulfate. The solvent was removed from the reaction mixture to give an oily residue, which was distilled under reduced pressure to give 11.8 g of I, bp 80—82°C/5—6 mmHg, $\lambda_{max}$ 1780 cm$^{-1}$ (carbonic ester $\nu_{C=O}$), $\tau$ ($CDCl_3$): 8.60 (3H, triplet), 7.85 (3H, singlet), 5.70 (2H, quartet), and 2.39 (1H, singlet).

Found: C, 49.08; H, 5.47; N, 8.46%. Calcd for

1) Merck Co., British Pat. 966804. R. A. Firestone, E. E. Harris and W. E. Reuter, *Tetrahedron*, **23**, 943 (1967).
2) Merck Co., British Pat. 880595.
3) M. Brenner and K. Rufenacht, *Helv. Chim. Acta*, **37**, 203 (1954).
4) M. Bergmann, F. Stern and C. Witte, *Ann.*, **499**, 277 (1932).

$C_6H_9NO_4$: C, 49.12; H, 5.30; N, 8.18%.

Similarly, VII (170—171°C/7 mmHg, yield 6.2 g) was obtained from the reaction of VI[4] (6.1 g) with ethyl chlorocarbonate (3.1 g) in the presence of triethylamine (2.9 g).

Found: C, 64.44; H, 5.67; N, 5.31%. Calcd for $C_{13}H_{13}NO_4$: C, 64.36; H, 5.79; N, 5.36%.

**The Reaction with Diethyl Maleate, Diethyl Fumalate or Dimethyl Thiofumarate.** A mixture of 0.85 g of I and 1.7 g of diethyl maleate was heated at 120°C for 6 hr. After cooling, 20 m*l* of ethyl alcohol and 1 m*l* of 5 N ethanolic hydrochloric acid were added to the solution. The substance, which was obtained by evaporation of ethanol from the reaction mixture, was recrystallized from acetone to give 1.2 g of 2-methyl-3-hydroxy-4, 5-diethoxy carbonylpyridine, mp 149°C. It was identified with an authentic sample[5] by the mixed melting point.

Similarly, I reacted with diethyl fumarate to give 60% of 2-methyl-3-hydroxy-4, 5-diethoxycarbonylpyridine, and with dimethyl thiofumarate to give 1.2 g of 2-methyl-3-hydroxy-4, 5-dicarboxylic acid methyl thioester hydrochloride, mp 210—212°C.

Found: C, 40.53; H, 4.29; N, 4.79%. Calcd for $C_{10}H_{11}NO_3S_2$: C, 40.88; H, 4.12; N, 4.77%.

**The Reaction with Maleic Anhydride.** A solution of 1.7 g of I and 1.2 g of maleic anhydride in 20 m*l* of benzene was heated under refluxed for 30 min. After cooling, 2 m*l* of 5 N ethanolic hydrochloric acid was added to the solution. The solvent was evaporated at reduced pressure. The oily residue was dissolved in water and extracted with ether. After drying over anhydrous magnesium sulfate, the ether was removed. The residue was recrystallized from ethyl acetate to give 0.8 g of 2-methyl-3-hydroxy-5-ethoxycarbonylpyridine, mp 205—207°C.

Found: C, 59.65; H, 6.00; N, 7.25%. Calcd for $C_9H_{11}NO_3$: C, 59.70; H, 6.08; N, 7.44%.

5) E. E. Harris and R. A. Firestone, *J. Org. Chem.*, **27**, 2075 (1962).

**The Reaction with Maleimide.** A solution of 2.0 g of I and 1.0 g of maleimide in benzene was heated under reflux for 4 hr. The solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to give 1.8 g of 2-methyl-3-hydroxypyridine-4, 5-dicarboximide, mp 250—252°C.

Found: C, 53.93; H, 3.49; N, 15.50%. Calcd for $C_8H_5NO_3$: C, 53.93; H, 3.40; N, 15.73%.

**The Reaction with Fumaronitrile.** A mixture of 1.0 g of I and 2.0 g of fumaronitrile was dissolved in 4 m*l* of acetic acid in a sealed tube. After heating at 140°C for 3 hr, the solvent was removed from the reaction mixture to give an oily residue, which was taken up in ether. The ethereal layer was dried over anhydrous magnesium sulfate and the ether was evaporated to give 0.6 g of 2-methyl-3-hydroxy-4, 5-dicyanopyridine, mp 189—191°C. It was identified with an authentic sample[5] by the IR spectra and the mixed melting point.

**2-Methyl-3-hydroxy-4, 5-diaminomethylpyridine Trihydrochloride.** A mixture of 1.3 g of 2-methyl-3-hydroxy-4, 5-dicyanopyridine and 1.0 g of palladium charchoal (1 : 10) was suspended in 100 m*l* of methanol. The reduction was carried out for 6 hr under hydrogen of the atomospheric pressure at room temperature. After absorption of 4 mol of $H_2$ was over, the catalyst was filtered off and 1 m*l* of 5 N methanolic hydrochloric acid was added to the filtrate. The solvent was removed from the reaction mixture to give 1.7 g of 2-methyl-3-hydroxy-4, 5-diaminomethylpyridine trihydrochloride, mp 296°C dec. (lit., 296°C dec.)[5] It was identified with an authentic sample by the IR spectra.

**Pyridoxine Hydrochloride.** To a solution of 4.9 g of 2-methyl-3-hydroxy-4, 5-diaminomethylpyridine trihydrochloride dissolved in 80 m*l* of 2 N hydrochloric acid, 1.7 g of sodium nitrite in 10 m*l* of water was added in small portions at room temperature. After stirring for 4 hr, the solvent was evaporated *in vacuo* below 40°C. Pyridoxine hydrochloride was obtained from the residue by recrystallization from dilute ethanol, mp 206—208°C. It was identified with an authentic sample by the mixed melting point and IR spectra.