BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1435—1437 (1969)

The Synthetic Intermediate of Pyridoxine. I. A Novel Synthesis of 5-Alkoxy-2-carboxy-4-methyloxazole

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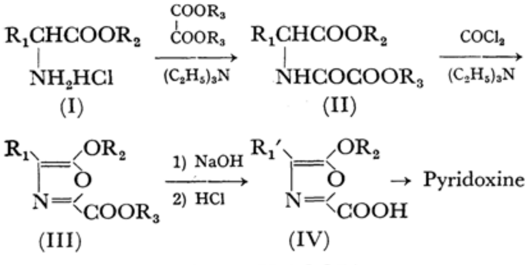
(Received July 2, 1968)

Recently, a few attempts have been reported to develop a new route to pyridoxine by modifying the original Harris report.[1] Most of these methods have dealt with the Diels-Alder reaction of 5-alkoxy-4-methyloxazole with various dienophiles except a few reports.[2,3] This 5-alkoxy-4-methyloxazole has been prepared from alkyl *N*-formylalaninate with phosphorus pentoxide.[4,5] However, the procedure is troublesome, for the reaction mixture forms a hard mass in the vessel.



R_1 (CH_3 or CH_2COOR)
R_1' (CH_3 or CH_2COOH)
R_2 (CH_3, C_2H_5 or C_4H_9)
R_3 (CH_3 or C_2H_5)

The present authors have found an excellent method for preparing a new oxazole, 5-alkoxy-2-alkoxycarbonyl-4-methyloxazole, as an intermediate of pyridoxine. Namely, 5-alkoxy-2-alkoxycarbonyl-4-methyloxazole was prepared from alkyl *N*-alkoxalylalaninate with phosgen and triethylamine as the dehydrating agents. Other dehydrating agents

TABLE 1. THE REACTION OF METHYL *N*-METHOXALYLALANINATE[a] WITH DEHYDRATING AGENTS IN CHLOROFORM

Dehydrating agents[b]	Reaction condition		Yield[f] %
	Temp., °C	Time	
$COCl_2$[c]	20	10 min	80
$POCl_3$[d]	20	10 min	0
$POCl_3$	50	4.5 hr	23.2
$SOCl_2$[c]	20	10 min	0
$SOCl_2$	50	2 hr	18.0
$ClCOOC_2H_5$[c]	50	1 hr	25.2
P_2O_5[e]	60	3 hr	24.5

a) 0.03 mol
b) Triethylamine was used equiv. to the chlorine atom of the dehydrating agent.
c) 0.045 mol
d) 0.03 mol
e) 0.06 mol (P_2O_5) and 0.12 mol (triethylamine)
f) The yield of 5-methoxy-2-methoxycarbonyl-4-methyloxazole which was analyzed by gas chromatography (5% carbowax 20 M on chromosorb T, 4 mmφ × 2 m; column temperature, 160°C; flow rate of He, 75 ml/min; internal standard, dimethyl terephthalate).

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1) E. E. Harris and R. A. Firestone, *J. Org. Chem.*, **27**, 2705 (1962).

2) M. Murakami and M. Iwanami, This Bulletin, **41**, 726 (1968).

3) T. Miki and T. Matsuo, *Yakugaku Zasshi* (*J. Pharm. Soc. Japan*), **87**, 323 (1967).

4) Merck Co., Belg. 617499; *Chem. Abstr.*, **59**, 634 (1926).

5) F. Hoffmann-La Roche and Co., Neth. Appl. 6508673; *Chem. Abstr.*, **64**, 14193(1931).

Table 2. 5-Alkoxy-2-alkoxycarbonyl-4-substituted oxazole

	R_1	R_2	R_3	Bp °C/mmHg (Mp °C)	Found (%)			Calcd (%)			Yield %
					C	H	N	C	H	N	
IIIa	CH_3	CH_3	CH_3	113—115/5 (75—76)	49.37	5.20	8.13	49.12	5.30	8.18	75.5
IIIa	CH_3	CH_3	C_2H_5	116—118/4 (45—48)	—	—	7.88	—	—	7.56	71.0
IIIae	CH_3	C_2H_5	C_2H_5	128/4	54.54	6.89	7.13	54.26	6.58	7.03	70.0
IIIa	CH_3	C_4H_9	CH_3	134—137/3	—	—	7.10	—	—	6.57	63.7
IIIb	CH_2COOCH_3	CH_3	CH_3	156—157/3 (56—59)	47.28	4.67	6.12	47.16	4.84	6.11	50.6
IIIbe	$CH_2COOC_2H_5$	C_2H_5	C_2H_5	166—167/2	53.23	6.46	5.14	53.13	6.32	5.16	77.2

Table 3. 5-Alkoxy-2-carboxy-4-substituted oxazole

	R_1	R_2	Mp °C	Found (%)			Calcd (%)		
				C	H	N	C	H	N
IVa	CH_3	CH_3	91—92	45.58	4.65	8.86	45.86	4.49	8.92
IVae	CH_3	C_2H_5	83—84	49.50	5.23	8.24	49.12	5.30	8.18
IVa	CH_3	C_4H_9	47—49	—	—	—	—	—	—
IVbe	CH_2COOH	C_2H_5	112	44.62	4.06	6.36	44.66	4.22	6.51

gave unsatisfactory results, as is shown in Table 1. No method of synthesizing oxazole derivatives by a reaction with phosgen and triethylamine has yet been reported.

Alkyl DL-alaninate hydrochloride (Ia, $R_1=CH_3$) reacted with alkoxalylchloride to produce alkyl *N*-alkoxalylalaninate (IIa, $R_1=CH_3$),[6] but the following improved method was adopted. A mixture of 1 mol of alkyl DL-alaninate hydrochloride, 2 mol of dialkyl oxalate, and 1 mol of triethylamine was heated to give compound IIa. Compound IIa then reacted with phosgen and triethylamine to give 5-alkoxy-2-alkoxycarbonyl-4-methyloxazole (IIIa, $R_1=CH_3$). The results are summarized in Table 2. Compound IIIa was saponified with sodium hydroxide and neutralized with hydrochloric acid to crystallize 5-alkoxy-2-carboxy-4-methyloxazole (IVa, $R_1=CH_3$), as is shown in Table 3.

In a similar manner, the oxazole derivative could be obtained from dialkyl aspartate hydrochloride (Ib, $R_1=CH_2COOR$). The results are shown in Table 2 and Table 3.

Pyridine derivatives were obtained by Diels-Alder reactions with 5-alkoxy-2-carboxy-4-methyloxazole (IVa) or 5-alkoxy-2-carboxy-4-carboxymethyloxazole (IVb) and with such dienophiles as diethyl maleate, fumaronitrile, 2,5-dihydrofuran, and 4,7-dihydro-1,3-dioxepine. These pyridine derivatives were introduced to pyridoxine by the usual methods.

Experimental[*1]

Ethyl *N*-Ethoxalylalaninate (Iae). Ethyl DL-alaninate hydrochloride (12.3 g, 0.08 mol) was dissolved in ethanol, and then diethyl oxalate (23.4 g, 0.16 mol) and triethylamine (8.1 g, 0.08 mol) were added. After the mixture had been heated at 50°C for 5 hr, the solvent was removed by distillation and chloroform was added to the residue. The triethylamine hydrochloride was removed by washing with water. On fractional distillation, ethyl *N*-ethoxalylalaninate was obtained (bp 127°C/2 mmHg, yield, 15.7 g, 90.5%). Similarly, alkyl *N*-alkoxalylalaninate and alkyl *N*-alkoxalylaspartate were obtained.

5-Ethoxy-2-ethoxycarbonyl-4-methyloxazole (IIIae). In 100 m*l* of chloroform, ethyl *N*-ethoxalylalaninate (21.7 g, 0.1 mol) and triethylamine (30.0 g, 0.3 mol) were dissolved. Into the solution, a 100-m*l* portion of chloroform solution containing phosgen (14.8 g, 0.15 mol) was then stirred, drop by drop, at 20°C, and the mixture was heated to 50°C for 1 hr. After the reaction mixture had been washed with water to remove the triethylamine hydrochloride, the chloroform was distilled off; on fractional distillation, 5-ethoxy-2-ethoxycarbonyl-4-methyloxazole was obtained (bp 128°C/4 mmHg; yield, 13.9 g, 70.0%). Similarly, 5-alkoxy-2-alkoxycarbonyl-4-methyloxazole and 5-alkoxy-2-alkoxycarbonyl-4-alkoxycarbonylmethyloxazole were obtained from alkyl *N*-alkoxalylalaninate and alkyl *N*-alkoxalylaspartate.

2-Carboxy-5-ethoxy-4-methyloxazole (IVae). Into 9.9 g (0.05 mol) of 5-ethoxy-2-ethoxycarbonyl-4-methyloxazole, an 11.4-m*l* portion of a 5N aqueous sodium hydroxide solution (0.057 mol) was stirred. After 20 min, 9.56 m*l* of 5.95N hydrochloric acid (0.057 mol) were added to the mixture. Crystals of 2-carboxy-5-ethoxy-4-methyloxazole were filtered out and dried over phosphorus pentoxide at 30°C under reduced pressure (mp 83—84°C; yield, 7.7 g, 90%). Similarly, 5-alkoxy-2-carboxy-4-methyloxazole and 5-alkoxy-2-carboxy-4-carboxymethyloxazole were obtained.

The Diels-Alder Reaction of 2-Carboxy-5-ethoxy-4-methyloxazole. *With Diethyl Maleate.* A mixture of 2-carboxy-5-ethoxy-4-methyloxazole (IVae, 1.7 g) and

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[6] W. Kerp and K. Unger, *Ber.*, **30**, 579 (1897).

[*1] The boiling and melting points are uncorrected.

diethyl maleate (5.2 g) was kept at 100°C for 6 hr. Upon the addition of ethanol containing hydrogen chloride and upon the further addition of ether to the reaction mixture, crystals of 4,5-diethoxycarbonyl-3-hydroxy-2-methylpyridine hydrochloride (V) were formed (mp 144—145°C; yield, 2.5 g, 86.2%).

Found: C, 49.63; H, 5.34; N, 4.88%. Calcd for $C_{12}H_{15}NO_5HCl$: C, 49.74; H, 5.57; N, 4.84%.

Similarly, a mixture of 2-carboxy-4-carboxymethyl-5-ethoxyoxazole (IVbe, 2.2 g) and diethyl maleate (5.2 g) was kept at 130°C for 4 hr. From the reaction mixture, V was obtained (mp 145—146°C; yield, 1.1 g).

With Fumaronitrile. A mixture of IVae (1.7 g), fumaronitrile (0.78 g), and methanol (20 m*l*) was refluxed for 5 hr. After the reaction mixture had then cooled, 4 m*l* of concentrated hydrochloric acid were added. The solvent was then distilled off, and the residue was dried with benzene. When recrystallized from a mixed solvent of methanol and benzene, it formed yellow crystals, 4,5-dicyano-3-hydroxy-2-methylpyridine (mp 187—188°C; yield, 0.9 g).

Found: C, 60.54; H, 3.08; N, 26.49%. Calcd for $C_8H_5N_3O$: C, 60.37; H, 3.17; N, 26.41%.

With 4,7-Dihydro-1,3-dioxepine. A mixture of 4,7-dihydro-1,3-dioxepine (20.3 g) and IVae (1.7 g) was kept at 190°C for 3 hr. After the unreacted compounds had been distilled off, a 120-m*l* portion of 2N hydrochloric acid was added to the residue and the mixture was refluxed for 2 hr. After the solvent had been distilled off, crystals of pyridoxine hydrochloride were obtained when ethanol and acetone were added to the residue (mp 202—204°C; yield, 1.0 g).

Found: C, 46.89; H, 6.15; N, 6.76%. Calcd for $C_8H_{11}NO_3HCl$: C, 46.72; H, 5.88; N, 6.81%.