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The Synthetic Intermediate of Pyridoxine. III.[1] The Simple Synthesis of Ethyl *N*-Ethoxalylalaninate and Ethyl *N*-Formylalaninate

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Ethyl *N*-ethoxalylalaninate (I), which is an important intermediate on the synthesis of pyridoxine, had been obtained from alanine through two steps. That is compound I had been prepared by the treatment of ethyl alaninate hydrochloride with ethoxalyl chloride[2] or with diethyloxalate in the presence of triethylamine, as was in our previous paper.[3] Our further investigation was undertaken to determine a simple method. Compound I and ethyl *N*-formylalaninate (II) could be obtained by heating a mixture of alanine, oxalic acid, and ethanol at various temperatures, as is shown in Fig. 1.

The yield of Compound I increased when the mixture was heated in the range from 110 to 140°C, while at temperatures above 150°C the yield of Compound I decreased and that of Compound II increased remarkably. After the water formed and the unreacted ethanol had been distilled off from the reaction mixture, ethanol was added again to the residue and the

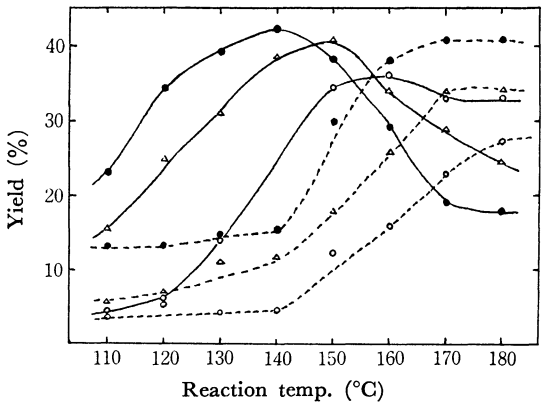

Fig. 1. One-step method of synthesizing ethyl *N*-ethoxalylalaninate.

The yield of ethyl *N*-ethoxalylalaninate ——
The yield of ethyl *N*-formylalaninate .....
Reaction time: ○—○, 1 hr; △—△, 3 hr; ●—●, 5 hr.

TABLE 1. SIMPLE METHOD OF THE SYNTHESIS OF *N*-ALKOXALYLAMINO ACID ESTERS

RCHCOOR′ NHCOCOOR′		Reaction conditions			Yield (%)	
R	R′	Temp. (°C)	Time (hr)	Repeat (times)	FAE[a]	OXE[b]
H	C_2H_5	120	3	3	3.6	80.9
		180	3	1	31.9	29.8
CH_3	C_2H_5	120	3	3	10.6	58.0
		120	3	3	trace	70.1[c]
		150	3	3	15.9	65.3
		150	3	3	trace	70.5[c]
$(CH_3)_2CHCH_2$	C_2H_5	120	3	3	5.5	78.4
		140	3	3	4.3	74.8
		180	5	1	37.2	24.3
$C_6H_5CH_2$	C_2H_5	180	5	1	28.5	12.9

a) *N*-Formylamino acid ester.
b) *N*-Alkoxalylamino acid ester.
c) Alanine (0.15 mol), oxalic acid (0.15 mol), diethyl oxalate (0.75 mol), and ethanol (138 g) were used.

1) Part II of this series: I. Maeda, M. Takehara and R. Yoshida, This Bulletin, **44**, 1407 (1971).
2) W. Kerp and K. Unger, *Ber.*, **30**, 579 (1897).
3) I. Maeda, M. Takehara, K. Togo, S. Asai, and R. Yoshida, This Bulletin, **42**, 1435 (1969).

mixture was heated again. When the mixture was heated at 120°C and the above treatment was repeated three times, the yield of Compound I amounted to 58.0%, while the yield of Compound II was 10.6%. A mixture of alanine (0.15 mol), oxalic acid (0.15 mol), diethyl oxalate (0.75 mol), and ethanol was heated at 120°C, and the treatment described above was repeated three times. The yield of Compound I was 70.1%, while the amount of Compound II was a trace. The results of these methods preparing *N*-alkoxalylamino acid esters are shown in Table 1.

Compound II, which is also an important intermediate for the synthesis of pyridoxine, can be obtained by heating a mixture of alanine, formic acid, and ethanol. *N*-Formylamino acid esters have been prepared from amino acids in two steps. In general, they are prepared by the esterification of *N*-formylamino acids with diazomethane[4] or by the formylation of amino acid esters with formic acid and acetic anhydride.[5]

By a similar simple method, these various *N*-formylamino acid esters could be synthesized from amino acid, formic acid, and alcohol in one step. The results are shown in Table 2.

Table 2. Simple method of the synthesis of *N*-formylamino acid esters

RCHCOOR′ NHCHO		Reaction conditions		
R	R′	Temp. (°C)	Time (hr)	Yield[a] (%)
CH_3	CH_3	160	5	71.0
CH_3	C_2H_5	160	8	70.0
CH_3	C_4H_9	170	5	50.2
$(CH_3)_2CHCH_2$	C_2H_5	170	5	56.4
H	CH_3	160	5	62.8
H	C_2H_5	170	5	56.4
$C_6H_5CH_2$	C_2H_5	170	3	52.7
CH_3SCH_2	CH_3	160	5	35.5

a) Based on amino acid.

Experimental[6]

Ethyl N-ethoxalylalaninate. A mixture of DL-alanine (13.35 g, 0.15 mol), oxalic acid (39.5 g, 0.45 mol), and ethanol (138 g) was put into a 300-m*l* autoclave. The autoclave was kept at 120°C by electrical heating for 3 hr, and then it was chilled. The ethanol and water formed in the reaction mixture were distilled off under reduced pressure. Then ethanol (138 g) was added to the residue, and the mixture was again treated in a manner similar to that used in the experiment described above. This treatment was repeated three times. After the unreacted ethanol and diethyl oxalate, which was one of the by-products, had been removed, the residue was distilled under reduced pressure to afford ethyl *N*-formylalaninate (bp 115—120°C/4 mmHg; yield, 2.3 g; 10.6%) and ethyl *N*-ethoxaylalaninate (bp 140—145°C/4 mmHg; yield, 18.9 g; 58.0%). The following *N*-alkoxylalamino acid esters were prepared by the same method. Ethyl *N*-ethoxalylglycinate (bp 135—138°C/5 mmHg; yield, 24.6 g; 80.9%). Found: C, 47.31; H, 6.65; N, 7.04%. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89%. Ethyl *N*-ethoxalylleucinate (bp 150—154°C/4 mmHg; yield, 29.1 g; 74.8%). Found: C, 55.89; H, 8.40; N, 5.69%. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40%. Ethyl *N*-ethoxalylphenylalaninate (bp 180—185°C/1 mmHg; yield, 5.7 g; 12.9%). The results are summarized in Table 1.

The investigation of the reaction temperature and time shown in Fig. 1 was carried out as follows. A mixture of DL-alanine (4.45 g, 0.05 mol), oxalic acid (13.5 g, 0.15 mol), and ethanol (46.0 g, 1 mol) was put into a 100-ml autoclave. The reaction was then carried out at 110—180°C at intervals of 10°C for 1, 3, or 5 hr respectively. The reaction mixtures were diluted with ethanol to 100 m*l* after which the amounts of ethyl *N*-formylalaninate and ethyl *N*-ethoxalylalaninate were analyzed by gas chromatography, which was carried out with 4% Versamid 900 on Chromosorb T (4 mmϕ × 1 m; column temperature, 190°C; flow rate of He, 60 m*l*/min; internal standard, benzophenone).

N-Formylamino Acid Esters. A mixture of amino acid (0.2 mol), 98.5% formic acid (0.6 mol), and ethanol (4 mol) was put into a 300-m*l* autoclave. The autoclave was then kept under the conditions listed in Table 2. After the removal of the solvent from the reaction mixture, the product was obtained as a syrup; the *N*-formylamino acid ester was then distilled at reduced pressure, as will be described below.

Methyl *N*-formylalaninate (bp 102—105°C/2 mmHg. Found: C, 45.79; H, 7.18; N, 10.82%). Ethyl *N*-formylalaninate (bp 110°C/2 mmHg. Found: C, 49.84; H, 7.91; N, 9.61%). Butyl *N*-formylalaninate (bp 131—133°C/2 mmHg. Found: C, 55.51; H, 9.02; N, 8.29%. Calcd for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 8.09%). Ethyl *N*-formylleucinate (bp 143°C/8 mmHg. Found: C, 58.09; H, 9.45; N, 7.60%). Methyl *N*-formylglycinate (bp 137°C/28 mmHg. Found: C, 41.26; H, 6.43; N, 11.76%). Ethyl *N*-formylglycinate (bp 136°C/5 mmHg. Found: C, 45.61; H, 7.22; N, 10.87%). Ethyl *N*-formylphenylalaninate (bp 158—159°C/1 mmHg. Found: C, 65.29; H, 7.07; N, 6.50%). Methyl *N*-formylmethionate (bp 152—153°C/1 mmHg. Found: C, 44.05; H, 7.02; N, 7.22%).

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4) D. S. Tarbell, H. P. Hirschler, and R. B. Carlin, *J. Am. Chem. Soc.*, **72**, 3138 (1950).
5) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 644 (1949).
6) All the boiling points are uncorrected.