BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 44, 1407—1410(1971)

The Synthetic Intermediate of Pyridoxine. II.[1] The Thermal Cyclization of Ethyl α-Isocyanopropionate to 5-Ethoxy-4-methyloxazole[2]

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(Received December 9, 1970)

The thermal cyclization of ethyl α-isocyanopropionate (I) was performed to 5-ethoxy-4-methyloxazole (II) as an intermediate for the synthesis of pyridoxine. The similar reaction of several new alkyl esters of α-isocyanocarboxylic acid to the corresponding 5-alkoxy-4-substituted oxazole was also carried out. The reaction products of the thermal cyclization of I were investigated. When the cyclization was carried out at 180°C for 5 hr, the maximum yield of the main product, II, was 20%; unreacted I (30%), ethyl α-cyanopropionate (20%), and dimer of I (5%) were also obtained. The α-hydrogen of ethyl α-isocyanosuccinate (X) can be more easily removed than that of I, so X may be expected to be more readily converted to 5-ethoxy-4-ethoxycarbonylmethyloxazole (XI), which is also an intermediate of pyridoxine. The yield of XI from X did not exceed 30% because of the side reaction.

By Firestone *et al*,[3] 5-ethoxy-4-methyloxazole, an important intermediate for the synthesis of pyridoxine by the Diels-Alder reaction with dienophiles, has been prepared from ethyl *N*-formylalaninate and phosphorus pentoxide. Recently, as a modification[4] of this procedure, it has been reported that ethyl *N*-formylalaninate was converted to its boron trifluoride complex, after which the complex was treated with phosphorus pentoxide to prepare 5-ethoxy-4-methyloxazole. However these methods have the defect that the reaction mixture forms a hard or powderlike mass which is difficult to remove from the vessel.

The present investigation was undertaken in an attempt to prepare this oxazole without the use of phosphorus pentoxide. This paper will present our findings on the thermal cyclization of ethyl α-isocyanopropionate to produce 5-ethoxy-4-methyloxazole.

Results and Discussion

Ethyl *N*-formylalaninate was converted to ethyl α-isocyanopropionate (I) following the methods of Ugi *et al.* for the synthesis of the derivatives of isonitrile.[5] Several new alkyl esters of α-isocyanocarboxylic acid were synthesized from the alkyl esters of *N*-formylamino acid. The results are listed in Table 1. In order to examine the possibility of the thermal cyclization of I, the solution of I was kept at 170°C. Upon being heated, the solution gradually turned brown-red. In order to analyze the reaction products, the resulting solution was submitted to gas chromatography. Various kinds of 5-alkoxy-4-substituted oxazoles were obtained through the cyclization of the alkyl esters of α-isocyanocarboxylic acid by external heating. The yield of 5-alkoxy-4-substituted oxazoles was calculated on the basis of the area of each peak in a gas chromatograph after a usual calibration using authentic samples; the results are listed in Table 2.

The thermal cyclization from ethyl α-isocyanopropionate (I) to 5-ethoxy-4-methyloxazole (II) was carried out at various temperatures in order to determine the temperature at which the maximum conversion can be obtained. The set of curves in Fig. 1 is presented to show; (A) the conversion of I to II; (B) the decrease in I, and (C) the residue of II at various temperatures. The maximum conversion of I to II, obtained by

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2) Presented in part at the 22nd Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1969.

3) R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron* **23**, 943 (1967).

4) F. Hoffmann-La Roche and Co., Neth. Appl. 6508673 (1966); *Chem. Abstr.*, **64**, 14193 (1966).

5) I. Ugi, W. Betz, U. Fetzer, and K. Offermann, *Chem. Ber.*, **94**, 2814 (1961).

TABLE 1. ALKYL ESTERS OF α-ISOCYANOCARBOXYLIC ACID

RCHCOOR′ | NC		Bp °C/mmHg	n_D(°C)	Yield %	Elementary analysis					
					Calcd %			Found %		
R	R′				C	H	N	C	H	N
CH_3	CH_3	77—79/19	1.4100 (30)	69.4	53.09	6.24	12.38	53.06	6.32	12.58
CH_3	C_2H_5	85—86/20	1.4105 (30)	70.4	56.58	7.14	11.02	56.65	7.39	11.36
CH_3	$CH(CH_3)_2$	86—87/20	1.4076 (30)	71.5	59.55	7.85	9.92	59.59	7.98	9.86
CH_3	C_4H_9	105—108/20	1.4190 (30)	76.9	61.91	8.44	9.03	61.54	8.24	8.95
$(CH_3)_2CHCH_2$	C_2H_5	88—90/10	1.4268 (22)	55.9	63.88	8.94	8.28	63.66	9.21	8.28
H	C_2H_5	89—91/20	1.4180 (22)	50.5	53.09	6.24	12.38	52.44	6.56	12.27
$C_6H_5CH_2$	C_2H_5	118—123/1	1.5000 (29)	74.2	70.91	6.45	6.89	70.77	6.17	6.89
CH_3SCH_2	CH_3	100—113/1	1.4783 (27)	71.0	48.55	6.40	8.09	48.76	6.53	8.01
CH_3OOCCH_2	C_2H_5	114—115/3	1.4369 (22)	58.8	54.26	6.58	7.03	54.54	7.00	7.09

TABLE 2. 5-ALKOXY-4-SUBSTITUTED OXAZOLES

RC=C(OR′)–O–CH=N		Reaction		Yeild (%)
		Temp.	Time	
R	R′	(°C)	(hr)	
CH_3	CH_3	160	3	15.6
CH_3	C_2H_5	170	3	16.6
CH_3	$CH(CH_3)_2$	180	3	22.1
CH_3	C_4H_9	180	3	28.2
H	C_2H_5	150	3	5.1
$(CH_3)_2CHCH_2$	C_2H_5	180	3	21.2

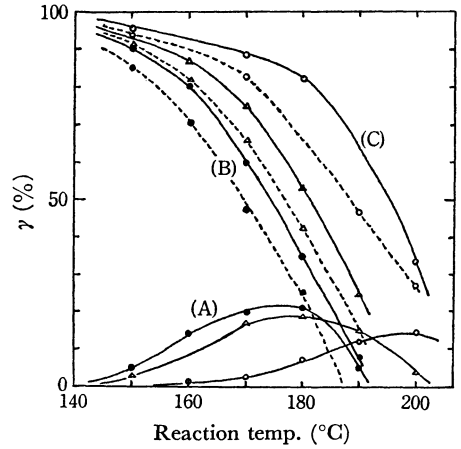


Fig. 1. The thermal cyclization from ethyl α-isocyanopropionate (I).
(A) conversion of I to II ——
(B) decrease of I ----
(C) residue of II ——
Reaction time; ○—○ 1 hr, △—△ 3 hr, ●—● 5 hr

keeping the compound I for 5 hr at 180°C was 21.4%. The results suggest that the compound II first formed from compound I is decomposed by further subsequent reactions and that the thermal conversion of I to II is accompanied by a side reaction. In order to investigate the side-reaction products compound I (30 g) was heated at 180°C for 5 hr and then distilled. The results are shown Table 3. The products of each fraction were identified by gas chromatography, NMR, and IR-spectra analyses. The gas chromatograms of fraction 2 (low-boiling materials) and fraction 5 (high-boiling materials) are shown in Fig. 2. Compounds I and II were identified as ethyl α-isocyanopropionate and 5-ethoxy-4-methyloxazole respectively by comparing their retention times with those of authentic samples. Compound I and III were observed in fraction 3 by gas chromatography. The IR spectrum of fraction 3 showed bands at 2270 cm^{-1} ($\nu_{C\equiv N}$), 2180 cm^{-1} ($\nu_{N\equiv C}$) and 1750 cm^{-1} ($\nu_{C=O}$), while the NMR spectrum exhibited peaks at 8.70τ (triplet 6H, $CH_2\underline{CH_3}$), 8.48τ (doublet 3H, $C\underline{H_3}CH$), 8.38τ (doublet 3H, $C\underline{H_3}CH$), 6.36τ (quartet, 1H, $CH_3C\underline{H}$) 5.88τ (quartet, 4H, $CH_3C\underline{H_2}$), and 5.62τ (quartet, 1H, $CH_3C\underline{H}$). These facts show that the fraction 3 was a mixture of I and ethyl α-cyanopropionate (III). The compound V in fractions 4 and 5 was identified as ethyl *N*-formylalaninate by a comparison of its retention time with that of an authentic sample. For the identification of the unknown product, compound VI, each of the components of fractions 4 and 5 was collected by preparative

TABLE 3. EACH FRACTION OF THE DISTILLATE

Fraction	Bp °C/mmHg	Weight g
1	64—80/20	7.4
2	80—88/20	7.3
3	88—92/20	5.7
4	92—142/6	0.9
5	142—170/6	3.1
6	residue	3.7

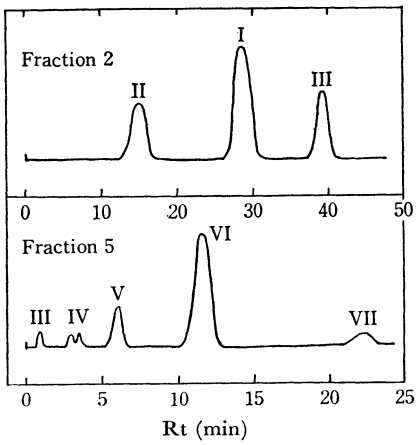
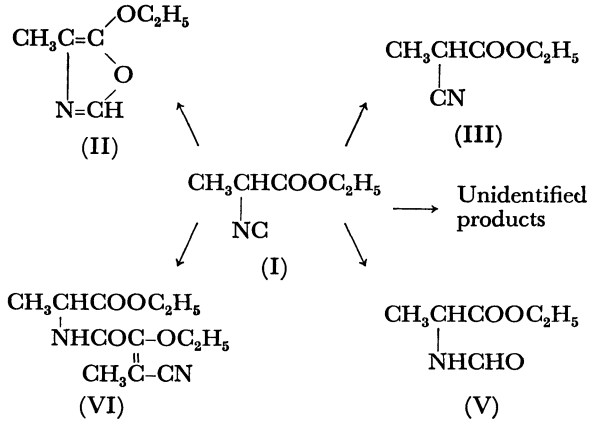


Fig. 2. The gas chromatograms of fraction 2 (low boiling materials) and fraction 5 (high boiling materials).

gas chromatography. The mass spectrum of compound VI showed a molecular ion peak at *m/e* 254, supporting the molecular formula of $C_{12}H_{18}N_2O_4$ (mol wt 254.28) obtained by elementary analysis. The IR spectrum of compound VI showed bands at 2270 cm^{-1} ($\nu_{C\equiv N}$), 1740 cm^{-1} ($\nu_{C=O}$), 1670 cm^{-1} ($\nu_{C=O}$), and 1600 cm^{-1} ($\nu_{C=C}$, $\nu_{C=O}$). The NMR spectrum showed peaks at 8.70τ (double triplet, 6H, $CH_2C\underline{H}_3$), 8.50τ (doublet, 3H, $CHC\underline{H}_3$), 8.00τ (singlet, 3H, $C\underline{H}_3C=$), 5.80τ (double quartet, 4H, $C\underline{H}_2CH_3$), 5.75τ (quartet, 1H, $C\underline{H}CH_3$), and 1.73τ (broad doublet, 1H, NH). The UV spectrum indicated a maximum absorption at 316 mμ. Futhermore, compound VI was hydrolyzed by heating it at 180°C for 30 min with an aqueous solution of sodium hydroxide. The resulting compound was identified as alanine by paper chromatography. On the basis of these data, compound VI was identified as ethyl *N*-(3-cyano-2-ethoxy-2-butenoyl)-alaninate. The amount of each product was determined by the usual gas-chromatography method using authentic samples. The results are shown in Table 4 and Scheme 1.

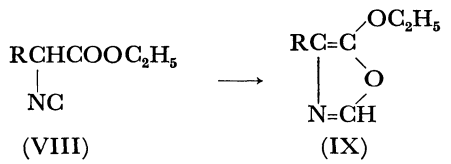


Scheme 1. Thermal reaction products of ethyl α-isocyanopropionate.

Table 4. The amount of the thermal cyclization products

Product number	Fraction	Per cent based on I
II	1, 2	20.4 mol%
I(unreacted)	1, 2, 3	30.4
III	1, 2, 3, 4	18.7
IV	4, 5	—
V	4, 5	0.9
VI	4, 5	5.0
VII	5	—
residue		12.3 wt%

The oxazole derivative (IX) seems to be formed by α-hydrogen abstraction from isocyano derivatives (VIII).



The facility of the cleavage of the α-carbon–hydrogen linkage depends on the electron density around the α-carbon. An electrophilic effect of R, such as $CH_2COOC_2H_5$, can reduce the electron density around the α-carbon. Therefore, diethyl α-isocyanosuccinate ($R=CH_2COOC_2H_5$) may be expected to be more readily converted to an oxazole derivative than ethyl α-isocyanopropionate ($R=CH_3$). At various temperatures diethyl α-isocyanosuccinate (X) was converted to 5-ethoxy-4-ethoxycarbonylmethyloxazole (XI), which is an intermediate for the synthesis of pyridoxine. The results are shown in Fig. 3. The rate of decrease in the starting material, X, was larger than that of I, though the rate of decrease in the residue of XI was similar to that of II. This indicates that the side reaction of X to XI occurs much more than that of I to II. Therefore, the maximum conversion of X to XI did not exceed 30% in spite of the facility of the cleavage of the αC–H linkage.

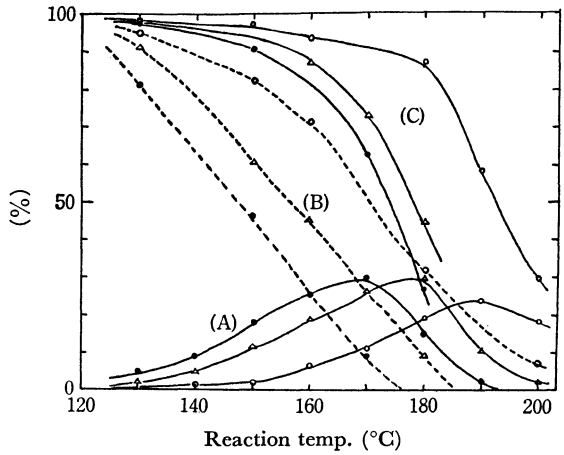


Fig. 3. The thermal cyclization from ethyl α-isocyanosuccinate (X)
(A) conversion of X to XI ——
(B) decrease of X ----
(C) residue of XI ——
Reaction time; ○—○ 1 hr, △—△ 3 hr, ●—● 5 hr

Experimental[6]

Ethyl α-Isocyanopropionate (I). Ethyl *N*-formylalaninate (43.5 g, 0.3 mol) and 100 m*l* of triethylamine were dissolved in 50 m*l* of chloroform. To the solution, 238 g of a chloroform solution containing phosgene (30 g, 0.3 mol) was added, drop by drop under ice-cooling at 25°C over a 1 hr period. The reaction mixture was stirred a further 30 min at room temperature and then washed with 160 m*l* of water to remove triethylamine hydrochloride. The chloroform layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The residue was distilled to give ethyl α-isocyanopropionate (bp 85—86°C/20 mmHg; yield; 26.8 g, 70.4%). Similarly, alkyl esters of α-isocyanocarboxylic acids were synthesized from alkyl esters of *N*-formyl amino acids, as is shown in Table 1.

The Thermal Cyclization of Alkyl Esters of α-Isocyanocarboxylic Acids to 5-Alkoxy-4-substituted Oxazoles. The alkyl ester of α-isocyanocarboxylic acid (2 g) was poured into a 10-m*l* ampoule. The ampoule was then sealed and placed in an oil bath equipped with a thermometer. The temperature was maintained as is shown in Table 2. The resulting liquid

6) All the boiling points are uncorrected.

TABLE 5. GAS CHROMATOGRAPHIC ANALYSIS OF OXAZOLE DERIVATIVES

R	R′	Column[a] length (m)	Column[a] temp. (°C)	Flow rate of He (ml/min)	Type[b]	Internal standard
CH_3	CH_3	1.5	85	75	1C	diethyleneglycol diethyl ether
CH_3	C_2H_5	2.25	85	60	1C	isoamyl acetate
CH_3	$CH(CH_3)_2$	2	90	75	2B	isoamyl acetate
CH_3	C_4H_9	1.5	100	75	1C	diethyleneglycol diethyl ether
H	C_2H_5	2	85	75	2B	isoamyl acetate
$(CH_3)_2CHCH_2$	C_2H_5	1.5	110	75	1C	diethyleneglycol diethyl ether

a) 5% Dinonyl phthalate on Chromosorb T b) 1C (2mmϕ) 2B (4mmϕ)

was analyzed by gas chromatography. Gas chromatography was carried out on a model GC-2B and 1C compact chromatographic analysis unit of Shimadzuseisakujo, Ltd. The operation conditions are shown in Table 5. The authentic samples were prepared, using the technique for 5-ethoxy-4-methyloxazole from ethyl *N*-formylalaninate, using phosphorus pentoxide.[3] All of the above authentic samples were confirmed by gas-chromatographic analysis to have no impurity affecting the results.

5-Ethoxy-4-methyloxazole from Ethyl α-Isocyanopropionate. Ethyl α-isocyanopropionate (1 g) was added to an ampoule. The ampoule was then sealed and placed in an oil bath. The reaction was carried out at 140—190°C at intervals of 10°C for 1, 3, and 5 hr. After the reaction, the contents of the ampoule were diluted with benzene to 50 m*l*; then, the 5-ethoxy-4-methyloxazole and the unreacted ethyl α-isocyanopropionate were analyzed by gas chromatography, using a stainless-steel column packed with 5% dinonyl phthalate on Chromosorb T (2 mmϕ × 3.75 m; column temperature: 85°C; flow rate of He: 20 m*l*/min; internal standard: isoamyl acetate). The curves (A) and (B) in Fig. 1 were thus drawn. Similarly, 5-ethoxy-4-methyloxazole (1 g) was heated under the above reaction conditions and analyzed; the curve (C) in Fig. 1 was thus drawn.

The Products of the Thermal Cyclization of Ethyl α-Isocyanopropionate. Ethyl α-isocyanopropionate (30 g) was put into a dried autoclave with a 100 m*l* capacity by means of a magnetic stirrer. The autoclave was kept at 180°C by electrical heating for 5 hr and then it was chilled. The reaction mixture was distilled under reduced pressure. The fractions of the distillate shown in Table 3 were thus obtained. Each fraction of the distillate was analyzed by gas chromatography; the compounds shown in Table 4 were identified by comparing their retention times with those of authentic samples. The yields of the compounds I, II, V, and VI were calculated from the total weight of the mixture on the basis of the calibration curves of the gas chromatography for an authentic sample. The authentic samples were prepared as follows: 5-ethoxy-4-methyloxazole (II) was prepared from ethyl *N*-formylalaninate with phosphorus pentoxide. Ethyl *N*-formylalaninate (V) was prepared from ethyl alaninate hydrochloride and formic acid. Compound VI was separated from the fractions 4 and 5 by preparative gas chromatography (10% Carbowax 20 M on Diasolid L; 8 mmϕ × 3 m; column temperature, 190°C; flow rate of He, 75 m*l*/min); it was shown to be $C_{12}H_{18}N_2O_4$ by elementary analysis.

Found: C, 56.77; H, 7.35; N, 10.76%. Calcd: C, 56.68; H, 7.14; N, 11.02%.

The yield of ethyl α-cyanopropionate (III) was calculated from the calibration curves of compound I.

5-Ethoxy-4-ethoxycarbonylmethyloxazole from Diethyl α-Isocyanosuccinate. The reaction and analysis of 5-ethoxy-4-methyloxazole from ethyl α-isocyanopropionate were similar to those described above except that gas chromatography was carried out with 3% Silicone XE-60 on Chromosorb T (4 mmϕ × 1.875 m glass column; column temperature, 140°C; flow rate of He, 70 m*l*/min; internal standard, dibenzyl ether).

The authors wish to thank Professor Dr. M. Matsui of Tokyo University and Professor Dr. Y. Nakatani of Ochanomizu University for their many helpful discussions and suggestions.