*A New Rearrangement Reaction of β-Hydroxy-α-amino Acid N-Carboxy Anhydrides to 2-Oxazolidone Derivatives**

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An α-amino acid *N*-carboxy anhydride polymerizes into poly-α-amino acid, which is a model substance of protein. The synthesis of β-hydroxyl-containing poly-α-amino acids is of interest, because the polymers provide models of water-soluble proteins.

Polymers containing protected β-hydroxyl groups, viz., poly-*O*-acetyl-DL-serine,[1] poly-*O*-acetyl-L-serine,[2,3] and poly-*O*-acetyl-L-threonine,[3] have been prepared by the polymerization of the corresponding *N*-carboxy anhydrides by using a trace amount of a suitable amine, e. g., triethylamine. The subsequent complete deacetylation of the resultant protected polymers was, however, accompanied by many difficulties. An attempt to polymerize DL- and L-serine *N*-carboxy anhydrides with a free β-hydroxyl group was unsuccessful in obtaining poly-DL- and L-serine, as has been reported by Fasman and Blout.[2]

The present paper will describe a rearrangement of the *N*-carboxy anhydrides of several α-amino acids with free β-hydroxyl groups to 2-oxazolidone derivatives.

Two cyclic compounds, *N*-carboxy anhydride (III) and 2-oxazolidone derivative (VII), are supposed to be produced by the reaction of β-hydroxyl-α-amino acid (I) with phosgene, in which reaction *N*-chlorocarbonyl-β-hydroxy-α-amino acid (II) is a possible intermediate (Scheme A).

The reaction of L-serine, DL-threonine, L-threonine, and DL-β-phenylserine with phosgene

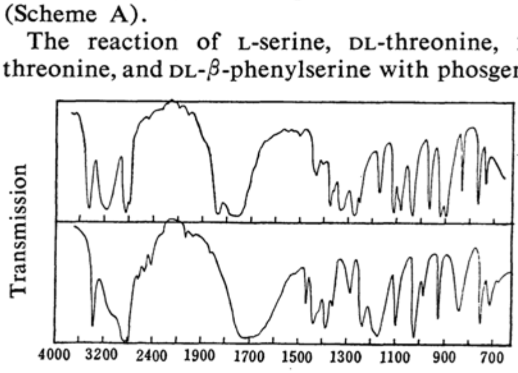

Fig. 1. The infrared spectra of L-serine-*N*-carboxy anhydride (IIIa) (upper) and L-2-oxazolidone-4-carboxylic acid (VIIa) (lower).

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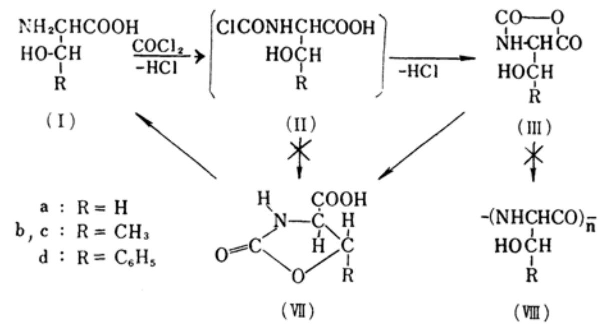
* This work was partly repoted in short communication on *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **84**, 441 (1963).

[1] M. Frankel, M. Breuer and S. Cardova, *Experientia*, **8**, 299 (1952); M. Frankel, S. Cardova and M. Breuer, *J. Chem. Soc.*, **1953**, 1991.

[2] G. D. Fasman and E. R. Blout, *J. Am. Chem. Soc.*, **82**, 2262 (1960).

[3] J. Noguchi and T. Saito, will be published.



Scheme A

in anhydrous dioxane at 50°C afforded exclusively products corresponding to III. The structure III of these substances was inferred from the following data. The equivalent weights determined for the substances III, by anhydrous sodium methylate titration using thymol blue as an indicator,[4] agreed with those of the corresponding *N*-carboxy anhydrides (III) (Table I), and the ready elimination of carbon dioxide by the action of dilute hydrochloric acid under mild conditions was observed for the substance III, while the use of this reaction in the qualitative identification for *N*-carboxy anhydrides is well known. The infrared absorption spectra showed two typical carbonyl-stretching absorption bands[5] for the cyclic acid anhydride, at 1860~1850 cm^{-1} and at 1780 cm^{-1}, and a hydroxyl-stretching absorption band at 3540 cm^{-1} (Figs. 1—4).

III did not polymerize into polyamino acids under the conditions suitable for the polymerization of *N*-carboxy anhydrides of general amino acids; rather, it was rearranged into a 2-oxazolidone derivative (VII). The evidence is as follows. Some physical constants (Table II) for the products derived from III attracted our special attention and led us to suggest a rearranged product, VII. Confirmatory support was given to the suggested structure VII by the infrared absorption spectra (Figs. 1—4), which indicated two carbonyl-stretching vibration bands at 1770~1650 cm^{-1} assignable to vibrations of cyclic lactone[5] and the free carboxyl group[5] and to the lack of the hydroxyl vibration at 3540 cm^{-1}.

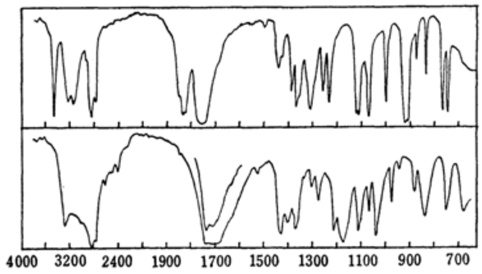


Fig. 2. The infrared spectra of DL-threonine *N*-carboxy anhydride (IIIb) (upper) and DL-*trans*-5-methyl-2-oxazolidone-4-carboxylic acid (VIIb) (lower).

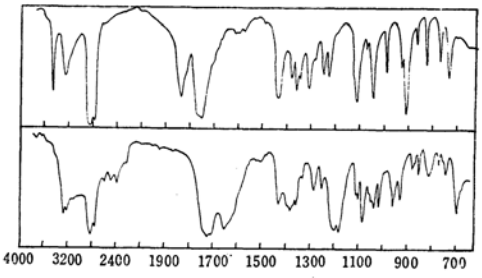


Fig. 3. The infrared spectra of L-threonine *N*-carboxy anhydride (IIIc) (upper) and L-*trans*-5-methyl-2-oxazolidone-4-carboxylic acid (VIIc) (lower).

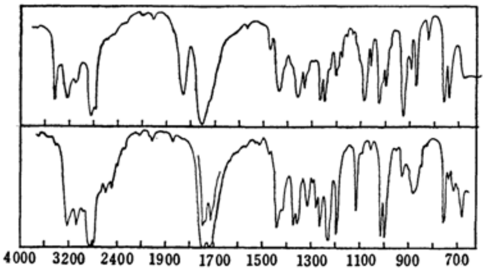


Fig. 4. The infrared spectra of DL-β-phenylserine *N*-carboxy anhydride (IIId) (upper) and DL-*trans*-5-phenyl-2-oxazolidone-4-carboxylic acid (VIId) (lower).

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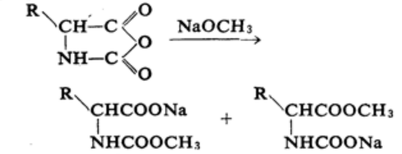
[4] A. Berger, M. Sela and E. Katchalski, *Anal. Chem.*, **25**, 1554 (1953). They reported that *N*-carboxy anhydride could be titrated with sodium methylate in non-aqueous solvent, and the reaction proceeds according to the following equation:



[5] N. B. Colthup, *J. Opt. Soc. Am.*, **40**, 397 (1950); L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co., Ltd., London (1958), pp. 95, 125.

TABLE I

β-Hydroxy-α-amino acid *N*-carboxy anhydrides

III	R		Yield %	M. p. °C	Equiv. wt. (NaOCH$_3$ tit.)	
					Found	Calcd.
a	-H	(L)	72	115 (decomp.) [115 (decomp.)][2]	127	131.1
b	-CH_3	(DL)	41	117 (decomp.)	141	145.1
c	-CH_3	(L)	82	111∼112 (decomp.)	147	145.1
d	-C_6H_5	(DL)	98	195 (decomp.)	200	207.2

TABLE II

2-Oxazolidone-4-carboxylic acid 5-derivatives

VII	R		Yield %	M. p. °C	Equiv. wt. (NaOCH$_3$ tit.)		$[\alpha]_D$	Hydrolysis by 6 N HCl
					Found	Calcd.		
a	-H	(L)	36	118	134	131.1	−10.95°	L-Serine
b	-CH_3	(DL)	78	128∼129 (127∼128)[6,10]	143	145.1		DL-Threonine
c	-CH_3	(L)	90	139 (139)[7]	146	145.1	+41.0° (+41.7°)[7]	L-Threonine
d	-C_6H_5	(DL)	96	204 (decomp.) [206∼207 (decomp.)][6]	208	207.2		DL-β-Phenyl-serine

Thus, rearranged products VII, viz., L-2-oxazolidone-4-carboxylic acid (VIIa), DL- and L-*trans*-5-methyl-2-oxazolidone-4-carboxylic acid (VIIb and VIIc), and DL-trans-5-phenyl-2-oxazolidone-4-carboxylic acid (VIId), were derived from the corresponding *N*-carboxy anhydrides (III) under the influence of the basic reagent.

Incidentally, Kaneko and Inui[6] have reported the preparation of DL-*trans*-5-methyl-2-oxazolidone-4-carboxylic acid (m. p. 127∼128°C) in the different way, from DL-threonine, and they have also obtained its optically active form (m. p. 138.5∼139.5°C) by resolution of the DL-compound.[7] VIIb and VIIc, respectively, were also identified with these two oxazolidones by melting point and infrared absorption spectra.

All of the compounds VII are all easily soluble in water, with the exception of the 5-phenyl derivative (VIId), which is slightly soluble, without decomposition, and their aqueous solutions indicate a strong acidity.

Hydrolysis by heating with 6 N hydrochloric acid converted VII into the starting β-hydroxy-α-amino acid (I). Optically-active VIIa and VIIc[7] gave optically-pure L-serine[8] and L-threonine[8] respectively.

Therefore, during the rearrangement, the configurations at both asymmetric centers remain unchanged. This rearrangement resulted in the formation of VIIb, VIIc, and VIId from the corresponding structures, IIIb, IIIc, and IIId, the rearrangement was especially smooth in the last two cases. However, L-serine *N*-carboxy anhydride (IIIa) gave a considerable amount of amorphous polymeric material, which showed a positive Biuret reaction. This material was characterized as *O*-acyl-polyamino acid by its infrared absorption spectra, but this polymer was not investigated further.

The rearrangement never proceeds exclusively without a side reaction affording a polymer, and the facility of the latter reaction depends on the β-substituted group within the anhydride molecule III. The order of such an effect of decreasing the yield of 2-oxazolidones was as follows:

$$C_6H_5\text{-(DL-)} < CH_3\text{-(L-)} < CH_3\text{-(DL-)} \ll H\text{-(L-)}$$

The mechanism of the rearrangement from III to VII is not certain, but the following hypothesis may be proposed. In the initial stages of the polymerization of general α-amino acid *N*-carboxy anhydrides by using a trace amount of amine (cf. Scheme B), the first step is the reversible formation of a complex IV′ by the addition of the base to carbonyl-5; this complex may coexist with its tautomeric form V′. The reaction of the latter with an *N*-carboxy anhydride molecule is supposed to lead to the dimer VI′ with a scission of the tertiary base molecule. The subsequent addition of

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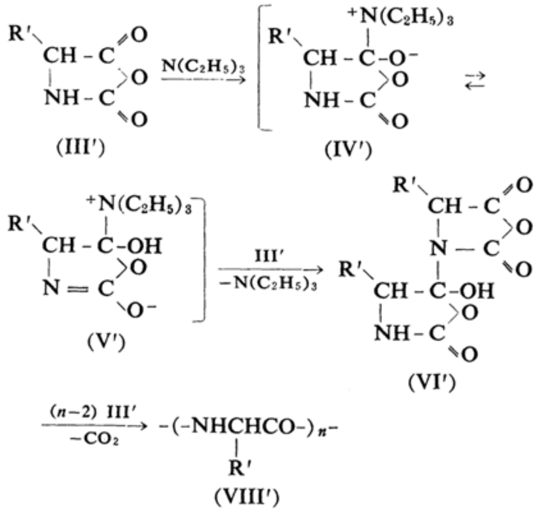
[6] T. Kaneko and T. Inui, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 1075 (1961).

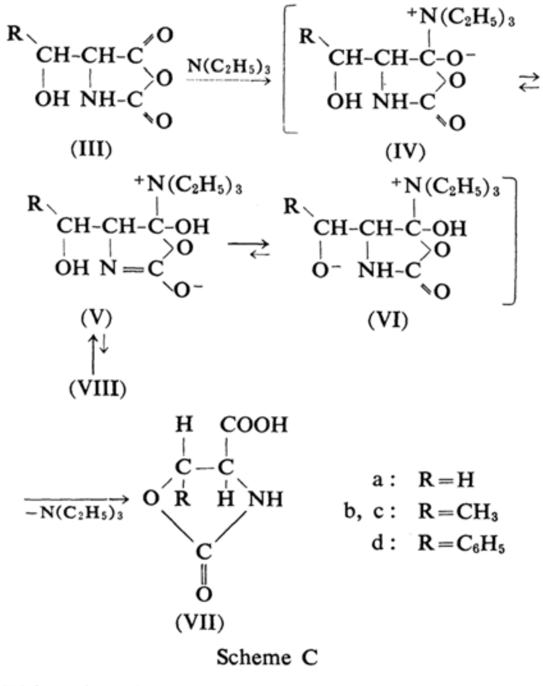
[7] T. Inui and T. Kaneko, ibid., **82**, 1078 (1961).

[8] L-Serine: $[\alpha]_D^{25} = +14.5°$ (in 1N hydrochloric acid), L-Threonine: $[\alpha]_D^{26} = -28.3°$ (in water). S. Akabori and S. Mizushima (Eds.), "Protein Chemistry" (Tanpakushitu Kagaku), Vol. 1, Kyoritsu Shuppan K. K., Tokyo (1952), p. 112.



Scheme B

N-carboxy anhydrides to the dimer VI' leads to a polyamino acid VIII'.[9] However, in the case of an *N*-carboxy anhydride which possesses a free β-hydroxy group (cf. Scheme C), the tautomer of a complex V corresponding to V' in Scheme B transfers rapidly with the proton migration to another tautomeric form, VI.



Scheme C

This migration rate is supposed to be greater than that which affords polyamino acid (VIII) and which is caused by the addition of *N*-carboxy anhydride to V. Then the rearrangement may proceed smoothly with the elimination of a tertiary base molecule from VI to VII as a stable form. In the case of IIIa it seems probable that the same intermediate Va in Scheme C affords VIIa through VIa, and VIII by two competing paths.

Experimental

All melting points are uncorrected.

Infrared Measurements. — All infrared spectra were recorded in Nujol mulls with a Koken DS 301-type double-beam spectrometer using a sodium chloride prism.

L-Serine *N*-Carboxy Anhydride (IIIa).[2]—Phosgene was bubbled into a suspension of L-serine (Ia) (10 g.) in dry dioxane (200 ml.) for three hours, while the temperature was maintained at 50°C. Then carbon dioxide was passed through the solution until it was phosgene-free. After filtration, the solvent was evaporated under reduced pressure, with the temperature kept below 40°C. The resultant oil solidified on rapeated trituration with petroleum ether. The solid was collected, dried, and recrystallized from ethyl acetate and petroleum ether; yield, 4.5 g. (72%) ; m. p. 115°C (decomp.). Found: N, 10.53; equiv. wt. 127 (determined by anhydrous sodium methylate titration). Calcd. for $C_4H_5O_4N$: N, 10.69%; equiv. wt. 131.1.

DL-Threonine *N*-Carboxy Anhydride (IIIb), L-Threonine *N*-Carboxy Anhydride (IIIc), and DL-β-Phenylserine *N*-Carboxy Anhydride (IIId). — IIIb, IIIc, and IIId were produced, by minor alterations of the method used in the preparation of IIIa, from DL- and L-threonine, and DL-β-phenylserine (m. p. 190°C (decomp.))[11,12] respectively. IIIb: yield, 41%; m. p. 117°C (decomp.). Found: N, 9.70; equiv. wt. 141. Calcd. for $C_5H_7O_4N$: N, 9.65%; equiv. wt. 145.1. IIIc: yield, 82%; m. p. 111∼112°C (decomp.). Found: N, 9.61; equiv. wt. 147. Calcd. for $C_5H_7O_4N$: N, 9.65%; equiv. wt. 145.1. IIId: yield, 98%; m. p. 195°C (decomp.). Found: N, 6.68; equiv. wt. 200. Calcd. for $C_{10}H_9 \cdot O_4N$: N, 6.76%; equiv. wt. 207.2.

L-2-Oxazolidone-4-carboxylic Acid (VIIa).—To a solution of IIIa (2.0 g.) in anhydrous dioxane (20 ml.), triethylamine (0.015 ml.) was added, and the mixture was stirred at room temperature for three days. Some polymeric precipitate was filtered off; this substance gave a positive Biuret reaction and showed not only amide I and II absorption spectra at 1625 cm^{-1} and 1545 cm^{-1} respectively, but also a carbonyl band at 1750 cm^{-1} which may be assignable to the ester. The solvent was evaporated under reduced pressure below 35°C. The resultant crystals were recrystallized from ethyl acetate and petroleum ether; yield, 0.72 g. (36%); m. p. 118°C, $[\alpha]^{15}_{D} = -10.95°$ (*c* 4.20, water). Found: C, 36.60; H, 3.91; N, 10.59; equiv. wt. 134 (determined by

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[9] C. H. Bamford, A. Elliott and W. E. Hanby, "Synthetic Polypeptides," Academic Press Inc., New York (1956), p. 86; E. Katchalski and M. Sela, "Advances in Protein Chemistry," Vol. 13, Academic Press Inc., New York (1958), p. 244.

[10] F. Bergel and R. Wade, *J. Chem Soc.*, **1959**, 941.

[11] E. Erlenmeyer, Jr., *Ber.*, **25**, 3445 (1892); E. Erlenmeyer, Jr., and E. Früstück, *Ann.*, **284**, 36 (1894); M. O. Forster and K. A. N. Rao, *J. Chem. Soc.*, **1926**, 1943.

[12] K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3417 (1953).

anhydrous sodium methylate titration). Calcd. for $C_4H_5O_4N$: C, 36.65; H, 3.85; N, 10.69%; equiv. wt. 131.1.

DL-*trans*-5-Methyl-2-oxazolidone-4-carboxylic Acid (VIIb), L-*trans*-5-Methyl-2-oxazolidone-4-carboxylic Acid (VIIc), and DL-*trans*-5-Phenyl-2-oxazolidone-4-carboxylic Acid (VIId).—VIIb, VIIc, and VIId were obtained from IIIb, IIIc, and IIId respectively in the same way as VIIa, but in the case of the preparation of VIIc and VIId, no polymeric materials were produced. VIIb: yield, 78%; m. p. 128~129°C.[6,10] Found: C, 41.40; H, 4.92; N, 9.69; equiv. wt. 143. Calcd. for $C_5H_7O_4N$: C, 41.38; H, 4.86; N, 9.65%; equiv. wt. 145.1. VIIc: yield, 90%; m. p. 139°C, $[\alpha]_D^{15}=+41.0°$ (*c* 3.97, water).[7] Found: C, 41.42; H, 4.92; N, 9.68; equiv. wt. 146. Calcd. for $C_5H_7O_4N$: C, 41.38; H, 4.86; N, 9.65%; equiv. wt. 145.1. VIId: yield, 96%; m. p. 204°C (decomp.).[6] Found: C, 58.01; H, 4.41; N, 6.73%; equiv. wt. 208. Calcd. for $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76%; equiv. wt. 207.2.

The Hydrolysis of 2-Oxazolidone Derivatives (VII) by Hydrochloric Acid. — VII (1.0 g.) was dissolved in 6 N hydrochloric acid (20 ml.), and the solution was heated on a boiling water bath. After three hours, the solution was decolorized with active charcoal and concentrated to dryness. The residue was dissolved in absolute alcohol, and the addition of a suitable amount of pyridine to this solution gave crystalline products in an almost theoretical yield. The recrystallization of them was carried out from water and alcohol. The products were identified by comparison with respective authentic samples in all their characteristics. Ia from VIIa: m. p. 220°C (decomp.), $[\alpha]_D^{18}=+14.4°$ (*c* 2.3, 1 N hydrochloric acid);[8] Ib from VIIb: m. p. 233°C (decomp.); Ic from VIIc: m. p. 254°C (decomp.), $[\alpha]_D^{18}=-28.0°$ (*c* 2.6, water);[8] Id from VIId: m. p. 202°C (decomp.).

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