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Oxazolidone Derivatives of Hydroxyamino Acids. V.[1] New Synthesis of *threo*- and *erythro*-β-Hydroxy-DL-aspartic Acids*[1]

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threo- and *erythro*-β-Hydroxy-DL-aspartic acids (VI and X) were synthesized by oxidation and subsequent hydrolysis of DL-*trans*- and DL-*cis*-5-furyl-2-oxo-oxazolidine-4-carboxylic acids (IV and VIII) derived from *threo*- and *erythro*-β-furyl-DL-serines (III and VII) respectively.

β-Hydroxyaspartic acids were first synthesized by Dakin.[2] Later, Kornguth[3] synthesized these amino acids by condensation of glyoxalic acid with copper glycinate. Recently, *threo*- and *erythro*-β-hydroxy-DL-aspartic acids were synthesized stereochemically by the reaction of *cis*- and DL-*trans*-epoxysuccinic acids with ammonia[4] or benzylamine[5] respectively.

1) Part IV: T. Inui, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **83**, 493 (1962).

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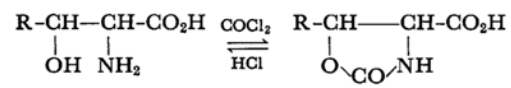
2) H. D. Dakin, *J. Biol. Chem.*, **48**, 273 (1921); **50**, 410 (1922).

3) M. L. Kornguth and H. J. Sallach, *Arch. Biochem. Biophys.*, **91**, 39 (1960).

4) T. Kaneko and H. Katsura, This Bulletin, **36**, 899 (1963); H. Okai, N. Imamura and N. Izumiya, *ibid.*, **40**, 2154 (1967).

5) Y. Liwschitz, Y. Rabinsohn and A. Haber, *J. Chem. Soc.*, **1962**, 3589.

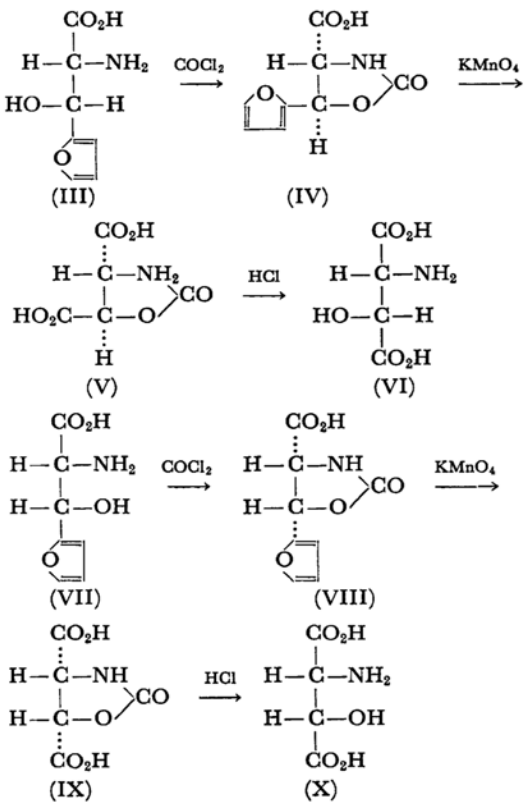
The present paper is concerned with another stereospecific synthesis of *threo*- and *erythro*-β-hydroxy-DL-aspartic acids from the corresponding β-furyl-DL-serines respectively.



(I) (II)

In the previous report,[6] hydroxyamino acids (I) such as threonine were easily cyclized with phosgene to the corresponding oxazolidone derivatives (II) without any configurational change at the either asymmetric center. If *trans*- and *cis*-furyloxazolidone-carboxylic acids (II, R=C_4H_3O) derived from *threo*- and *erythro*-β-furylserines (I, R=C_4H_3O) were oxidized to the corresponding oxazolidone-dicarboxylic acids (II, R=CO_2H), the dicarboxylic acids thus obtained would be hydrolyzed to *threo*- and *erythro*-β-hydroxyaspartic acids (I, R=CO_2H) maintaining the same configurations with those of the starting β-furylserines.

threo-β-Furyl-DL-serine (III) was prepared from furfural and glycine by the directions of Hayes.[7] On the other hand, *erythro*-β-furyl-DL-serine (VII)



(III) (IV) (V) (VI) (VII) (VIII) (IX) (X)

was separated as its dioxane adduct from the mixture of III and VII, which was obtained by condensation of furfural with copper glycinate, by applying the method for separation of *erythro*-β-phenyl-DL-serine from its *threo*-isomer.[8] The R_f values of III and VII on paper chromatogram were compared with those of threonine, allothreonine and *threo*- and *erythro*-β-phenylserines (Table 1), and their structures were confirmed as the assigned ones. Then, III and VII were cyclized with phosgene to DL-*trans*- and DL-*cis*-5-furyl-2-oxo-oxazolidine-4-carboxylic acids (IV and VIII) respectively. Oxidation of IV with aqueous potassium permanganate solution provided DL-*trans*-2-oxo-oxazolidine-4,5-dicarboxylic acid (V) as a crystalline state in a yield of 30%, which was hydrolyzed with hydrochloric acid to *threo*-β-hydroxy-DL-aspartic acid (VI). However, oxidation and subsequent hydrolysis of IV without isolation of V gave VI in an overall yield of 40%. Similarly, *erythro*-β-hydroxy-DL-aspartic acid (X) was obtained by oxidation and subsequent hydrolysis of VIII in a yield of 39%. The properties tested of VI and X were identical with those of the corresponding authentic samples.

Table 1. R_f Values on paper chromatogram

threo-Isomer	R_f	*erythro*-Isomer	R_f
III	0.28	VII	0.18
threo-β-Phenyl-DL-serine	0.42	*erythro*-β-Phenyl-DL-serine	0.27
Threonine	0.18	Allothreonine	0.13

Solvent: *n*-Butanol-acetone-concentrated aqueous ammonia-water (8:1:1:6).[8]

Experimental*5

***threo*-β-Furyl-DL-serine (III).** According to the directions of Hayes,[7] III was prepared by condensation of 293 g (3.05 mol) of furfural with 115 g (1.53 mol) of glycine in the presence of 170 g (3.03 mol) of potassium hydroxide in 1200 m*l* of ethanol. Yield, 126 g (48%), mp 197°C (decomp.) after recrystallization from water and ethanol.

Found: C, 49.47; H, 5.41; N, 8.28%. Calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18%.

***erythro*-β-Furyl-DL-serine (VII).** Using the method for preparation of threonine by Akabori,[9] a mixture of 10.2 g (0.106 mol) of furfural and 11.3 g (0.0534 mol) of copper glycinate in 200 m*l* of 1 N potassium hydroxide was stirred for 2 hr at 10—20°C. After it had been kept overnight at room temperature, undissolved material was filtered off and the filtrate was acidified with 20 m*l* of acetic acid. The acidic solution was washed with ether and bubbled with a stream of hydrogen sulfide to decompose the resulting copper complex. The filtrate from copper sulfide was evaporated *in vacuo* to a small

6) T. Kaneko and T. Inui, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **82**, 1075 (1961); T. Inui and T. Kaneko, *ibid.*, **82**, 1078 (1961).

7) K. Hayes and G. Geber, *J. Org. Chem.*, **16**, 269 (1951).

8) K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3421 (1953).

*5 All melting points are uncorrected.

9) M. Sato, K. Okawa and S. Akabori, This Bulletin, **30**, 937 (1957).

volume and diluted with ethanol to separate *threo*-isomer III (9.1 g; 50%), which was collected by filtration. The residue obtained by evaporation of solvent from the filtrate was dissolved into 30 m*l* of water and 30 m*l* of dioxane was added to the aqueous solution to precipitate VII as its dioxane adduct. Yield, 5.0 g (22%). Recrystallization from water-dioxane (1 : 1) gave 3.3 g of chromatographically pure VII melting at 169°C (decomp.).

Found: C, 50.44; H, 6.06; N, 6.55%. Calcd for $C_7H_9NO_4 \cdot \frac{1}{2}C_4H_8O_2$: C, 50.23; H, 6.09; N, 6.51%.

DL-*trans*-5-Furyl-2-oxo-oxazolidine-4-carboxylic Acid (IV). To a solution of 29.0 g (0.168 mol) of III in 645 m*l* (0.645 mol) of 1 N potassium hydroxide, a solution of 20.2 g (0.204 mol) of phosgene in 80 m*l* of toluene was added dropwise over 30 min with stirring at 0—3°C and the reaction mixture was stirred for an additional 3 hr below 5°C. The aqueous layer separated from organic layer was acidified with 14 m*l* of concentrated hydrochloric acid to separate a crude product (28.0 g, mp 199—200°C (decomp.)), which was shown to be a mixture of IV and its potassium salt by detecting with flame test.

A stream of dry hydrogen chloride was passed through a suspension of the crude product in about 30 volumes of ethyl acetate and the resulting mixture was washed thoroughly with water. Evaporation of the dried solution provided IV as a pure state. Yield, 21.0 g (63%); mp 126—128°C (decomp.) after recrystallization from ethyl acetate - petroleum ether.

Found: C, 48.70; H, 3.64; N, 7.12%. Calcd for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.11%.

DL-*cis*-5-Furyl-2-oxo-oxazolidine-4-carboxylic Acid (VIII). In a similar way, a solution of 5.0 g (0.0232 mol) of dioxane adduct of VII in 50 m*l* (0.0891 mol) of 10% aqueous potassium hydroxide solution was treated with a solution of 2.8 g (0.0283 mol) of phosgene in 15 m*l* of toluene. The aqueous layer separated from organic layer was acidified with concentrated hydrochloric acid and the acidic solution was extracted with ethyl acetate. The dried extract was evaporated *in vacuo* leaving VIII as a crystalline solid. Yield, 2.8 g (61%); mp 143—144°C (decomp.) after recrystallization from ethyl acetate.

Found: C, 48.77; H, 3.71; N, 6.78%. Calcd for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.11%.

DL-*trans*-2-Oxo-oxazolidine-4, 5-dicarboxylic Acid (V). Three grams (0.0152 mol) of IV was dissolved into 200 m*l* of water and neutralized with 15 m*l* (0.0150 mol) of 1 N potassium hydroxide. The resulting solution was oxidized with 270 m*l* (0.0683 mol; 96% of required ammount) of 4% aqueous potassium permanganate solution for 2 hr at 15—20°C. After manganese dioxide precipitated had been removed, the aqueous solution was acidified with 10 m*l* of concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The residue was extracted three times with 50-m*l* portions of hot dioxane and the combined extracts were evaporated *in vacuo* to give crystals. Yield, 0.8 g (30%); mp 159—160°C (decomp.) after recrystallization from ethyl acetate - petroleum ether.

Found: C, 34.90; H, 3.07; N, 7.95%; mol wt (titration with alkali), 177, 180. Calcd for $C_5H_5NO_6$: C, 34.29; H, 2.88; N, 8.00%, mol wt, 175.1.

The treatment of V with an ethereal diazomethane solution gave dimethyl DL-*trans*-2-oxo-oxazolidine-4,5-dicarboxylate melting at 97—99°C after recrystallization from benzene.

Found: C, 41.96; H, 4.54; N, 6.96%. Calcd for $C_7H_9NO_6$: C, 41.38; H, 4.47; N, 6.90%.

***threo*-β-Hydroxy-DL-aspartic Acid (VI).** *By Hydrolysis of V.* A solution of 1.0 g (0.0057 mol) of V in 20 m*l* of 6 N hydrochloric acid was refluxed for 6 hr and VI was isolated from the hydrolyzate in an usual way. Yield, 0.6 g (70%).

It was identified by comparing its physical properties such as infrared spectra with those of an authentic sample. Analytical sample was recrystallized from water and dried over phosphorus pentoxide in a vacuum desiccator.

Found: C, 32.53; H, 4.81; N, 9.55%. Calcd for $C_4H_7NO_5$: C, 32.22; H, 4.73; N, 9.41%.

By Oxidation and Subsequent Hydrolysis of IV. In the same way as the above, a neutralized solution of 5.0 g (0.0254 mol) of IV in 240 m*l* of water was oxidized with 475 m*l* (0.120 mol; 101% of required ammount) of 4% aqueous potassium permanganate solution. After manganese dioxide precipitated had been removed, the residue obtained from the filtrate was hydrolyzed with 30 m*l* of 6 N hydrochloric acid under refluxing for 6 hr. Yield, 1.5 g (40% based on IV).

***erythro*-β-Hydroxy-DL-aspartic Acid (X).** A neutralized solution of 3.0 g (0.0152 mol) of VIII in 200 m*l* of water was oxidized with 290 m*l* (0.0734 mol; 103% of required ammount) of 4% aqueous potassium permanganate solution. After removing manganese dioxide, the residue obtained from the filtrate by evaporation of the solvent was dissolved into 30 m*l* of 6 N hydrochloric acid and the resulting solution was refluxed for 6 hr. From the hydrolyzate, X was isolated as its hydrochloride in an usual way. Yield, 1.1 g (39%), mp 215°C (decomp.).

The properties tested of this compound such as infrared spectra were identical with those of an authentic sample.

Found: C, 25.86; H, 4.40; N, 7,66; Cl, 19.49%. Calcd for $C_4H_7NO_5 \cdot HCl$: C, 25.89; H, 4.35; N, 7.55; Cl, 19.11%.