2. On the Asymmetric Synthesis of Amino Acids.

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(Comm. by R. MAJIMA, M.J.A., Jan. 12, 1951.)

On the asymmetric synthesis of amino acids there are not many reports. Knoop and Martius¹⁾ obtained oktopine of the same optical activity as the natural substance by the catalytic reduction of a mixture of L-arginine and pyruvic acid. Bergmann and Tiethman²⁾ described the formation of acetyl-L-phenylalanyl-L-prolinamide and L-phenylalanyl-L-proline anhydride by hydrogenation of acetyldehydro-phenylalanyl-L-prolinamide and dehydro-phenylalanyl-L-proline anhydride respectively, but they mentioned nothing about the "asymmetric synthesis" of amino acids.

We tried to synthesize optically active phenylalanine by Sasaki's method³⁾, namely, by condensing optically active asymmetric diketopiperazine with benzaldehyde to monobenzal-diketopiperazine, followed by hydrogenation and hydrolysis. It has been described by Sasaki and Hashimoto⁴⁾, and Bergmann and Ensslin⁵⁾ that they obtained racemic monobenzal-diketopiperazine by the condensation of benzaldehyde with glycyl-L-tyrosine anhydride and with ethyl anhydro-glycyl-L-aspartate. We preferred glycyl-L-isovaline anhydride (II) as an asymmetric diketopiperazine, because this compound was reported by Levene and Steiger⁶⁾ to be resistant against alkaline racemization.

By condensing glycyl-L-isovaline anhydride (I) with benzaldehyde in the usual way we obtained optically active dehydrophenylalanyl-L-isovaline anhydride (II), which was catalytically reduced to phenylalanyl-L-isovaline anhydride (III), and finally, by the hydrolysis of III, we obtained L-phenylalanine (IV), $[\alpha]_D^{25} - 34^\circ$ (in water).

If the yields were high in each procedure L-isovaline may be repeatedly used for the synthesis, but the actual yields in our experiments were very poor. Further studies are now in progress.

in the author's laboratory in the hope of improving the process and methods.

Experimental.

(1) **Formyl-L-isovaline.** Formyl-DL-isovaline, which was prepared by the treatment of DL-isovaline with formic acetic anhydride according to Buelmann⁷⁾, was resolved by brucine. $[\alpha]_D^{25} + 7.17^\circ$ (in 3/4 N KOH). According to Fiseher and Graevenitz⁸⁾ $[\alpha]_D^{25} + 7.14^\circ$.

(2) **Chloracetyl-L-isovaline.** Formyl-L-isovaline was hydrolyzed by hydrochloric acid, and without isolating L-isovaline, this was chloracetylated to chloracetyl-L-isovaline according to Levene and Steiger⁴⁾. M.P. 157–160°.

(3) **Glycyl-L-isovaline anhydride (I):** This optically active asymmetric diketopiperazine was prepared by Rosenmund's method⁹⁾. 6.5 gm. chloracetyl L-isovaline was suspended in absolute methanol, dry hydrogen chloride was saturated in it, methanol was distilled off under reduced pressure, and this esterification procedure was repeated once again. The residual sirup was dissolved in 80 ml. of methanolic ammonia and heated in a pressure bottle at 100° for 1.5 hours. On cooling the solution, crystalline glycyl-L-isovaline anhydride deposited, which was collected and washed with water. This first crop weighed 3.2 gm., melting at 268–271°. From the mother liquor 0.6 gm. of crude product was obtained.

Calcd. for $C_7H_{12}O_2N_2$ N 17.94%. Found N 17.64%. $[\alpha]_D^{25} + 21.6^\circ$ (in pyridine-water).

(4) **Dehydrophenylalanyl-L-isovaline anhydride (II):** 6.0 gm. glycyl-L-isovaline anhydride, 16.5 gm. anhydrous sodium acetate, 12.5 gm. fresh distilled benzaldehyde and 20 ml. acetic anhydride were mixed in a round bottomed flask and heated to 160–170° (bath temperature) for 7 hours under reflux. To the reaction mixture 100 ml. warm water added and the insoluble residue was treated with 100 ml. ether, where 3.5 gm. of white crystalline products were deposited. After recrystallization from absolute alcohol, the crystals melted at 212–214°.

Calcd. for $C_{14}H_{16}O_5N_2$ N 11.47%. Found N 11.23%. $[\alpha]_D^{25} - 98.0^\circ$ (in pyridine).

(5) **L-Phenylalanyl-L-isovaline anhydride (III):** 1.2 gm. dehydrophenylalanyl-L-isovaline anhydride was dissolved in 65 ml. acetic acid. 0.2 gm. palladium oxide was added and hydrogenated. In 4 hours 120 ml. (1.1 mole equivalent) hydrogen were taken up. The crude product, remained on distilling off the solvent, was recrystallized from absolute methanol, where 0.62 gm. of white needles were obtained. After recrystallization from absolute methanol,

the crystals melted at 280-282°.

Calcd. for $C_{14}H_{18}O_2N_2$ N 11.37%. Found N 11.18%.

$[\alpha]_D^{25} + 49.5^\circ$ (in glacial acetic acid).

(6) L-phenylalanine(IV): 0.5 gm. L-phenylalanyl-L-isovaline anhydride were refluxed with 10 ml. of concentrated hydrochloric acid for 7 hours. On cooling 0.15 gm. L-phenylalanine hydrochloride deposited, and from the mother liquor 0.05 gm. more crystals were obtained. By neutralizing the aqueous solution of the hydrochloride 70 mg. L-phenylalanine was obtained. D.P. 260-270°.

Calcd. for $C_9H_{11}O_2N$ N 8.47%. Found N 7.91%.

$[\alpha]_D^{25} - 34.0^\circ$ (in water°).

E. Fischer and Schoeller⁽⁹⁾ described $[\alpha]_D^{25} - 35.14^\circ$ for L-phenylalanine. Rf value on paperchromatograph developed by butanol-acetic acid. was 6.0-6.1. Rf of a authentic specimen was 6.0.

References.

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