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Asymmetric Reduction of Some Dehydrophenylalanyl Peptides[1]

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Recently, Sheehan *et al.*[2] reported the stereoselective reduction of *N*-acetyldehydrovaline *S*-α-phenylethylamide by means of Raney-nickel catalyst. To clear stereochemical factors of this type of asymmetric reduction, authors carried out stereospecific reduction of a dehydropeptide, *N*-acetyldehydrophenylalanyl-D-valine and its esters. After saponification, D-phenylalanine was afforded, having specific rotation between +6.29°—+15.88° (optical purity 18—45%).

N-Acetyldehydrophenylalanyl-D-valine, prepared by the condensation reaction[3] of 4-benzal-2-methyl-5-oxazolone[4] and D-valine, was esterified in alcohols by treatment with a small amount of hydrochloric acid. The dehydropeptide and its esters were hydrogenated with palladium on charcoal, then hydrolyzed by refluxing with hydrochloric acid. From the reaction mixtures, D-valine and D-phenylalanine were separated in chemically pure states according to the method of Partridge.[5] Following table shows these results.

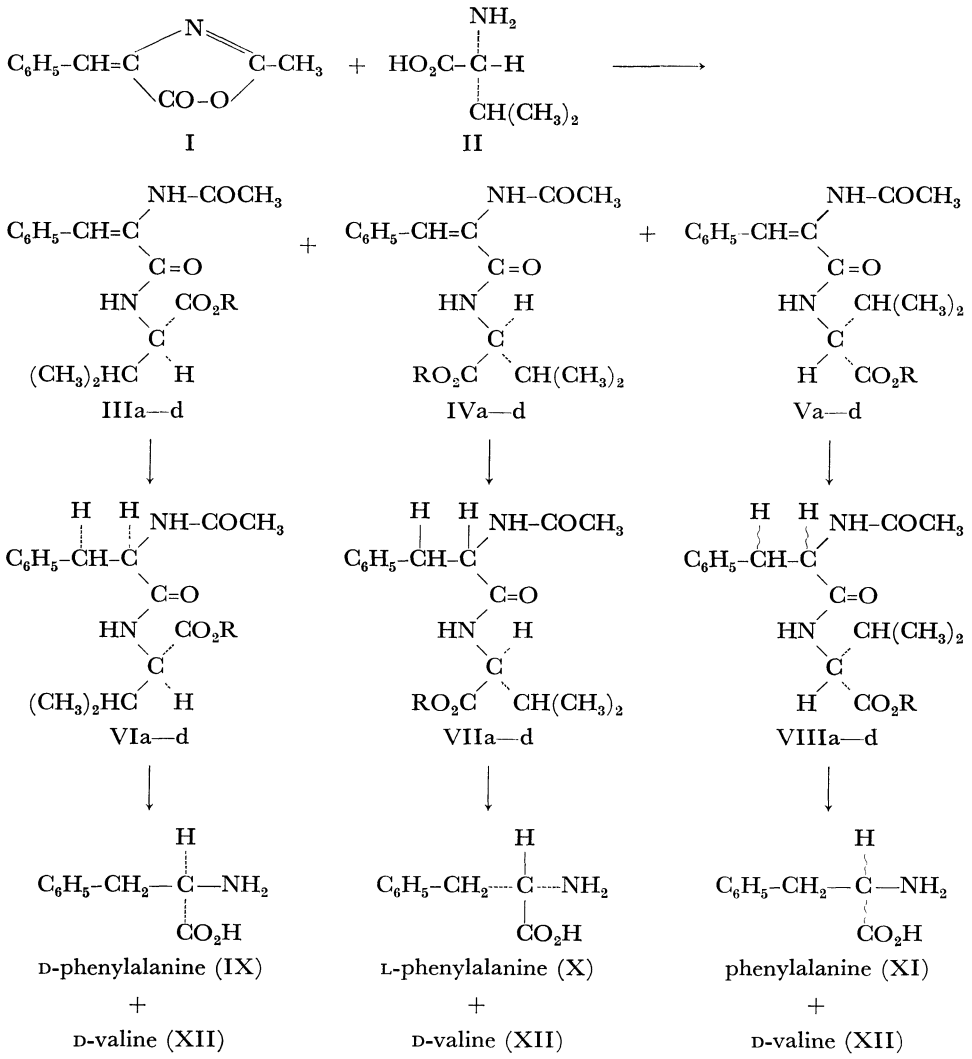
1) This paper is dedicated to Emeritus Professor Munio Kotake in Commemoration of his 75th birthday, November 30, 1969.

2) J. C. Sheehan and R. E. Chandler, *J. Amer. Chem. Soc.*, **83,** 4795 (1961).

3) O. K. Behrens, D. G. Doherty, and M. Bergmann, *J. Biol. Chem.*, **136,** 61 (1940).

4) R. M. Herbst and D. Shemin, "Organic Syntheses," Coll. Vol. II, p. 1 (1948).

5) S. M. Partridge, *Biochem. J.*, **44,** 521 (1949).



a, R=H; b, R=CH_3; c, R=C_2H_5; d, R=n-C_3H_7

Table 1. Asymmetric reduction of dehydrophenylalanyl peptides

	R	$[\alpha]_D$ (Py)	IX $[\alpha]_D$ (H_2O)	Optical[a] yield %	XII $[\alpha]_D$ (6N HCl)
IIIa	H	−35.96	+14.23	40.7	—
IIIa	H	−35.94	+12.12	34.6	−22.90
IIIb	CH_3	−24.14	+15.88	45.3	−21.80
IIIb	CH_3	−22.92	+13.83	39.5	−21.43
IIIc	C_2H_5	−34.44	+8.84	25.2	−21.40
IIIc	C_2H_5	−32.49	+10.42	29.8	−21.44
IIId	C_3H_7	−38.93	+6.29	18.0	−21.05
IIId	C_3H_7	−38.12	+8.87	25.3	−20.83

a) Specific rotations of optically pure L-phenylalanine and L-valine are −35.0° (H_2O) and +23.0° (6N HCl), respectively.

Experimental

N-Acetyldehydrophenylalanyl-D-valine (IIIa). To a solution of 11.7g (0.1mol) of D-valine ($[\alpha]_D$ −23.0°) in 200m*l* of 0.5N sodium hydroxide solution, was added 18.8 g (0.1mol) of 4-benzal-2-methyl-4-oxazolone[4] followed by about 190 m*l* of acetone until the mixture became clear. After standing overnight, the reaction mixture was acidified by adding 100m*l* of 1N hydrochloric acid. Crude crystals separated were recrystallized from 99% ethanol; pure crystals (yield, 19.5g (64%)) mp 218°C, $[\alpha]_D^{27}$ −24.0° (*c* 2.32, 99% ethanol), $[\alpha]_D^{25.5}$ −35.94° (*c* 2.96, pyridine). Found: C, 63.14; H, 6.62; N, 9.21%. Calcd for $C_{16}H_{20}O_4N_2$: C, 62.95; H, 6.69; N, 9.22%.

N-Acetyldehydrophenylalanyl-D-valine Esters (IIIb, c, and d). To a solution of 5.0g of above peptide (IIIa) in 100 m*l* of methanol was added 2m*l* of concentrated hydrochloric acid at 0°C. After standing for 2 days at room temperature, separated crystals were filtered off, and pure crystals were obtained by recrystallization from a mixture of water and methanol.

Methyl Ester (IIIb): mp 195°C (yield, 76%), $[\alpha]_D^{25}$ −24.13° (*c* 3.22, pyridine).
Found: C,64.16; H,7.01; N,8.63%. Calcd for $C_{17}H_{22}O_4N_2$: C, 64.13; H, 6.97; N, 8.80%.

Ethyl ester (IIIc) and *n*-propyl ester (IIId) were afforded by the analogous methods described above.

Ethyl Ester (IIIc): mp 154°C (yield, 82%), $[\alpha]_D^{25}$ −34.44° (*c* 3.20, pyridine).
Found: C, 65.19; H, 7.20; N, 8.43%. Calcd for $C_{18}H_{24}O_4N_2$: C, 65.04; H, 7.28; N, 8.43%.

n-Propyl Ester (IIId): mp 151°C (yield, 76%). $[\alpha]_D^{25}$ −38.73° (*c* 4.83, pyridine).
Found: C,65.34; H,7.52; N,8.27%. Calcd for $C_{19}H_{26}O_4N_2$:

C, 65.87; H, 7.57; N, 8.09%.

Asymmetric reduction and hydrolysis. A solution of 1.5g of the peptide or its esters in 100m*l* of ethanol was hydrogenated with 0.1g of 5% palladium on charcoal under atmospheric pressure at room temperature. After absorption of hydrogen was ended (about 45 min), catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was hydrolyzed by refluxing with 15m*l* of concentrated hydrochloric acid for 50 min, and the hydrolysate was evaporated at below 40°C to dryness under reduced pressure. To the residue water was added and evaporated again as described above. These procedures were repeated until free hydrochloric acid was removed completely from the residue. The hydrolysate was treated with the activated charcoal prepared according to the method of Partridge.[5] From the aqueous layer D-valine was obtained, and from the charcoal D-phenylalaine was eluted. These amino acid fractions were neutralized by means of Amberite IR-4B resin. The optical rotation of D-valine was measured in solution of 6N hydrochloric acid.

As the solubility of optically active phenylalanine in water is larger than that of racemic isomer, to avoid fractional crystallization a part of a solution of phenylalanine obtained above was completely evaporated to dryness and weighed, then the residue was dissolved in a definite volume of water and optical rotation of this solution was measured. In each instance the identity and purity of the amino acids were confirmed by paper chromatography developed by 80% phenol. The phenylalanine (R_f=0.87) and valine (R_f=0.79) obtained above, showed single ninhydrin-positive spots which had the same R_f values as those of authentic samples, respectively.

Discussion

As dehydrophenylalanyl peptides may be regarded as derivatives of cinnamic acid, phenyl and carboxyl groups of the peptides should be oriented "trans" position to each other with regard to double bond, since the longest conjugated system is the most stable configuration. The peptides in this paper, would have three staggered conformations as shown by III, IV, and V. According to the assumptions by Prelog[6] and Sheehan,[2] hydrogen will be absorbed on the surface of catalyst and the substrate will approach the catalyst surface from the least sterically hindered side. From III, VI will be deduced, and from IV, VII will be expected. Stereostructure of VIII, the reduction product from V, is yet obscure, because of no significant difference between the bulkiness of "isopropyl" and "carboxylate" groups. After saponification, the products obtained from VI will be D-(R)-phenylalanine and D-(R)-valine, on the other hand L-(S)-phenylalanine and D-(R)-valine will be given from VII, but from VIII, D-valine and racemic or faintly optically active phenylalanine will be obtained. Because D-phenylalanine produced predominantly in these experiments, it is supposed that the conformer III is the most preferable one among the three probable conformers (III, IV, and V) of dehydrophenylalanyl peptides.

6) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953).