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SYNTHESIS OF A CHIRAL PYRIDOXAMINE ANALOG AND NONENZYMATIC STEREOSELECTIVE TRANSAMINATION

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A broad range of amino acid reactions that are catalyzed by vitamin B_6[1]-dependent enzymes has been duplicated by nonenzymatic model reactions in which pyridoxal (or pyridoxamine) and a suitable metal salt serve as catalyst[2]. These model reactions, however, are devoid of stereospecificity and/or stereoselectivity[3] which enzymatic reactions owe to apoprotein. In the course of our study pursuing enzyme mimics provided with such stereochemical characteristics, we recently reported the synthesis of a chiral pyridoxal analog with an "ansa chain"[4] (I) and the fact that I, in the presence of cupric salt, stereospecifically catalyzed racemization of enantiomorphs of an amino acid[5].

We now wish to describe the synthesis of (-)-15-aminomethyl-14-hydroxy-2,8-dithia[9](2,5)pyridinophane (III), a chiral pyridoxamine analog corresponding to I, and stereoselective transamination between III and an α-ketocarboxylic acid. This transamination can also be regarded as the biomimetic asymmetric synthesis of an amino acid that is widely applicable.

As a method for the preparation of III, reductive amination of I seemed most straightforward. Both treatment of I with NH_3-$NaBH_4$-CH_3OH and that with NH_4Cl-$NaBH_3CN$-CH_3OH[6], however, gave a considerable amount of by-product, pyridoxine analog (IV), m.p. 162-172°[7]; $[\alpha]_D^{19}$ -215° (c 0.369, C_2H_5OH); ν_{max}^{KBr} cm^{-1}: 3400, 3050 (OH); Found: C, 54.75; H, 6.68; N, 4.78; S, 22.21; Cacld. for $C_{13}H_{19}NO_2S_2$: C, 54.71; H, 6.71; N, 4.91; S, 22.47%, in addition to III. Therefore, two stages of reactions were undertaken for preventing production of IV. Compound I was treated with $NH_2OH \cdot HCl$-CH_3COONa-C_2H_5OH and the resulting compound was recrystallized from benzene to give the oxime (II) folding 1/4 equivalent of benzene, m.p. 189-191°; $[\alpha]_D^{23}$ -291° (c 0.081, $CHCl_3$); ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1630 (C=N-); δ ($CDCl_3$) ppm: 8.65 (1H, singlet), 7.99 (1H, singlet), 7.30 (6/4H, singlet); Found: C, 54.75; H, 6.33; N, 8.80; S, 20.27; Calcd. for $C_{13}H_{18}N_2O_2S_2$+1/4 C_6H_6: C, 54.77; H, 6.18; N, 8.81, S, 20.17%, in the yield of 89%. After a few unsuccessful attempts, reduction of the oxime (II) was finally fulfilled by treatment with sulfurated borohydride ($NaBH_2S_3$)[8] in tetrahydrofuran, giving III as colorless needles, m.p. 143-144°; $[\alpha]_D^{23}$ -202°

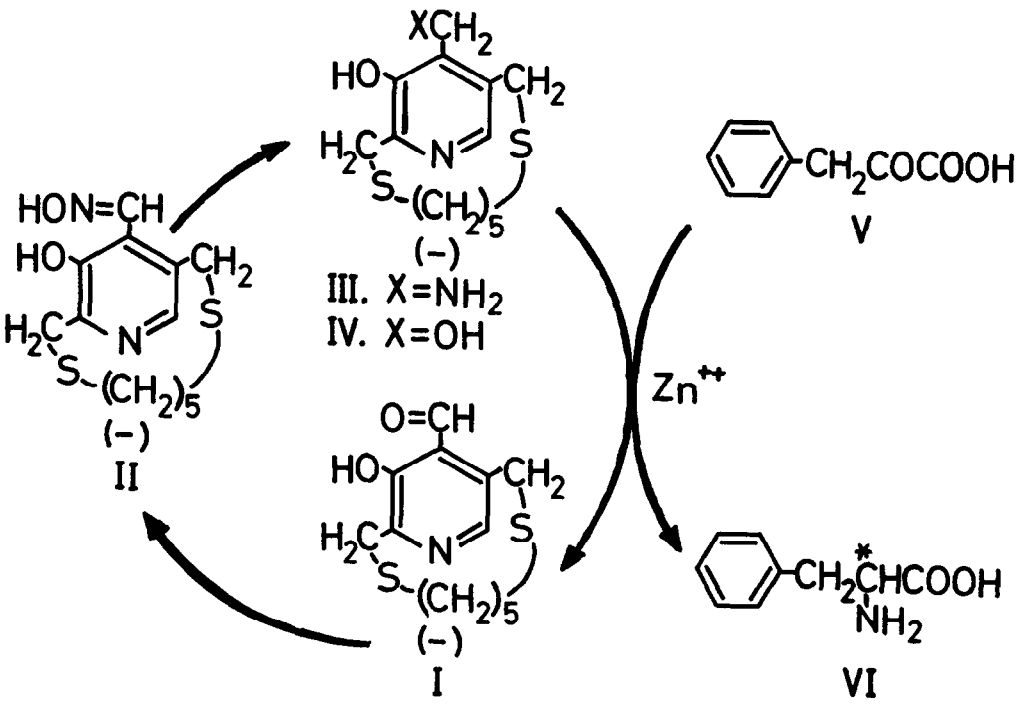

TABLE Reaction Solvents and Chemical Yields, Specific Rotations of the Products in Transamination.

REACTION SOLVENTS	ε*	PRODUCTS: PHENYLALANINE (VI) Chemical Yield %	PHENYLALANINE (VI) $[\alpha]_D^{**}$	PHENYLALANINE (VI) e.e.%	PYRIDOXAL ANALOG (I) Chemical Yield %
Methanol	32.6	83	-2.0	6	83
n-Butanol	17.5	61	-7.7	22	32***
Acetonitrile	32.6	71	+8.9	25	70
Nitromethane	35.9	55	+9.0	26	75

* Dielectric constant
** Measured with a Perkin-Elmer Model 241 MC porarimeter at 21-23°.
*** Partial decomposition by overheating might occur during isolation.

(c 0.26, $CHCl_3$); ν_{max}^{KBr} cm^{-1}: 3430, 3380, 3270 (OH, NH_2); δ (DMSO-d_6) ppm: 7.78 (1H, singlet), 4.27 (1H, doublet, J=12 Hz), 3.79 (1H, doublet, J=13 Hz), 3.59 (1H,doublet, J=13 Hz), 3.36 (1H, doublet, J=12 Hz); λ_{max}^{MeOH} (ε) nm: 230 (7480), 250 (sh) (3430), 305 (4140), 330 (sh) (2880); Found: C, 55.06; H, 7.19; N, 9.77; S, 21.96, Calcd. for $C_{13}H_{20}N_2OS_2$: C, 54.89; H, 7.09; N, 9.85; S, 22.54%, in the yield of 75%.

According to the spectrophotometric studies of Matsushima et al.[9], transamination between pyridoxamine and potassium α-ketoisovalerate proceeds quite smoothly and completely at room temperature in the presence of zinc ion in methanol solution, giving the zinc chelate of pyridoxylidenevaline. This prompted us to employ zinc salt as catalyst for transamination with III. On the other hand, phenylpyruvic acid (V) was chosen as an amino group acceptor because V would be converted into phenylalanine (VI), of which enantiomorphs had relatively large specific rotations ($[\alpha]_D$ -35° for authentic L-enantiomer). Reactions were carried out at room temperature in various organic solvents and a typical experiment is shown in the following.

A mixture of III, commercial sodium salt of V (monohydrate)[10], and $ZnClO_4 \cdot 6H_2O$ in ratio of 1:2:1.3 was stirred at room temperature for 20 hr in acetonitrile and then acidified (pH 2) with 1N hydrochloric acid. After evaporation in vacuo, water was added to the residue and the resulting mixture was extracted with ethyl acetate, from which pyridoxal analog (I) and an excess of V were recovered. Phenylalanine (VI) was isolated from the aqueous solution by treatment with strongly acidic and weakly acidic ion exchange resins[11].

Results of these experiments revealed several things. (Most of the results are tabulated.) Transamination between III and V proceeded smoothly in many organic solvents, giving VI generally in good yield. The enantiomeric excess in the product was up to 26%. The limited optical yield would be ascribable to the fact that the reaction center (imine carbon) was separated far from the "ansa chain" in an intermediate Schiff base[12]. This situation, however, will be altered by replacing the simple "ansa chain" of III with more bulky ones. On the other hand, it was interesting that there seemed some correlation between the choice of a solvent and the sign of rotation of the product. As far as the tabulated data are concerned, the dielectric constant of the solvent has no relationship to the rotational sign but whether the solvent is protic or aprotic corresponds to predominance of L- or D-amino acid respectively. Good recovery of I without any racemization can be regarded as one of the advantages of this biomimetic amino acid synthesis because I, as described, can be readily converted into III which is reused for the synthesis.

Finally, we would like to point out that this transamination should be also applicable to the asymmetric synthesis of other amino acids.

REFERENCES AND NOTES

1) The term "vitamine B_6" means pyridoxine, pyridoxal, pyridoxamine, and their 5'-O-phosphates.

2) D. E. Metzler, J. B. Longenecker, and E. E. Snell, J. Am. Chem. Soc., 76 , 639 (1954) and references cited therein.

3) The only reported instance of apparent stereoselectivity in model reactions using pyridoxal has been attributed to the asymmetry in the substrate. See J. B. Longenecker and E. E. Snell, Proc. Nat. Acad. Sci. U. S. A., 42, 221 (1956).

4) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill Co. Inc. (1962), P.175.

5) H. Kuzuhara, M. Iwata, and S. Emoto, J. Am. Chem. Soc., 99, 4173 (1977).

6) R. F. Borch, M. D. Bernstein, and H. D. Durst, J. Am. Chem. Soc., 93, 2897 (1971).

7) In this range of the temperature, the specimen of IV gradually colored and softened.

8) J. M. Lalancette, A. Frêche, and R. Monteux, Can. J. Chem., 46, 2754 (1968).

9) Y. Matsushima and A. E. Martell, J. Am. Chem. Soc., 89, 1331 (1967).

10) Sigma Chemical Co. Inc., St. Louis, Mo., U. S. A.

11) For removal of metal ions, the aqueous solution was passed through Dowex-50 (H^+) column, which was eluted with enough water and then with aqueous ammonium hydroxide. The ammonium hydroxide solution containing VI was lyophilized to give a powder, which was washed with chloroform. For removal of a small amount of residual III, the powder was dissolved again in water, passed through Amberlite IRC-50 (H^+) column, and lyophilized to yield VI which gave the satisfactory results of various analyses including elemental analysis.

12) It is generally accepted that a chelate complex of Shiff base is a common intermediate of the reaction of pyridoxal-enzyme models. See E. E. Snell and S. J. Di Mari, "The Enzymes 3rd. Ed.", Vol. 2, Academic Press (1970), P. 339.

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