CATALYTIC ASYMMETRIC SYNTHESIS OF LYSINE α-PHENYLETHYLAMIDE BY DIASTEREOSELECTIVE HYDROGENATION

E. I. Klabunovskii, E. S. Levitina, L. N. Kaigorodova, D. D. Gogoladze, L. F. Dodunova, E. I. Karpeiskaya, and G. O. Chivadze

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The diastereoselective hydrogenation of the C=N bond in chiral precursors of aminoacids is one of the most highly developed methods for the asymmetric synthesis of this type of compound [1]. There have, however, been no reports of the asymmetric synthesis of lysine.

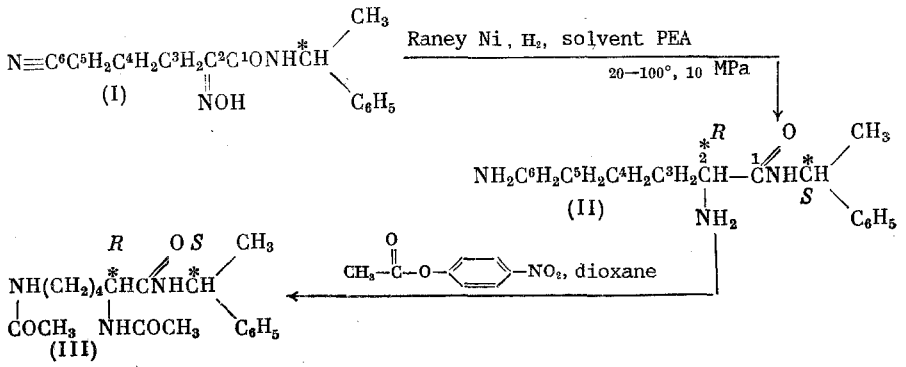
We have now examined the catalytic hydrogenation of the C=N–OH group in a chiral precursor of lysine, namely, 5-cyano-2-hydroxyiminovaleric acid S-α-phenylethylamide (I).

DISCUSSION OF RESULTS

Hydrogenation of the ethyl ester of 5-cyano-2-hydroxyiminovaleric acid (CHIV) over a skeletal nickel catalyst in Ac_2O in the presence of a strong base takes place under mild conditions to give quantitative yields of cyanoacetyllysine ethyl ester [2]. Using these conditions, we were unable to effect the anantioselective hydrogenation of CHIV, either by modifying the nickel catalyst, or by adding chiral bases in Ac_2O [3]. Hydrogenation of (I) as in [2] resulted in racemization of the desired product and side reactions, which substantially reduce the yield.

The use of a variety of palladium catalysts (5% Pd/C, 10% $Pd(OH)_2/C$ [4], and Pd–α-phenylethylamine [5]) for the selective hydrogenation of the C=N bond in (I) using a variety of reaction conditions, solvents, and additives to protect the amino-group did not give the desired results.

Lysine can also be obtained by the hydrogenation of CHIV over a skeletal nickel catalyst in ethanol saturated with ammonia [6]. This method is, however, unsuitable for the hydrogenation of (I) as a result of the transamination of (I) by the ammonia and loss of the chiral group. For this reason, instead of ammonia, the presence of which in the reaction mixture is necessary to prevent the cleavage of the ε-amino-group in the lysine molecule, we have used α-phenylethylamine (PEA). Hydrogenation of (I) was carried out over a Raney nickel catalyst in dioxane containing PEA. No reaction occurred at 0.1 MPa, but at higher pressures (I) was hydrogenated with the preferential formation of the RS-diastereoisomer of lysine α-phenylethylamide (II).



The stereoselectivity of the reaction was calculated from the excess of the diastereoisomer (e.d. %) as measured by PMR spectroscopy. For this purpose, the diastereoisomeric

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow. Institute of Physical and Organic Chemistry, Academy of Sciences of the Georgian SSR, Tbilisi. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 849-852, April, 1987. Original article submitted July 25, 1985.

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TABLE 1. Effect of Concentration of RS-α-phenylethylamine on Yields of (II) [(I) 2 mmole, Raney Ni 0.3-0.5 g, dioxane 10 ml, 30°C, 10.0 MPa]

Concentration of RS-α-phenylethylamine mole/liter	Reaction products, %			e.d. RS-(II), %
	(I)	(II)	polymer	
0,375	60	18	22	8
0,150	60	27	13	7
0,075	50	30	20	10
0,025	–	7	93	6

TABLE 2. Effect of Temperature on Yields of (II) and the Stereoselectivity of Hydrogenation [(I) 2 mmole, RS-α-phenylethylamine 0.75 mmole, dioxane 10 ml, skeletal Ni 0.3-0.5 g, 10.0 MPa]

T., °C	Reaction products, %*		e.d. RS-(II), %
	(I)	(II)	
20	90	7	9
50	50	30	10
70	40	38	12
100	–	71	6

*The other products were polymers.

TABLE 3. Effect of Solvent and Configuration of the Amine on the Stereoselectivity of Hydrogenation of (I) [(I) 2 mmole, α-phenylethylamine 0.75 mmole, solvent 10 ml, Raney nickel catalyst 0.3-0.5 g, 50°C, 10.0 MPa]

Solvent	Configuration of PEA	Reaction products, %*		e.d. RS-(II), %
		(II)	(I)	
EtOH	*RS*	30	50	3
i-PrOH	*RS*	28	40	6
t-BuOH	*RS*	40	30	10
Dioxane	*RS*	30	50	10
»	*S*	34	–	8
»	*R*	28	–	10

*The other products were polymers.

products of the hydrogenation (II) were converted into their diacetyl derivatives (III), for which the assignment of the SS- and RS-configurations in the PMR spectra has previously been carried out [7]. Acetylation of (II) was carried out with p-nitrophenyl acetate under conditions which avoid racemization [8].

The preferential formation of the isomer in which the α-center in (II) has the R-configuration is in agreement with the results reported in [4], where hydrogenation of the α-hydroxyimino-group under the steric control of the S-α-phenylethylamide group gave phenylglycine in the R-configuration in an optical yield of 5.5%.

Study of the hydrogenation of (I) at 50°C and 10.0 MPa showed that the extent of reaction of (I) and the yields of (II) were highly dependent on the concentration of PEA (Table 1). When PEA was used as solvent, no hydrogenation of (I) took place, and hydrogenation in dioxane in the absence of PEA gave polymers as the sole products.

Hence, PEA both inhibits the hydrogenation of (I), and prevents cleavage of the ε-amino-group from (II) which results in the formation of polymers. Varying the amounts of PEA showed that the highest yields of (II) (30%) were obtained at a PEA concentration of 0.075 mole/liter. Increasing the amount of PEA reduced the reaction rate and the extent of reaction of (I), and reducing the concentration resulted in low yields of the desired product (II). As will be seen from Table 1, the concentration of PEA has virtually no effect on the stereoselectivity of the reaction (e.d. RS-(II) 6-10%). As Table 2 shows that as the temperature is increased the extent of reaction of (I) increases, reaching complete conversion at 100°C, and the yield of (II) is 71%.

The use of different solvents for the hydrogenation of (I) at 50°C and 100.0 MPa, PEA concentration 0.075 mole/liter (Table 3) showed that the yields of (II) were independent of the solvent, but the stereoselectivity increased slightly in the solvent sequence EtOH < i-PrOH < t-BuOH < dioxane.

Since in addition to the asymmetric center of the S-α-phenylethylamide group in substrate (I), the reaction mixture also contains chiral PEA, which could make a contribution to the stereoselectivity of the reaction, the hydrogenation of (I) was examined in dioxane containing PEA of differing chirality (Table 3). No differences in stereoselectivity whatsoever were found when S-, R-, and RS-PEA were used. Consequently, the amine is not a chiral factor in this reaction, and is required solely to suppress cleavage of the ε-amino-group.

EXPERIMENTAL

PMR spectra were obtained on a Bruker WM-250 radiospectrometer, and IR spectra on Specord and UR-20 spectrometers. Optical rotatory dispersion was recorded on a Spectropol-1 spectropolarimeter.

Ethyl-5-cyano-2-hydroxyiminovalerate (CHIV), mp 74°C (from CCl_4) [3].

α-Phenylethylamine (PEA): S – $[\alpha]D^{20}$ = −40.4°; R – $[\alpha]D^{20}$ = +40° (no solvent).

5-Cyano-2-hydroxyiminovaleric acid S-α-phenylethylamide (I). In a glass ampul were placed 1.42 g (7.75 mmole) of (I), 10 ml of S-PEA, and 0.1 g of imidazole. The mixture was heated for 19 h in the sealed, evacuated ampul at 115°C. The PEA was removed under reduced pressure, and the residue dissolved in aqueous acetone and passed through a column of KU-2 in the H^+ form. The oily product in the eluate crystallized on cooling, mp 89-90°C, yield 69%. IR spectrum in $CHCl_3$ (ν, cm^{-1}): 3415 (OH), 3330 br (NH), 2250 w (C≡N), 1680 (amide I), 1520 (amide II). PMR spectrum in $CDCl_3$ (δ, ppm): 1.41 d ($C\underline{H}_3CH$, J = 7.5 Hz), 1.90 quint (C^4H_2, J = 7.5 Hz), 2.35 t (C^3H_2, J = 7.5 Hz), 2.73 t (C^5H_2, J = 7.5 Hz), 5.13 q ($C\underline{H}_3CH$, J = 7.5 Hz), 7.25 m (C_6H_5), 7.04 d (NH), 8.76 s (OH).

Found, %: C 64.72; H 6.64; N 16.22. $C_{14}H_{17}N_3O_2$. Calculated, %: C 64.86; H 6.56; N 16.19. $[\alpha]D^{17}$=+8°, $[\alpha]_{420}$ = +28° (C 0.71, EtOH).

Hydrogenation of (I) was carried out under a hydrogen pressure of 10.0 MPa in a rocking autoclave. A mixture of 0.267 g (2 mmole) of (II), 10 ml of dioxane containing 0.75 mmole of PEA, and 0.3-0.5 g of skeletal nickel catalyst was placed in a 100 ml glass ampul, and kept for 6 h at 50°C. The catalyst was separated, and the solvent removed under reduced pressure. The residue (an oil) was dissolved in 50 ml of water, and the PEA extracted with ether. The aqueous layer was evaporated under reduced pressure, and the residue dried over KOH to give a colorless oil, lysine α-phenylethylamide (II), yield 1.4 g (30%). PMR spectrum in CD_3OD (δ, ppm): 1.41 d ($C\underline{H}_3CH$, J = 7.5 Hz), 1.18-1.71 m ($C^{3,4,5}H_2$), 1.65 d.t. (C^6H_2), 4.95 q ($CH_3C\underline{H}$, 7.12-7.35 m (C_6H_5). To 0.5 mmole of (II), dissolved in dioxane, was added 0.5 mmole of p-nitrophenyl acetate, and the mixture kept at ~20°C for 12 h. The precipitated (III) was filtered off and analyzed by PMR spectroscopy for its SS- and RS-diastereoisomer content, as described in [7].

CONCLUSIONS

The catalyzed asymmetric synthesis of R-lysine S-α-phenylethylamide has been carried out by the diastereoselective hydrogenation of 5-cyano-2-hydroxyiminovaleric acid S-α-phenylethylamide over a skeletal nickel catalyst in a solvent containing α-phenylethylamine, at raised pressures. The excess of the RS-diastereoisomer was 6-12%.

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ASYMMETRIC SYNTHESIS OF (2S,4S)-2,4-DIAMINOGLUTARIC AND (2S,3S)-2,3-DIAMINO-2,3-DIMETHYLSUCCINIC ACIDS USING CHIRAL Ni(II) COMPLEXES

Yu. N. Belokon', N. I. Chernoglazova, A. S. Batsanov, N. S. Garbalinskaya, V. I. Bakhmutov, Yu. T. Struchkov, and V. M. Belikov

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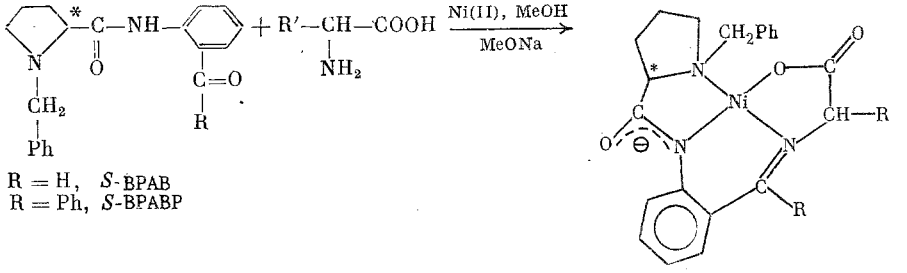
Diaminocarboxylic acids and their derivatives are components of certain antibiotics [1], their complexes with $PtCl_2$ possess antimicrobial activity [2], and diaminosuccinic acid is used in the synthesis of biotin [3].

Known methods of synthesis of diaminosuccinic [4, 5] and diaminoglutaric [1, 6] acids give mixtures of the meso- and (±)-forms, which are then resolved. We here report the enantio- and diastereoselective synthesis of (2S,4S)-2,4-diaminoglutaric and (2S,3S)-2,3-diamino-2,3-dimethylsuccinic acids, using Ni(II) complexes obtained from Schiff's bases of alanine and glycine with the chirally regeneratable reagents S-2-N-(N'-benzylprolyl)aminobenzaldehyde (S-BPAB) and S-2-N-(N'-benzylprolyl)aminobenzophenone (S-BPABP). Nickel complexes of similar structure have been used previously in the asymmetric synthesis of α-amino-β-hydroxy-acids [7, 8] and for the preparation of optically pure α-methyl-α-aminoacids [9]. 2,3-Diamino-2,3-dimethylsuccinic acid has been obtained by the oxidative dimerization of Ni(II) complexes, and 2,4-diaminoglutaric acid by the C-alkenylation of the aminoacid component of the complex with dibromomethane.

DISCUSSION OF RESULTS

The reaction of S-BPAB and S-BPABP with Gly or racemic Ala and $Ni(No_3)_2$ in methanol in the presence of MeONa gives red complexes

Diagram 1



R = H, R' = Me (*S*-BPAB-*SR*-Ala)Ni(II); R = Ph, R' = H (*S*-BPABP-Gly)Ni (II).

Whereas Gly gives a single complex, S,R-Ala forms a mixture of two diastereoisomeric complexes, which have also been used without prior resolution of the diastereoisomers. The structures of the complexes shown in Diagram 1 have been proved [7, 9].

(S-BPAB-S,R-Ala)Ni(II) is alkylated readily by alkyl halides to give mixtures of diastereoisomeric complexes containing S- and R-α-methyl-α-aminoacids [9]. We have found that the enolate (I), obtained from (S-BPAB-S,R-Ala)Ni(II) by treatment with butyllithium in THF,

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