Asymmetric Hydrogenolysis of Hydrazones. Synthesis of Optically Active α-Alanine

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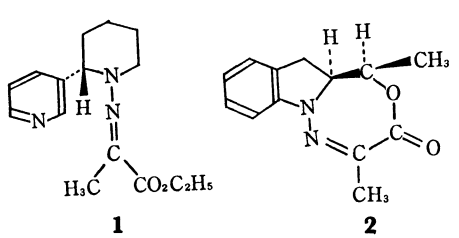
Optically active α-alanines have been synthesized by the asymmetric hydrogenolysis of the chiral hydrazones which were derived from chiral amines and ethyl pyruvate. Reduction of the C=N group in the hydrazones was carried out using PtO_2 catalyst in acetic acid at room temperature, followed by hydrogenolysis of the N–N linkage using the same catalyst in 1 M HCl at 100 °C (autoclave). The synthesis using (*S*)-bornylamine as a chiral reagent afforded L-alanine with optical purity of 46.5%. By using (*S*)-1,2-dimethylpropylamine as a simple chiral reagent, L-alanine was also obtained with optical purity of 32.2%. It has become apparent that the synthesis using (*S*)-alkylamine gave L-alanine, while D-alanine was obtained by using (*S*)-α-methylbenzylamine.

A number of methods for the asymmetric synthesis of α-amino acid have been reported and summarized in several reviews.[1] Among these, the reduction of hydrazide and hydrazone derivatives has the advantage of recovering the starting acids and amines without destruction of the optical activity. Akabori and his co-workers[2] reported the synthesis of L-alanine (8% e.e.) and L-phenylalanine (5% e.e.) using hydrazide of (*R*)-2-methyl-3-phenylpropanoic acid. Suzuki[3] also used hydrazide of *d*-tartaric acid to obtain L-alanine (12% e.e.). However, they did not recover the original optically active sources. On the other hand, Kost and his co-workers[4] used the hydrazone (**1**) derived from anabasine to obtain D-alanine (40% e.e., 10% yield) and recovered anabasine with optical purity of 90%. Corey and his co-workers[5] succeeded in an excellent asymmetric synthesis of D-alanine by using the compound (**2**) (96% e.e., 78% yield). Our present study deals with the asymmetric synthesis of α-alanine by the catalytic hydrogenolysis of the hydrazones derived from optically active hydrazines and ethyl pyruvate.

Results and Discussion

The reduction of *d*-camphoroxime with sodium in ethanol afforded the mixture of 70% of bornylamine (Ia) and 30% of isobornylamine (Ib). The mixture was separated into Ia and Ib by the treatment with glacial acetic acid in ether solution, using Hückel's method.[6] The optical purities of Ia and Ib were shown to be 99.7% and 98.6% by comparing their optical rotations with those in the literature.[7] Both amines, Ia and Ib, were respectively converted to the hydrazone derivatives, (Va) and (Vb), by the following procedures. I was condensed with benzaldehyde to give benzaldimine. The imine was treated with methyl iodide, followed by hydrolysis to give *N*-methyl compound (II). II was converted into hydrazine derivative (IV) through the reduction of its nitroso compound (III) with zinc dust. IV was condensed with ethyl pyruvate in a dry ether solution and gave the hydrazone (V). In the asymmetric reductions reported previously, Kost used zinc dust–hydrogen chloride and Corey used aluminum amalgam. Thus far the catalytic hydrogenolysis of the hydrazone has not been successful. The hydrogenation of Va and Vb did not proceed with 5% or 10% of palladium on carbon or platinum oxide in ethanol under the hydrogen pressure of 50 kg/cm² at room temperature or even at an elevated one. However, hydrogen was absorbed when the solvent was replaced with acetic acid using platinum oxide catalyst under atmospheric pressure. The colorless oil isolated from the above reaction was found to be the intermediate (VI) from its IR and NMR spectra. The NMR spectra of the diastereomers VI were so similar in their patterns of peaks that the optical yield of the asymmetric hydrogenation could not be calculated from the proportion of the NMR peaks of the particular protons, even with NMR shift reagents. Further, hydrogen was absorbed in the HCl solution of VI with PtO_2 when the temperature was elevated to 100 °C under a hydrogen



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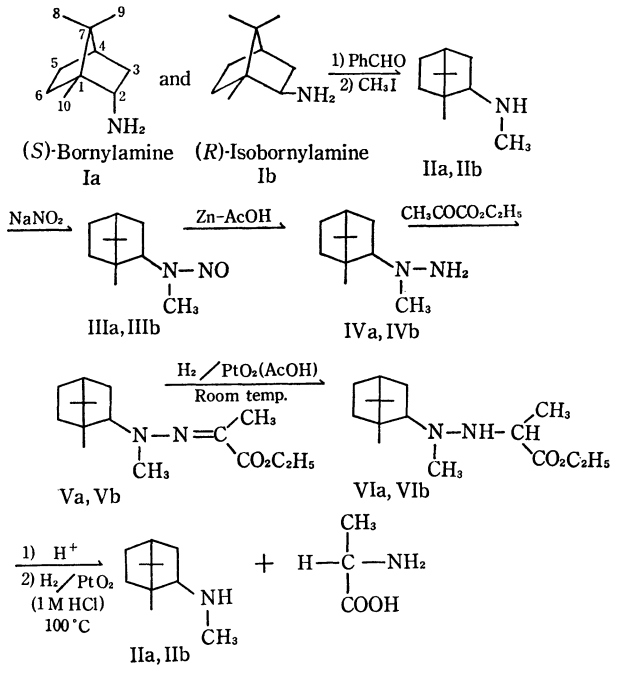


TABLE 1. ASYMMETRIC SYNTHESIS

Hydrazones	Methods	L-Alanine yield	Optical yield
Va (*S*)	Catalytic reduction	34%	46.5%
Va (*S*)	Chemical reduction	21%	10.9%
Vb(*R*)	Catalytic reduction	37%	9.2%

pressure of 50 kg/cm^2. Thus, the cleavage of the N–N linkage leading to α-alanine was carried out, and simultaneously *N*-methyl amine IV was recovered with 95% optical purity (38% yield). The reduction of the bornylhydrazone Va was also performed with zinc dust and hydrogen chloride in ethanol in order to compare the differences between the catalytic reduction and the "chemical" one (Zn–HCl). The resulting α-alanine was isolated by successive columns of an anion exchange resin (Amberlite IRA 410) and a cation exchange resin (Dowex 50W-X8) and the optical rotations of the eluted α-alanines were measured. The results of the asymmetric hydrogenolysis are shown in Table 1. Although the absolute configurations of the starting amines, Ia and Ib, were different at C-2 (asymmetric carbon), the catalytic reductions of Va and Vb, derived from the amines, gave alanines having the same configuration. This fact suggested that the conformation of the molecule adsorbed on the surface of the catalyst could not be predicted because of the difficulty in evaluating the extent of the intramolecular steric repulsions and the interactions between the molecule and the catalyst. What is known as the anchor effect[8] of the lone pair of nitrogen, the adsorption of the lone pair of the amino nitrogen on the surface of the catalyst, may be attributable to the fixing of the conformation of V and the amino nitrogen's tetrahedral character. However, the authors have been unable to find any detailed account of the asymmetric induction mechanism.

Next, as a simple alkylamine, (*S*)-1,2-dimethylpropylamine was chosen. The *dl*-1,2-dimethylpropylamine was synthesized and resolved into (*S*)-amine and (*R*)-amine with *d*-tartaric acid according to a recently reported method.[9] The synthetic method and experimental operation of the asymmetric synthesis using optically active 1,2-dimethylpropylamine was similar to that for (*S*)-bornylamine described above. L-Alanine (32.2% e.e.) was derived from the (*S*)-amine. As expected, from the (*R*)-antipode D-alanine was obtained in reasonable optical yield. Further, in order to examine the effect of an affinity[10] of the phenyl groups for the catalyst, (*S*)-α-methylbenzylamine was chosen and converted into its hydrazone derivative. The hydrazone absorbed two moles of hydrogen (PtO_2–AcOH) at ordinary temperature and pressure. Table 2 shows the results of the asymmetric reduction. Except for R_2= ethyl, the reductions of the hydrazones derived from (*S*)-α-methylbenzylamine gave D-alanine, contrary to the results for (*S*)-1,2-dimethylpropylamine. The cause of the low optical yields seemed to be a complex competition of the adsorption power between the lone pair of nitrogen and the phenyl group to fix the conformation of the molecule on the surface of the catalyst.

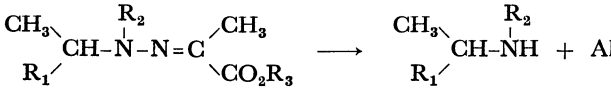
Experimental

Optical rotations were measured using an Applied Electric Lab. Automatic Polarimeter Model MP-IT and a Yanaco OR-50. IR spectra were recorded using a JASCO infrared spectrophotometer Model IRA-1. NMR spectra were measured using a JEOL-MH-100 spectrometer. The IR and NMR spectra supported the structures of all compounds used in this paper, but the data have not been written in the experimental section. Nitrogen was analyzed by the Kjeldahl method. Melting and boiling points are uncorrected. The α-alanines given by the asymmetric reductions were identified with pure L-alanine $[\alpha]_D^{21}$ +32.7° (*c* 0.5, acetic acid) by paper chromatography: the IR (KBr) spectra of the products agreed very closely with that of the authentic one.

(S)-*Bornylamine (Ia) and* (R)-*Isobornylamine (Ib).* *d*-Camphoroxime was prepared with *d*-camphor ($[\alpha]_D^{20}$ +44°, *c* 4.0, ethanol) and hydroxylamine.[11] The amines obtained on sodium metal–ethanol reduction[12] of the oxime were purified and separated into two parts (Ia and Ib) by fractional precipitation of their acetates, according to the procedure used by Hückel.[6] Bornylamine hydrochloride, $[\alpha]_D^{20}$ +23.1° (*c* 4.2, ethanol), (lit,[7] [α] +23.3°, *c* 4.0, ethanol) and isobornylamine hydrochloride, $[\alpha]_D^{20}$ −48.6° (*c* 4.0, ethanol), (lit,[7] [α] −49.4°, *c* 4.0, ethanol) were used in the following experiments.

(S)-N-*Methylbornylamine (IIa).* To a cooled solution of the *(S)*-bornylamine hydrochloride (50 g) in ethanol (350 ml), sodium hydroxide (30 g) was added with stirring. Benzaldehyde (30 g) was added to the solution containing the free amine. The mixture was heated under reflux for 4 h with stirring. The solvent was evaporated *in vacuo*. The concen-

TABLE 2.



Hydrazone	Absolute configuration of starting amine	R_1	R_2	R_3	Alanine	Yield	Optical yield
IX	(*S*)-1,2-Dimethylpropylamine (VIIa)	Isopropyl	Methyl	Ethyl	L	40%	32.2%
X	(*R*) (VIIb)	Isopropyl	Methyl	Ethyl	D	43%	31.8%
XI	(*S*)-α-Methylbenzylamine (VIII)	Phenyl	Methyl	Ethyl	D	37%	0.9%
XI[a)]	(*S*) (VIII)	Phenyl	Methyl	Ethyl	D	32%	6.3%
XII	(*S*) (VIII)	Phenyl	Methyl	Isobutyl	D	35%	15.4%
XIII	(*S*) (VIII)	Phenyl	Ethyl	Ethyl	L	30%	3.2%
XIV	(*S*) (VIII)	Phenyl	Benzyl	Ethyl	D	38%	7.5%

a) Using the solvent of acetic acid–ethanol (1 : 1), the temperature (0 °C) of the reaction was kept through reduction. In the other cases, the initial addition of one mole of hydrogen was carried out at room temperature using the catalyst of PtO_2 in acetic acid.

trate was cooled and diluted with water (100 ml), followed by extraction with ether. The extract after drying (sodium sulfate), on evaporation, gave the Schiff base quantitatively. The Schiff base obtained was heated with methyl iodide (36 g) in an autoclave (100 °C) for 24 h. The mixture was washed out with aqueous ethyl acetate (200 ml) from the autoclave and then the solution containing aqueous ethyl acetate was heated at 70 °C. The cooled mixture was added into a solution of 1 M hydrochloric acid (200 ml). After separation from the organic layer, the aqueous portion was made basic to litmus with 3 M sodium hydroxide with cooling, and extracted with ether. After drying (sodium sulfate) and evaporating the solvent, the oil obtained was distilled under reduced pressure (22 mmHg) at 95—110 °C (28 g). Found: N, 8.54%. Calcd for $C_{11}H_{21}N$: N, 8.37%.

(S)-N-*Nitroso*-N-*methylbornylamine (IIIa).* *N*-Methylbornylamine hydrochloride (25 g) was dissolved in water (200 ml) containing concd hydrochloric acid (0.5 ml). To the solution obtained, sodium nitrite (13 g) was added little by little at room temperature and then the mixture was heated to 70—80 °C for 3 h. After cooling to room temperature, the floating yellow oil was extracted with ether. The extract after drying (calcium chloride) gave on evaporation a yellow solid (mp 26 °C) (20 g).

(S)-N-*Methylbornylhydrazine (IVa).* To water (40 ml) maintained at 15 °C with zinc (30 g), IIIa (15 g) dissolved in acetic acid (32 ml) was added dropwise over 0.5 h with stirring. After this addition, the reaction mixture was stirred for 1 h at room temperature and heated for 1 more h at 80 °C. The unreacted zinc was filtered from the cooled mixture. Forty per cent solution of sodium hydroxide was added in large excess to the filtrate which was extracted with ether. After drying (potassium hydroxide), the residual oil on evaporation of the solvent was distilled at 195—200 °C to give a colorless oil (13 g). Found: N, 15.21%. Calcd for $C_{11}H_{22}N_2$: N, 15.37%.

Ethyl (S)-2-*(*N-*Methyl*-N-*bornylhydrazono)propionate (Va).* A cooled solution of IVa (4.7 g) in dry ether (300 ml) was added dropwise to a stirred ice-cooled solution of ethyl pyruvate (3 g) in dry ether (500 ml). The solution was kept at 5 °C for 12 h and then at room temperature for 5 h. Anhydrous magnesium sulfate was added to the ethereal solution. After evaporation of the solvent, a deep yellow oil (8 g) was obtained, which had $[\alpha]_D^{22}$ +278° (*c* 2.50, ethanol). Found: N, 9.99%. Calcd for $C_{16}H_{26}O_2N_2$: N, 10.51%.

The General Procedure for Catalytic Reduction. Hydrazone (1 g) and platinum oxide (150 mg) were placed in a 100 ml-round-bottomed flask, which was then filled with hydrogen under ordinary pressure. The solution obtained was hydrogenated at room temperature for 12 h. After filtration of the catalyst, the resulting solution was made alkaline to litmus with 1 M sodium hydroxide solution and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate. The evaporation of ether afforded a colorless oil (500 mg), which was assigned to a hydrazino compound by IR and NMR data. The hydrazino-compound was successively dissolved in 1 M hydrochloric acid (50 ml) with platinum oxide (100 mg) in a 200 ml-autoclave. The autoclave was then filled with hydrogen at 50 kg/cm² (room temperature) and stirred magnetically at 100 °C for 4 h. After cooling, the catalyst was filtered and the filtrate was evaporated *in vacuo* to dryness. The residue was redissolved in water (100 ml) and basified to pH 9 with 1 M ammonia. The *N*-methyl compound (optically active source) extracted with ether maintained its 95% optically activity (35% yield). The aqueous solution was passed through an ion exchange column packed with IRA-410. The elute was evaporated *in vacuo* to dryness. The residue obtained was redissolved in water (200 ml) and passed through a column packed with Dowex 50W-X8. The amino acid was eluted with 1 M ammonia. The basic solution was concentrated to dryness to give a white solid (30—40% yield). The IR (KBr) spectrum of the synthesized alanine was superimposable with that of an authentic sample. Paper chromatography of the synthesized alanine showed only the one spot having the R_f value as an authentic sample.

L-*Alanine from* (S)-*Hydrazone (Va) by Catalytic Reduction.* One gram of Va gave 109 mg (34% yield) of L-alanine of 46.5 % optical purity, $[\alpha]_D^{22}$ +15.21° (*c* 0.56, acetic acid).

L-*Alanine from Ethyl* (R)-*2*-(N-*Methyl*-N-*isobornylhydrazono*) *propionate (Vb) by Catalytic Reduction.* One gram of Vb, $[\alpha]_D^{20}$ −293° (*c* 2.7, ethanol), gave 118 mg (37% yield) of L-alanine of 9.2% optical purity, $[\alpha]_D^{22}$ +3.0° (*c* 0.56, acetic acid).

Zn–HCl Reduction of (Va). A mixture of Va (2.2 g), ethanol (40 ml), and zinc dust (2.7 g) was treated slowly with a saturated alcoholic solution of hydrogen chloride at 10 °C. When this zinc was completely dissolved, an additional amount (1.3 g) of zinc was added and the mixture was stirred at room temperature for 1 h. The filtered solution was evaporated *in vacuo* and the residue was dissolved in water. Hydrogen sulfide was introduced into the solution at pH 4. After precipitating ZnS, the mixture was separated by a centrifuge, then the supernatant was made alkaline at pH 9 with 1 M ammonia extracted with ether. The aqueous solution was passed through an ion exchange column packed with IRA-410 and the crude amino acid was eluted with 1 M acetic acid. The dried solid was disolved in water again and treated by passing through a Dowex-50W-X8 column. The L-alanine (140 mg), $[\alpha]_D^{21}$ +3.6° (*c* 0.55, acetic acid) of 10.9% optical purity, was obtained by elution with 1 M ammonia and evaporation.

Catalytic Reduction of Hydrazones (IX—XIV). The same procedure as in the experiment of bornylamine system Va was applied to the hydrazones IX—XIV, which were derived from *(S)*-1,2-dimethylpropylamine (VIIa): $[\alpha]_D^{20}$ −3.4° (neat) (lit,[13] $[\alpha]_D$ −3.45°); *(R)*-(VIIb): $[\alpha]_D^{20}$ +3.2° (neat); and *(S)*-α-methylbenzylamine (VIII): $[\alpha]_D^{22}$ −38.5° (neat).[14]

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15) XIV was derived from *(S)*-*N*-benzyl-α-methylbenzylamine, which was given by the reduction of *(S)*-*N*-benzilidene-α-methylbenzylamine with H_2/PtO_2 in ethanol at room temperature.