cient mixing to ensure homogeneity. The half-shade angle on the instrument was set at 5°, which normally gives an error of ±0.02° in α_{obsd}; since the readings had to be made rapidly, an error of ±0.04° was assigned. Error in the pseudo-first-order rate constant was evaluated by the method of limiting slopes. Results are summarized in Table I.

A. Triethylamine in Chloroform.—Runs were made at two temperatures: 33.7° ± 0.3 and 24.0° ± 0.1.

B. Triethylamine in 80% Dioxane–Water.—In this case the ester was dissolved in pure dioxane and the amine in 60% dioxane–water; the temperature was 32.1° ± 0.2.

C. Tribenzylamine in Chloroform.—There was no change in optical rotation after 24 hr at 33°.

D. Tribenzylamine Hydrochloride in 20% Methanol–Chloroform.—There was no change in optical rotation after 24 hr at 33°.

Registry No.—**1**, 17659-10-8; **2**, 17659-11-9; **3**, 17659-18-6; **4**, 17730-92-6.

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Synthesis of Optically Active Alanine from Oxaloacetic Acid by Hydrogenolytic Asymmetric Transamination[1]

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Hiskey and Northrop published a method for synthesizing optically active α-amino acids from the corresponding α-keto acids. They employed optically active α-methylbenzylamine and subsequent catalytic hydrogenation and hydrogenolysis.[2] In the previous study from this laboratory, the possible steric courses of the asymmetric synthesis have been studied.[3,4] Also, the formation of optically active amino acids from α-keto acids and optically active α-phenylglycine in alkaline aqueous solution by catalytic hydrogenation and subsequent hydrogenolysis has been studied.[5]

In this investigation, reactions of oxaloacetic acid with (*S*)(−)-α-methylbenzylamine and with (*S*)(−)-α-ethylbenzylamine in alcoholic solution were used to obtain optically active aspartic acid. However, the resulting amino acid was found to be only optically active α-alanine (optical purity 69 and 52%, respectively). No aspartic acid was identified in the reaction product. Therefore, very fast decarboxylation of oxaloacetic acid during the reaction is inferred.

To clarify the decarboxylation during the asymmetric synthesis, several amines and solvent systems were used. Benzylamine resulted in racemic alanine

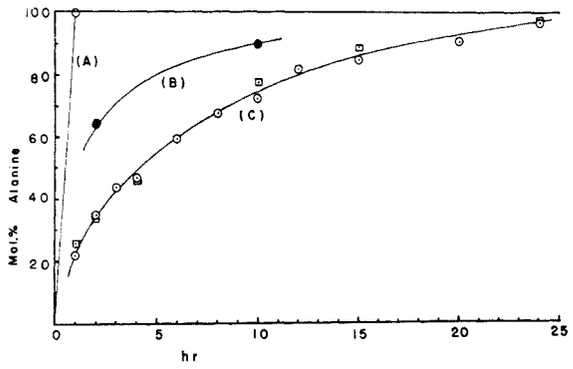
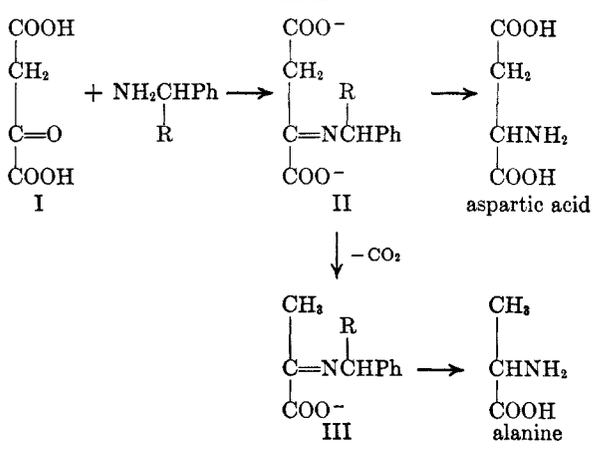


Figure 1.—Decarboxylation during the reductive amination of oxaloacetic acid. (A) oxaloacetic acid (1.32 g, 0.01 mol) + (*S*)(−)-α-methylbenzylamine (3.63 g, 0.03 mol). (B) Oxaloacetic acid (0.66 g, 0.05 mol) + pyridoxamine dihydrochloride (1.2 g, 0.005 mol). (C) Oxaloacetic acid (1.32 g, 0.01 mol) + (*R*)(−)-phenylglycine (1.51 g, 0.01 mol). ⊙, determined by amino acid analyzer; ⊡, determined by DNP method.

in an alcoholic solution, the same as the optically active α-methyl- and α-ethylbenzylamine did. When optically active (*S*)(+)-or (*R*)(−)-α-phenylglycine was used in the reaction with oxaloacetic acid in aqueous solution, the products were found to be a mixture of (*S*)(+)-alanine–(*S*)(+)-aspartic acid or (*R*)(−)-alanine–(*R*)(−)-aspartic acid. The decarboxylation rate in this reaction is relatively slow compared with that in the reaction with α-alkylbenzylamine in alcoholic solution. The observed results are shown in Figure 1, in which the ratios of the resulting alanine and aspartic acid, depending on time in the reaction, are presented. The summarized results of yield and optical purity are presented in Table I.

The inferred route of this reaction is shown in Scheme I. Oxaloacetic acid reacts with benzylamines to form

SCHEME I



the Schiff base (II). The structure II might lose its β-carboxyl group easily to convert it into the Schiff base of pyruvic acid (structure III).[6] In the reaction with benzylamine, α-alkylbenzylamine, or α-(1-naphthyl)-ethylamine, the decarboxylation rate seems to be very fast in alcoholic solution. When an aqueous solvent was used, decarboxylation was not so fast that the re-

(1) Sterically controlled synthesis of optically active organic compounds VII. Part VI: K. Harada and K. Matsumoto, *J. Org. Chem.*, **33**, 4467 (1968). Contribution No. 079 from the Institute of Molecular Evolution, University of Miami.

(2) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).

(3) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

(4) Part VI.[1]

(5) K. Harada *Nature*, **212**, 1571 (1966); K. Harada, *J. Org. Chem.*, **32**, 1790 (1967).

(6) The decarboxylation reaction mechanism could be similar to those of enzymatic β-decarboxylation proposed by A. Meister, J. S. Nishimura, and A. Novogradsky, "Chemical and Biological Aspects of Pyridoxal Catalysis," E. E. Snell, P. M. Fasella, A. Braunstein, and A. Rossi Fanelli, Ed., The Macmillan Co., New York, N. Y., 1963, p 229.

TABLE I

FORMATION OF OPTICALLY ACTIVE ALANINE FROM OXALOACETIC ACID

Reaction	Confign of amine[a]	Solvent	Yield,[b] %	Confign of amino acid	Isolated amino acid, $[\alpha]^{25}D$, deg (c, 5 N HCl)[c]	Optical purity,[d] %	DNP-amino acid, $[\alpha]^{25}D$, deg (c, 1 N NaOH)[e]	Optical purity,[f] %
1	(S)(−)-Me	EtOH	78 (30 min)	(S)-Ala	+10.8 (3.30)	74	+98.6 (0.44)	69
2	(S)(−)-Me	H_2O, EtOH (1:1), NaOH	60 (30 min)	(S)-Ala	+7.4 (2.99)	50	+73.8 (0.40)	51
				(R)-Asp	−11.1 (2.84)	44	−41.0 (0.39)	45
3	(S)(−)-Et	EtOH	75 (30 min)	(S)-Ala	+6.2 (3.47)	42	+74.6 (0.45)	52
4	(S)(−)-Et	H_2O, EtOH (1:1), NaOH	56 (30 min)	(S)-Ala	+5.5 (2.80)	38	+52.9 (0.31)	37
				(R)-Asp	−6.8 (2.50)	27	−23.0 (0.37)	25
5	(R)(+)-Naph	EtOH	75	(R)-Ala	−11.1 (4.10)	76	−120 (0.35)	83
6	(R)(+)-Naph	H_2O, EtOH (1:1), NaOH	65 (30 min)	(R)-Ala	−10.9 (3.13)	74	−105 (0.45)	73
7	(S)(+)-Ph-gly	H_2O, NaOH	40	(S)-Ala	+8.2 (3.00)	56	+85.3 (0.39)	60
				(S)-Asp	+12.3 (2.51)	48	+48.9 (0.60)	53
8	(R)(−)-Ph-gly	H_2O, NaOH	38	(R)-Ala	−7.9 (3.91)	54	−89.5 (0.57)	62
				(R)-Asp	−12.8 (3.14)	53	−49.1 (0.56)	53
9	Benzylamine	EtOH	78	(±)-Ala				
10	Pyridoxamine	H_2O, NaOH	20	(±)-Ala, -asp				

[a] (S)(−)-Me, (S)(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3° benzene); (S)(−)-Et, (S)(−)-α-ethylbenzylamine ($[\alpha]^{25}D$ −21.0° benzene); (S)(+)-Ph-gly, $[\alpha]^{25}D$ +164.2° (5 N HCl); (R)(−)-Ph-gly, $[\alpha]^{25}D$ −168° (5 N HCl); (R)(+)-naph, (R)(+)-α-(1-naphthyl)ethylamine, ($[\alpha]^{25}D$ +88.0° benzene). [b] Reaction time, 2 hr except reactions mentioned. [c] Optical rotations of first isolated amino acids were listed. [d] Defined as ($[\alpha]$p obsd/$[\alpha]$D lit.) × 100. (S)-Ala, $[\alpha]^{25}D$ +14.6° (5 N HCl); (S)-asp, $[\alpha]^{24}D$ +25.39° (5 N HCl). J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1961: alanine, p 1819; aspartic acid, p 1856. [e] DNP-amino acids were isolated by column chromatography. Specific rotations were measured without further purification. [f] Defined as ($[\alpha]$D obsd/$[\alpha]$D lit.) × 100. DNP-(S)-ala, $[\alpha]$D +143.9° (1 N NaOH); DNP-(S)-asp, $[\alpha]^{25}D$ +91.9° (1 N NaOH). K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

sulting ketimine could be a mixture of II and III which would give a mixture of aspartic acid and alanine. The decarboxylation reaction also took place in the reaction of oxaloacetic acid with pyridoxamine in aqueous solution. The rate of decarboxylation was found to be lower than that from the use of α-alkylbenzylamine in alcohol, but faster than with phenylglycine in aqueous solution. It was found also that structure II combined with pyridoxamine could be hydrogenated and hydrogenolyzed by the use of palladium hydroxide on charcoal, as could N-benzyl, N-α-alkylbenzyl,[2-4] or N-α-carboxybenzyl[5] groups. After hydrogenolysis, structure II, combined with pyridoxamine, gave a mixture of alanine and aspartic acid in a ratio of 63:37.

N-Benzylideneaspartic acid was prepared to check whether the compound was decarboxylated. The N-benzylidene compound did not evolve any carbon dioxide under the same conditions employed in this study. This fact suggests that this type of compound is not a suitable structure for the decarboxylation reaction and also that the N-benzylidene compound does not convert into a structure II by migration of the double bond.

It is known that optically active phenylglycine is one of the most easily racemizable amino acids, and it is also known that in general amino acids racemize more easily when they combine with a carbonyl compound. Therefore, it was necessary to examine the racemization of optically active phenylglycine during the decarboxylation reaction. After allowing the reaction mixtures of oxaloacetic acid and (R)(−)-phenylglycine to stand for 2, 12, and 24 hr, hydrogenation and hydrogenolysis were carried out. Specific rotations of resulting DNP-alanine were −89.5, −88.9, and −89.5°, respectively (in 1 N NaOH). These results suggest that the racemization of phenylglycine during the reaction is very small or none. Free (R)(−)-phenylglycine, $[\alpha]^{25}D$ −166.8° (c 1.10, 5 N HCl), was also isolated from the reaction mixture in 97.3% yield after standing at room temperature for 24 hr. The optical purity is almost the same as that of the original (R)(−)-phenylglycine, $[\alpha]^{25}D$ −168.0° (c 1.11, 5 N HCl).

Experimental Section[7]

(S)(+)-Alanine from Oxaloacetic Acid and (S)(−)-α-Methylbenzylamine.—Oxaloacetic acid (1.32 g, 0.01 mol) in ethanol (40 ml) was added to a solution of (−)-α-methylbenzylamine[8,9] (3.63 g, 0.03 mol, $[\alpha]^{25}D$ −42.3° benzene) in ethanol (30 ml). The mixture was allowed to stand for 30 min at room temperature. Hydrogenation using 10% palladium on charcoal (1.5 g) was carried out for 6 hr at room temperature. The catalyst was removed by filtration and then washed with hot water. The filtrate was concentrated to 30 ml *in vacuo*. Ethanol was added to the concentrate until the suspended material was dissolved completely. Palladium hydroxide on charcoal (2.0 g) was added to the mixture, and hydrogenolysis was carried out at room temperature for 10 hr. The catalyst was filtered and washed with water, The combined solution was evaporated to 10 ml. The concentrate was applied to a Dowex 50 × 2 column (hydrogen form, 100–200 mesh, 1.5 × 18 cm). Acidic nonamino acid components were eluted with water; then alanine was eluted with 1 N aqueous ammonia. Fractions containing the amino acid were evaporated to dryness. (S)(+)-Alanine was obtained [0.70 g (78%); $[\alpha]^{25}D$ +10.8° (c 3.30, 5 N HCl)]. The expected aspartic acid was not found by paper chromatography in the butanol–water–acetic acid system nor by the automatic amino acid analyzer (Phoenix Model K-5000). A part of the product (0.10 g) was treated with 1-fluoro-2,4-dinitrobenzene. The resulting DNP-alanine was separated in the same way as described in previous reports:[3,10] $[\alpha]^{25}D$ +98.6° (c 0.44, 1 N NaOH); mp 172–175° dec.

Isolation of N-(α-Methylbenzyl)alanine.—A mixture of oxaloacetic acid (1.32 g, 0.01 mol), (−)-α-methylbenzylamine (3.63 g, 0.03 mol), and ethanol (70 ml) was allowed to stand for 1 hr. Hydrogenation using 10% palladium on charcoal (1.5 g) was carried out for 6 hr. The catalyst was removed by filtration and washed with water and ethanol. The filtrate was evaporated to dryness. The residue was washed with a small amount of water. The crude crystals were purified by sublimation: mp 265° dec; $[\alpha]^{25}D$ −50.5° (c 0.455, 50% EtOH) [lit.[2] mp >275°;

(7) All optical rotation measurements were carried out by the use of the Rudolph Model 80 polarimeter with PEC-101 photometer.

(8) W. Theilacker and H. Hinkler, *Ber.*, **87**, 690 (1954).

(9) W. Leithe, *ibid.*, **64**, 2831 (1931).

(10) K. Matsumoto and K. Harada, *J. Org. Chem.*, **31**, 1956 (1966); K. Harada and K. Matsumoto, *ibid.*, **31**, 2985 (1966).

$[\alpha]^{25}D$ +87.5° (*c* 1.02, 50% EtOH) from (+)-α-methylbenzylamine].

Anal. Calcd for $C_{11}H_{15}NO_2$: N, 7.27; Found: N, 7.23.

(*R*)(−)-Alanine and (*R*)(−)-Aspartic Acid from Oxaloacetic Acid and (*R*)(−)-Phenylglycine.[5]—A mixture of oxaloacetic acid (1.32 g, 0.01 mol), (−)-phenylglycine [1.51 g, 0.01 mol; $[\alpha]^{25}D$ −168° (5 *N* HCl)], and water (5 ml) was dissolved in 2 *N* sodium hydroxide (15.5 ml). The mixture was allowed to stand for 2 hr at room temperature. To the mixture, 10% palladium on charcoal (2.5 g) was added, and hydrogenation and hydrogenolysis were carried out at room temperature for 24 hr. The catalyst was filtered and washed with water. To the solution, 6 *N* hydrochloric acid was added to bring the pH to about 2. Ether extraction was carried out to remove the phenylacetic acid. The aqueous solution was evaporated to dryness. Absolute alcohol (50 ml) was added to the residue to extract the amino acid hydrochloride. Sodium chloride was removed by filtration. The alcoholic solution was evaporated, and the residue was dissolved in water (15 ml). The aqueous solution was treated with a Dowex 50 × 2 column in the same way described above. A mixture of alanine and aspartic acid was obtained (0.46 g, 38%). (Yields of amino acids at various times are almost constant: 12 hr, 36%; 24 hr, 35%.) The amino acid mixtures (0.36 g) were separated into alanine and aspartic acid by the use of an AG 1 × 8 column (formate form, 100–200 mesh, 1.5 × 16 cm). Alanine was eluted with water; then aspartic acid was eluted with 1 *N* formic acid. (*R*)(−)-Alanine (0.09 g) and (*R*)(−)-aspartic acid (0.26 g) were obtained, respectively: (*R*)(−)-alanine, $[\alpha]^{25}D$ −7.9° (*c* 3.91, 5 *N* HCl); (*R*)(−)-aspartic acid, $[\alpha]^{25}D$ −12.8° (*c* 3.14, 5 *N* HCl); alanine:aspartic acid = 35:65.

Separation of DNP-Alanine and DNP-Aspartic Acid.—The alanine and aspartic acid mixture (0.10 g) was treated with 1-fluoro-2,4-dinitrobenzene (0.4 g) and sodium hydrogen carbonate (0.4 g) by the usual method. Crude DNP-amino acid was separated by Celite column chromatography by the method described in previous reports:[3,10] DNP-(*R*)(−)-alanine, yield 0.073 g, $[\alpha]^{25}D$ −89.5° (*c* 0.57, 1 *N* NaOH); DNP-(*R*)(−)-aspartic acid, yield 0.184 g, $[\alpha]^{25}D$ −49.1° (*c* 0.56, 1 *N* NaOH); DNP-alanine:DNP-aspartic acid = 33:67.

Alanine from Oxaloacetic Acid and Pyridoxamine.—A mixture of oxaloacetic acid (0.66 g, 0.005 mol), pyridoxamine dihydrochloride (1.2 g, 0.005 mol), 2 *N* sodium hydroxide (10 ml), and water (10 ml) was allowed to stand for 2 hr at room temperature. To the mixture, palladium hydroxide (2.0 g) was added, and hydrogenation and hydrogenolysis were performed for 24 hr at room temperature. The reaction mixture was treated as above. Amino acid mixture was obtained (0.15 g, 20%). The ratio of alanine and aspartic acid was determined by the use of the automatic amino acid analyzer: alanine:aspartic acid = 63:37. Separation of DNP-amino acids was carried out as above: DNP-alanine:DNP-aspartic acid = 65:35.

Isolation of Barium Carbonate.—In a three-necked flask with a nitrogen gas inlet tube, outlet tube, and dropping funnel, a mixture of oxaloacetic acid (1.32 g, 0.01 mol), α-methylbenzylamine (3.63 g, 0.03 mol), and ethanol (70 ml) was placed. The carbon dioxide evolved was collected in traps containing 0.2 *M* barium hydroxide. After 30 min, 6 *N* hydrochloric acid (10 ml) was added to the mixture. Then nitrogen gas was passed through until the evolution of carbon dioxide ceased (30 min). Precipitated barium carbonate was collected by filtration and washed with water repeatedly. After the residue was dried, barium carbonate (1.90 g, 96.4%) was obtained.

Examination of Racemization of Phenylglycine.—A mixture of oxaloacetic acid (0.66 g, 0.005 mol), (*R*)(−)-phenylglycine [0.75 g, 0.005 mol; $[\alpha]^{25}D$ −168°, (5 *N* HCl)], water (2.5 ml), and 2 *N* sodium hydroxide (7.8 ml) was allowed to stand at room temperature. After 2 hr of standing, 6 *N* hydrochloric acid was added to the mixture to decompose the Schiff base. The mixture was evaporated to dryness *in vacuo*. The dried residue was extracted with absolute ethanol (50 ml). The ethanolic solution was kept in a freezer overnight, and the precipitated inorganic salt was removed by filtration. To the filtrate pyridine was added to precipitate phenylglycine. The precipitating solution was allowed to stand in a freezer overnight. The crystals were filtered to yield 0.73 g (97.3%): $[\alpha]^{25}D$ −166.8° (*c* 1.10, 5 *N* HCl).

Registry No.—(*S*)(+)-alanine, 10333-82-1; (*R*)(−)-alanine, 10353-30-7; oxaloacetic acid, 328-42-7; N-(α-methylbenzyl)alanine, 17791-40-1; (*R*)(−)-aspartic acid, 10333-84-3; (*S*)(+)-aspartic acid, 10353-31-8.

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A New Thiadiazepine Ring System

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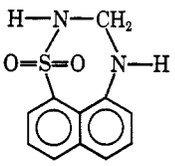
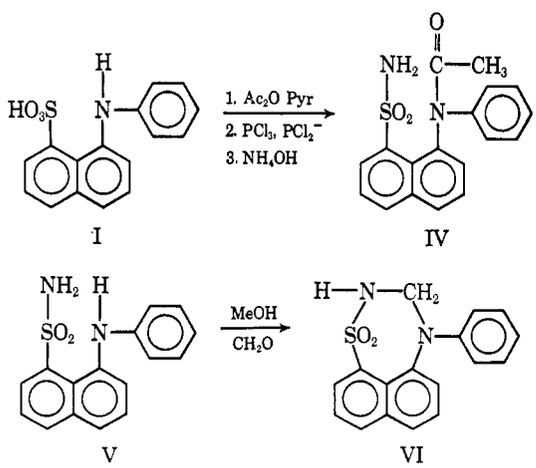
In connection with investigations dealing with the preparation of compounds for diuretic activity, we wish to report the synthesis of a new thiadiazepine ring system by two different methods, A and B. In method



A (Scheme I) the N-acetyl (II) compound was prepared from N-phenyl *peri* acid (I) by refluxing with acetic anhydride in pyridine solution, and II was converted into the corresponding sulfonyl chloride III by refluxing with PCl_5 in PCl_3. Ammoniation of III, using 10% ammonia solution, gave amide IV, and the acetyl group

SCHEME I



was then hydrolyzed by methanolic sodium hydroxide to give V. The ring closure to VI[2] was effected by condensing V with equal molar quantities of 55% Methyl Formcel in methanol.

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