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The Synthesis of Optically-active Valine by the Stereoselective Decarboxylation of α-(α-Methylbenzylamino)-α-isopropylmalonic Acid*

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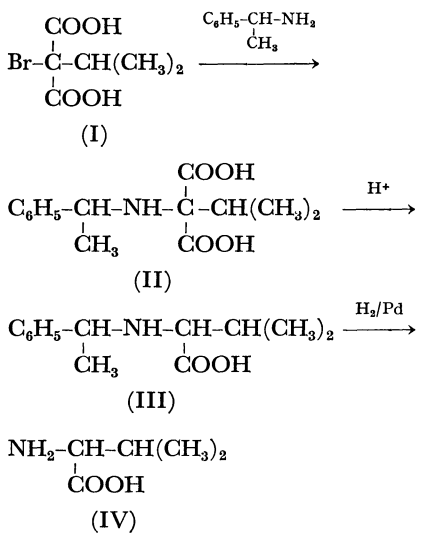
Many studies of the syntheses of optically-active α-amino acids have been reported.[1-2] Syntheses using optically-active α-methylbenzylamine as an optically-active moiety have been reported in many types of stereochemical studies.[2]

In this study, the synthesis of optically-active valine was examined by the stereoselective decarboxylation of (*S*)(−)- and (*R*)(+)-α-(α-methylbenzylamino)-α-isopropylmalonic acids.

The route of synthesis is as follows:



α-(α-Methylbenzylamino)-α-isopropylmalonic acid (II) was prepared by the reaction of α-brom-α-isopropylmalonic acid (I)[3] with optically-active α-methylbenzylamine. The product, II, was decarboxylated by heating it in 6 M hydrochloric acid to give *N*-(α-methylbenzyl)-valine (III). In order to check the influence of the reaction temperature on the steric effect of the decarboxylation, the reactions were carried out at various temperatures. The resulting *N*-(α-methylbenzyl)-valine was hydrogenolyzed into valine by the use of palladium hydroxide on charcoal. A part of the isolated valine (IV) was converted to DNP-valine by the use of 2,4-dinitrofluorobenzene in the usual manner.[4] The reactions of II→III→IV proceeded to give a quantitative yield. To avoid the fractionation of the partially-active valine and its methylbenzyl derivative thus synthesized, the purification of the compounds was carried out by the use of a Dowex 50×2 column (hydrogen form). The optical rotations of the valine and DNP-valine thus isolated, their optical purities, and the experimental conditions are listed in Table 1. When a decarboxylation reaction was carried out at room temperature, the higher optically-active valine (20—26%) was obtained. The optical purities of the resulting valines decreased with the rise in the reaction temperature. It is considered that, at lower reaction temperatures, the steric hindrance between the methylbenzyl group and the two carboxyl groups of the malonic acid derivative may contribute to the stereoselective decarboxylation more than at higher temperatures. The configurations of the resulting valines are also shown in Table 1. When (*S*)(−)-amine was used, (*R*)-rich valines were obtained, while (*R*)(+)-amine gave (*S*)-rich valines. In order to clarify the mechanism of this selective decarboxylation, the synthesis of another optically-active α-amino acid is now under investigation.

Experimental

α-[(S)(−)-α-Methylbenzylamino]-α-isopropylmalonic Acid (II) To a solution of 2.0 g of α-brom-α-isopropylmalonic acid (I)[3] in 7.12 ml of a 10% sodium hydroxide solution, 5.40 ml of (*S*)(−)-methylbenzylamine was added. After the mixture had been allowed to stand for 3 weeks, the unreacted amine was extracted with ether, and an aqueous layer was placed in a Dowex 50×2 column (hydrogen form). The column was washed with water. Then methylbenzylaminomalonic acid was eluted with 3 M aqueous ammonia and evaporated to dryness *in vacuo*. The residual product was dissolved in 20 ml of water, and the insoluble material was removed by filtration. After the filtrate had been acidified to congo red by the addition of dilute hydrochloric acid, the crystals thus precipitated were filtered and dried; yield, 1.0 g (38%); mp 181—183 °C (decomp.), $[\alpha]_D^{20} = -33.5°$ (*c* 1.01, 1 M NaOH).

Found: C, 63.66; H, 7.24; N, 5.31%. Calcd for $C_{14}H_{19}O_4N$: C, 63.88; H, 7.22; N, 5.28%.

α-[(*R*)(+)-α-Methylbenzylamino]-α-isopropylmalonic acid was prepared from I (2.0 g) and (*R*)(+)-methylbenzylamine

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Table 1. Optically-active valines prepared from (*S*) (−)- and (*R*) (+)-α-(α-methylbenzylamino)-α-isopropylmalonic acids at various temperatures

Reaction temp. (°C)	Config. of amine[a]	Config. of isolated valine	$[\alpha]_D$ of isolated valine (5 M HCl)	Optical purity (%)[b]	$[\alpha]_D$ of DNP-valine (1 M NaOH)	Optical purity (%)[b]
90	*S*(−)	*R*	−1.1	3.9	−4.3	3.9
	R(+)	*S*	+1.2	4.2	+5.8	5.3
70	*S*(−)	*R*	−1.9	6.7	−9.4	8.6
	R(+)	*S*	+1.8	6.4	+7.9	7.2
60	*S*(−)	*R*	−2.2	7.8	−11.0	10.1
	R(+)	*S*	+2.8	9.9	+13.5	12.4
50	*S*(−)	*R*	−2.6	9.2	−15.1	13.8
	R(+)	*S*	+3.1	11.0	+15.6	14.3
20	*S*(−)	*R*	−5.6	19.8	−23.2	21.2
	R(+)	*S*	+6.5	23.0	+28.8	26.4

a) (*S*) (−)-α-Methylbenzylamine ($[\alpha]_D^{25}$ −41.5°, benzene); (*R*) (+)-α-Methylbenzylamine ($[\alpha]_D^{25}$ +41.0°, benzene).
b) Defined as ($[\alpha]_D$ obsd/$[\alpha]_D$ lit) × 100. *S*-Val, $[\alpha]_D^{25}$ +28.3° (5 M HCl); DNP-(*S*)-Val, $[\alpha]_D$ +109.2° (1 M NaOH). (J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons Inc., New York, N. Y., 1961. valine, Vol. 3 p. 2368; DNP-valine, Vol. 2 p. 1564.)

(5.40 ml) in the same way as above. Yield, 0.8 g (30%); mp 180—183 °C (decomp.), $[\alpha]_D^{20}$ = +34.0° (*c* 1.02, 1 M NaOH).

Found: C, 63.73; H, 7.18; N, 5.35%. Calcd for $C_{14}H_{19}O_4N$: C, 63.88; H, 7.22; N, 5.28%.

N-[(S)-α-Methylbenzyl]-valine (III). A solution of 0.3 g of α-[(*S*)(−)-α-methylbenzylamino]-α-isopropylmalonic acid (II) in 30 ml of 6 M hydrochloric acid was heated at room temperature (20 °C) for 24 hr, at 50 °C for 6 hr, at 60 °C for 5 hr, at 70 °C for 4 hr, and at 90 °C for 3 hr. The solution was then evaporated to dryness *in vacuo*, and the residue was dissolved in 10 ml of water. The solution was then placed in a Dowex 50×2 column (hydrogen form). The column was washed with water until the effluent became neutral. Then the methylbenzylvaline was eluted with 3 M aqueous ammonia. The effluent was evaporated to dryness *in vacuo*. The yield was nearly quantitative.

Found: C, 70.37; H, 8.63; N, 6.27%. Calcd for $C_{13}H_{19}O_2N$: C, 70.56; H, 8.65; N, 6.33%.

The *N*-[(*R*)-α-methylbenzyl]-valines were prepared by the decarboxylation of α-[(*R*)(+)-α-methylbenzylamino]-α-isopropylmalonic acids at various temperatures in the same way as above. The yields averaged 95—99%. The elemental analytical values were in good agreement with the theoretical value.

(R)(−)-Valine (IV) and DNP-(R)(−)-valine. To a solution of 0.25 g of *N*-[(*S*)-α-methylbenzyl]-valine in 30 ml of 50% ethanol containing 0.096 ml of 12 M hydrochloric acid, 0.3 g of 10% palladium hydroxide on charcoal was added; the solution was then hydrogenated at room temperature until the absorption of gas had ceased. The catalyst was removed by filtration and washed with hot water. The combined solution was evaporated to dryness *in vacuo*. After the residue had then been dissolved in 10 ml of water, the solution was placed in a Dowex 50×2 column (hydrogen form) and the valine was eluted with 3 M aqueous ammonia. The effluent was evaporated to dryness; the yields averaged 95—99%. This valine was found by paper chromatography to have the same purity as the authentic optically-active valine. The analytical sample was obtained by one recrystallization from water and ethanol.

Found: C, 51.02; H, 9.50; N, 11.84%. Calcd for $C_5H_{11}O_2N$: C, 51.26; H, 9.47; N, 11.96%.

A part of the unrecrystallized valine was converted into DNP-valine in the usual manner,[4] and the resulting DNP-valine was purified by the use of a Celite column treated with a pH 7.0 citrate buffer.[5] The DNP-valine was extracted with ether and crystallized.

Found: C, 46.81; H, 4.58; N, 14.71%. Calcd for $C_{11}H_{13}O_6N_3$: C, 46.64; H, 4.62; N, 14.84%.

The (*S*)(+)-valines were prepared by the hydrogenation of *N*-[(*R*)-α-methylbenzyl]-valines obtained under several conditions and were then converted to DNP-(*S*)(+)-valine by dinitrophenylation in the way described above. The optical rotations of the resulting valines and DNP-valines, and their optical purities and configulations, are shown in Table 1.

5) J. C. Perron, *Nature*, **167**, 513 (1951); A. Court, *Biochem. J.*, **58**, 70 (1954).