BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 2720—2722 (1969)

Studies on Hydroxy Amino Acids. II.*1 The Optical Resolution of α-Amino-β-hydroxy-γ-benzyloxybutyric Acid*2

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(Received March 8, 1969)

The optical resolution of α-amino-β-hydroxy-γ-benzyloxybutyric acid (I_{ab}) into the four stereoisomers was investigated with success as a study related to the synthesis of homoserine analogues. The synthesis and the stereochemistry of α-amino-β,γ-dihydroxybutyric acid were first investigated by Niemann[1] and by Hamel[2,3] in order to clarify the structure of Sphingosine; they succeeded in synthesizing three isomers of this amino acid, the D-erythro, L-threo, and D-threo forms, from D-mannitol. However, another isomer, the L-erythro form, could not be obtained.

The present authors prepared α-amino-β-hydroxy-γ-benzyloxybutyric acid (I_{ab}) by the condensation reaction of copper glycinate[4] with benzyloxyacetaldehyde,[5] while diastereoisomeric DL-erythro and DL-threo forms were isolated by the partial crystallization from *s*-butyl alcohol. We studied the optical resolution of both of the racemic modifications; we thus confirmed that the DL-erythro form (I_a) could be resolved by the use of Takadiastase, but the threo form (I_b) could not, though the latter could be resolved by Vogler's method[6] using the diastereoisomeric salt formation of the *N*-acyl-DL-threo amino acid (III) with L-tyrosine hydrazide (Fig. 1).

CH_2OR
|
$CHOH$ I $R=CH_2C_6H_5$, $R'=H$
|
$CHNHR'$ II $R=H$, $R'=H$
|
$COOH$ III $R=CH_2C_6H_5$,
$R'=COOCH_2C_6H_5$ (CHA salt)

The four stereoisomers obtained were reduced by catalytic hydrogenation to give free α-amino-β,γ-dihydroxybutyric acids (II); γ-lactone derivatives (IV) of these isomers were also obtained by treatment with dry hydrogen chloride in methanol. The melting points and specific rotations of these isomers are summarized in Tables 1 and 2.

Experimental

α-Amino-β-hydroxy-γ-benzyloxybutyric acid (I_{ab}) was prepared by the glycine - copper method in a 14% yield; mp 205—207°C.

Found: C, 58.43; H, 6.63; N, 6.07%. Calcd for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22%.

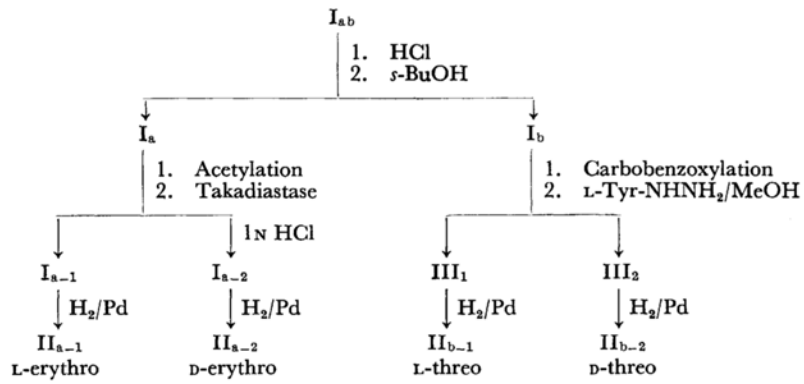

Fig. 1.

*1 Part I: K. Okawa, S. Sakai and T. Kinutani, This Bulletin, **41**, 1353 (1968).

*2 *Cf.* Original Paper: K. Okawa, K. Hori, K. Hirose and Y. Nakagawa, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **89**, 998 (1968).

1) C. Niemann and P. Nichols, *J. Biol. Chem.*, **143**, 191 (1942).

2) E. E. Hamel and E. P. Painter, *J. Am. Chem. Soc.*, **75**, 1362 (1953).

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4) K. Okawa and S. Akabori, This Bulletin, **30**, 937 (1957).

5) K. Okawa and H. Tani, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Japan, Pure Chem. Sect.*), **75**, 1199 (1954).

6) K. Vogler and P. Lanz, *Helv. Chim. Acta*, **49**, 1348 (1966).

Table 1. Melting points and specific rotations of the four isomers of α-amino-β,γ-dihydroxybutyric acid (II)

		II_{a-1}	II_{a-2}	II_{b-1}	II_{b-2}
Author	Mp (°C)	194—195	194	214	214—215
	$[\alpha]_D^{23}$ (°)	−11.3	+11.3	−13.5	+13.6
		L-erythro	D-erythro	L-threo	D-threo
Hamel	Mp (°C)	——	193—194	214—215	214—215
	$[\alpha]_D^{23}$ (°)		+15.3	−13.6	+13.1
Niemann	Mp (°C)	——	192—194	215	——
	$[\alpha]_D^{24}$ (°)		+16.0	−13.7	

Table 2. Melting points and specific rotations of the four isomers of α-amino-β-hydroxy-γ-butyroractone hydrochloride (IV)

		IV_{a-1}	IV_{a-2}	IV_{b-1}	IV_{b-2}
Author	Mp (°C)	176	176.5—177	173—174	175—175.5
	$[\alpha]_D^{23}$ (°)	+55.6	−56.6	−26.2	+26.0
		L-erythro	D-erythro	L-threo	D-threo
Hamel	Mp (°C)	174—175	174—175	Oil	——
	$[\alpha]_D^{23}$ (°)	+50.4	−51.2		

Separation of Diastereomers. A suspended solution of I_{ab} hydrochloride (29 g) in *s*-butyl alcohol (300 m*l*) was stirred for 2 hr at 50°C. The undissolved crystals, I_a hydrochloride (19 g), were then filtered off. From the mother liquor, I_b hydrochloride (10 g) was obtained. Both of the amino acid hydrochlorides were decomposed with a pyridine-methanol solution; subsequent recrystallization from hot water gave I_a (11 g; mp 202—203°C), and I_b (6 g; mp 195—196°C).

Resolution of Racemic I_a. *N*-Acetyl-I_a was prepared in an 88% yield by the usual Schotten-Baumann method, mp 151—153°C, as CHA*3 salt. The salt obtained (7.33 g, 0.02 mol) was dissolved in 2N sodium hydroxide, and the liberated CHA was extracted with ether. After the pH of the aqueous layer had been adjusted to 6.8, the solution was incubated with Takadiastase at 37°C for 4 days. The precipitate was then filtered off, and the filtrate was concentrated under reduced pressure until crystals appeared. The crystals of I_{a-1} were obtained in a 67% yield and were recrystallized from hot water; mp 194—195°C; $[\alpha]_D^{23}$ +21.9° (*c* 5.7, 1N HCl).

Found: C, 58.62; H, 6.75; N, 6.20%. Calcd for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22%.

The mother liquor of I_{a-1} was acidified to pH 2.0 and was extracted with ethyl acetate. *N*-Acetyl-I_{a-2} was obtained from the concentrated extract as CHA salt in an 84% yield. Recrystallization from methanol-ethyl acetate gave pure crystals; mp 145—146°C; $[\alpha]_D^{23}$ −12.5° (*c* 2.5, EtOH). The partial hydrolysis of the CHA salt of *N*-acetyl-I_{a-2} with 1N hydrochloric acid gave free amino acid I_{a-2} in a 82% yield; mp 194°C; $[\alpha]_D^{23}$ −21.9° (*c* 5.5, 1N HCl).

Found: C, 58.78; H, 6.67; N, 6.25%. Calcd for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22%.

***N*-Carbobenzoxy-I_b (III).** *N*-Carbobenzoxy-I_b was prepared from I_b and carbobenzoxychloride by the usual method; it was obtained as CHA salt in a 79% yield; mp 158—159°C.

L-Tyrosine Hydrazide Salt of III. The free acid (III) was obtained from CHA salt (13.7 g, 0.03 mol) by the use of 3N hydrochloric acid and by ethyl acetate extraction. L-Tyrosine hydrazide (5.86 g, 0.03 mol) was added to a solution of III in methanol (50 m*l*), and the solution was warmed at 65°C. After the removal of insolubles, the solution was concentrated; the subsequent addition of ethanol gave L-tyrosine hydrazide salt of III in a quantitative yield (16.6 g), $[\alpha]_D^{23}$ +36° (*c* 1.0, water).

Four recrystallizations of this salt (5.96 g) from methanol gave a small amount (310 mg) of optically-pure L-tyrosine hydrazide salt (V_1), mp 158.5—159°C; $[\alpha]_D^{23}$ +30.6° (*c* 1.0, water). V_1 was used as the seed of the following partial crystallization.

Resolution of Racemic III. A solution of L-tyrosine hydrazide salt of III in methanol (50 m*l*) was similarly prepared from the CHA salt of III (6.88 g, 0.015 mol). After the insolubles had been filtered off, a small amount of V_1 was seeded to the filtrate; then the mixture was stirred for 1.5 hr and kept at 25°C for 22.5 hr. The precipitated first crop (V_1) was then collected (2.12g); mp 158.5°C; $[\alpha]_D^{23}$ +30.5° (*c* 1.0, water). The mother liquor was concentrated, and the resulting crystals were dissolved in methanol (50 m*l*). After the solution had been stirred at 25°C for 4 hr and then kept at 25—17°C for 20 hr, the second crop (V_2) was obtained (2.66 g, 64%); mp 163—165°C; $[\alpha]_D^{23}$ +39.3° (*c* 1.0, water). From the filtrate of V_2, an additional crop of V_1 was obtained; the total yield of V_1 was 73%.

III_1 was obtained from V_1 by treatment with 3N hydrochloric acid; it was purified as CHA salt; mp 138.0°C; $[\alpha]_D^{23}$ +10.9° (*c* 2.0, EtOH).

Found: C, 65.61; H, 7.60; N, 6.18%. Calcd for $C_{25}H_{34}O_6N_2$: C, 65.48; H, 7.47; N, 6.11%.

The CHA salt of III_2 was obtained from V_2 in the same way; mp 137—138°C; $[\alpha]_D^{23}$ −10.3° (*c* 2.0, EtOH)

Found: C, 65.62; H, 7.57; N, 6.14%.

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*3 CHA=cyclohexylamine

mixture of I_{a-1} (675 mg, 3 mmol), water (10 m*l*), palladium charcoal (160 mg), and N hydrochloric acid (3 m*l*) was stirred for 5 hr at room temperature under the bubbling of hydrogen gas. After the removal of the catalyst, the solution was neutralized and subsequently concentrated under reduced pressure. The resulting crystals were recrystallized twice from water-methanol to give II_{a-1} (305 mg, 75%); mp 194—195°C; $[\alpha]_D^{23}$ −11.3° (*c* 7.2, water).

Found: C, 35.56; H, 6.77; N, 10.30%. Calcd for $C_4H_9O_4N$: C, 35.55; H, 6.71; N, 10.37%.

II_{a-2}, II_{b-1}, and II_{b-2} were obtained from I_{a-2}, III_1, and III_2 by the catalytic hydrogenation described above.

II_{a-2}: mp 194°C; $[\alpha]_D^{23}$ +11.3° (*c* 7.0, water).

Found: C, 35.99; H, 6.91; N, 10.63%.

II_{b-1}: mp 214°C; $[\alpha]_D^{23}$ −13.5° (*c* 2.0, water).

Found: C, 35.32; H, 6.72; N, 10.21%.

II_{b-2}: mp 214—215°C; $[\alpha]_D^{23}$ +13.6° (*c* 4.8, water).

Found: C, 35.61; H, 6.74; N, 10.98%.

α-Amino-β-hydroxy-γ-butyrolactone Hydrochlorides (IV). IV_{a-1}, IV_{a-2}, IV_{b-1}, and IV_{b-2} were prepared from II_{a-1}, II_{a-2}, II_{b-1}, and II_{b-2} respectively in the way described by Hamel and Painter.[2]

IV_{a-1}: mp 176°C; $[\alpha]_D^{23}$ +55.6° (*c* 1.5, water).

Found: C, 31.31; H, 5.24; N, 9.58; Cl, 22.73%. Calcd for $C_4H_8O_3NCl$: C, 31.28; H, 5.25; N, 9.12; Cl, 23.09%.

IV_{a-2}: mp 176.5—177°C; $[\alpha]_D^{23}$ −56.6° (*c* 1.5, water).

Found: C, 31.23; H, 5.51; N, 9.18; Cl, 23.05%.

IV_{b-1}: mp 173—174°C; $[\alpha]_D^{23}$ −26.2° (*c* 1.0, water).

Found: C, 31.24; H, 5.26; N, 9.13; Cl, 23.23%.

IV_{b-2}: mp 175—175.5°C; $[\alpha]_D^{23}$ +26.0° (*c* 1.0, water).

Found: C, 31.39; H, 5.27; N, 9.13; Cl, 23.15%.