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Synthesis of Tricholomic Acid. VII.[1] Synthesis of Four optically Active Isomers of Tricholomic Acid[2]

TAKAAKI KAMIYA

Chemical Research Laboratories, Research and Development Division, Takeda Chemical Industries, Ltd.[3]

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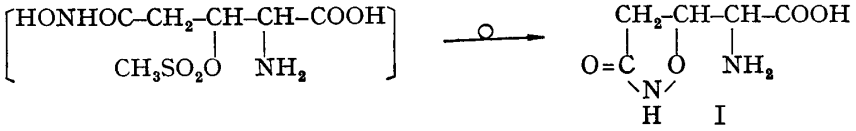
Four optically active isomers (I) of tricholomic acid were synthesized by the method reported previously for the synthesis of its racemates starting with the corresponding optically active isomers of β-hydroxyglutamic acid (VII). A new resolution technique was used for the synthesis of the starting materials.

DL-Tricholomic acid and its *threo*-isomer (I) have been synthesized in the previous paper.[1] Accordingly, it has become obvious that the reactions proceeded stereospecifically with only one inversion at the β-asymmetric carbon, and that all the four optically active congeners of I could possibly be synthesized from the optically active isomers of β-hydroxyglutamic



acid. This paper reports the realization of this expectation together with the optical resolution of β-hydroxyglutamic acid.

Optical resolution of β-hydroxyglutamic acid was effected with racemic diastereoisomers of 3-hydroxy-5-oxo-pyrrolidine-2-carboxylic acid (V). Of the racemates (Va, b), the *trans*-isomer (Va) was obtained by alkaline hydrolysis of methyl *trans*-3-hydroxy-5-oxo-pyrrolidine-

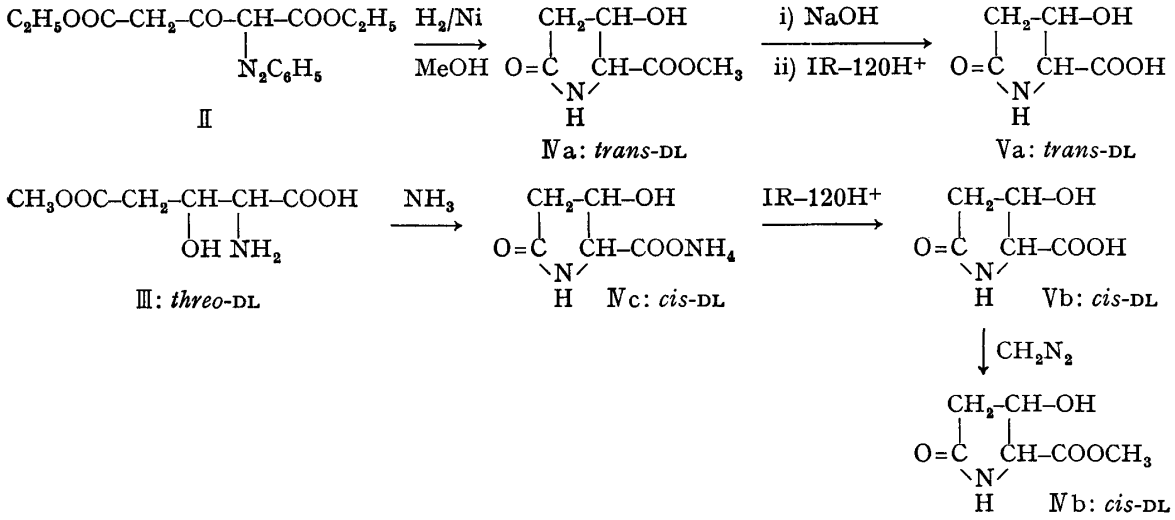
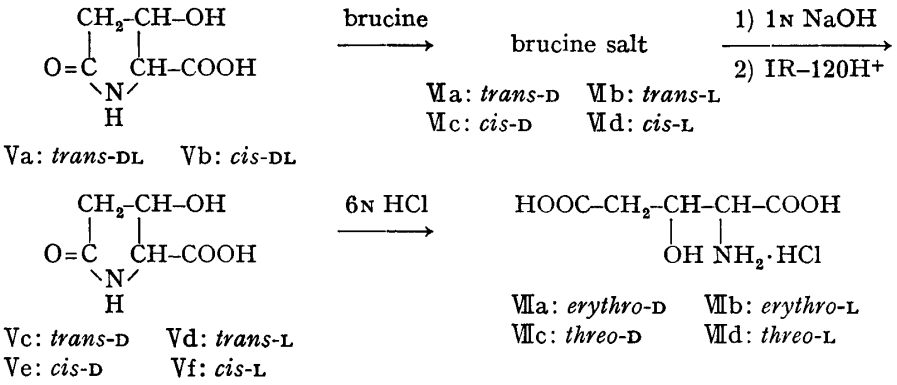


Chart 1

1) Part VI: T. Kamiya, *Chem. Pharm. Bull.* (Tokyo), 17, 886 (1969).
2) This work was presented at the 86th Annual Meeting of Pharmaceutical Society of Japan, Tohoku, Oct. 1966 and published as preliminary communication in *Chem. Pharm. Bull.* (Tokyo), 14, 1307 (1966).
3) Location: *Jusonishino-cho, Higashiyodogawa-ku, Osaka.*
4) H. Iwasaki, T. Kamiya, O. Oka and J. Ueyanagi, *Chem. Pharm. Bull.* (Tokyo), 13, 753 (1965).



Va: *trans*-DL Vb: *cis*-DL

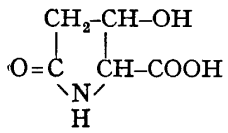
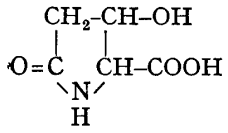
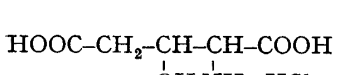
Ⅵa: *trans*-D Ⅵb: *trans*-L
Ⅵc: *cis*-D Ⅵd: *cis*-L

Vc: *trans*-D Vd: *trans*-L
Ve: *cis*-D Vf: *cis*-L

Ⅶa: *erythro*-D Ⅶb: *erythro*-L
Ⅶc: *threo*-D Ⅶd: *threo*-L

Chart 2

TABLE I

		Configuration	mp (°C)	Yield (%)
	Va	*trans*-DL	170—172 (d.)	89
	Vb	*cis*-DL	215 (d.)	87.5
	Vc	*trans*-D	96—100	95.5
	Vd	*trans*-L	96—100	93
	Ve	*cis*-D	171—174 (d.)	93.5
	Vf	*cis*-L	169—173 (d.)	94
	Ⅵa	*trans*-D	185 (d.)	72.5
	Ⅵb	*trans*-L	151 (d.)	85
	Ⅵc	*cis*-D	157—158	70
	Ⅵd	*cis*-L	238 (d.)	52.5
	Ⅶa[a]	*erythro*-D	183—184 (d.)	78.5
	Ⅶb[b]	*erythro*-L	197—198 (d.)	75
	Ⅶc[c]	*threo*-D	204 (d.)	74
	Ⅶd[d]	*threo*-L	203 (d.)	72.5

	$[\alpha]_D$ °(H_2O)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va		$C_5H_7O_4N$	41.38	4.86	9.65	41.64	4.97	9.82
Vb		$C_5H_7O_4N$	41.38	4.86	9.65	41.51	4.80	9.73
Vc	−28 (c=1, MeOH)	$C_5H_7O_4N$	41.38	4.86	9.65	41.53	4.79	9.53
Vd	+34.8 (c=1, MeOH)	$C_5H_7O_4N$	41.38	4.86	9.65	41.25	4.59	9.71
Ve	− 1.0 (c=1, MeOH)	$C_5H_7O_4N$	41.38	4.86	9.65	41.58	4.94	9.81
Vf	*ca.* 0 (c=1, MeOH)	$C_5H_7O_4N$	41.38	4.86	9.65	41.54	4.73	9.51
Ⅵa	−25.9 (c=1)	$C_{28}H_{33}O_4N_3 \cdot 2H_2O$	60.15	6.67	7.51	60.34	6.58	7.65
Ⅵb	−16.5 (c=1)	$C_{28}H_{33}O_4N_3 \cdot 2H_2O$	60.15	6.67	7.51	60.15	6.35	7.44
Ⅵc	−13.8 (c=1)	$C_{28}H_{33}O_4N_3$	62.22	6.16	7.79	61.91	6.31	7.90
Ⅵd	−32.0 (c=1)	$C_{28}H_{33}O_4N_3$	62.22	6.16	7.79	61.84	6.13	7.80
Ⅶa[a]	−11.5 (c=2)							
Ⅶb[b]	+20.7 (c=2.5)							
Ⅶc[c]	−10.0 (c=2.5)							
Ⅶd[d]	+ 9.7 (c=2)							

a) lit.[8] mp 192—193° (decomp.), $[\alpha]_D$ −18.70° (c=1.97, H_2O) *b*) lit.[8] mp 194° (decomp.), $[\alpha]_D$ +19.8° (c=1.86, H_2O)
c) lit.[8] $[\alpha]_D$ −7.3° (c=2.53, H_2O) *d*) lit.[8] mp 200—201° (decomp.), $[\alpha]_D$ +9.7° (c=2.58, H_2O)

2-carboxylate (IVa), which was previously synthesized[4] by hydrogenation of the phenylazo-compound (II). On the other hand, the *cis*-isomer (Vb)[5] was prepared by ring closure of *threo*-β-hydroxyglutamic acid γ-methyl ester (III)[6] according to the procedure described in the synthesis of pyroglutamic acid[7] (Chart 1).

Among several salts examined, the brucine salts of *cis*- and *trans*-V were found suitable for optical resolution. Removal of brucine from the salts (VI) gave the optically active 4-hydroxypyrrolidonecarboxylic acids. Acid hydrolysis of the pyrrolidones (Vc, d, e, f) with 6N HCl gave the optically active β-hydroxyglutamic acids (VII), and their physical properties were in good accord with those reported by Kaneko, *et al.*[8] as shown in Table I.

The optically active β-hydroxyglutamic acids (VII), thus obtained, were converted to the final products by the same process as described in the preceding paper.[1] Protection of the α-amino group by carbobenzoxylation, selective partial esterification of the α-carboxyl group and condensation of the γ-carboxyl group with O-benzylhydroxylamine in the case of the *threo*-compounds and the latter two reactions in the case of the *erythro*-compounds were performed in one step, and each of the four γ-benzyloxyamides (X) was purified by column chromatography on silicagel. Each amide afforded the optically active mesylate (XI) by the usual procedure in a good yield. Hydrogenolysis of XI to hydroxamic acids (XII) and subsequent cyclization of XII to the optically active isomers of I were also performed according to the procedures reported previously.[1]

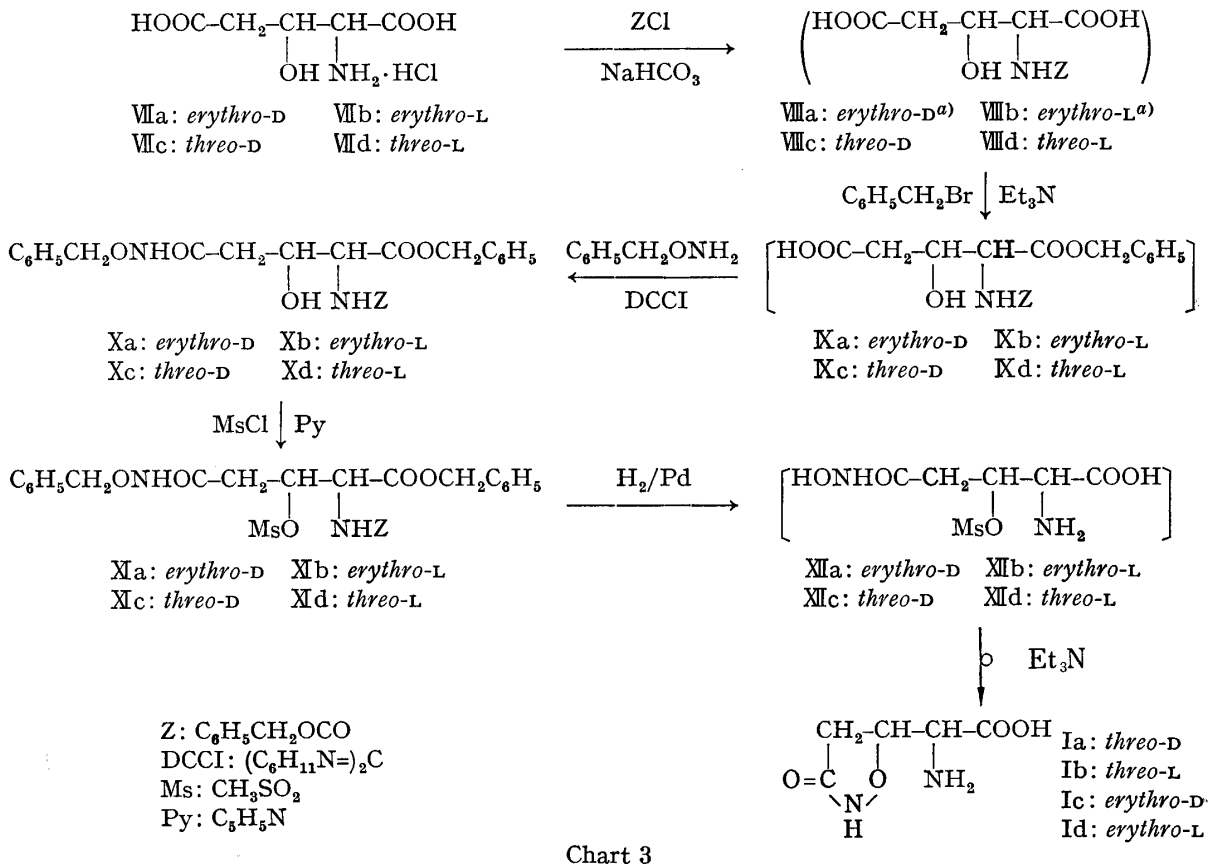


Chart 3

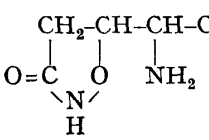
a) Isolated as crystals.

As in reactions with the racemates the reactions occurred stereoselectively with almost complete inversion of the configuration at the β-carbon in the cyclization of XII. Thus,

5) Vb afforded the methyl ester (IVb), the diastereoisomer of IVa by treatment with diazomethane.
6) Synthesis of III will be described in the next paper (Part VIII).
7) A.F. Beecham, *J. Am. Chem. Soc.*, **76**, 4615 (1954).
8) T. Kaneko, R. Yoshida and H. Katura, *Nippon Kagaku Zasshi*, **75**, 942 (1954).

erythro-D-, -L-, *threo*-D-, and -L-I were obtained from *threo*-D-, -L-, *erythro*-D- and -L-XI, respectively. Of the four optically active isomers of I, *erythro*-L-I was identified with the natural tricholomic acid[9] by the mixed melting point determination, the comparison of infrared spectra and optical rotation.

Table II. $R^1OC-CH_2-CH(R^2O)-CH(NHZ)-COOR^3$

R^1	R^2	R^3		Configuration	mp (°C)	Yield (%)
HO	H	H	VIIIa	*erythro*-D	108 —112	85
HO	H	H	VIIIb	*erythro*-L	110 —115	92
HO	H	H	VIIIc	*threo*-D	oil	94
HO	H	H	VIIId	*threo*-L	oil	96
$C_6H_5CH_2NH$	Ms	$C_6H_5CH_2$	XIa	*erythro*-D	144 —146	79[a]
$C_6H_5CH_2NH$	Ms	$C_6H_5CH_2$	XIb	*erythro*-L	146.5	74[a]
$C_6H_5CH_2NH$	Ms	$C_6H_5CH_2$	XIc	*threo*-D	124 —125	90
$C_6H_5CH_2NH$	Ms	$C_6H_5CH_2$	XId	*threo*-L	125.5—126.5	92
			Ia	*threo*-D	194 —195(d.)	74
			Ib	*threo*-L	196 (d.)	76
			Ic	*erythro*-D	203 (d.)	78
			Id	*erythro*-L[c]	205 (d.)	85

	$[\alpha]_D$ °(MeOH)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIIa	− 6.5 (c=2)	$C_{13}H_{15}O_7N$			4.71			4.51
VIIIb	+ 5.9 (c=2)	$C_{13}H_{15}O_7N$			4.71			4.53
VIIIc	—	$C_{13}H_{15}O_7N$						
VIIId	—	$C_{13}H_{15}O_7N$						
XIa	+ 15.5 (c=1)	$C_{28}H_{30}O_9N_2S$	58.93	5.30	4.91	58.71	5.29	4.71
XIb	− 17.0 (c=1)	$C_{28}H_{30}O_9N_2S$	58.93	5.30	4.91	58.96	5.31	4.69
XIc	− 25.0 (c=1)	$C_{28}H_{30}O_9N_2S$	58.93	5.30	4.91	59.18	5.26	4.71
XId	+ 27.0 (c=1)	$C_{28}H_{30}O_9N_2S$	58.93	5.30	4.91	59.21	5.28	4.60
Ia	+ 63 (c=0.2)[b]	$C_5H_8O_4N_2$	37.50	5.04	17.50	37.43	5.13	17.38
Ib	− 65 (c=0.2)[b]	$C_5H_8O_4N_2$	37.50	5.04	17.50	37.36	5.09	17.41
Ic	−101 (c=0.2)[b]	$C_5H_8O_4N_2$	37.50	5.04	17.50	37.47	5.08	17.51
Id	+103 (c=0.2)[b]	$C_5H_8O_4N_2$	37.50	5.04	17.50	37.61	5.15	17.61

a) overall yield of three steps from VIII *b*) solvent: H_2O *c*) lit.[9] mp 207° (decomp.), $[\alpha]_D$ +80.0° (c=0.2, H_2O)

Experimental[10]

Racemic Diastereoisomers of 3-Hydroxy-5-oxopyrrolidine-2-carboxylic Acid (V, see Table I)——a) To a solution of 16 g of IVa[4] in 100 ml of H_2O was added 100 ml of 1N NaOH and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was passed through a column of a cation exchanger (Amberlite IR-120, H^+-form) and the column was washed with H_2O. Va was eluted with dil. HCl and the effluent was evaporated under reduced pressure. The residue was crystallized from EtOH to give 13 g (89%) of Va.

9) T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, **84**, 1183 (1964).
10) Melting points are uncorrected. Procedures and instrumentation used were the same as previously reported,[1,4] unless otherwise indicated.

b) Compound III (2 g) was dissolved in 70 ml of MeOH saturated with NH_3 and the solution was allowed to stand overnight at room temperature. Precipitates were collected by filtration and washed with MeOH to give 1.6 g (87.5%) of IVc, mp 210—211° (decomp.). *Anal.* Calcd. for $C_5H_{10}O_4N_2$: C, 37.03; H, 6.22; N, 17.28. Found: C, 36.87; H, 6.06; N, 17.35. A solution of 0.5 g of VII in 5 ml of H_2O was treated with a cation exchanger as described above, and the residue obtained was crystallized from MeOH to give a quantitative yield of Vb.

Methyl *cis*-3-Hydroxy-5-oxopyrrolidine-2-carboxylate (IVb)——To a suspension of 1.5 g of Vb in 30 ml of MeOH was added an excess of CH_2N_2 in ether at room temperature. After evaporation of the solvent *in vacuo*, a crystalline residue was recrystallized from MeOH to yield a quantitative yield of IVb, mp 172—174°. *Anal.* Calcd. for $C_6H_9O_4N$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.28; H, 5.72; N, 8.74.

General Procedure for Resolution of 3-Hydroxy-5-oxopyrrolidine-2-carboxylic Acid (see Table I)——To a warm solution of 4.3 g of brucine ($2H_2O$) in 200 ml of MeOH was added 1.45 g of V, and the mixture was heated until the solid materials had dissolved. After being left standing overnight at room temperature, crystals were collected by filtration and recrystallized from MeOH to give one optically active salt. The first mother liquor was concentrated to 9 ml under reduced pressure and placed overnight at room temperature to give the second crystals. Recrystallization of the crystals from MeOH yielded the other optically active salt.

General Preparation of optically Active Isomers of 3-Hydroxy-5-oxopyrrolidine-2-carboxylic Acid (V, see Table I)——To a solution of 1.15 g of VI in 15 ml of H_2O was added slowly 2.1 ml of 1N NaOH (with vigorous stirring), and the solution was stirred for additional an hour. After chilling in an ice-bath for 1 hr, the brucine was collected by filtration and washed throurhgly with cold H_2O. The filtrate and the washing were combined and treated with a cation exchanger as described in the synthesis of Va. The residue obtained was crystallized from EtOH to yield V quantitatively.

General Preparation of Optically Active Isomers of β-Hydroxyglutamic Acid Hydrochloride (VII, see Table I)——A solution of 1.46 g of an optically active V in 15 ml of 6N HCl was refluxed for 12 hr and concentrated to give crystals. The crystals were recrystallized from conc. HCl to yield an optically active VII.

Optically Active Isomers of N-Carbobenzoxy-β-hydroxyglutamic Acid (VIII, see Table II)——Carbobenzoxylation of VII was performed according to the procedure reported previously[1] to yield VIII.

N-Carbobenzoxy-β-hydroxyglutamic Acid α-Benzylester γ-Benzyloxyamide (Xa, b, c, d)——a) To a solution of 1 g of VIIIa and 0.46 ml of triethylamine in 1.5 ml of dimethylformamide was added 0.4 ml of benzylbromide, and the mixture was allowed to stand overnight at room temperature. After completion of the reaction, 13 ml of H_2O was added to the mixture. An oil separated was extracted with AcOEt, and the extract was washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent from the extract under reduced pressure yielded oily IXa. This oil was dissolved in 15 ml of THF, and to this was added 0.45 g of O-benzylhydroxylamine and 0.7 g of DCCI. The mixture was stirred for 5 hr and precipitated dicyclohexylurea was removed by filtration. The filtrate was evaporated under reduced pressure to give an oil. The oil was chromatographed with a solvent of benzene–AcOEt (7:3) on silicagel. The eluate, which gave the same *Rf*-value on TLC as the racemic congener[1] gave 1 g (60.5%) of Xa. Similarly, from VIIIb, VIIIc, VIIId were obtained Xb, Xc, and Xd.

b) Xb: yield 61.5%. Each Xa and Xb was obtained as crystals, but converted to XIa and XIb respectively without purification and characterization due to the small amount available.

c) Xc: yield 57.5%, mp 132—134°, $[\alpha]_D$ −12.5° ($c=1$, MeOH).

d) Xd: yield 58%, mp 133—134°, $[\alpha]_D$ +12.7° ($c=1$, MeOH).

Optically Active Isomers of N-Carbobenzoxy-β-mesyloxyglutamic Acid α-Benzylester γ-Benzyloxyamide (XI, see Table II)——Mesylation of X was performed according to the procedure reported previously[1] to yield XI.

Optically Active Isomers of α-Amino-3-oxo-5-isoxazolidineacetic Acid (I, see Table II)——Hydrogenation of XI and subsequent cyclization was performed according to the procedure reported previously[1] to yield I.