[Chem. Pharm. Bull. 14(5) 537～549 (1966)]

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77. Kazuo Achiwa and Shun-ichi Yamada : Studies on Optically Active Amino Acids. Ⅷ.*1,*2 Studies on α-Alkyl-α-amino Acids. Ⅲ.*3 Determination of Absolute Configuration of Optically Active Isovaline.

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Studies on naturally occurring α-amino acids in the chemical and biochemical fields have been advanced greatly in the decades, and recently on those studies of α-alkyl-α-amino acids much attentions have begun to be attracted. A few of them were found in natural resources. α-Methylalanine (Ⅰ) was isolated from the hydrolysates of horse muscle protein[1] and of antibiotic I.C.I. No. 13959,[2] (+)-α-methylserine (Ⅱ) was also obtained as a component of antitubercular antibiotic, Amicetin,[3] 1-amino-1-cyclopropane carboxylic acid (Ⅲ) from berries of cowberry,[4] cider apple and perry juices[5] as a free amino acid. Furthermore, (−)-3-amino-3-pyrrolidinecarboxylic acid (Ⅳ) was isolated from the seeds of Cucurbita moschata.[6]

On the other hand, some sorts of the amino acids of this series were synthesized and much attention has been paid on them from biochemical and pharmacological points of view,[7~14] for example, 1-amino-1-cyclopentanecarboxylic acid (Ⅴ) showed anti-cancer activities[15,16] and several of its derivatives have been synthesized in order to minimize its toxicity.[16] On the contrary, some of the DL-α-methylcysteine derivatives (Ⅶ) and DL-α-methylethionine (Ⅶ) were reported to promote the tumor growth.[17] α-Methyl-DOPA (Ⅵ), which is the optical isomer with a negative rotation, was found to show an hypotensive activity.[18~22] The same isomer also inhibits the decarboxylation

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*1 A part of this work was published as a communication to the Editor in this Bulletin, **12**, 1525 (1964).
*2 Part Ⅶ : This Bulletin, **14**, 243 (1966).
*3 Part Ⅱ : *Ibid.*, **13**, 1399 (1965).
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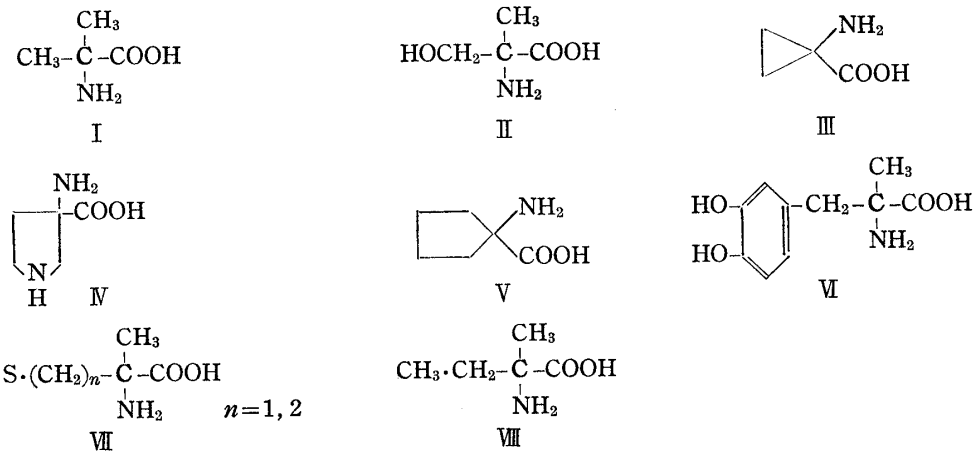
of L-DOPA by mammalian decarboxylase while the other isomer is totally inactive.[19~22]



I II III IV V VI

VII VIII

However, the absolute configuration of the amino acids of this series is either still unknown or only just suggestive[23~27] and even mutual chemical correlation of absolute configuration among these amino acids has not been clarified yet. The absolute configurations of α-methylphenylglycine,[26] N-acetyl-α-methylphenylalanine, N-acetyl-α-methyltyrosine and N-acetyl-α-methyl-β-(2-naphthyl)-alanine[27] were presented by the Freudenberg displacement rule, and further the absolute configuration of α-methyl-DOPA[23] (VI) was also suggested from various points of optical behavior. Surprisingly enough, in some cases, the opposite absolute configuration was proposed to the same optically active amino acids, that is, the absolute configuration of (+)-α-methylserine proposed respectively by Greenstein, *et al.*[25] and Wilson, *et al.*[24] was opposite, and the absolute configuration of the above-mentioned α-methylphenylgylcine suggested by Cram, *et al.*[26] was in contradiction with the formula postulated by Maeda.[28]

Moreover, some confusions have occurred in the nomenclature of these amino acids, that is, the absolute configuration of enanthiomeric α-methyl-α-amino acids has often been designated with prefix D- or L-, similar to the case of optically active α-amino acids with an α-hydrogen substituent. However, a single isomer of optically active α-methyl-α-amino acids is considered to belong to both an L- and a D- series depending on the drawing by Fischer convention.

For example, it is evident that the absolute configuration of isovaline shown in Chart 1 can be assigned to be either an L- or a D-configuration, IX, or X, depending upon whether it is considered to be a derivative of L-butyrine or D-alanine, and thus it could arbitrarily be designated as L-α-methylbutyrine or as D-α-ethylalanine. When viewed in this manner, the assignment of a D- or an L-configuration for these amino acids in which an alkyl substituent replaces the α-hydrogen, becomes meaningless.

As mentioned above, the absolute configuration and the designation of all optically active α-methyl-α-amino acids, found so far, have been remained still ambiguous.

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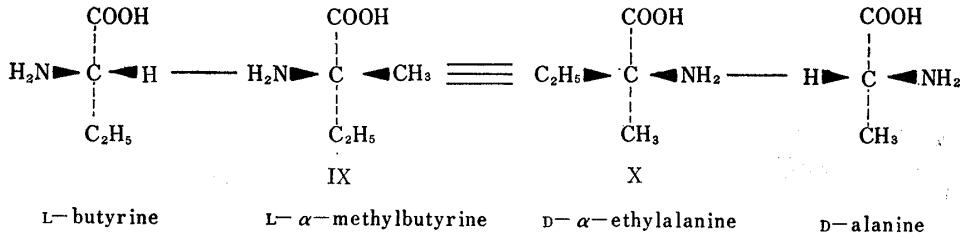

Chart 1.

This work therefore was undertaken with an objective of establishing the absolute configuration of optically active α-methyl-α-amino acids and further of elucidating relationships between the absolute configuration and its biochemical activities. The authors chose (+)-isovaline, the simplest and well-known optically active α-methyl-α-amino acid as a reference amino acid of this series. (−)-Isovaline was isolated by Ehrlich, *et al.*[29] from the yeast fermentation of racemic isovaline, and (+)-isomer was assimilated during the fermentation, therefore (+)-isovaline was supposed to be a "natural isomer" which was later called as "L-series". The absolute configuration of (+)-isovaline has also been proposed as an L-series from its taste,[30] and also its hydrolytic specificity of the N-acyl derivative to the action of hog kidney acylase.[31] The latter assignment was based on the fact that the hydrolysis of N-chloroacetyl -DL-isovaline by hog kidney acylase yielded (+)-isovaline, and designation of (+)-isovaline as an L-series has long been recognized. But the absolute configuration of (+)-isovaline designated as an L-series by the above biochemical behavior cannot be written in the conventional Fischer diagram because of the reason mentioned above.

Nevertheless, the absolute configuration of L-(+)-isovaline was assigned tentatively as IX by Greenstein, *et al.* without any convincing evidence in his book.[25a] It may only be said that (+)-isovaline exhibits the same metabolic susceptibility as L-amino acids whose hydrogen atom is attached to the α-asymmetric carbon atom. On the other hand, an aqueous solution of, so-called L-(+)-isovaline" showed a small negative shift in molecular rotation $[M]_D$ value on addition of acids.[32] This phenomenon is certainly contrary to Clough-Lutz-Jirgensons rule applicable to L-amino acids whose hydrogen atom is attached to the α-asymmetric atom. Thus, nothing definitive is known about the absolute configuration of isovaline.

The establishment of the absolute configuration of (+)-isovaline ((+)-VIII) by correlating it to D-(−)-quinic acid ((−)-XI)[33] whose absolute configuration has been clearly demonstrated, is presented in this paper. The schemes are shown in Charts 2 and 3.

Isopropylidene lactone (−)-XII which was synthesized from D-(−)-quinic acid (XI) by the action of conc. sulfuric acid in anhydrous acetone according to the method of Eberle, *et al.*[34] was tosylated with 2 moles of tosyl chloride in pyridine at 37° for a week to give an 0-tosyl derivative (+)-XV m.p. 96~97°. Its IR spectrum exhibited absorption bands due to 5-membered lactone at 1809 cm^{-1}, and sulfonic ester at 1352 and 1174 cm^{-1}. The reaction of (+)-XV with ethanol, saturated with ammonia at room temperature gave amino acid amide XVI which, without further purification, was hydrolyzed with barium hydroxide and followed by ion exchanger (Amberlite IR-120,

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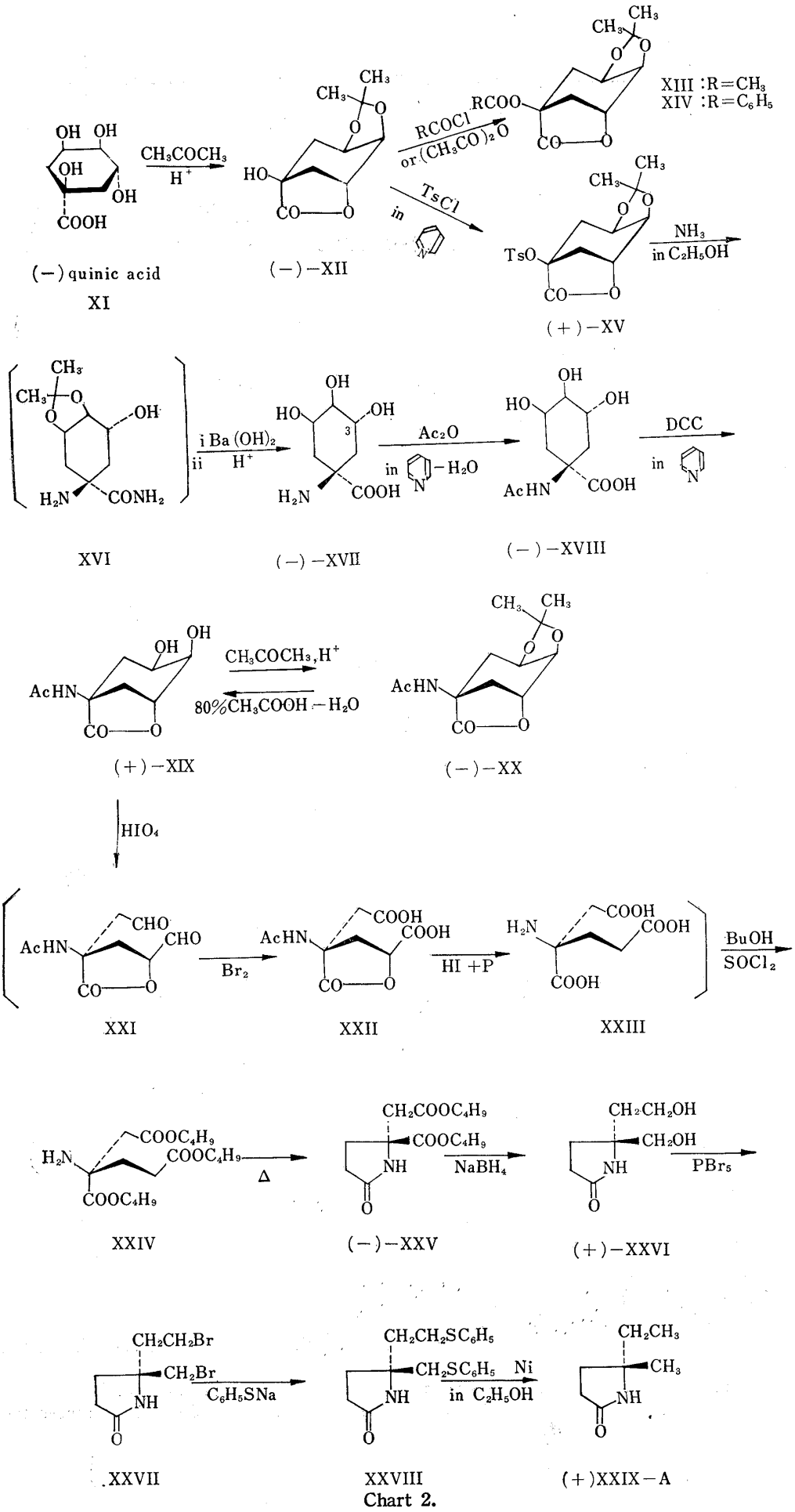


Chart 2.

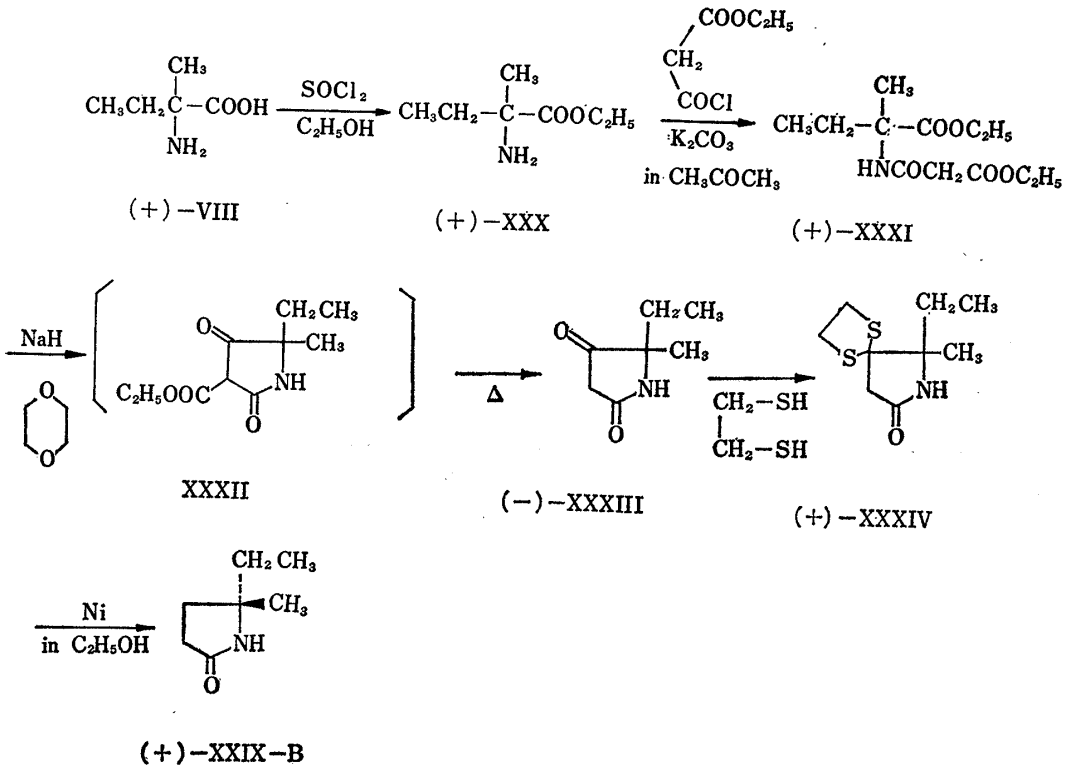


Chart 3.

H form) purification to yield the free amino acid (−)-XVII, monohydrate $C_7H_{13}O_5 \cdot H_2O$, m.p. 260~261°, $[\alpha]_D^{24} -65°(H_2O)$, as an only isolatable product, which proved to be pure by paper partition chromatography. Two diastereomers, XVII and XVIIa, should be considered to be this product, but the product obtained was demonstrated to show the structure (−)-XVII by nuclear magnetic resonance (NMR) spectroscopy*[5] after leading to (−)-XX and comparing its NMR spectrum with that of XIII[35] which is stereochemically well established. Even though the amino acid would be represented as XVIIa, it would be led to the same derivative XXI *via* XVIIa and XIXa as it is derived from (−)-XVII by the same reaction sequences shown in Chart 4.

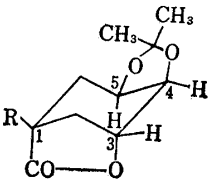
Therefore, for the present purpose, it is not so important whether the amino acid is represented by XVII or XVIIa. The OH group at 3 position of (−)-XVII did not epimerize in the course of lactone ring opening to afford a meso-compound XXXV since XVII showed an optical activity and the properties of (−)-XVII were quite different from such amino acids as XXXVI and XXXVII which were previously prepared from shikimic acid by Plieninger, *et al.*[36] The structure of (−)-XVII was also confirmed by the chemical identification with pyrrolidone derivative (+)-XXIX- A and B prepared from (−)-XVII and (+)-isovaline ((+)-VIII).

*[5] Detail of NMR studies of this compound will be published in near future in this Bulletin.

XIII : $J_{H_3-H_4}$ 2.5 c.p.s. $J_{H_4-H_5}$ 6.4 c.p.s.

(−)-XX : $J_{H_3-H_4}$ 2.3 c.p.s. $J_{H_4-H_5}$ 5.7 c.p.s.

Therefore C_4-H of XIX was conformationally equatorial as same as the C_4-H of XIII :



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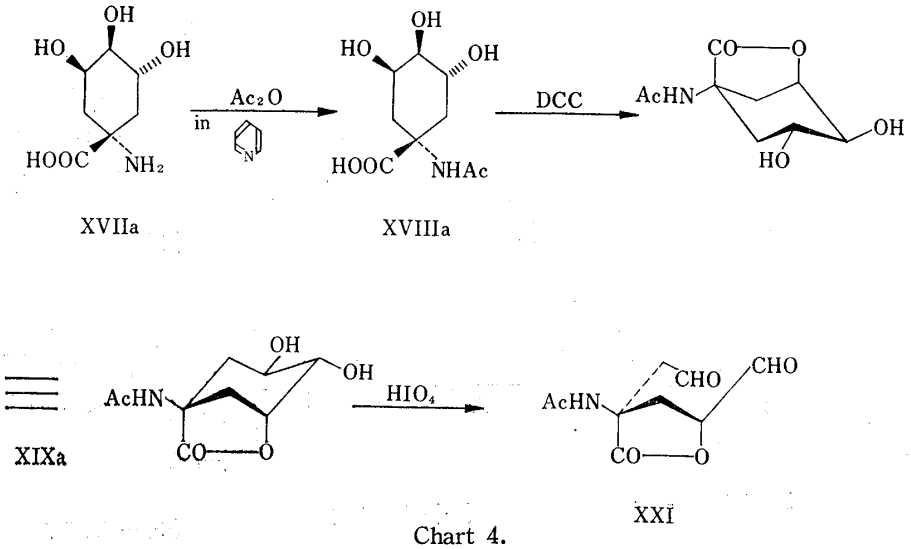
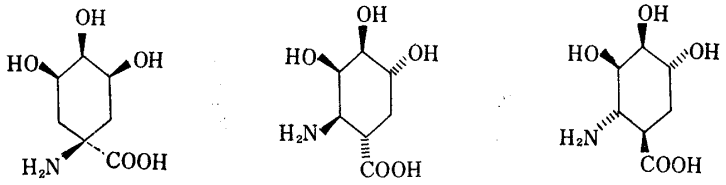


Chart 4.



XXXV XXXVI XXXVII

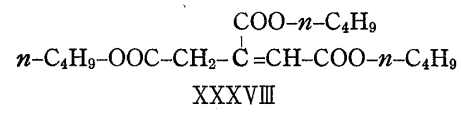
(−)-XVII was N-acetylated with acetyl anhydride in aqueous pyridine to afford (−)-N-acetyl derivative (−)-XVIII, which was lactonized with an equimolecular amount of N, N-dicyclohexylcarbodiimide in anhydrous pyridine to give the (+) *cis*-diol lactone (+)-XIX, m.p. 206~207° (decomp.). The purification of (+)-XIX by recrystallization was found to be difficult, because of its contamination with dicyclohexylurea. Therefore (+)-XIX was purified either by leading it to isopropylidine lactone derivative (−)-XX by the reaction of crude (+)-XIX with acetone in sulfuric acid or by column chromatography of crude (+)-XIX on silicic acid with 20% ethanol-chloroform. (+)-XIX was also regenerated by the reaction of (−)-XX with 80% acetic acid. Oxidation of diol lactone (+)-XIX with periodic acid gave dialdehyde XXI which was subsequently converted to α-aminotricarboxylic acid (XXIII) by the successive oxidation with bromine and the reduction with hydroiodic acid and red phosphorus without separating the intermediate XXII. As the tricarboxylic acid (XXIII) did not solidify, XXIII underwent the esterification with *n*-butanol and thionyl chloride without further purification to afford an oily substance $b.p_5$ 190~195°.

This distillate exhibited 3 spots by thin-layer chromatography on silicic acid, developed by ethyl ether-benzene (1:1), and also by gas chromatography,[*6] whose retention time was 9.6, 10.7, and 11.2 minutes respectively. The distillate was chromatographed on silicic acid and eluted first with benzene and then with ethyl ether-benzene (1:1), to separate three substances. The second portion of the eluates was redistilled to give the expected product, lactam ester (−)-XXV, $b.p_{4.5}$ 199~201°, $[\alpha]_D^{21}$ −27.4°(c=0.576, benzene) as a colorless oil, which was identified by IR spectrum showing the absorption bands at 3423 (amide NH), 1744, 1731 (ester), and 1713 cm^{-1} (5-membered lactam) in chloroform and also by elementary analysis. The lactamization seemed to take place during the distillation prior to the chromatography on silicic acid. IR spectrum of (−)-XXV, was completely superimposable with the racemic lactam

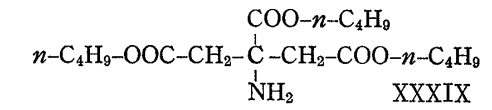
[*6] Column, 1.5% SE-30 on chromosorb W (60~80 mesh), 2.25 m. × 4 mm. Sample heater temp., column temp. and detector temp. were 340°, 201° and 240° respectively, and carrier gas (N_2) flow rate was 20 ml./min. (2 kg./cm^2).

ester XXV, in chloroform, which was synthesized from the DL-tricarboxylic acid (XXIII).*7 Before establishing the synthetic route from optically active (+)-XIX to (+)-XXIX-A, racemic XXIII was prepared from diethyl 3-oxoadipate[37] alternatively, and the synthetic route from racemic XXIII to racemic XXIX-A had been successfully established but the results on the racemic compounds from XXIII to XXIX-A are not described in this report.

The first (retention time 9.6 minutes)*6 and the third fractions (retention time 11.2 minutes) *6 of the eluates were supposed to have the structure of XXXVIII and XXXIX from IR spectra and elementary analyses.



XXXVIII



XXXIX

Reduction of lactam ester (−)-XXV with sodium borohydride afforded the diol (+)-XXVI as a colorless oil $[\alpha]_D^{26}$ +8.8°(c=1.9, methanol) which showed a single spot by thin-layer chromatography on Kiegel G, developed by 20% ethanol-chloroform, and gave the di-*p*-nitrobenzoate derivative, m.p. 191~192°, and its IR spectrum was superimposed with that of DL-XXVI*7 in chloroform. Bromination of diol (+)-XXVI with phosphorus pentabromide gave crude dibromide XXVII which underwent the thioetherification with sodium thiophenolate in dimethylformamide to afford crude dithioether XXVIII. Crude XXVII and XXVIII were used in the following steps without purification. Desulfurization of crude dithioether with Raney Ni in alcohol afforded 5-ethyl-5-methyl-2-pyrrolidinone ((+)-XXIX-A) as a colorless oil, b.$p_{15.5}$ 135~138°, $[\alpha]_D^{28}$ +8.9°(c=0.56, benzene), its elemental analysis and IR spectrum*1 were consistent with that expected for the structure XXIX-A, optical rotatory dispersion (ORD) curve of (+)-XXIX-A was shown in Fig. 1.

On the other hand, a successful attempt afforded the same lactam XXIX-B from (+)-isovaline monohydrate[38] $[\alpha]_D^{28}$ +8.9 (H_2O) as shown in Chart 3. Esterification of (+)-isovaline (VIII) with alcohol and thionyl chloride yielded isovaline ethyl ester ((+)-XXX), which was submitted to Schotten-Baumann reaction with malonic half ester chloride[39] in the presence of potassium carbonate in acetone to produce the amide ester (+)-XXXI as a colorless oil, b.$p_{5.5}$ 154~156°, $[\alpha]_D^{33}$ +4.6°(c=2.096, benzene). The different shapes of ORD curves of (+)-XXXI were observed according to the various solvents used (Fig. 2). The amide ester (+)-XXXI underwent the Dieckmann cyclization with 2 moles of sodium hydride in dioxane to afford ketoester which was readily decarboxylated under vacuum distillation to give the keto-lactam (−)-XXXIII, m.p. 105~106°, $[\alpha]_D^{29}$ −11.9°(c=0.115, CH_3OH). Remarkable

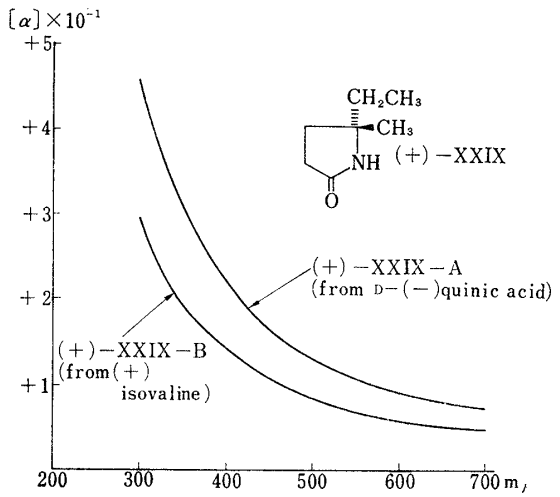


Fig. 1. Optical Rotatory Dispersion Curves of (+)-XXIX-A and (+)-XXIX-B (in benzene)

*7 Unpublished data.

37) S. F. MacDonald, R. F. Stedman : Can. J. Chem., **33**, 458 (1955).

38) E. Fischer, R. von Grävenitz : Ann., **406**, 1 (1914). $[\alpha]_D$ value of the pure isovaline containing no crystal water : $[\alpha]_D^{16}$ +11.8°(c=0.886, H_2O) S. Terashima, K. Achiwa, S. Yamada : This Bulletin, **13**, 1399 (1965).

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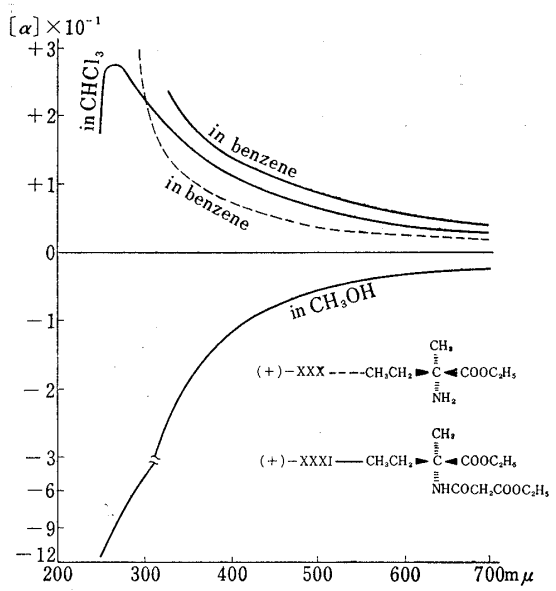


Fig. 2. Optical Rotatory Dispersion Curves of (+)-XXX (in benzene) and (+)-XXXI (in methanol, benzene and chloroform)

differences were observed between the IR spectra of (−)-XXXIII in solid state and that of in chloroform solution as shown in Fig. 3. This data and the NMR spectra in deuterium chloroform and water support the structure XL to exist in solid state and XLI in liquid state.

Ketalization of (+)-XXXIII with ethylene thioglycol in the presence of boron trifluoride etherate gave the thioketal (+)-XXXIV, m.p. 171~171.5°, $[\alpha]_D^{29}$+16.1° (c=0.31, CH_3OH). This thioketal (+)-XXXIV was desulfurized with Raney nickel to give the lactam, 5-ethyl-5-methyl-2-pyrrolidinone ((+)-XXIX-B), b.$p_{11.5}$ 130~135°, $[\alpha]_D^{29}$+5.7° (c=0.847, benzene).

The two lactams ((+)-XXIX-A and (+)-XXIX-B) which were obtained by the different routes, from D-(−)-quinic acid and (+)-isovaline, were found to be identical in every respect, infrared spectra,*1 optical rotatory dispersion curves (Fig. 1) and retention times by gas chromatography (Table 1).

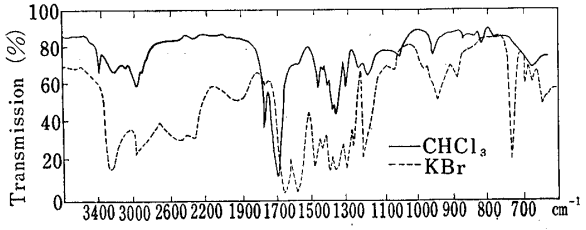


Fig. 3. Infrared of spectra XXXIII

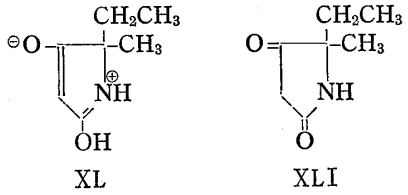


Table I. Gas Chromatographic Identification of (+)-XXIX-A and (+)-XXIX-B

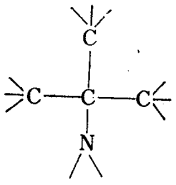
Compd. (in ether)	Retention Time (min.) 1.5% SE-30[a] (2.25 m.×4 mm.)	0.7% QF-1[a] (1.5 m.×4 mm.) (on Chromosorb-W)	0.7% QF-1[b] (3.0 m.×4 mm.)
XXIX-A	1.25	0.95	2.6
XXIX-B	1.25	0.95	2.6
XXIX-A / XXIX-B mixture	1.25	0.95	2.6

a) Sample heater temp.: 340°, column temp.: 172°, detector temp.: 220°, carrier gas (N_2): 20 ml./min. at 2 kg./cm², sens.: 100, range 0.8 v.
b) Sample heater temp.: 340°, column temp.: 201°, detector temp.: 240°, carrier gas (N_2): 20 ml./min. at 2 kg./cm², sens.: 100, range 0.8 v.

Accordingly, the absolute configuration of (+)-isovaline was obviously determined to be either IX or X, in which the formula IX corresponds to L-α-methylbutyrine and the formula X to D-α-ethylalanine. This conclusion is accidentally consistent with the proposal without clear evidences by Greenstein, *et al.*[25a] Therefore, when (+)-isovaline would be designated as belonging to an L-series according to the usual designation based on the biochemical properties, L-(+)-isovaline should be considered

to be such an amino acid, in which L-butyrine skeleton is the main chain and the α-hydrogen is replaced by a methyl group with the retention of the stereochemical configuration. However, since the absolute configuration of isovaline has been unequivocally established in this paper as a reference amino acid of this series, the arbitrary D and L nomenclature adopted for the amino acids of this series based on biochemical activity may now be abandoned.

Various nomenclature scheme has long been employed in this α-substituted-α-amino acid field, for example, homoaspartic acid[40a] DL-C-methylasparagine[40b] α-methyl-DL-aspartic acid,[9] α-methyl-L-serine,[24] DL-α-methylhistidine[40c] and L-(−)-α-methyl-3,4-dimethoxyphenylalanine.[40d] The present authors should like to propose the general nomenclature scheme of these amino acids including the designation of the absolute configuration. First, an L-α-substituted amino acid, such as L-(+)-α-methylaspartic acid, is the one in which a hydrogen at α position of a protein-derived L-amino acid is replaced by a substituted group with the retention of absolute configuration, regardless the biochemical activity, and a prefix D or L is to be used before the trivial name which is combined with the α-substituted group, and if an additional symbol to denote the direction of rotation is required, a plus or a minus sign enclosed in parentheses should be put immediately before the trivial name. Secondly, if the α-substituent and/or the chemical structure of the stem amino acid are complicated, the absolute configuration should be based on the Cahn-Ingold-Prelog *R* and *S* convention*[8] and moreover, in the case where a trivial name is applied to a α-substituted amino acid, *i.e.* isovaline, the absolute configuration should be also based on *R* and *S* convention. In this respect, (+)-isovaline, determined above, is represented as *S*(+)-isovaline.



XLII

And this is the first report to determine the absolute configuration of tertiary carbinamine skeleton XLII by a direct correlation with

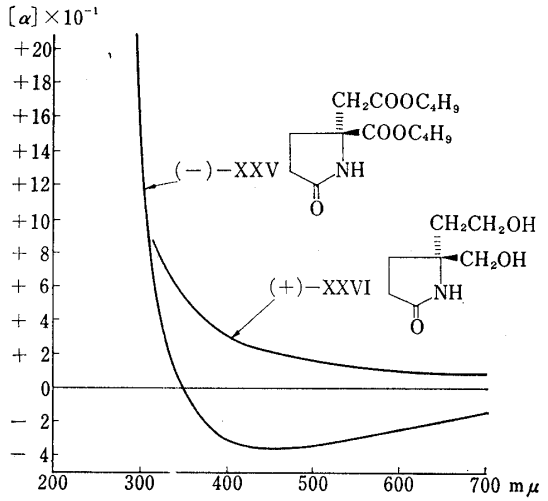


Fig. 4. Optical Rotatory Dispersion Curves of (−)-XXV (in benzene) and (+)-XXVI (in methanol)

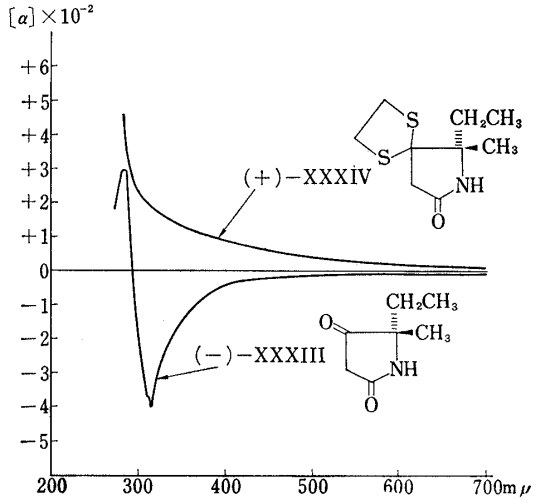


Fig. 5. Optical Rotatory Dispersion Curves of (−)-XXXIII (in methanol) and (+)-XXXIV (in methanol)

*[8] For a full discussion of the *R* and *S* notation for defining absolute configuration, see R. S. Cahn, C. K. Ingold, V. Prelog : Experientia, **12**, 81 (1956).

40) *a*) P. Pfeiffer, E. Heinrich : J. prakt. Chem., **146**, 105 (1936). *b*) G. Adembri, M. Ghelardoni : Gazz. chim. ital., **89**, 1763 (1959). (C. A., **55**, 4371[e] (1961)). *c*) B. Robinson, D. M. Shepherd : J. Chem. Soc., **1961**, 5037. *d*) H. L. Slates, D. Taub, C. H. Kuo, N. L. Wendler : J. Org. Chem., **29**, 1424 (1964).

glyceraldehyde. ORD spectra of some tertiary carbinamine type compounds are shown in Figs. 1, 2, 4 and 5.

Experimental*9

D(−)-Quinic Acid (XI)——This compound was purchased from Tokyo Kasei Co., Ltd., m.p. 164～166°. IR ν_{max}^{KBr} cm^{-1} : 3529, 3400, 3360 (OH), 2600～2500 (COOH), 1686 (-COOH), 1082, 1065, 1057.

(−)-4,5-O-Isopropylidene-1, 3, 4, 5-tetrahydroxy-1-cyclohexanecarboxylic Acid γ-Lactone ((−)-XII)——This compound was synthesized according to the method of Eberle, *et al.*,[34] m.p. 137～138° (crude product), in 77.3% yield. Recrystallization from a mixture of AcOEt and *n*-hexane gave (−)-XII, colorless needles, m.p. 140～141°, $[\alpha]_D^{15.5}$ −35.9°(c=2.12, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1} : 3480 (ν_{OH}), 1782 (5-membered lactone). *Anal.* Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found : C, 55.89, H, 6.43 (Lit., m.p. 142～143°, $[\alpha]_D$ −32° (c=1.6, $CHCl_3$),[34] m.p. 140～141°, $[\alpha]_D^{18}$ −36.6° (acetylene tetrachloride)).[41]

(−)-4,5-O-Isopropylidene-1,3,4,5-tetrahydroxy-1-cyclohexanecarboxylic Acid γ-Lactone 1-Acetate ((−)-XIII)——This compound was synthesized from (−)-XII and acetic anhydride in dry pyridine according to the method of Josephson,[35] colorless scales, m.p. 100～101°(ethyl ether-*n*-hexane), $[\alpha]_D^{33}$ −6.5°(c=1.174, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1} : 1795 (5-membered lactone), 1754 (acetyl). (Lit., m.p. 109°, $[\alpha]_D^{20}$ −4.4° ($CHCl_3$)).[35]

(+)-4,5-O-Isopropylidene-1,3,4,5-tetrahydroxy-1-cyclohexanecarboxylic Acid γ-Lactone 1-Benzoate ((−)-XIV)——This compound was synthesized from (−)-XII and benzoyl chloride in dry pyridine according to the method of Josephson,[35] colorless plates (ethanol), m.p. 137～138°, $[\alpha]_D^{33}$ +12°(c=0.96, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1} : 1800 (5-membered lactone), 1730 (benzoyl). (Lit., m.p. 140°)[35]

(+)-4,5-O-Isopropylidene-1,3,4,5-tetrahydroxy-1-cyclohexanecarboxylic Acid γ-Lactone 1-Tosylate ((+)-XV)——To a solution of (−)-XII (20 g., 0.094 mole) in dry pyridine (100 ml.) was added tosyl chloride (40 g., 0.21 mole) in small portions at room temperature. It was then shaken until the crystals dissolved, and was kept standing for 7 days. Crystals appeared again. The reaction mixture was poured onto ice-water (1 L.), to give an oily substance which soon solidified. Recrystallization from a benzene-hexane mixture afforded colorless pillars (33.6 g., 97.1%), m.p. 96～97°, $[\alpha]$ +23.1°(c=2.54, benzene). IR ν_{max}^{KBr} cm^{-1} : 1809 (5-membered lactone), 1599 (arom.), 1352, 1174 (-SO_3R), 814 (*p*-disubstituted benzene). *Anal.* Calcd. for $C_{17}H_{20}O_7S$: C, 55.45, H, 5.47. Found : C, 55.55; H, 5.27.

(−)-1-Amino-3,4,5-trihydroxy-1-cyclohexanecarboxylic Acid ((−)-XVII)——A suspension of O-tosyl derivative (+)-XV (150 g., 0.407 mole) in EtOH (1 L.) was saturated with NH_3 under cooling, to give a clear solution. This was kept standing for 2 days at room temperature and EtOH was removed *in vacuo*. The residual caramel was dissolved in 50% aq. EtOH, and the solution was passed through a column of Amberlite IR-120 (H-form) (1 L.). After washing with 50% aq. EtOH, the amine was eluted with 10% NH_4OH (2 L.). Evaporation of the eluate *in vacuo* gave a residue, which was hydrolyzed with $Ba(OH)_2 \cdot 8H_2O$ (180 g.) in H_2O (800 ml.) by heating on a water bath for 8 hr. The reaction mixture was passed through a column of Amberlite IR-120 (H-form) (1 L.) and, after being washed with H_2O until the effluent became neutral, the amino acid was eluted with 10% NH_4OH (2 L.), and the eluate was evaporated to give the crude amino acid (−)-XVII. Recrystallization of the product from aq. EtOH gave needles (44.5 g., 52.9%), m.p. 252～253.5° (decomp.). Further recrystallization from the same solvent afforded pure (−)-XVII, m.p. 260～261° (decomp.), $[\alpha]_D^{24}$ −65.0°(c=0.5, H_2O). *Anal.* Calcd. for $C_7H_{13}O_5N \cdot H_2O$: C, 40.19; H, 7.23; N, 6.70. Found : C, 39.90; H, 6.84; N, 6.72. The amino acid showed a single spot developed by two different solvent systems on paper chromatography. Solvent system : *n*-BuOH-CH_3COOH-H_2O=4:1:1, Rf value 0.11, *n*-BuOH-CH_3COOH-H_2O =4:1:2 (v/v), Rf value 0.22 (Toyo Roshi No. 50. filler paper, 17 hr.), IR ν_{max}^{KBr} cm^{-1} : 3469 (ν_{OH}), 2915 (NH_3^+), 1657 (NH_3^+), 1607 (COO^-).

(−)-1-Acetamido-3,4,5-trihydroxy-1-cyclohexanecarboxylic Acid ((−)-XVIII)——To the solution of the amino acid (−)-XVII (9.0 g., 0.043 mole) in a mixture of pyridine (80 ml.) and H_2O (100 ml.) was added Ac_2O (15 ml.) at room temperature. The mixture was stirred for 7 hr., evaporated *in vacuo* and the residue dissolved in H_2O (100 ml.) was passed through a column of Amberlite IR-120 (H-form) (100 ml.) which was washed with H_2O. The effluent and washings were evaporated to dryness (7.0 g.) *in vacuo*. The residue was recrystallized from aq. EtOH to give colorless pillars (4.9 g.), m.p. 193～194° (decomp.). An additional crop (1.2 g.) of (−)-XVIII was obtained from the mother liquor, m.p. 189～190° (decomp.). Total yield, 5.1 g. (51%). $[\alpha]_D^{29}$ −92.3°(c=0.234, MeOH). *Anal.* Calcd. for $C_6H_{15}O_6N$: C, 46.35; H, 6.48; N, 6.01. Found : C, 46.22; H, 6.89; N, 6.14. IR ν_{max}^{KBr} 3469, 3394 (ν_{OH}), 3270 (ν_{NH}), 2800～2500, 1707 (-COOH), 1638, 1533 (-CONH-), 1072, 1053.

*9 All melting points were uncorrect. IR spectra measurements were carried out with a Spectrophotometer, Model. DS-301 equipped with NaCl optics. Nippon Bunko Co., Ltd. Optical activities were measured with a Yanagimoto Photo Magnetic Direct Reading Polarimeter, Model OR-20 and an automatic recording ORD/UV-5. Gas chromatographic analysis were carried out with a Shimadzu Gas Chromatograph Model GC-IB with hydrogen flame detector.

41) H. O. L. Fischer : Ber., **45**, 775 (1921).

The unreacted amino acid (−)-XVII was recovered from a column of Amberlite IR-120 by elution with 10% NH_4OH. The effluents were collected and evaporated *in vacuo* to give the starting amino acid. Recrystallization from aq. EtOH gave needles (2.4g., 27%), m.p. 255～256° (decomp.). The IR spectrum and Rf value of this material were completely identical with the starting material.

(+)-1-Acetamido-3,4,5-trihydroxy-1-cyclohexanecarboxylic Acid γ-lactone ((+)-XIX). A) from (−)-XVIII——A mixture of (−)-XVIII (0.5 g., 0.0021 mole) and dicyclohexylcarbodiimide (0.5 g., 0.002 mole) in dry pyridine (20 ml.) was refluxed for 5 hr. and concentrated to a volume of one third and it was kept standing overnight. The crystallized dicyclohexylurea (ca. 0.53 g.) was filtered off and the mother liquor was evaporated to dryness *in vacuo*. Recrystallization from EtOH gave (+)-XIX (280 mg., 61%), m.p. 202～204° (decomp.). Further recrystallization from EtOH gave colorless prisms, m.p. 206～207.5°, $[\alpha]_D^{19}$ +5.3° (c=0.524, EtOH). *Anal.* Calcd. for $C_9H_{13}O_5N$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.13; H, 6.03; N, 6.51. IR ν_{max}^{KBr} cm^{-1}: 3536, 3407, 3224 (ν_{OH}, ν_{CONH-}), 1788 (5-membered lactone), 1661, 1533 (amide).

B) from (−)-XX——A mixture of (−)-XX (2.0 g., 0.008 mole) and 80% CH_3COOH (v/v) (20 ml.) was heated on a water bath for an hour and then evaporated to dryness *in vacuo*. The residue was washed with EtOH–ether (1:1) (12 ml.) to give crude (+)-XIX (1.2 g., 71%), m.p. 205～207° (decomp.). Recrystallization from EtOH afforded colorless prisms, m.p. 206～207.5° (decomp.). IR spectra of (+)-XIX obtained from both A and B were completely imposed.

(−)-1-Acetamido-3,4-O-isopropylidene-3,4,5-trihydroxy-1-cyclohexanecarboxylic Acid γ-Lactone ((−)-XX)——To a suspension of (+)-XIX (1.0 g.) in anhyd. acetone (10 ml.) was added conc. H_2SO_4 (0.2 ml.), and the whole was stirred for 4 hr. at room temperature (at 15°) and diluted with $CHCl_3$ (400 ml.). The organic layer was washed with aq. Na_2CO_3 and H_2O, and dried over Na_2SO_4. $CHCl_3$ was evaporated *in vacuo* to give a solid (920 mg., 78%), m.p. 197～198°. Recrystallization from $CHCl_3$–Et_2O afforded (−)-XX as prisms, m.p. 198～199°, $[\alpha]_D^{30}$ −14.7° (c=0.19, MeOH). *Anal.* Calcd. for $C_{12}H_{17}O_5N$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.38; H, 6.41; N, 5.66. IR ν_{max}^{KBr} 3367 (ν_{NH}), 1780 (5-membered lactone), 1684, 1537 (amide).

(−)-2-Butoxycarbonyl-5-oxo-5-pyrrolidineacetic Acid Butyl Ester ((−)-XXV)——To a solution of amide-lactone ((+)-XIX) (4.0 g., 0.019 mole) in H_2O (65 ml.) was added $HIO_4 \cdot 2H_2O$ (5.0 g., 0.022 mole) at room temperature. It was kept standing for 7 hr., Br_2 (10 ml.) was added to the solution to oxidize dialdehyde (XXI), and without separation, the reaction mixture was after standing for 2 days, concentrated, and treated with 57% HI (100 ml.) and red P (5 g.). The whole was refluxed for 20 hr. in an oil bath and then evaporated to dryness. The residue was dissolved in H_2O (100 ml.) and the unreacted red P was filtered off. The filtrate was passed through a column of ion exchanger Amberlite IR-120 (H-form) (300 ml.) which was washed with H_2O until the effluent became neutral. The amino acid (XXIII) was eluted with 10% NH_4OH from a column. The effluents were collected and evaporated to dryness to give powdery residue (ammonium salt of XXIII) (2.6 g.). To the suspension of the residue in *n*-BuOH (50 ml.) was added $SOCl_2$ (15 g.) and it was stirred for 30 min. at room temperature, refluxed for 4.5 hr. and subsequently *n*-BuOH was removed *in vacuo* to give an oily residue which was dissolved in ether. The ethereal solution was washed with 10% $NaHCO_3$, H_2O, being dried over Na_2SO_4 and distilled at $b.p_5$ 190～195° (1.8 g.). The distillate contained three substances which were separated by chromatography on silicic acid (50 g.) employing benzene or 50% ether–benzene (v/v) as eluting solvent systems. The eluate (50 ml.) was collected in each fraction. The results are listed in Table II. Substance A, B and C were redistilled, respectively.

Table II. Chromatographic Results of Crude (−)-XXV

Fraction No.[a]	Elution solvent	Substances obtained[b]	Rt[c] (min.)
1～15	benzene		
16～17	ether–benzene (1:1)	substance A (300 mg.)	9.6
22～25	〃	substance C (313 mg.)	11.2
28～38	〃	substance B (653 mg.)	10.7

a) Fifty milliliter each of the eluate was collected as a fraction.
b) Each fraction was examined by gas chromatography.
c) Column, 1.5% SE-30 on Chromosorb W (60～80 mesh) 2.25 m.×4 mm. Sample heater temp., column temp. and detector temp. were 340°, 201° and 240° respectively, and carrier gas (N_2) flow rate was 20 ml./min. at 2 kg./cm^2.

Substance B gave (−)-XXV, $b.p_{4.5}$ 199～201°, a colorless oil (560 mg., 10% based on (+)-XIX), ORD $[\alpha]^{21}$(mμ) (c=0.576, benzene): −17°(700), −28°(589), −35°(500), −38°(450), −35°(400), −10°(350), 0°(345), +143°(300), +229°(290). IR ν_{max}^{cap} cm^{-1}: 3460, 3276 (ν_{NH}), 1749, 1742 (ester), 1718 (5-membered lactam). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3423 (ν_{N-H}), 1744, 1731 (ester), 1713 (5-membered lactam). *Anal.* Calcd. for $C_{15}H_{25}O_5N$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.53; H, 8.33; N, 4.92.

Substance A (XXXVIII): $b.p_{5.0}$ 180～181°, a colorless oil (270 mg., 5.0% based on (+)-XIX), ORD (700～300 mμ), $[\alpha]^{25}$ 0° (c=0.5, benzene). IR ν_{max}^{cap} 1747 (ester), 1727 (conjugated ester), 1659 (conjugated double bond). *Anal.* Calcd. for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 62.90; H, 8.61.

Substance C (XXXIX): b.$p_{5.0}$ 180~183°, a colorless oil (160 mg., 2.4% based on (+)-XIX). ORD (700~300 mμ), $[\alpha]^{26}$ 0°(c=0.94, benzene). IR ν_{max}^{cap} cm^{-1}: 3393, 3380 (ν_{NH_2}), 1741 (ester). *Anal.* Calcd. for $C_{18}H_{33}O_6N$: C, 60.14; H, 9.25; N, 3.90. Found: C, 60.22, H, 9.28, N, 3.79.

(+)-5-Hydroxyethyl-5-hydroxymethyl-2-pyrrolidinone ((+)-**XXVI**)——A solution of pyrrolidinone ester (−)-XXV (4.5 g., 0.015 mole) in EtOH (40 ml.) was added to a solution of $NaBH_4$ (2.3 g., 0.06 mole) in EtOH (60 ml.) which was refluxed for 7 hr. The reaction mixture was diluted with H_2O (100 ml.) and passed through a column of Amberlite IR-120 (H-form) (100 ml.) which was washed with 50% aq. EtOH. The effluent and washings were collected and concentrated *in vacuo* to give crystalline residue to which EtOH (30 ml.) was added and concentrated repeatedly *in vacuo* to remove boric acid. The residual oil (2.5 g.) was purified by chromatography on silicic acid (75 g.) employing 20% EtOH-$CHCl_3$ (v/v) as an eluting solvent system. The eluate (25 ml.) was collected as each fraction. The fractions from No. 25 to No. 45 gave, after evaporation of the solvents, a pure diol (+)-XXVI (1.86 g., 78%), as a colorless oil which exhibited one spot by thin-layer chromatography (Kiegel G, solvent 20% EtOH-$CHCl_3$, Rf-value 0.29). IR ν_{max}^{cap} cm^{-1}: 3329 (broad) (ν_{OH}), 1674 (5-membered lactam), 1054 (C-O). ORD $[\alpha]^{26}$(mμ) (c=1.90, MeOH): +8°(700 mμ), +10°(589), +16°(500), +31°(400), +51°(350), +88°(310).

Di-*p*-nitrobenzoate, needles, m.p. 191~192° from $CHCl_3$-ether. *Anal.* Calcd. for $C_{21}H_{19}O_9N_3$: C, 55.14; H, 4.19; N, 9.19. Found: C, 54.91; H, 4.08; N, 9.08. IR ν_{max}^{KBr} cm^{-1}: 1727 (ester), 1704 (5-membered lactam), 1605 (arom.), 1529, 1350 (nitro), 1297 (ester). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3418 (ν_{NH}), 1729 (ester), 1700 (5-membered lactam), 1607 (arom.), 1528, 1352, 1280, 1113, 1104, 1015, 871.

5-Bromoethyl-5-bromomethyl-2-pyrrolidinone (**XXVII**)——A mixture of pyrrolidinone diol (+)-XXVI (1.6 g., 0.01 mole) and PBr_5 (13 g., 0.03 mole) was stirred at 120° for 3 min., PBr_5 dissolved and a homogeneous solution was obtained under an evolution of HBr. After cooling, ether (100 ml.) was added and the ethereal solution was shaken with $NaHCO_3$ solution, washed with H_2O, dried over Na_2SO_4. Evaporation of ether gave crude XXVII as a brownish oil (2.46 g.) which was used for the subsequent step without purification.

5-Phenylthioethyl-5-phenylthiomethyl-2-pyrrolidinone (**XXVIII**)——Dibromide derivative XXVII (2.46 g., 0.009 mole) was refluxed in dimethylformamide (50 ml.) with φSNa (prepared from Na (450 mg., 0.019 mole) and φSH (2.1 g., 0.019 mole) in abs. CH_3OH) for 9.5 hr. under N_2 atmosphere. The solvent was removed *in vacuo*, the residue dissolved in H_2O was extracted with $CHCl_3$ (50 ml.×2). The combined $CHCl_3$-layer was washed with H_2O, dried over Na_2SO_4, and concentrated to give a brownish oil XXVIII (3.2 g.) which was used for the following steps without purification.

(+)-5-Ethyl-5-methyl-2-pyrrolidinone ((+)-**XXIX-A**)——A mixture of crude thioether XXVIII (3.2 g.) and Raney Ni[42] (50 ml.) in EtOH (20 ml.) was refluxed for 5 hr. After filtration of Raney Ni, the solvent was evaporated to give an oil which was taken in ether. Ethereal layer was washed with H_2O, dried over Na_2SO_4 and distilled at b.$p_{7.0}$ 120~122° to give an oil (+)-XXIX-A (480 mg., 38% based on XXVI). Redistillation gave pure (+)-XXIX-A as a colorless oil, b.$p_{15.5}$ 135~138°, IR ν_{max}^{cap} 3436 (sh), 3264 (broad) (ν_{NH}), 1695 (5-membered lactam), 1461, 1423, 1386, 1368 (sh), 1337, 1298, 1248, 1223, 1193, 1166, 1151, 1112, 1060, 999, 952, 917, 886, 822, 790 (broad). ORD $[\alpha]^{29}$(mμ) (c=0.56, benzene): +7°(700), +9°(589), +13°(500), +21°(400), +30°(350), +49°(300). *Anal.* Calcd. for $C_7H_{13}ON$: C, 66.10; H, 10.30; N, 11.01. Found: C, 65.83; H, 10.03; N, 11.35.

(+)-Isovaline ((+)-**VIII**)——Racemic modification was resolved into antipodes according to the procedure of Fischer, *et al.*[38] Monohydrate $[\alpha]_D^{28}$ +6.7°(c=1.86, H_2O). Anhydride was used as a starting material after drying over 120°, 5 mm. Hg.

(+)-Isovaline Ethyl Ester ((+)-**XXX**)——To a suspension of anhydrous (+)-isovaline (7.0 g.) in anhyd. EtOH was added $SOCl_2$ (14 g.) dropwise, isovaline gradually dissolved. The whole was refluxed for 6 hr. After being kept standing overnight, EtOH was removed *in vacuo*, and anhyd. $CHCl_3$ (200 ml.) saturated with NH_3 was added to the residue. The separated NH_4Cl was filtered off and the filtrate was evaporated and distilled, b.$p_{20~30}$ 75~80° to give colorless liquid (+)-XXX (5.1 g., 59%). ORD $[\alpha]^{30}$(mμ) (c=1.75, benzene): +1°(700), +2°(589), +3°(500), +7°(400), +11°(350), +29°(300). IR ν_{max}^{cap} cm^{-1}: 3379, 3342 (ν_{NH_2}), 1730 (ester), 1600 (δ_{NH_2}), 1245, 1145 (ester). *Anal.* Calcd. for $C_7H_{15}O_2N$: C, 57.90; H, 10.41; N, 9.65. Found: C, 57.78; H, 10.88; N, 9.37. Picrate, m.p. 145~146° from EtOH (a small amount)-benzene, pale yellow needle. IR ν_{max}^{KBr} cm^{-1}: 3000 (broad) (NH_3^+), 1740 (ester). *Anal.* Calcd. for $C_7H_{15}O_2N \cdot C_6H_3O_7N_3$: C, 41.71; H, 4.85; N, 14.97. Found: C, 41.85; H, 4.82; N, 14.96.

(+)-N-(Ethoxycarbonylacetyl)isovaline Ethyl Ester ((+)-**XXXI**)——Malonic ester chloride (11 g., 0.069 mole) was added dropwise to a solution of amino ester (+)-XXX (5.0 g., 0.0345 mole) in anhyd. acetone (100 ml.) in the presence of anhyd. K_2CO_3 (19.5 g., 0.139 mole). It was refluxed for 6 hr., and kept standing overnight. Acetone was removed *in vacuo* to give an oily residue which was diluted with H_2O (100 ml.) and extracted with ether (200 ml.). The ethereal layer was washed with NaCl satd. H_2O, 10% HCl and NaCl satd. H_2O successively, dried over Na_2SO_4, and concentrated. Distillation of a residual oil gave (+)-XXXI (7.7 g., 86%) as a colorless oil, b.$p_{5.5}$ 154~156°. IR ν_{max}^{cap} cm^{-1}: 3360 (ν_{NH}), 1740 (ester), 1658, 1548 (amide), 1259 (ester). ORD $[\alpha]^{28}$(mμ) (c=2.096, benzene): +3°(700); +5°(589), +8°(500), +13°(400), +18°(350).

42) R. Mozingo, D. E. Wolf, S. A. Harris, K. Folkers: J. Am. Chem. Soc., **65**, 1013 (1943).

+23°(330). ORD $[\alpha]^{11.5}$(mμ)(c=0.404, MeOH): −3°(700), −4°(589), −6°(500), −12°(400), −19°(350), −36°(300), −113°(250). ORD $[\alpha]^{12}$(mμ)(c=0.348, $CHCl_3$): +4°(589), +6°(500), +11°(400), +15°(350), +24°(300), +28°(266), +16°(250). *Anal.* Calcd. for $C_{12}H_{21}O_5N$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.20; H, 8.22; N, 5.35.

(−)-5-Ethyl-5-methyl-2,4-pyrrolidinedione ((−)-XXXIII)——To a suspension of 50% NaH in oil(3.5 g., 0.072 mole) in anhyd. dioxane (100 ml.) was added (+)-XXXI (7.5 g., 0.029 mole) dropwise with stirring. The whole was stirred at room temperature for 30 min. and refluxed for 13.5 hr. After being kept standing overnight, the solvent was removed *in vacuo*, and under cooling, H_2O (100 ml.) was added to the residue, then extracted with benzene (100 ml.). Benzene layer was washed with H_2O (50 ml.×2) and the aq. layer and washings were made acidic with conc. HCl and extracted with $CHCl_3$ (200 ml.). The $CHCl_3$ layer was washed with NaCl satd. H_2O, dried over Na_2SO_4, and concentrated. Distillation of residual oil gave (−)-XXXIII as a faint yellow viscous oil (1.5 g., 37%), b.p_{10} 135～155°, which solidified into crystalline product, m.p. 88～90°. During the distillation, an evolution of gas was observed. Recrystallization from benzene-isopropyl ether gave colorless prisms, m.p. 105～106°. IR ν_{max}^{KBr} cm^{-1}: 3236 (ν_{OH}), 2500～2290, 1920 (⩾NH^+), 1662 (C=$\overset{+}{N}$-), 1591 (conjugated-C=C-), 793 $\left(>C=C<_{H}\right)$. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3411, 3238 (ν_{NH}), 1771 (5-membered lactone), 1702 (5-membered lactam). ORD $[\alpha]^{31}$(mμ)(c=0.118, MeOH): −21°(589), −38°(400), −127°(350), −331°(320), −394°(315) (trough), −356°(312)(peak), −372°(308)(trough), 0°(294), +305°(280)(peak), +178°(270). *Anal.* Calcd. for $C_7H_{11}O_2N$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.72; H, 7.96; N, 10.02.

(+)-5-Ethyl-5-methyl-4,4-ethylenedithiopyrrolidine ((+)-XXXIV)——To a mixture of the keto amide (−)-XXXIII (3.0 g., 0.021 mole) in ethylene dithiol (6 ml.) was added $BF_3\cdot(C_2H_5)_2O$ (6.0 g.) under stirring at room temperature. A slight exothermic reaction occurred to give a homogeneous solution and it was maintained between 90～100° for 5 hr. The mixture became slightly a reddish transparent solution. $BF_3\cdot(C_2H_5)_2O$ was removed *in vacuo*, and the residual oil was chromatographed on Al_2O_3 (150 g.) and eluted with 5% EtOH-benzene (v/v). Each eluate (25 ml.) was collected as a fraction. The fractions from No. 5 to No. 12 were combined and evaporated to dryness. The residue was washed with ether-isopropyl ether to give white crystals (+)-XXXIV (1.0 g., 22%), m.p. 160～163°. Recrystallization from EtOH-isopropyl ether gave scales, m.p. 171～171.5°. ORD $[\alpha]^{28}$(mμ)(c=0.31, MeOH): +9°(700), +13°(589), +34°(500), +81°(400), +230°(300), +440°(280). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3422, 3245 (ν_{NH}), 1711, 1698 (5-membered lactam). *Anal.* Calcd. for $C_9H_{15}ONS_2$: C, 49.76, H, 6.96 N, 6.45, S, 29.46. Found: C, 50.17; H, 7.15; N, 6.09; S, 29.39.

(+)-5-Ethyl-5-methyl-2-pyrrolidinone ((+)-XXIX-B)——A mixture of (+)-XXXIV (960 mg., 0.0044 mole) and Raney Ni[42] (10 ml.) in EtOH (80 ml.) was refluxed on a water bath for 5 hr. Raney Ni was filtered off, filtrate was concentrated *in vacuo* to give residual oil which was again dissolved in benzene (100 ml.). The benzene layer was washed with H_2O saturated with NaCl and dried over Na_2SO_4. The solvent was removed and the residue was distilled to give (+)-XXIX-B (370 mg., 66%) as a colorless oil, b.$p_{11.5}$ 130～135°. $[\alpha]_D^{29}$ +5.7°(c=0.848, benzene). IR ν_{max}^{cap} cm^{-1}: 3436 (sh), 3262 (ν_{NH}), 1695 (5-membered lactam), 1462, 1425, 1387, 1337, 1298, 1248, 1223, 1190, 1165, 1151, 1111, 1059, 998, 951, 918, 856, 822, 790. ORD $[\alpha]^{32}$(mμ)(c=0.848, benzene): +5°(700), +6°(589), +9°(500), +14°(400), +18°(350), +31°(300).

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Summary

The absolute configuration of (+)-isovaline ((+)-Ⅷ) was correlated with D-(−)-quinic acid ((−)-Ⅺ) by leading to (+)-5-ethyl-5-methyl-2-pyrrolidinone ((+)-XXIX-A and B) from (+)-isovaline and D-(−)-quinic acid. It was recommended that (+)-isovaline should be shown by the formula Ⅸ or Ⅹ, that is, *S*(+)-isovaline. The solvent effects on ORD curves of (+)-XXXI were also observed.

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