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224. Hatsuhiko Mizuno, Shiro Terashima, Kazuo Achiwa, and Shun-ichi Yamada*1 : Studies on Optically Active Amino Acids. XIV.*2 Studies on α-Alkyl-α-amino acids. VII.*3 Determination of Absolute Configuration of Optically Active α-Methylphenylglycine and 1-Methyl-1-phenylpropylamine.*4

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The absolute configuration of (+)-α-methylphenylglycine was proved to be S series by the chemical correlation with R(−)-isovaline. Chemical scheme employed was shown in Chart 1. Moreover, in the course of the chemical correlation, the absolute configuration of (+)-1-methyl-1-phenylpropylamine was also proved to be R series. Preliminary experiments using racemic compounds were also described.

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The absolute configuration of (+)-isovaline ((+)-I)[1] has been unequivocally estalished in our laboratory by chemical correlation with D-(−)-quinic acid whose absolute configuration had been clearly demonstrated. Subsequently, the absolute configurations of (+)-α-methylaspartic acid ((+)-II),[2] (−)-α-methyl-3,4-dihydroxyphenylalanine ((−)-III)[2] and (−)-α-methylphenylalanine hydrochloride ((−)-IV)[3] have also been determined by chemically correlating them with S(+)-I.*5

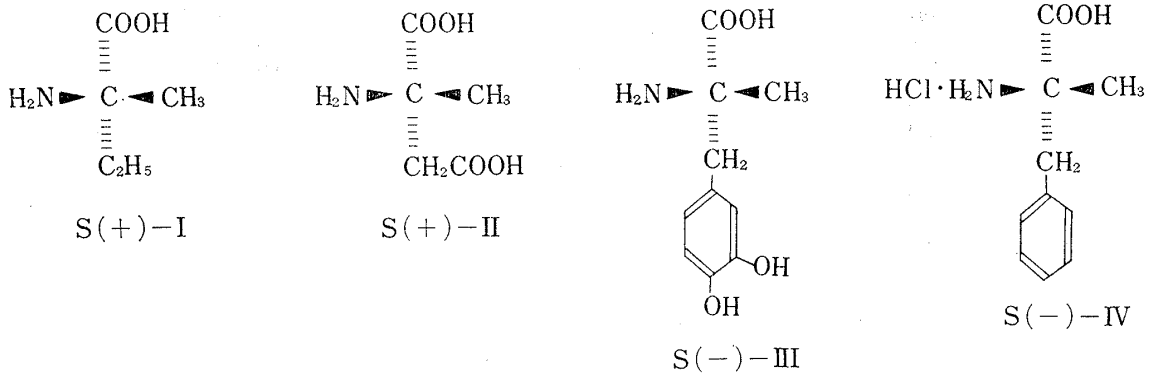

Fig. 1.

It is the present purpose to present the establishment of the absolute configuration of optically active α-methylphenylglycine (V), one of the important α-methyl-α-amino acids by chemical correlation with S(+)-I, by way of 1-methyl-1-phenylpropylamine. Optically active α-methylphenylglycine (V) was first resolved by McKenzie, *et al.*[4] in 1912,

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*2 Part XIII : This Bulletin, **15**, 350 (1967).
*3 Part VI : *Ibid.*, **14**, 1138 (1966).
*4 This work was presented at the 86 th Annual Meeting of Pharmaceutical Society of Japan, October, 1966, Sendai.
*5 For the expression of the absolute configurations of amino acids in this series, we have proposed to use the Cahn-Ingold-Prelog R and S convention (K. Achiwa, S. Yamada : This Bulletin **14**, 537 (1966)).

1) S. Yamada, K. Achiwa : *Ibid.*, **12**, 1525 (1964). K. Achiwa, S. Yamada : *Ibid.*, **14**, 537 (1966).
2) *a*) S. Yamada, S. Terashima, K. Achiwa : *Ibid.*, **13**, 227 (1965). *b*) S. Terashima, K. Achiwa, S. Yamada : *Ibid.*, **14**, 572 (1966). *c*) *Idem* : *Ibid.*, **14**, 579 (1966).
3) *Idem* : *Ibid.*, **14**, 1138 (1966).
4) A. McKenzie, G.W. Clough : J. Chem. Soc., **101**, 390 (1912).

and since then this amino acid has often been employed as the substrate[5~9] on the various kinds of stereochemical studies because of its chemical structure having an asymmetric center at the benzyl position. However, its absolute configuration has not yet been clearly established and only suggestive, curiously, the opposite suggestions on the absolute configuration of the same optically active V were proposed. That is, Maeda[6] suggested the positive isomer as R-series,*6 wihle Cram, *et al.*[7] proposed the same isomer as S series by Freudenberg's displacement rule and carbanion reaction mechanism, our group[9] also proposed the positive isomer to be the same absolute configuration as

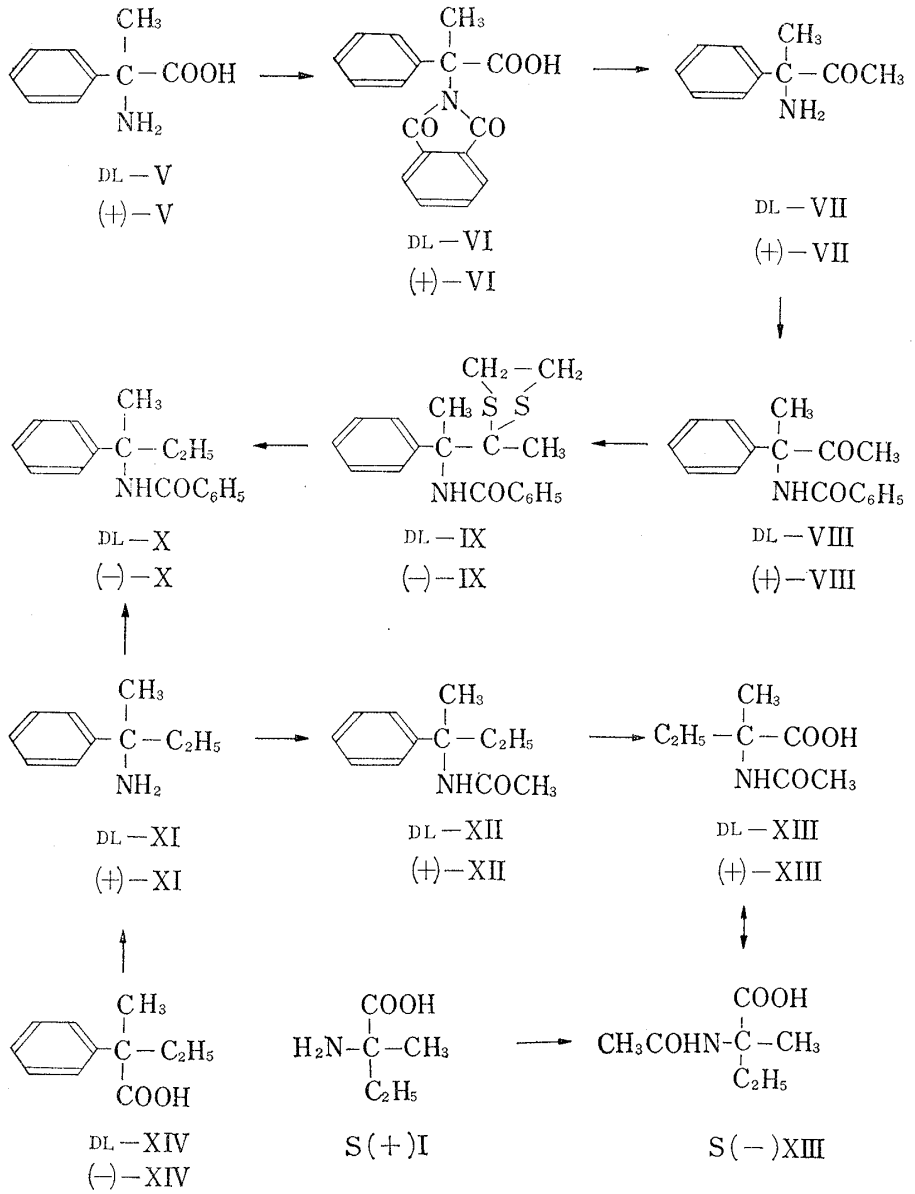


Chart 1.

*6 In reference 6), this amino acid was written as D(+)-α-amino-α-phenylpropionic acid $[\alpha]_D^{18}$ +70.3°(H_2O), and considering the reaction mechanism proposed in this paper, the present author supposed this amino acid to be R series.

5) A. McKenzie, J.R. Myles: Chem. Ber., **65**, 209 (1932).
6) G. Maeda: Nippon Kagaku Zasshi, **77**, 1011 (1956).
7) D.J. Cram, L.K. Gaston, H. Jäger: J. Am. Chem. Soc., **83**, 2183 (1961).
8) S. Mitsui, E. Sato: Nippon Kagaku Zasshi, **86**, 416 (1965).
9) S. Yamada, S. Terashima, K. Achiwa: This Bulletin, **14**, 800 (1966).

Cram, *et al.* by the reaction mechanism of thermal decomposition on azidoformate.

As described above, even though optically active V has long been recognized, its absolute configuration is still under question. In our laboratory the clear establishment of the absolute configuration of optically active V is urgent for our rearrangement studies at the asymmetric center of carbinamine type compounds in addition to the mentioned reasons.

We undertook the determination of the absolute configuration of optically active V by chemical correlation with S(+)-I following the route as shown in Chart 1.

According to Akabori's[11] method, DL-α-methylphenylglycine (DL-V) prepared from acetophenone,[10] was converted to N-formyl-DL-α-methylphenylglycine which was resolved with quinine by McKenzie procedure,[4] and followed by hydrolysis to give (+)-V, m.p. >250°, $[\alpha]_D^{22}$+86.3° (*N*HCl). Only the following among various attempts to obtain methyl ketone derivative (VII) from V was successful. (+)-N-Phthaloyl-α-methylphenylglycine ((+)-VI) was obtained from the fusion of (+)-V with phthalic anhydride in 45% yield and identified as cyclohexylammonium salt, m.p. 218° (decomp.), $[\alpha]_D^{10.5}$+17.6° (CH_3COOH). Reflux of (+)-VI with thionyl chloride gave the corresponding acid chloride which was used in the subsequent experiment after the complete evaporation of excess thionyl chloride. (+)-3-Amino-3-phenyl-2-butanone ((+)-VII) was obtained in the acylation of the ethoxymagnesium salt of diethyl malonate with the above mentioned acid chloride, followed by acid hydrolysis, decarboxylation of the resulting β-keto diester and simultaneous dephthaloylation. (+)-VII was a colorless oil, α_D^{10}+5.1° (l=0.1, neat), and the yield was 26% based on (+)-VI. The reaction of (+)-VII with benzoyl chloride in pyridine gave (+)-3-benzamido-3-phenyl-2-butanone ((+)-VIII) as colorless prisms m.p. 113~114.5°, $[\alpha]_D^{14.5}$+15.9° (C_2H_5OH), which was followed by thioketalization with ethanedithiol and boron trifluoride etherate to give (−)-3-benzamido-3-phenyl-2-butanone ethylenedithioketal ((−)-IX), m.p. 118~119°, $[\alpha]_D^{19}$−119° (C_6H_6). Desulfurization of (−)-IX with Raney Ni in anhyd. ethanol gave (−)-2-benzamido-2-phenylbutane ((−)-X), m.p. 108~108.5°, $[\alpha]_D^{17}$−22.9° (C_2H_5OH) in 47% yield.

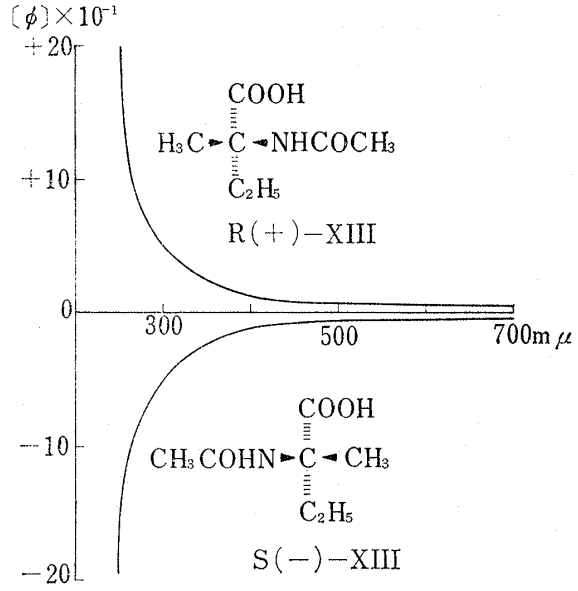


Fig. 2. Optical Rotatory Dispersion Curves of R(+)- and S(−)-N-Acetyl-isovaline (R(+)-XIII and S(−)-XIII)

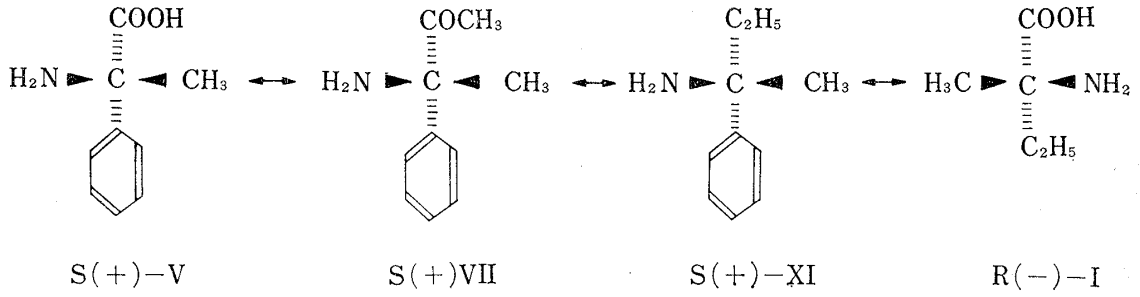
On the other hand, (+)-1-Methyl-1-phenylpropylamine ((+)-XI) was prepared from DL-2-methyl-2-phenylbutyric acid (DL-XIV) obtained according to the Bonner and Greenlee direction,[12] followed by the resolution[13] of DL-XIV with (−)-quinine and Curtius rearrangement of (−)-XIV by Cram's procedure.[14] The benzoylation of (+)-XI thus obtained gave (−)-X, m.p. 108~109°, $[\alpha]_D^{16}$−24.4° (C_2H_5OH) in 97% yield, which was identical with the one obtained from (−)-IX by the desulfurization with Raney Ni. Accordingly the absolute configuration of (+)-V was chemically correlated to (+)-XI.

(+)-2-Acetamino-2-phenylbutane ((+)-XII), m.p. 83~84°, $[\alpha]_D^{14}$+15.1° (benzene), obtained from (+)-XI with acetic anhydride in

10) "Org. Synth.," Coll. Vol., III, p. 88.
11) S. Akabori, T. Ikenaka, K. Matsumoto: Nippon Kagaku Zasshi, **73**, 112 (1952).
12) W.A. Bonner, T.W. Greenlee: J. Am. Chem. Soc., **81**, 3336 (1959).
13) E. Wallis, P. Bowman: J. Org. Chem., **1**, 383 (1936).
14) D.J. Cram, J.S. Bradshaw: J. Am. Chem. Soc., **85**, 1108 (1963).

pyridine was treated with ozone in acetic acid, and then with 30% hydrogen peroxide to give (+)-N-acetylisovaline ((+)-XIII), m.p. 188~189°, $[\alpha]_D^{19.5}$ +1.33° (methanol) in 19% yield. Since specific rotation of this compound, (+)-XIII, obtained from (+)-XII, was too small to get the accurate value at D line wave length, the ORD measurement was carried out from 700 mμ to 250 mμ. The ORD curve of (+)-XIII was found to be positive plain curve and completely antipodal with that of (−)-XIII obtained from S(+)-I, as shown in Fig. 2.

Consequently, the absolute configuration of (+)-α-methylphenylglycine ((+)-V) was proved to be S series as shown in Chart 2. It was found that Cram's and our suggestions on the absolute configuration of V were correct. In the course of the present study, (+)-1-methyl-1-phenylpropylamine ((+)-XI) was also proved to be R series. Optically active XI is supposed to be the important key compound from the point of absolute configuration. Cram, *et al.*[14] have proposed the absolute configuration of (+)-XI to be R series since the Curtius rearrangement of (−)-XIV whose absolute configuration is assumed to be R-series,[12,15,16] proceeded to (+)-XI under the retention of configuration.*7 As the consequence of our present experiments, Cram's proposal[14] was proved to be correct, and among the tertiary carbinamine type compounds 1-Methyl-1-phenylpropylamine (XI) is the first whose absolute configuration has been established clearly.



S(+)−V S(+)VII S(+)−XI R(−)−I

Chart 2.

Preliminary experiments about all reactions were carried out with racemic compounds in order to find out favorable reaction conditions before optically active compounds were attempted. The results obtained with racemic compounds are described in the experimental section.

Experimental*8

DL-α-Methylphenylglycine (DL-V) and Its N-Acetyl Derivative (DL-XV)——DL-V prepared from acetophenone[10] was treated with Ac_2O-pyridine as usual to give DL-XV in 90% yield. Recrystallization of DL-XV from aq. EtOH afforded the dimorphism. The one of them was colorless needles, m.p. 194~196°, which was obtained by rapid cooling, and the other obtained by slow cooling was colorless granules, m.p. 197.5~199° (lit.[17] m.p. 202~203°). These two DL-XV gave the different IR spectrum in a solid state respectively.

(+)-α-Methylphenylglycine ((+)-V) and Its (+)-N-Acetyl Derivative ((+)-XV)——N-Formyl-DL-α-methylphenylglycine prepared from DL-V according to Akabori method[11] was resolved with quinine[4] and

*7 It is well known that Curtius rearrangement of the compounds >CH-CONHNH$_2$ proceeds under the retention of configuration. However in the case of the compounds >C-CONHNH$_2$ that have no hydrogen atom at α-position, it is not evident whether Curtius rearrangement proceeds with the retention of configuration because of uncertainty of absolute configuration of tertiary carbinamide type compounds.

*8 All melting points are uncorrected. IR spectra measurements were performed with a Spectrometer, Model DS-402. Japan Spectroscopic Co., Ltd. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20.

15) D. J. Cram, J. Allinger : J. Am. Chem. Soc., **76**, 4516 (1954).
16) D. J. Cram, K. R. Kopecky, F. Hauck, A. Langemann : *Ibid.*, **81**, 5754 (1959).
17) R. L. Levene, R. E. Steiger : J. Biol. Chem., **93**, 581 (1931).

hydrolysed to (+)-V. Recrystallization from H_2O gave (+)-V as needles. (+)-V (m.p. >250°, $[\alpha]_D^{22}$ +86.3° (c=1.00, *N* HCl)) was treated as same as DL-V to give crude (+)-XV in 67% yield, m.p. 201~204°, $[\alpha]_D^{19.5}$ +47.2°(c=1.32, MeOH). After decolorization with charcoal, several recrystallizations from EtOH-*n*-hexane gave colorless prisms. m.p. 208~209°, $[\alpha]_D^{14}$ +47.1°(c=0.642, MeOH). *Anal.* Calcd. for $C_{11}H_{13}O_3N$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.83; H, 6.29; N, 6.59. IR ν_{max}^{KBr} cm^{-1}: 3373, 3351, 1713, 1612, 1515, 1303, 731, 697. IR spectrum of (+)-XV in a solid state was remarkably different from that of DL-XV.

N-Phthaloyl-DL-α-methylphenylglycine (DL-VI)——A mixture of DL-V (15.0 g., 0.0908 mole) and phthalic anhydride (20.2 g., 0.136 mole) was kept at 200° being molten for 1 hr., to the somewhat cooled reaction mixture was added MeOH (80 ml.). The whole was triturated and the undissolved material was filtered off. To the warm filtrate was added H_2O (120 ml.) and the clear solution was kept in a refrigerator overnight. Precipitated brown solid was filtered and recrystallized from Ac_2O-AcOH (1:4) to give DL-VI as yellow massive crystals (12.3 g., 46%), m.p. 182~185°(lit.[18] m.p. 186~187°, yield 47%). This DL-VI was used for next procedure.

(+)-N-Phthaloyl-α-methylphenylglycine ((+)-VI)——Crude (+)-VI was obtained from the fusion of (+)-V (m.p. >250°, $[\alpha]_D$ +84.6°(*N* HCl)*[9]) (17.2 g., 0.104 mole) and phthalic anhydride (23.1 g., 0.156 mole) followed by treatment with MeOH and H_2O as same as the case of DL-VI. This crude (+)-VI was dissolved in H_2O saturated with $NaHCO_3$, the undissolved material was filtered off, the filtrate was acidified with conc. HCl to separate out (+)-VI (13.8 g., 45%), m.p. 130~143°, $[\alpha]_D^{16}$+14.7°(c=1.13, EtOH). Because of unsuccessful recrystallization (+)-VI was converted to cyclohexylammonium salt. Pure cyclohexylammonium salt was obtained as colorless needles after several recrystallizations from H_2O-EtOH, m.p. 218°(decomp.), $[\alpha]_D^{10.5}$ +17.6°(c=1.00, AcOH). *Anal.* Calcd. for $C_{23}H_{25}O_4N_2$: C, 70.21; H, 6.40; N, 7.12. Found: C, 69.92; H, 6.61; N, 7.05. IR ν_{max}^{KBr} cm^{-1}: 1773, 1727, 1635, 1561, 723, 699.

DL-3-Amino-3-phenyl-2-butanone (DL-VII)——A mixture of DL-VI (17.7 g., 0.060 mole) and $SOCl_2$ (17 ml.) was refluxed for 1 hr. Then excess $SOCl_2$ was evaporated in reduced pressure under N_2 atmosphere, and addition of anhyd. benzene followed by evaporation of it was repeated several times to remove $SOCl_2$ completely. The acid chloride of DL-VI obtained as above was used for further experiment. On the other hand, CCl_4 (0.5 ml.) was added to Mg (1.8 g., 0.075 atom) in abs. EtOH (30 ml.) in order to accelerate the initiation of reaction. The whole was refluxed for 2.5 hr. until all of Mg was dissolved in EtOH. EtOH was evaporated and anhyd. benzene was added to the residue and distilled off to dryness to remove EtOH completely. To the residue was added anhyd. ether (30 ml.) and the whole was refluxed for 10 min., to which diethyl malonate (12.03 g., 0.075 mole) in anhyd. ether (30 ml.) was added under stirring in an ice bath. After stirring for 3 hr. at room temperature nearly clear solution was obtained, to which the solution of acid chloride obtained above in anhyd. benzene (90 ml.) was added under stirring in an ice bath. The reaction mixture was stirred for 18.5 hr. at room temperature and treated with *N* H_2SO_4 (100 ml.), the organic layer separated out was washed with sat. NaCl (60 ml.×2) and evaporated *in vacuo* to give a remaining oil, which was refluxed in a mixture of AcOH (80 ml.), 48% HBr (55 ml.) and conc. HCl (15 ml.) for 3 hr. The reaction mixture was concentrated to *ca.* 60 ml. in reduced pressure, and phthalic acid precipitated out was filtered off and washed with H_2O. The combined washings and filtrate were extracted with ether (50 ml.×3) (discarded), and the aqueous layer was made alkaline to pH 8 with Na_2CO_3 and 10% NaOH to separate DL-VII as an oil. After the oil was extracted with ether (50 ml.×3), the aqueous layer was again alkalined to pH 10 by 10% NaOH and extracted with ether (50 ml.). The combined ether extracts were washed with sat. NaCl (60 ml.×2), dried over anhyd. K_2CO_3, and evaporated to dryness under N_2 atmosphere to give a brown residue, which was distilled fractionally under reduced pressure to give DL-VII as a pale pink oil (4.9 g., 50%), b.$p_{11.5}$ 123~124°, IR ν_{max}^{cap} cm^{-1}: 3362, 3293, 1713, 759, 701.

(+)-3-Amino-3-phenyl-2-butanone ((+)-VII)——(+)-VI (m.p. 116~137°, $[\alpha]_D^{14.5}$ +14.3°(c=0.894,EtOH)) (11.0 g., 0.0373 mole) was treated similarly to the case of DL-VI to give (+)-VII as a colorless oil (1.6 g., 26%), b.$p_{.4}$ 94~97°, α_D^{10} +5.104°(*l*=0.1, neat), IR ν_{max}^{cap} cm^{-1}: 3369, 3300, 1714, 759, 702.

DL-3-Benzamido-3-phenyl-2-butanone (DL-VIII)——To the pyridine solution of DL-VII (6.2 g., 0.038 mole) was added benzoyl chloride (6.4 g., 0.046 mole) under cooling in an ice bath. The mixture was warmed for 3 hr. on a steam bath, left for 2 hr. at room temperature, and poured onto ice and water (250 ml.). After kept overnight at room temperature the pH was adjusted to 8 by the addition of Na_2CO_3 and extracted with ether (50 ml.). The aqueous layer was made further alkaline to pH 10 with 10% NaOH, and extrcted with ether (50 ml.×2). The combined ether layers were washed with sat. NaCl (100 ml.), 5% HCl (50 ml.×2, 25 ml.×5), sat. NaCl (100 ml.), 5% Na_2CO_3 (50 ml.) and sat. NaCl (50 ml.), dried over anhyd. Na_2SO_4 overnight, and evaporated to dryness. Resulted residue was recrystallized twice from iso-Pr_2O to afford DL-VIII (8.5 g., 83%), m.p. 82~83.5°, which was purified on column chromatogrphy using silica gel (solvent, benzene-CH_2Cl_2). Fractions containing only DL-VIII were collected and recrystallized from isoPr_2O to give pure DL-VIII

*9 In this case six lots of (+)-V were mixed and used directly, so the specific rotation cited here was calculated as an arithmetical mean from the specific rotations of them.

18) S.D. Upham, O.C. Dermer: J. Org. Chem., **22**, 799 (1957).

as nearly colorless pillars, m.p. 82~84.5°. *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.69; H, 6.68; N, 5.13. IR ν_{max}^{KBr} cm^{-1}: 3390, 1712, 1662, 1578, 1278, 760, 717, 707, 693.

(+)-3-Benzamido-3-phenyl-2-butanone ((+)-VIII)——A portion of (+)-Ⅶ ($[\alpha]_D^{13}$ +5.1°(l=0.1, neat)) (1.84 g., 0.0113 mole) was benzoylated by the same procedure as above except that a mixture of EtOH, *n*-hexane and petroleum ether was used as the solvent of recrystallization, to give (+)-Ⅷ, slightly yellow prisms (2.47 g., 82%), m.p. 114~116°, $[\alpha]_D^{13}$ +14.3°(c=0.994, EtOH). Analytical sample was purified similarly to the case of DL-Ⅷ and finally recrystallized from EtOH-*n*-hexane-petroleum ether. Colorless prisms, m.p. 113~114.5°, $[\alpha]_D^{14.5}$ +15.9°(c=1.01, EtOH). *Anal.* Calcd. for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.49; H, 6.22; N, 5.53. IR ν_{max}^{KBr} cm^{-1}: 3389, 1713, 1664, 1579, 1280, 761, 717, 707, 693. This IR spectrum was superimposable with that of DL-Ⅷ in a solid state.

DL-3-Benzamido-3-phenyl-2-butanone Ethylenedithioketal (DL-IX)——A mixture of DL-Ⅷ (1.0 g., 0.0037 mole), ethanedithiol (1 ml.) and $BF_3 \cdot OEt_2$ (1 ml.) was warmed at 65~70° for 13 hr. and treated with 10% NaOH (10 ml.) to precipitate crystals. The whole was treated again with 5% NaOH (10 ml.), and extracted with benzene (20 ml., 10 ml.×2). The benzene extracts were combined, washed with sat. NaCl (20 ml.), 5% HCl (15 ml.) and sat. NaCl (15 ml.×2) successively, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to afford a pale yellow viscous oil, which was triturated with $isoPr_2O$. The colorless powder undissolved was filtered and recrystallized from $isoPr_2O$-benzene to give DL-Ⅸ as colorless needles (770 mg., 60%), m.p. 139.5~140.5°. Purification on column chromatography using silica gel (solvent, benzene) followed by recrystallization from $isoPr_2O$-benzene gave pure DL-Ⅸ as colorless needles, m.p. 140~141°. *Anal.* Calcd. for $C_{19}H_{21}ONS_2$: C, 66.44; H, 6.16; N, 4.08. Found: C, 66.67; H, 6.26; N, 4.00. IR ν_{max}^{KBr} cm^{-1}: 3397, 1666, 1578, 768, 741, 713, 702.

(−)-3-Benzamido-3-phenyl-2-butanone Ethylenedithioketal ((−)-IX)——(+)-Ⅷ (m.p. 114~116°, $[\alpha]_D^{13}$ +14.3°(c=0.994, EtOH)) (1.4 g., 0.0052 mole) was treated as same as DL-Ⅷ to give crude (−)-Ⅸ, which was submitted to column chromatography using silica gel and recrystallized from benzene-$isoPr_2O$-*n*-hexane to afford (−)-Ⅸ as colorless prisms (1.00 g., 56%), m.p. 118~120°, $[\alpha]_D^{12}$ −120° (c=0.496, benzene). Further twice recrystallizations from the same solvent gave pure (−)-Ⅸ as colorless prisms, m.p. 118~119°, $[\alpha]_D^{19}$ −119°(c=0.396, benzene). *Anal.* Calcd. for $C_{19}H_{21}ONS_2$: C, 66.44; H, 6.16; N, 4.08. Found: C, 66.27; H, 6.18; N, 3.84. IR ν_{max}^{KBr} cm^{-1}: 3375, 1666, 1579, 1276, 769, 713, 702. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3397, 1665, 1510, 1485, 1283. This IR spectrum was similar to that of DL-Ⅸ but not identical in a solid state, but in chloroform solution IR spectra of (−)-Ⅸ and DL-Ⅸ were superimposable each other.

DL-2-Benzamido-2-phenylbutane (DL-X) (by Desulfurization of DL-IX)——A mixture of DL-Ⅸ (800 mg., 0.0023 mole) and Raney Ni[19] (*ca.* 10 g.) in EtOH (100 ml.) was refluxed for 5 hr. Raney Ni was filtered off and washed with EtOH. The combined washings and filtrate were evaporated to dryness *in vacuo* to give a residual oil, which was extracted with benzene (30 ml., 10 ml.) and ether (10 ml.). The combined organic layers were washed successively with sat. NaCl (20 ml.), 5% HCl (20 ml.), sat. NaCl (20 ml.), 5% NaOH (20 ml.) and sat. NaCl (20 ml.×2), dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*. The resulting residue was submitted to column chromatography using silica gel (solvent, $isoPr_2O$-*n*-hexane) and recrystallized from $isoPr_2O$ to give DL-X as colorless fine needles (110 mg., 19%), m.p. 108~111°. Pure sample was obtained by several recrystallizations from $isoPr_2O$-*n*-hexane as colorless needles, m.p. 113~114°. *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.65; H, 7.62; N, 5.72. IR ν_{max}^{KBr} cm^{-1}: 3320, 1641, 1536, 1310, 756, 714, 694.

(−)-2-Benzamido-2-phenylbutane ((−)-X) (by Desulfurization of (−)-IX)——(−)-Ⅸ (m.p. 118~120°, $[\alpha]_D^{12}$ −120°(c=0.496, benzene)) (950 mg., 0.0028 mole) was treated as same as DL-Ⅸ to afford (−)-X (330 mg., 47%), m.p. 90~103°, $[\alpha]_D^{15}$ −20.9°(c=0.850, EtOH). Further five times recrystallizations from benzene-$isoPr_2O$-*n*-hexane gave an analytical sample as colorless minute needles, m.p. 108~108.5°, $[\alpha]_D^{17}$ −22.9° (c=0.558, EtOH). *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.45; H, 7.41; N, 5.66. IR ν_{max}^{KBr} cm^{-1}: 3340, 1642, 1532, 1309, 755, 713, 692.

DL-1-Methyl-1-phenylpropylamine (DL-XI)——According to the procedure reported by Newman and Clossen,[20] hydratropanitrile was obtained from hydratropaldehyde[21] which was prepared from acetophenone by way of ethyl β-methyl-β-phenylglycidate.[22] The reaction of this nitrile with C_2H_5Br in the presence of sodium amide gave DL-2-methyl-2-phenylbutyronitrile which was refluxed with KOH (3 molar equivalent) in diethyleneglycol for 3 hr. to give DL-2-methyl-2-phenylbutyric acid (DL-XIV) in 79~92% yield (Almost similar procedure was reported by Bonner and Greenlee[12]). DL-XIV thus obtained was converted to DL-Ⅺ under the condition of Curtius rearrangement.[14] Hydrochloride (DL-Ⅺ-HCl), m.p. 237.5~238°(from MeOH-ether). *Anal.* Calcd. for $C_{10}H_{16}NCl$: C, 64.63; H, 8.68; N, 7.54. Found: C, 64.78; H, 8.47; N, 7.52. IR ν_{max}^{KBr} cm^{-1}: *ca.* 2900 (broad), 1617, 1519, 784, 760, 698.

19) R. Mozingo, D. E. Wolf, S. A. Harris, K. Folkers: J. Am. Chem. Soc., **65**, 1013 (1943).
20) M. S. Newman, R. O. Clossen: *Ibid.*, **66**, 1554 (1944).
21) "Org. Synth.," Coll. Vol. Ⅲ. p. 733.
22) *Idem*: *Ibid.*, p. 727.

(+)-1-Methyl-1-phenylpropylamine ((+)-XI)——According to the procedure of Wallis and Bowman,[13] DL-XIV obtained as above was submitted to optical resolution *via* quinine salt to afford (−)-XIV, which was treated as same as DL-XIV to give (+)-XI as colorless oil in 56% yield, b.p.$_{10.5}$ 95～96°, $\alpha_D^{9.5}$ +1.516°(l=0.1, neat) (lit.[14] b.p.$_2$ 50～52°, α_{546}^{27} −18.2°(l=1, neat),*[10] lit.[23] $[\alpha]_D^{25}$ −15.7°(l=1, neat),*[10] lit.[24] α_{546}^{25} +18.2°(l=1, neat)). Hydrochloride ((−)-XI-HCl), m.p. 228～230°(from EtOH–ether), $[\alpha]_D^{11.5}$ −6.24°(c=0.994, EtOH). *Anal.* Calcd. for $C_{10}H_{16}NCl$: C, 64.63; H, 8.68; N, 7.54. Found: C, 64.64; H, 8.56; N, 7.62. IR ν_{max}^{KBr} cm^{-1}: *ca.* 3000 (broad), 1615, 1519, 761, 698. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: *ca.* 3000 (broad), 1616. IR spectrum of (−)-XI-HCl was different from that of DL-isomer in a solid state, but in chloroform solution it was identical with that of DL-XI-HCl.*[11]

DL-2-Benzamido-2-phenylbutane (DL-X) (by Benzoylation of DL-XI)——To a solution of DL-XI (8.0 g., 0.054 mole) in pyridine (80 ml.) was added benzoyl chloride (9.0 g., 0.064 mole) under cooling. The mixture was warmed in a water bath for 2.5 hr., kept at room tempetature for 2 hr., and poured onto H_2O (240 ml.) under cooling. After standing overnight the whole was made alkaline to pH 9 with 40% NaOH, and extracted with benzene (50 ml., 30 ml.×2). The combined benzene extracts were washed with sat. NaCl (50 ml.), 10% HCl (50 ml.) and sat. NaCl (50 ml.×3), dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to afford yellow solid, which was recrystallized twice from isoPr$_2$O-benzene to give DL-X as slightly yellow needles (10.9 g., 80%), m.p. 112.5～113.5°. An analytical sample was obtained by repeated recrystallizations from benzene–isoPr$_2$O–*n*-hexane as colorless needles, m.p. 111～113°. *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.58; H, 7.46; N, 5.53. The mixed m.p. with DL-X obtained from the desulfurization of DL-IX showed no depression. IR ν_{max}^{KBr} cm^{-1}: 3305, 1642, 1537, 1311, 756, 713, 694. This IR spectrum was superimposable with that of DL-X prepared from DL-IX by the desulfurization in the same state.

(−)-2-Benzamido-2-phenylbutane ((−)-X) (by Benzoylation of (+)-XI)——(+)-XI (b.p.$_{17}$ 95～97°, α_D^{18} +1.576°(l=0.1, neat)) (0.7 g., 0.0047 mole) was treated as same as DL-XI to give crude (−)-X, which was purified on column chromatography using silica gel (solvent, $CHCl_3$) to afford (−)-X as pale yellow crystals (1.15 g., 97%), m.p. 106～108°, $[\alpha]_D^{16}$ −23.9°(c=0.986, EtOH). The mixed m.p. with (−)-X obtained from (−)-X and Raney Ni showed no depression. Further three times recrystallizations from benzene–isoPr$_2$O–*n*-hexane gave pure (−)-X as colorless minute needles, m.p. 108～109°, $[\alpha]_D^{19}$ −24.4°(c=0.874, EtOH), $[\alpha]_D^{17}$ −19.7°(c=0.852, benzene) (lit.[23] $[\alpha]_D^{25}$ −19.2° (c=7.0, $CHCl_3$), lit.[24] m.p. 108～109°, $[\alpha]_D^{25}$ −20.2° (c=5.2, benzene), $[\alpha]_D^{25}$ −18.1° (c=0.99, benzene)). *Anal.* Calcd. for $C_{17}H_{19}ON$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.84; H, 7.78; N, 5.52. IR ν_{max}^{KBr} cm^{-1}: 3336, 1643, 1533, 1310, 756, 714, 693. This IR spectrum was superimposable with that of (−)-IX prepared from (−)-IX by the desulfurization, and different from that of DL-X in a solid state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3436, 1665. This IR spectrum was identical with that of DL-X in the same state.

DL-2-Acetamido-2-phenylbutane (DL-XII)——To a solution of DL-XI (3.7 g., 0.025 mole) in pyridine (20 ml.) was added Ac_2O (20 ml.) under cooling. The mixture was warmed in a water bath for a while, kept overnight at room temperature, and then poured onto ice and water (120 ml.). The whole was left standing at room temperature for 4.5 hr., made alkaline to pH 11 with Na_2CO_3 and 40% NaOH, and extracted with benzene (30 ml.×2, 20 ml.). The combined benzene extracts were washed with sat. NaCl (50 ml.), 10% HCl (30 ml.×3) and sat. NaCl (40 ml.×2), dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give DL-XII as a solid (3.9 g., 82%), m.p. 68～72°. This solid was purified on column chromatography using silica gel (as the eluting solvent *n*-hexane, isoPr$_2$O and AcOEt were used successively). The fractions which contained DL-XII only were collected and recrystallized from EtOH–H_2O, to give pure DL-XII as colorless needles, m.p. 68～70°. *Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.42; H, 8.70; N, 7.55. IR ν_{max}^{KBr} cm^{-1}: 3291, 1650, 1553, 1310, 765, 708.

(+)-2-Acetamido-2-phenylbutane ((+)-XII)——(+)-XI (α_D^{14} +1.526 (l=0.1, neat)) (3.7 g., 0.025 mole) was treated similarly to DL-XI to give (+)-XII (4.1 g., 87%), m.p. 82～85°, $[\alpha]_D^{10}$ +8.50°(c=1.04, EtOH). Analytical sample was obtained by several recrystallizations from isoPr$_2$O–*n*-hexane as colorless prisms, m.p. 83～84°, $[\alpha]_D^{16.5}$ +9.97° (c=1.12, EtOH), $[\alpha]_D^{14}$ +15.1° (c=1.06, benzene) (lit.[24] m.p. 85～86°, $[\alpha]_D^{25}$ +16.1°(c=6.4, benzene), $[\alpha]_D^{25}$+15.5°(c=0.97, benzene)). *Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.26; H, 9.00; N, 7.22. IR ν_{max}^{KBr} cm^{-1}: 3317, 1657, 1546, 1292, 756, 735, 694. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435, 1672. IR spectra of (+)-XII and DL-XII in a solid state showed some difference each other, but in $CHCl_3$ solution both were found to be superimposable.

N-Acetyl-DL-isovaline (DL-XIII)——An O_2 stream containing ozone passed into a solution of DL-XII (2.0 g., 0.010 mole) in AcOH (35 ml.) at room temperature for 15 hr. during which time the volume of AcOH solution was maintained at *ca.* 35 ml. To the reaction mixture was added 30% H_2O_2 (1.05 ml., S.G. 1.11, 1.17 g., 0.0104 mole) and kept standing for 1 hr. An excess of H_2O_2 was decomposed by adding a small amount of reduced Pt. Filtration and evaporation gave a brown viscous oil, which was triturated with H_2O (10 ml.). After standing overnight in refrigerator DL-XIII precipitated out was collected (290 mg.), m.p. 179～

*[10] These amines were prepared from (+)-XIV.

*[11] Optical active and racemic hydrochlorides (DL-XI-HCl and (−)-XI-HCl) were freely soluble in $CHCl_3$.

23) E.H. White, J.E. Stuber: J. Am. Chem. Soc., **85**, 2169 (1963).

24) H.P Fischer: Helv. Chim. Acta, **48**, 1279 (1965).

181°. The filtrate was treated with charcoal, concentrated and cooled to give the second crop of DL-XIII (380 mg.), m.p. 179~182°. A total amount of DL-XIII was 670 mg. (40%). The combined crude DL-XIII thus obtained was treated with charcoal, and recrystallized successively from H_2O and EtOH-*n*-hexane to give pure DL-XIII as colorless prisms, m.p. 183~184°. The mixed melting point with the authentic DL-XIII prepared from DL-isovaline (DL-I) showed no depression (lit.[2b] m.p. 187.5~189°). *Anal.* Calcd. for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8.80. Found: C, 53.01; H, 8.12; N, 8.45. IR ν_{max}^{KBr} cm^{-1}: 3355, 1950 (broad), 1694, 1614, 1533.

(+)-N-Acetylisovaline ((+)-XIII)——(+)-XII (m.p. 82~85°, $[\alpha]_D^{16}$ +8.50°(c=1.04, EtOH)) (2.5 g., 0.013 mole) was treated as described above to afford (+)-XIII (390 mg., 19%), m.p. 184~187°, $[\alpha]_D^{19}$ +1.18°(c=1.49, MeOH).*12 Several recrystallizations from EtOH-*n*-hexane gave pure (+)-XIII as colorless fine needles, m.p. 188~189°, $[\alpha]_D^{19.5}$+1.33°(c=1.50, MeOH) (lit.[2b] S-(−)-XIII, m.p. 193~193.5°, $[\alpha]_D^{18}$ −1.3° (c=1.32, MeOH). *Anal.* Calcd. for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.92; H, 8.14; N, 8.76. IR ν_{max}^{KBr} cm^{-1}: 3335, 1707, 1625, 1554. This IR spectrum was superimposable with that of authentic S(−)-XIII,[2b] but different from that of DL-XIII remarkably in a solid state. A mixture of (+)-XIII and authentic S(−)-XIII prepared previously[2b] showed m.p. 183~184.5° which was identical with melting point of DL-XIII.

Optical rotatory dispersion*13 in MeOH at 22°(c=1.50), $[\alpha]_{700}$ +1.00°, $[\alpha]_{600}$ +1.50°, $[\alpha]_D$ +1.50°, $[\alpha]_{500}$ +2.74°, $[\alpha]_{400}$ +7.17°, $[\alpha]_{350}$ +14.0°, $[\alpha]_{300}$ +32.0°, $[\alpha]_{250}$ +123°. ORD curve measurement of S(−)-XIII[2b] in MeOH at 22°(c=1.37), $[\alpha]_{700}$ −0.913°, $[\alpha]_{600}$ −1.00°, $[\alpha]_D$ −1.28°, $[\alpha]_{500}$ −2.74°, $[\alpha]_{400}$ −6.94°, $[\alpha]_{350}$ −11.6°, $[\alpha]_{300}$ −30.7°, $[\alpha]_{250}$ −121°.

The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analysis and spectral data.

*12 This specific rotation was calculated from the optical rotatory dispersion chart.

*13 ORD curve measurements were carried on with a Spectrophotometer Model ORD/UV-5, Japan Spectroscopic Co., Ltd.