[Chem. Pharm. Bull. 14(10)1138~1143(1966)] UDC 547.466.02.07 : 541.653

156. Shiro Terashima, Kazuo Achiwa, and Shun-ichi Yamada :

Studies on Optically Active Amino Acids. XI.*1 Studies on α-Alkyl-α-amino Acids. VI.*2 Chemical Correlation of Absolute Configuration of α-Methylphenylalanine to α-Methylaspartic Acid.

*(Faculty of Pharmaceutical Sciences, University of Tokyo*3)*

On α-alkyl-α-amino acids much attention has been paid from the biochemical point of view, since α-methyl-3,4-dihydroxyphenylalanine (α-methyl-DOPA) which is one of the important α-alkyl-α-amino acids, is known as a hypotensive agent[1] and some others show anticancer activities.[2] In the series of the systematic studies on the α-alkyl-α-amino acids in our laboratory[3,4], the absolute configuration of the pharmacologically active (-)-α-methyl-DOPA was elucidated to be *S*-configuration by the chemical correlation with *S*(+)-isovaline.[3,4] However, the absolute configuration of α-methylphenylalanine (I), being a fundamental structure of aromatic α-methyl-α-amino acid series, has not been unequivocally established yet. It became necessary in our laboratory to establish the absolute configuration of I from the studies of the optical properties and the reaction mechanisms of carbinamine compounds derived from I. The present authors found only one reference for the absolute configuration of I, namely, Almond, *et al.*[5] reported that (−)-N-acetyl-α-methylphenylalanine ((−)-III) is assumed to be L-series by the comparison of the optical rotations of its derivatives with those of L-phenylalanine derivatives according to Freudenberg's rule of shift, even though their data seem not to be conclusive. Therefore the present authors undertook to determine the absolute configuration of optically active α-methylphenylalanine (I) by the chemical correlation with α-methylaspartic acid (II) whose absolute configuration had been established in our laboratory.[3a,c]

The chemical scheme which we employed is shown in Chart 1. Before the chemical correlation was studied using optically active compounds, preliminary experiments on racemic compounds were carried out in order to ascertain the working conditions. N-Acetyl-DL-α-methylphenylalanine (DL-III) obtained from DL-α-methylphenylalanine (DL-I)[5,6] using pyridine-acetic anhydride was treated with ozone in acetic acid,[7] and then with 30% hydrogen peroxide solution to give N-acetyl-DL-α-methylaspartic acid (DL-IV) which was followed by deacetylation with 10% hydrochloric

*1 Part X : This Bulletin, 14, 579 (1966).
*2 Part V : *Ibid.*, 14, 579 (1966).
*3 Hongo, Tokyo, Japan (寺島孜郎, 阿知波一雄, 山田俊一).

1) *a*) A. Sjoerdsma, S. Udenfriend : Biochem. Pharmacol., 8, 164 (1961). *b*) L. Gillespie, Jr. : Ann. N. Y. Acad. Sci., 88, 1011 (1960). *c*) I.A. Oates, L. Gillespie, S. Udenfriend, A. Sjoerdsma : Science, **131**, 1890 (1960). *d*) E.M. Tristram, J. ten Broeke, D.F. Reinhold, M. Sletzinger, D.E. Williams : J. Org. Chem., **29**, 2053 (1964).
2) *a*) T.A. Conners, L.A. Elson, W.C.J. Ross : Biochem. Pharm., **1**, 239 (1958). *b*) T.A. Conners, L. A. Elson, A. Haddow, W.C.J. Ross : *Ibid.*, **5**, 108 (1960). *c*) T.A. Conners, W.C.J. Ross : J. Chem. Soc., **1960**, 2119. *d*) *Idem* : Chem. Ind. (London), **1960**, 492.
3) *a*) S. Yamada, S. Terashima, K. Achiwa : This Bulletin, **13**, 277 (1965). *b*) S. Terashima, K. Achiwa, S. Yamada : *Ibid.*, **13**, 1399 (1965). *c*) *Idem* : *Ibid.*, **14**, 572 (1966). *d*) *Idem* : *Ibid.*, 579 (1966).
4) *a*) S. Yamada, K. Achiwa : *Ibid.*, **12**, 1525 (1964). *b*) K. Achiwa, S. Yamada : *Ibid.*, **14**, 537 (1966).
5) H.R. Almond, Jr., D.T. Manning, C. Niemann : Biochem., **1**, 243 (1962).
6) G.A. Stein, H.A. Bronner, K. Pfister, III : J. Am. Chem. Soc., **77**, 700 (1955).
7) H.E. Smith, T.C. Willis : J. Org. Chem., **30**, 2654 (1965).

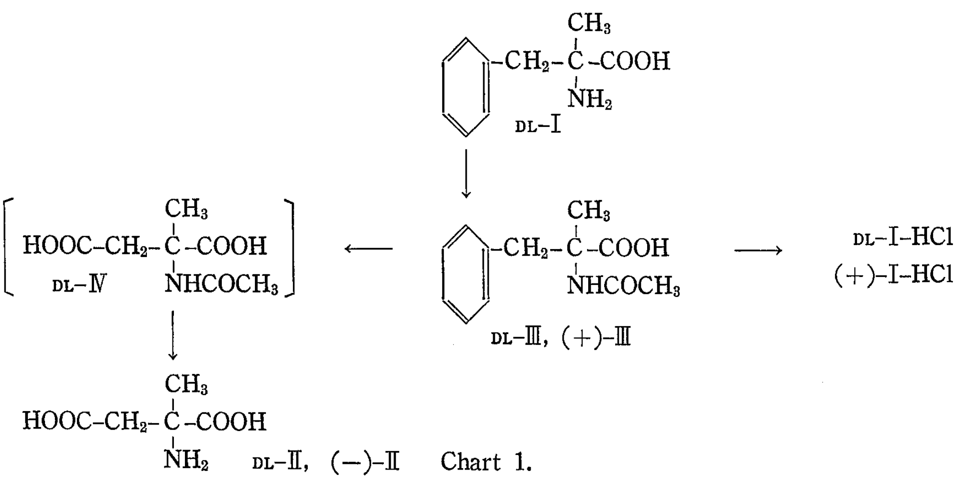


Chart 1.

acid without isolation to afford DL-α-methylaspartic acid hydrochloride (DL-II-HCl). DL-II-HCl thus obtained was purified through a cellulose powder column, and neutralization of the pure DL-II-HCl with pyridine in alcohol afforded DL-α-methylaspartic acid (DL-II) in a 38% yield. On the other hand, DL-III was hydrolyzed with 10% hydrochloric acid to give DL-α-methylphenylalanine hydrochloride (DL-I-HCl). This amino acid hydrochloride did not show a sharp melting point being different from the reported value,[5,6,8,9] but it was identified from infrared spectrum, nuclear magnetic resonance spectrum and elemental analysis.

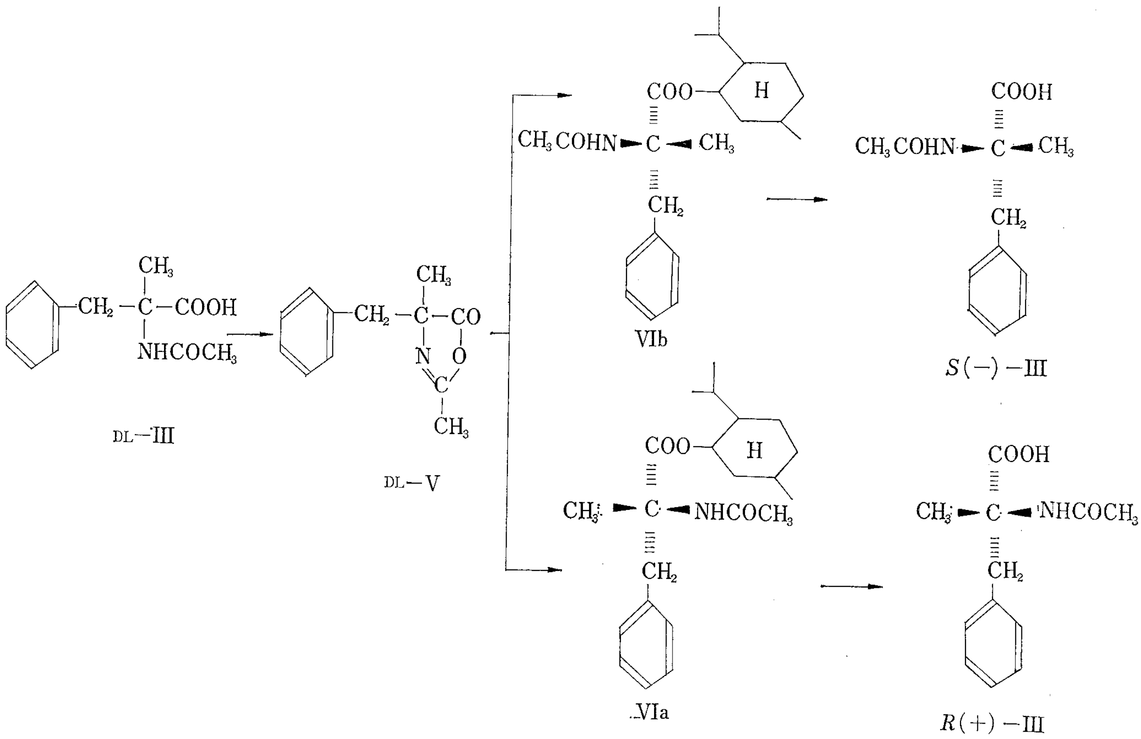


Chart 2.

In order to obtain the optically pure III as a starting material, the resolution of DL-III was performed through l-menthyl ester method[3b)] previously reported from our laboratory. As shown in Chart 2, DL-4-benzyl-2,4-dimethyl-2-oxazolin-5-one (DL-V)

8) R.M. Herbest, T.B. Johnson: J. Am. Chem. Soc., **54**, 2463 (1932).
9) A.M. Yurkevich, A.V. Dombrovskiĭ, A.P. Terent'ev: Zhur. Obshcheĭ Khim., **28**, 227 (1958) (C.A., **52**, 12797h (1958)).

derived from DL-III by the reflux in acetic anhydride was treated with sodium l-menthoxide in benzene to give a mixture of two diastereoisomers (VIa, VIb), which was separated into two sorts of crystals by fractional crystallization, VIa, m.p. 171.5~172.5°, $[\alpha]_D^{22}$ +37.4° (CH_3OH), in a 40% yield, and VIb, m.p. 121.5~123.5°, $[\alpha]_D^{19}$ −80.9° (CH_3OH), in a 9.9% yield. The former, VIa, thus obtained was optically pure, since even by the repeated recrystallization VIa did not change its optical rotation and melting point, however the latter, VIb, was found to be contaminated with some amount of VIa because the dementhylation of VIb gave partially resolved (−)-N-acetyl-α-methylphenylalanine ((−)-III). Reflux of VIa with 10 equivalent potassium hydroxide in 50% aq. ethanol gave pure (+)-N-acetyl-α-methylphenylalanine ((+)-III), m.p. 200.5~202.5°, $[\alpha]_D^{20}$ +79.3° (CH_3OH), and the same treatment of VIb afforded (−)-III, m.p. 187~190°, $[\alpha]_D^{21}$ −46.9° (CH_3OH).

Furthermore, (+)-III was treated as same as DL-III to afford *R*(−)-α-methylaspartic acid (*R*(−)-II), m.p. 256.5~257° (decomp.), $[\alpha]_D^{17}$ −52.9° (H_2O), in a 40% yield. Infrared spectrum of *R*(−)-II was superimposable with that of authentic *S*(+)-II previously obtained in our laboratory,[3a,c] and its optical rotatory dispersion curve was just

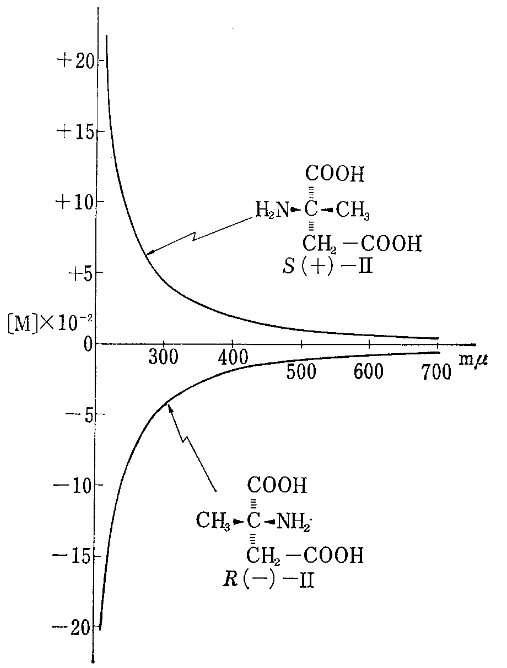


Fig. 1. Optical Rotatory Dispersion Curves of *R*(−)- and *S*(+)-α-Methylaspartic Acid (*R*(−)- and *S*(+)-II)

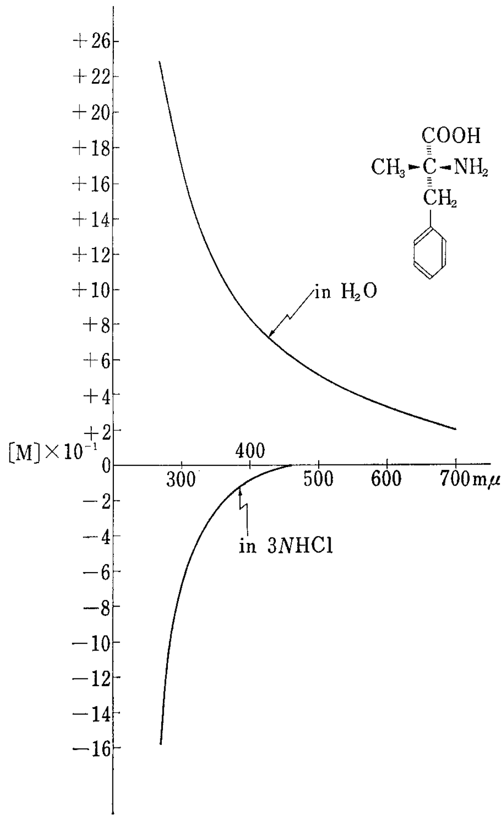
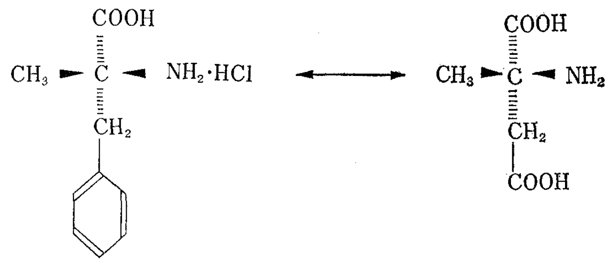


Fig. 2. Application of Clough-Lutz-Jirgensons Rule to *R*-α-Methylphenylalanine

opposite to that of *S*(+)-II. (+)-III was deacetylated with 10% hydrochloric acid to give (+)-α-methylphenylalanine hydrochloride ((+)-I-HCl), m.p. 210.5~214.5° (decomp.), $[\alpha]_D^{16}$ +6.7° (H_2O), which was identified from the elemental analysis and infrared spectrum.

Summarizing the results obtained above, (+)-I-HCl was correlated to *R*(−)-α-methylaspartic acid by way of (+)-N-acetyl-α-methylphenylalanine ((+)-III), accordingly the absolute configuration of (+)-I-HCl was demonstrated to be either *R* or D configuration.

The measurement of optical rotatory dispersion curves of *R*-I using *R*(+)-I-HCl showed that Clough-Lutz-Jirgensons rule[10] could be applicableto *R*-I in the region of 700~270 mμ when this compound was supposed to be D-α-methylphenylalanine, not L-α-benzylalanine.[4b] The optical properties of the α-alkyl-α-amino acids will be reported in detail in near future.



R(+)-I-HCl *R*(−)-II

Chart 3.

Experimental*4

DL-α-Methylphenylalanine (DL-I), Its N-Acetyl Derivative (DL-III), and Its Hydrochloric Acid Salt (DL-I-HCl)——DL-α-Methylphenylalanine, m.p. >250°(lit.,[5] m.p. 297°, lit.,[6] m.p. 294.5~295°(decomp.), lit.,[8] m.p. 293~294°, lit.,[13] m.p. 294~295°(decomp.), lit.,[14] m.p. 263~264°) was obtained[5,6,12] in a 57% yield from phenylacetone.[11] Crude DL-I thus obtained was treated with Ac_2O-pyridine to give N-acetyl-DL-α-methylphenylalanine (DL-III) in a 87% yield. Several recrystallizations from 50% aq. EtOH afforded pure DL-III as colorless prisms, m.p. 196~197°(lit.,[5] m.p. 195~197°, lit.,[14] m.p. 203~204°). IR ν_{max}^{KBr} cm^{-1}: 3270, 1713, 1648, 1562, 753, 700.

A mixture of pure DL-III and 10% HCl was refluxed for 3 hr. to give DL-α-methylphenylalanine hydrochloride (DL-I-HCl) in quantitative yield. DL-I-HCl thus obtained melted partially between 216.5° and 222° and decomposed gradually up to 243°. Several recrystallizations from 95% aq. EtOH-ether gave pure DL-I-HCl as white needles. This sample sintered at ca. 220° and decomposed at 234.5~241°*5(lit.,[5] m.p. 237°, lit.,[6] m.p. 241~243°(decomp.), lit.,[9] m.p. 236°(decomp.), lit.,[8] m.p. 244~246°). *Anal.* Calcd. for $C_{10}H_{14}O_2NCl$: C, 55.68; H, 6.54; N, 6.50. Found: C, 55.74; H, 6.64; N, 6.54. IR ν_{max}^{KBr} cm^{-1}: 3000, 2900, 1756, 1578, 1500, 772, 722, 701. NMR (solvent D_2O, 60 Mc., c.p.s. upperfield from H_2O): +202 (3H, singlet, >C-CH_3); +125, +111, +107, +92 (2H, quartet, -CH_2-, J_{AB}=15 c.p.s.); −140 (5H, singlet, benzene ring proton).

DL-4-Benzyl-2,4-dimethyl-2-oxazolin-5-one (DL-V)——A mixture of DL-III (68.0 g., 0.308 mole) and Ac_2O (408 ml.) was refluxed for 6 hr. avoiding moisture. After kept standing overnight at room temperature, the reaction mixture was evaporated to dryness ***in vacuo*** to afford reddish orange oil, which was submitted to fractional distillation to give DL-V as colorless oil (55.6 g., 89%) b.p.$_{6.5}$ 113~114.5° IR $\nu_{max}^{Cap.}$ cm^{-1}: 1823, 1689, 773, 739, 701. No band was observed in the region of 3500~3200 cm^{-1}. This DL-V was used immediately for the following step.[3b]

N-Acetyl-α-methylphenylalanine 1-Menthyl Esters (VIa, VIb)——To the suspension of Na powder (5.8 g., 0.25 mole) in anhyd. benzene (200 ml.) was added 1-menthol*6 (39.0 g., 0.25 mole). The reaction mixture was kept standing overnight at room temperature avoiding moisture and refluxed for 2 hr. Unreacted Na powder was decanted off and washed with anhyd. benzene (100 ml.). To the combined benzene solution of the supernatant and the washings was added a solution of DL-V (42.2 g., 0.208 mole) in anhyd. benzene (100 ml.). The reaction mixture was stirred at room temperature for 5 hr., and then kept standing overnight. The benzene solution was washed with 10% AcOH (300 ml.×2), H_2O (300 ml.×1), 2.5% Na_2CO_3 (300 ml.×1), and H_2O (300 ml.×2) successively, and then dried with anhyd. Na_2SO_4. Filtration and evaporation ***in vacuo*** of this benzene solution gave pale yellow oil, which solidified on standing. Recrystallization from iso-Pr_2O

*4 All melting points are uncorrected. IR spectra measurements were performed with a Spectrometer, Model DS-402. Japan Spectroscopic Co., Ltd. NMR spectra were determined with a Spectrometer, Model 3H-60, Japan Electron Optics Lab. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20.

*5 A sample showing a sharp melting point was not obtained, although recrystallization under several conditions were attempted.

*6 $[\alpha]_D^{19}$ −51.1°(c=3.326, EtOH).

10) J.P. Greenstein, M. Winitz: "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, London, 1961, Vol. 1, p. 83.
11) Org. Syn., Coll. Vol. II, p. 391, 487.
12) *Ibid.*, Coll. Vol. III, p. 88.
13) K.T. Pott: J. Chem. Soc., **1955**, 1632.
14) T.N. Ghosh, B. Bhattacharya, S. Datta: J. Indian Chem. Soc., **34**, 417 (1957).

(700 ml.) afforded colorless plates (42.6 g.), m.p. 123～147°, $[\alpha]_D^{25}$ −28.8°(c=1.366, MeOH). Another twice recrystallizations from iso-Pr_2O gave crude VIa as colorless needles (18.6 g., 50%), m.p. 169.5～172°, $[\alpha]_D^{21}$ +35.0°(c=1.618, MeOH). Recrystallization of crude VIa from iso-Pr_2O-AcOEt (5:4) afforded pure VIa as colorless needles (15.1 g., 40%), m.p. 171～173°, $[\alpha]_D^{23}$ +37.5°(c=1.588, MeOH). Analytical sample obtained from further twice recrystallizations from the same solvent showed m.p. 171.5～172.5°, $[\alpha]_D^{22}$ +37.4°(c=1.112, MeOH). *Anal.* Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.91; H, 9.16; N, 3.67. IR ν_{max}^{KBr} cm^{-1}: 3260, 1744, 1640, 1563, 1197, 735, 699. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3400, 1730, 1677, 1505.

The combined mother liquor of the first two recrystallizations was evaporated *in vacuo* to give yellow solid, which was recrystallized from hexane (300 ml.) to afford pale yellow crystals (30.0 g.), m.p. 114～118°, $[\alpha]_D^{22}$ −71.5°(c=1.122, MeOH). Successive recrystallization from hexane, iso-Pr_2O, 70% aq. EtOH, and iso-Pr_2O (×2) gave crude partially resolved VIb*[7] as white crystals (3.7 g., 9.9%), m.p. 121.5～123°, $[\alpha]_D^{21}$ −87.6° (c=1.242, MeOH). Another twice recrystallizations from hexane gave partially resolved VIb as white crystals, m.p. 121.5～123.5°, $[\alpha]_D^{19}$ −80.9°(c=1.318, MeOH). *Anal.* Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90. Found: C, 72.95; H, 9.04; N, 4.14. IR ν_{max}^{KBr} cm^{-1}: 3360, 1727, 1672, 1535, 1122, 749, 709. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3400, 1727, 1677, 1504.

(+)-N-Acetyl-*R*-α-methylphenylalanine (*R*(+)-III)——A mixture of (+)-VIa (m.p. 171～172.5°, $[\alpha]_D^{22}$ +37.4°(c=1.168, MeOH)) (11.0 g., 0.0307 mole) and KOH (17.2 g., 0.307 mole) in 50% aq. EtOH (200 ml.) was refluxed for 5 hr., condenced to ca. half volume and extracted with benzene (50 ml.×3). Aqueous layer was acidified with dil. HCl and kept in an ice bath for 2 hr. to crystallize out the crude *R*(+)-III as white powdery crystals (5.5 g., 81%), m.p. 200～201.5°, $[\alpha]_D^{21}$ +78.2° (c=1.334, MeOH). Recrystallization from 50% aq. EtOH gave pure *R*(+)-III as colorless needles (5.0 g., 74%), m.p. 200.5～202°, $[\alpha]_D^{19}$ +80.3°(c=1.052, MeOH). Analytical sample was prepared by the repeated recrystallization from the same solvent, m.p. 200.5～202.5°, $[\alpha]_D^{20}$ +79.3°(c=1.082, MeOH) (lit.,[5]) m.p. not described. $[\alpha]_D$ +74.4°(c=1, MeOH)). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.14; H, 6.76; N, 6.36. IR ν_{max}^{KBr} cm^{-1}: 3340, 1722, 1633, 1560, 752, 706. This IR spectrum was different from that of DL-III in solid state. Another hydrolysis using 70% aq. EtOH as a solvent raised the yield of the crude *R*(+)-III up to 97%.

(−)-N-Acetyl-*S*-α-methylphenylalanine (*S*(−)-III)——A mixture of (−)-VIb (m.p. 120.5～122.5°, $[\alpha]_D^{25}$ −83.5°(c=1.424, MeOH)) (2.5 g., 0.00696 mole) and KOH (3.9 g., 0.0696 mole) in 50% aq. EtOH (45 ml.) was treated similarly to the case of *R*(+)-III to give crude partially resolved *S*(−)-III as white powdery crystals (1.5 g., 97%), m.p. 187～190°, $[\alpha]_D^{21}$ −46.8°(c=1.034, MeOH) (optical purity 59%).*[8] Recrystallization from 50% aq. EtOH afforded colorless needles (1.1 g., 72%), m.p. 189.5～193.5°, $[\alpha]_D^{18}$ −55.6° (c=1.012, MeOH) (optical purity 70%).*[8] Further recrystallization from the same solvent gave analytical sample as colorless needles, m.p. 196.5～200.5°, $[\alpha]_D^{19}$ −78.4° (c=1.036, MeOH) (optical purity 99%)*[8] (lit.,[5]) m.p. not described, $[\alpha]_D$ −74.3°(c=1, MeOH)). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.18; H, 6.99; N, 6.37. IR ν_{max}^{KBr} cm^{-1}: 3440, 1721, 1633, 1577, 752, 706. This IR spectrum was identical with that of *R*(+)-III in solid state.

DL-α-Methylaspartic Acid (DL-II)——AcOH (50 ml.) containing DL-III (2.0 g., 0.00906 mole) was bubbled through with O_3 gas at room temperature for 9 hr. After kept standing overnight, additional AcOH (10 ml.) was added to the reaction mixture. The bubbling of O_3 gas was continued for additional 9 hr. The reaction mixture was mixed with 30% H_2O_2 (1.0 g., 0.00906 mole) and it was kept standing at room temperature for 2 hr. An excess of H_2O_2 was decomposed with Pt. Filtration and evaporation gave a reddish brown oil (2.6 g.), which was dissolved in 10% HCl (30 ml.). The HCl solution was refluxed for 2 hr. and evaporated to dryness *in vacuo* to give reddish brown caramel (1.7 g.). This caramel showed 4 spots on paper chromatogram,*[9] whose Rf values were 0.20 (very pale orange), 0.12 (violet), 0.05 (violet), and 0.00 (brown). By the comparison of the Rf value with the authentic DL-II the product showing Rf value 0.05 was assingned to be DL-II. Purification of this caramel on column chromatography was undertaken using cellulose powder (100 g.) and *n*-BuOH-EtOH-2*N* NH_4OH (5:1:2) as eluting system. Fractions which contained DL-II only, were detected using ninhydrin test and paper chromatography,*[9] combined and then evaporated to dryness *in vacuo* to give brownish white solid. After addition of H_2O (30 ml.), evaporation to dryness afforded reddish brown caramel (1.03 g.). 25 w/w% NaOH (8 ml.) was added to this caramel and evaporated *in vacuo* to ca. half volume. Acidification with conc. HCl and evaporation to dryness gave a reddish brown solid, which was extracted with a mixture of H_2O (2 ml.) and EtOH (18 ml.). Reddish brown extract thus obtained was treated with charcoal and evaporated to ca. 5 ml. Addition of pyridine (25 drops) and trituration in an ice-salt bath gave white powder, which was filtered after 2 hrs.' cooling, washed with EtOH (2 ml.×3), and ether (2 ml.×3) and dried. Crude DL-II obtained was pale yellow powder (0.56 g., 38%), m.p. 222.5°(decomp.). This sample showed a single spot on paper chromatogram,*[9] whose Rf value was exactly as same as that of the

---

*7 Partial resolution of (−)-1-menthyl ester VIb was deduced from the fact that VIb showing $[\alpha]_D^{25}$ −83.5° (c=1.424, MeOH) gave *S*(−)-III whose optical purity was 59%.

*8 Optical purity was calculated based on the assumption that *R*(+)-III showing $[\alpha]_D^{20}$ +79.3° (MeOH) was optically pure.

*9 Solvent system: *n*-BuOH-EtOH-2*N* NH_4OH (5:1:2). 0.5% ninhydrin in acetone was used for coloring.

authentic DL-II. Several recrystallizations from H_2O–acetone gave pure DL-II as colorless fine needles, m.p. 233~234°(decomp.) (lit.,[3c] m.p. 235°(decomp.)). *Anal.* Calcd. for $C_5H_9O_4N \cdot H_2O$: C, 36.36; H, 6.71; N, 8.48. Found : C, 36.47; H, 6.61; N, 8.74. IR ν_{max}^{KBr} cm^{-1} : 3530, 1690, 1612, 1594, 1451, 1414. This IR spectrum was superimposable with that of authentic DL-II. Paper chromatography with two different solvent systems*[10] gave one spot respectively. Rf value : 0.06 (solvent A), 0.32 (solvent B).

***R*(−)-α-Methylaspartic Acid (*R*(−)-II)**——*R*(+)-III (m.p. 200.5~202°, $[\alpha]_D^{19}$ +80.3°(c=1.052, CH_3OH)) (2.0 g., 0.00906 mole) was treated as same as DL-III to give crude *R*(−)-II as pale yellow powder (0.53 g., 40%), m.p. 244~245°(decomp.), $[\alpha]_D^{22}$ −52.0°(c=0.500, H_2O). Several recrystallizations from H_2O–acetone afforded pure *R*(−)-II as colorless needles, m.p. 256.5~257°(decomp.), $[\alpha]_D^{17}$ −52.9°(c=0.680, H_2O) (lit.,[3a,c] m.p. 256~257°(decomp.), $[\alpha]_D^{18}$ +49.0°(c=0.518, H_2O) as *S*(+)-II). *Anal.* Calcd. for $C_5H_9O_4N$: C, 40.81; H, 6.17; N, 9.52. Found : C, 40.55; H, 5.93; N, 9.84. IR ν_{max}^{KBr} cm^{-1} : 1720, 1621, 1603, 1560, 1496, 1410, *S*(+)-II in solid state. Paper chromatography with two different solvent systems*[10] showed one spot respec- 1400. This IR spectrum was identical with that of tively. Rf value : 0.07 (solvent A), 0.32 (solvent B).

Optical rotatory dispersion curve measurement.*[11] $[M]^{14}$ (mμ) (c=0.210, H_2O) : −56.0°(700), −77.0° (589), −115°(500), −147°(450), −197°(400), −284°(350), −431°(300), −770°(250), −2030°(211).

Optical Rotatory Dispersion Curve Measurement of Authentic *S*(+)-II[3a,c]——$[M]^{14}$ (mμ) (c=0.204, H_2O) : +50.4° (700), +72.1° (589), +112° (500), +144° (450), +191° (400), +277° (350), +425° (300), +865° (250), +2160° (213).

***R*(+)-α-Methylphenylalanine Hydrochloride (*R*(+)-I-HCl)**——A mixture of *R*(+)-III (m.p. 200.5~202°, $[\alpha]_D^{19}$ +80.3°(c=1.052, CH_3OH)) (2.0 g., 0.00906 mole) and 10% HCl (40 ml.) was refluxed for 3 hr. and evaporated to dryness *in vacuo* to afford *R*(+)-I-HCl monohydrate as white solid (1.9 g., 90%), m.p. 210~215° (decomp.), $[\alpha]_D^{17}$ +6.8°(c=0.976, H_2O). Recrystallization from 95% aq. EtOH (6 ml.)-ether (50 ml.) gave white crystals (1.6 g.), m.p. 209~213.5°(decomp.), $[\alpha]_D^{17}$ +6.3°(c=1.280, H_2O). Another several recrystallizations from the same solvent gave pure *R*(+)-I-HCl monohydrate as white crystals, m.p. 210~213.5° (decomp.), $[\alpha]_D^{15}$ +6.6°(c=1.034, H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_2NCl \cdot H_2O$: C, 51.40; H, 6.90; N, 5.99. Found : C, 51.31; H, 6.77; N, 6.46. IR ν_{max}^{KBr} cm^{-1} : 3385, 3310, 3025, 1743, 1603, 1590, 1523, 726, 695. Pure *R*(+)-I-HCl monohydrate was dried overnight *in vacuo* at ca. 60° to afford *R*(+)-I-HCl, m.p. 210~214.5°(decomp.), $[\alpha]_D^{16}$ +6.7°(c=0.920, H_2O). *Anal.* Calcd. for $C_{10}H_{14}O_2NCl$: C, 55.68; H, 6.54; N, 6.50. Found : C, 55.53; H, 6.39; N, 6.66. IR ν_{max}^{KBr} cm^{-1} : 3010, 1740, 1590, 1499, 729, 705, 696. This IR spectrum was different from those of DL-I-HCl and *R*(+)-I-HCl monohydrate in solid state.

Optical rotatory dispersion curve measurements*[11] of *R*-I. $[M]^{18.5}$ (mμ) (c=0.257, 3*N* HCl)*[12] : 0.0°(700), 0.0°(589), 0.0°(500), −0.7°(450), −8.4°(400), −22.9°(350), −68.8°(300), −158°(270). $[M]^{18.5}$ (mμ) (c=0.175, H_2O)*[13] : +20.4°(700), +34.8°(589), +51.2°(500), +65.3° (450), +83.8° (400), +115° (350), +168° (300),

The authors are grateful to the members of the Central Analysis Room of this Faculty for elemental analyses and spectral data. A part of this work was supported by a Grant-in-Aid for Fundamental Scientific Research from the Ministry of Education, to which the authors' thanks are due.
+238°(270).

Summary

The absolute configuration of (+)-α-methylphenylalanine hydrochloride has been elucidated to be either *R*- or D-configuration by the chemical correlation with (−)-α-methylaspartic acid, whose absolute configuration had been cofirmed to be *R*-configuration. The resolution of N-acetyl-DL-α-methylphenylalanine through its menthyl esters was also reported.

(Received February 22, 1966)

*10 Solvent A : *n*-BuOH-EtOH-2*N* NH_4OH 5:1:2. Solvent B : *n*-BuOH-AcOH-H_2O 4:1:2.

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

*12 15.5 mg. of *R*(+)-I-HCl was dissolved directly in 3*N* HCl and total volume was made up to 5 ml.

*13 10.5 mg. of *R*(+)-I-HCl was dissolved in 4.9 ml. of 0.01*N* NaOH solution and total volume was made up to 5 ml. with H_2O.