that of IVb prepared from VIIb. It was too difficult to purify IVb by the recrystallization method,[14] so IVb was identified as its methiodide (IXb), colorless needles (recrystallized from MeOH–ether), mp 167—168°. *Anal.* Calcd. for $C_{13}H_{26}O_2N_3I$: C, 40.74; H, 6.84; N, 10.96. Found: C, 40.77; H, 6.79; N, 11.22. IR ν_{max}^{KBr} cm^{-1}: 3200, 2985, 1769, 1706, 1447. NMR[13]: +213 (3H, triplet, $J=7$ cps, $-CO-\underset{\underset{CO}{|}}{N}-CH_2\underline{CH_3}$), +206 (6H, triplet, $J=7$ cps, $(\underline{CH_3CH_2})_2\overset{+}{\underset{|}{N}}-$), +193 (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{CH_3}$), +149 (2H, triplet, $J=9$ cps, $-\underline{CH_2}-\overset{CH_3}{\overset{|}{C}}-$) +104 (3H, singlet, $-\overset{+}{\underset{H_3C}{\underset{|}{N}}}-$), +114~+57 (8H, multiplet, $(CH_3\underline{CH_2})_2\overset{+}{N}-\underline{CH_2}CH_2\overset{C_3H}{\overset{|}{C}}-CO$ $\underset{NH-CO}{\overset{|}{}}\diagdown N-\underline{CH_2}CH_3$).

2-Amino-2-methyl-4-dimethylaminobutyric Acid (VIIIa)——a) VIIIa from Va: A mixture of Va (1.85 g, 0.01 mole) and $Ba(OH)_2\cdot 8H_2O$ (15.8 g, 0.05 mole) in H_2O (50 ml) was refluxed and stirred for 50 hr. To the reaction mixture was added $(NH_4)_2CO_3$ (7.2 g, 0.075 mole), and the $BaCO_3$ which precipitated was filtered off. The combined filtrate and washings were concentrated to *ca.* 10 ml and poured through an ion exchange resin (Amberlite IR–120(H^+ form)). The column was washed thoroughly with H_2O and eluted with diluted NH_4OH. The fractions showing positive ninhydrin tests were combined and evaporated to dryness to give crude VIIIa as pale yellow crystals (1.37 g, 86%), mp 253° (decomp.). Three recrystallizations from MeOH–acetone gave pure VIIIa as colorless needles, mp 255° (decomp.). *Anal.* Calcd. for $C_7H_{16}O_2N_2$: C, 52.47; H, 10.07; N, 17.49. Found: C, 52.55; H, 9.99; N, 17.52. IR ν_{max}^{KBr} cm^{-1}: 3420, 2970, 2780, 1610, 1399, 1287, 1186. A paper chromatogram, developed with BuOH—CH_3COOH—H_2O, 4:1:2 as the solvent system, showed one spot. *Rf* value 0.31.

b) VIIIa from IVa: IVa was treated in a manner similar to Va to afford crude VIIIa (1.5 g, 94%), mp 251—252° (decomp.), which was recrystallized several times from MeOH–acetone to give pure VIIIa as colorless needles, mp 255° (decomp). *Anal.* Calcd. for $C_7H_{16}O_2N_2$: C, 52.47; H, 10.07; N, 17.49. Found: C, 52.57; H, 9.90; N, 17.43. The infrared spectrum of this sample was superimposable with that of VIIIa obtained from Va. A paper chromatogram, developed with the same solvent system as in the case of a), showed one spot whose *Rf* value was identical with that of VIIIa from Va.

5-(2-Dimethylaminoethyl)-5-methylhydantoin Na Salt (XI)——A mixture of Va (0.37 g, 0.002 mole) and NaH (50% oil dispersion, 0.1 g, 0.002 mole) in dioxane (20 ml) was stirred at room temperature for 30 min, and refluxed for 2 hr. The reaction mixture was evaporated to dryness *in vacuo* to give hygroscopic crystals (0.42 g), whose infrared spectrum showed characteristic carbonyl bands at 1692, and 1585 cm^{-1} in a solid state.

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Studies on Optically Active Amino Acids. XVI.[1] Studies on α-Alkyl-α-amino Acids. XI.[2] Synthesis of *R*-α-Methylphenylalanine from *S*(+)-2-Methyl-3-phenylpropionic Acid by the Direct Conversion of the optically Active C-H Bond into the C-N Bond

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In the previous report,[4] optically active 2-oxazolidinone (III) was prepared by photochemical decomposition of azidoformate (II), which had been synthesized from carboxylic

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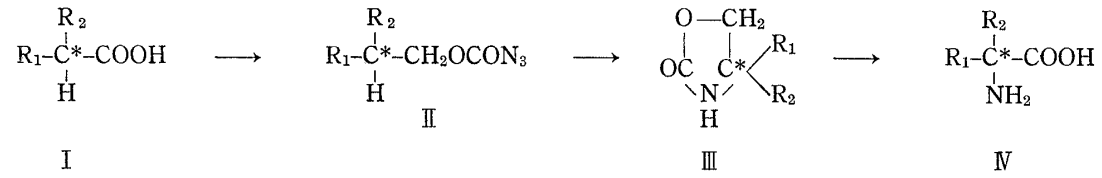
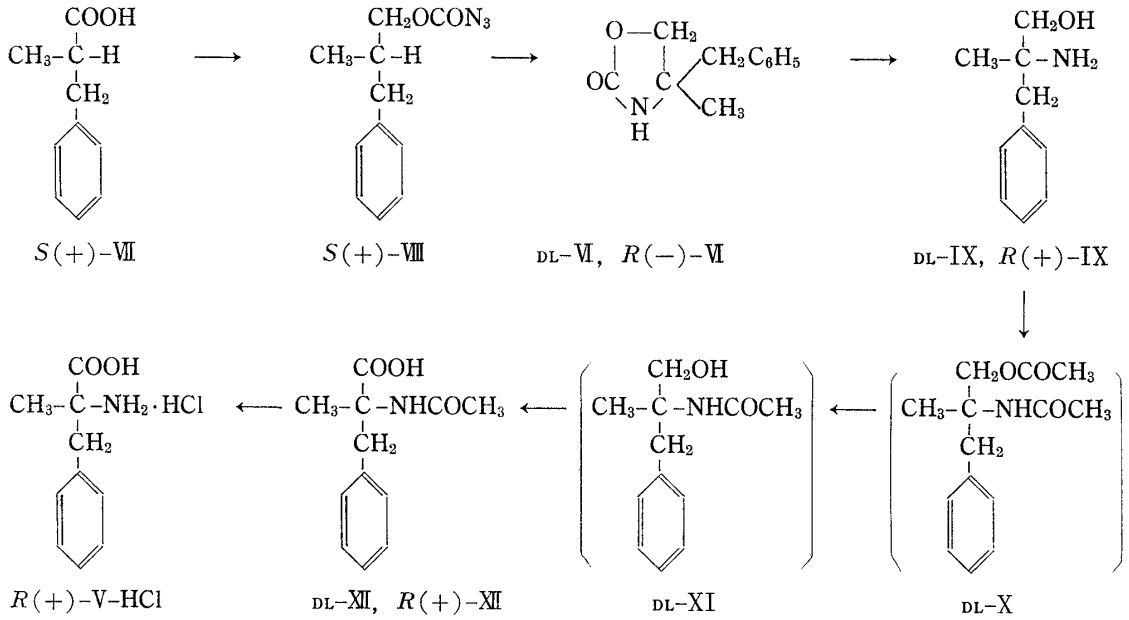
2) Part X: N. Takamura, S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2059 (1968).
3) Location: *Hongo, Tokyo.*
4) S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968).



I II III IV

acid (I) involving the optically active C–H bond at the α–position. This result prompted us to examine the preparation of optically active α–alkyl–α–amino acid (IV) from III, since this syhthesis would become a useful method for the preparation of IV if the yield of IV from III was found to be good. Then, we studied whether or not R–α–methylphenylalanine (R–V) was prepared in a good yield from $R(-)$–4–benzyl–4–methyl–2–oxazolidinone($R(-)$–VI) obtained from $S(+)$–2–methyl–3–phenylpropionic acid($S(+)$–VII) through photochemical decomposition of $S(+)$–2–methyl–3–phenylpropyl azidoformate ($S(+)$–VIII). Before examinations using optically active compounds were performed, preliminary studies on racemic compounds were carried out in order to ascertain the best working conditions.

As shown in Chart 1, a reflux of DL–4–benzyl–4–methyl–2–oxazolidinone (DL–VI) with 20 eq. potassium hydroxide in 50% aq. ethanol for 8 hr[5] afforded DL–2–amino–2–methyl–3–phenylpropanol(DL–IX) in a 87% yield. DL–IX was identified with the authentic[4] from its infrared spectrum and its mixed melting point, and as its hydrochloride.[4] By the treatment with acetic anhydride and pyridine, DL–IX was converted to the diacetate (DL–X), which, without isolation, was partially hydrolysed with diluted potassium hydroxide solution to afford DL–2–acetamido–2–methyl–3–phenylpropanol(DL–XI). DL–XI was oxidized immediately with potassium permanganate[6] to give N–acetyl–DL–α–methylphenylalanine(DL–XII)[7] in a 75% yield from DL–IX. DL–XII was identified with the authentic sample[7] from its infrared spectrum and its mixed melting point.



$S(+)$–VII $S(+)$–VIII DL–VI, $R(-)$–VI DL–IX, $R(+)$–IX

$R(+)$–V–HCl DL–XII, $R(+)$–XII DL–XI DL–X

Chart 1

Then, $R(-)$–VI, $[\alpha]_D^{32}$ $-24.2°$ (ethanol), obtained by the photochemical decomposition of $S(+)$–VIII[4] was treated in the same way as DL–VI, to give $R(+)$–2–amino–2–methyl–3–phenylpropanol($R(+)$–IX), $[\alpha]_D^{25}$ $+3.8°$ (ethanol), in a 84% yield, which was identified with the authentic $R(+)$–IX[4] from its infrared spectrum and its mixed melting point. $R(+)$–IX was converted to (+)–N–acetyl–R–α–methylphenylalanine($R(+)$–XII),[7] $[\alpha]_D^{27}$ $+64.8°$ (methanol), by the same treatment as in the case of DL–IX to give a 72% yield. Two recrystal-

lizations of this sample from aq. ethanol afforded $R(+)$–XII showing $[\alpha]_D^{20}$ +79.3° (methanol), which was identified with the authentic $R(+)$–XII prepared by the resolution of DL–XII through its menthyl ester[7] from its infrared spectrum, its optical rotatory dispersion curve, and its mixed melting point.

Since the preparation of $R(+)$–α–methylphenylalanine hydrochloride ($R(+)$–V–HCl) from $R(+)$–XII in a 90% yield on a reflux with 10% hydrochloric acid has already been reported,[7] it is evident that $R(+)$–V–HCl can be prepared from $R(-)$–VI in a fairly good yield. Accordingly, it was found that the preparation of IV from I especially from an optically active I, by way of the photochemical decomposition of II, now accomplished, is one of the fruitful new methods for the synthesis of IV.

Experimental[8]

DL-2-Amino-2-methyl-3-phenylpropanol (DL-IX)——A mixture of DL–VI (1.0 g, 0.0052 mole) and KOH (5.9 g, 0.11 mole) in 50% aq. EtOH (30 ml) was refluxed for 18 hr,[5] and then evaporated to *ca.* 15 ml. H_2O (20 ml) was added to the residual solution, and the aqueous layer was saturated with K_2CO_3. After the addition of NaCl (5 g), the aqueous layer was extracted with ether (30 ml, 20 ml×3). The combined ether layers were washed with satd. NaCl (20 ml×1), and extracted with 10% HCl (20 ml×2). The acidic layer was made alkaline by the addition of 20% NaOH, saturated with NaCl, and then extracted with ether (20 ml×3). The combined ether layers were washed with satd. NaCl (20 ml×3), and dried over anhyd. K_2CO_3. Filtration and evaporation in a N_2 atmosphere afforded a pale yellow oil, which solidified as a colorless solid (0.75 g, 87%), mp 88.5—93°. The mixed melting point, with the authentic DL–IX[4] (mp 93—94.5°), showed no depression (mp 90.5—93°). The infrared spectrum of this sample was identical with that of the authentic DL–IX[4] in a solid state.

Hydrochloride was prepared as a colorless powder, mp 155.5—156.5°. The mixed melting point, with the authentic compound[4] (mp 156—157°), showed no depression (mp 155.5—156.5°). The infrared spectrum of this sample was superimposable on that of the authentic sample[4] in the same state.

$R(+)$-2-Amino-2-methyl-3-phenylpropanol ($R(+)$-IX)——The same treatment of $R(-)$-VI (mp 92—94°, $[\alpha]_D^{32}$ −24.2° (c=1.398, EtOH), optical purity 86%)[4] (0.43 g, 0.0023 mole), as in the case of DL–IX, gave $R(+)$–IX as a colorless oil, which solidified as a colorless solid (0.31 g, 84%), mp 65—69°, $[\alpha]_D^{25}$ +3.8° (c=1.530, EtOH). The mixed melting point, with the authentic $R(+)$–IX[4] (mp 72.5—73.5°), showed no depression (mp 69—72°). IR ν_{max}^{KBr} cm^{-1}: 3335, 3275, 1603, 1584, 1073, 1061, 727, 702. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3355, 1603, 1583, 1043. These infrared spectra were identical with those of the authentic sample[4] in the same state.

N-Acetyl-DL-α-methylphenylalanine (DL-XII)——A mixture of DL–IX (0.50 g, 0.0030 mole) and Ac_2O (5 ml) in pyridine (5 ml) was kept standing overnight at room temperature, avoiding moisture. The reaction mixture was poured onto crushed ice (10 g), and the whole was left at room temperature for 4 hr. The aqueous solution was evaporated to dryness *in vacuo*. Addition of H_2O (5 ml) to the residue and evaporation to dryness were repeated twice, and then addition of benzene (10 ml) and evaporation were repeated five times to afford a pale yellow oil (0.78 g), which seemed to be DL–2–acetamido–2–methyl–3–phenylpropyl acetate (DL–X) from its infrared spectrum. IR ν_{max}^{cap} cm^{-1}: 3290, 1745, 1656, 1549, 1240, 745, 704.

To an aqueous solution (30 ml) containing KOH (0.34 g, 0.0061 mole) was added a dioxane solution (2 ml) of the pale yellow oil obtained above. The whole was stirred for 10 min at room temperature, and $KMnO_4$ (1.05 g, 0.0061 mole) was added portionwise to the reaction mixture for 10 min below 40°. H_2O (10 ml) was added to the reaction mixture and the whole was stirred for 3 hr at room temperature. After standing overnight at room temperature, further $KMnO_4$ (0.20 g) and H_2O (5 ml) were added to the reaction mixture, which was stirred for 3 hr at room temperature. After an excess of $KMnO_4$ was converted to MnO_2 using EtOH, the MnO_2 was filtered. The MnO_2 was suspended in H_2O (30 ml), and the whole was refluxed for a short time and then filtered. The combined filtrates were concentrated to *ca.* 10 ml and filtered again. After being extracted with ether (10 ml×3), the filtrate was cooled in an ice bath and acidified to pH 2—3 by the addition of conc. HCl. The whole was kept in an ice bath for 2 hr, and then the white

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8) All the melting points were uncorrected. IR spectra measurements were performed with a Spectrometer, Model DS-402 and IR-S, Japan Spectroscopic Co., Ltd. Optical activities were measured with a Yanagimoto Photo Direct Reading Polarimeter, Model OR-20. ORD curve measurements were carried out with a Spectrometer Model ORD/UV-5, Japan Spectroscopic Co. Ltd.

powder precipitated was filtered, washed with H_2O (1 ml×2), and dried. DL-XIII which was obtained as a colorless powder (0.50 g, 75%) showed a mp of 191.5—193.5°. Recrystallization of DL-XII from aq. EtOH gave pure DL-XII as colorless prisms, mp 194—196°, which showed no depression (mp 194.5—196.5°) of the mixed melting point with the authentic DL-XII (mp 195—196.5°). The infrared spectrum of this sample was superimposable on that of the authentic sample[7] in a solid state.

(+)-N-Acetyl-*R*-α-methylphenylalanine(*R*(+)-XII)——*R*(+)-IX (mp 65—69°, $[\alpha]_D^{25}$ +3.8° (c=1.530, EtOH)) (0.29 g, 0.0018 mole) was treated in a similar way to DL-IX to afford *R*(+)-XII as a colorless powder (0.28 g, 72%), mp 185—192.5°, $[\alpha]_D^{27}$+64.8° (c=1.040, MeOH). The optical purity of this sample was calculated as 82% based on the assumption that *R*(+)-XII showing $[\alpha]_D^{20}$ +79.3° (c=1.082, MeOH) was 100% optically pure. IR ν_{max}^{KBr} cm^{-1}: 3340, 1720, 1633, 1558, 753, 706. This infrared spectrum was identical with that of the authentic *R*(+)-XII in the same state. ORD:$[M]^{28.5}$ (c=0.494, MeOH) (mμ): +103° (700), +143° (589), +215° (500), +279° (450), +380° (400), +586° (350), +1050° (300), +1750° (270). Two recrystallizations of *R*(+)-XII thus prepared from aq. EtOH, afforded pure *R*(−)-XII showing a mp of 199—200.5°, $[\alpha]_D^{24}$ +74.9° (c=0.614, MeOH). The mixed melting point, with the authentic *R*(+)-XII (mp 200—202°), showed no depression (mp 200.5—202°). The infrared spectrum of this sample was identical with that of the authentic *R*(+)-XII in a solid state.

Optical Rotatory Dispersion Curve Measurement of Authentic *R* (+)-XII——$[M]^{17}$ (c=0.512, MeOH) (mμ): +129° (700), +186° (589), +276° (500), +367° (450), +508° (400), +790° (350), +1425° (300), +2330° (270).

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Stability of Ascorbic Acid in Fused System Containing Ascorbic Acid and Mannitol[1]

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In manufacturing processes of ointments, suppositories and in spray chilling processes, or other processes including fusing step, one of the most important problem is the stability of the drug in the fused system.

The present paper is concerned with ascorbic acid and mannitol as an example. The stability of ascorbic acid dissolved in fused mannitol was studied in order to determine the condition of above processes, that is, the temperature and time range of fusion required to keep the drug decomposition within a certain limit.

The stability of ascorbic acid in its aqueous solution has been well studied.[3-6] Awata, *et al.*[7,8] and Ohtani[9,10] reported the mechanism of the color formation of ascorbic acid in

1) Presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, 1965. The study was made in relation to the investigation on air oxidation of ascorbic acid in mannitol conglomerate. (Part I: *Chem. Pharm. Bull.* (Tokyo), **16**, 1972 (1968); Part II: *Chem. Pharm. Bull.* (Tokyo), **16**, 1982 (1968).)
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