[Chem. Pharm. Bull. 17(12)2540—2547(1969)]

UDC 547.466.2.04

Stereochemical Studies. IV.[1,2] Studies on α-Alkyl-α-amino Acids. XII.[3] Hofmann and Curtius Rearrangements of S(+)-2-Cyano-2-methyl-3-phenylpropionic Acid

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(Received May 10, 1969)

Hofmann and Curtius rearrangements of (*S*)(+)-2-cyano-2-methyl-3-phenylpropionic acid ((*S*)(+)-Ia) having a quarternary asymmetric carbon at α position were made.

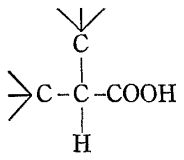
These rearrangements clearly proceeded with nearly 100% retention of configuration even if the migrating groups were quarternary.

Preliminary examinations using racemic compounds are also described.

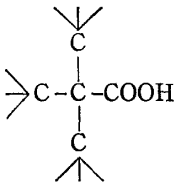
To study whether or not a rearrangement reaction proceeds with configuration retention of the asymmetric carbon where the migration reaction occurs, and to establish the accurate degree of asymmetry retention, the examination of the reaction system in which absolute configurations of the starting material and the product have been definitely established is unavoidable. Moreover, precise optical purity of these compounds must be easily determined. It is also desirable that the system contain no asymmetric carbon atom other than that rearranged in the reaction.

Hofmann and Curtius rearrangements of optically active carboxylic acids are frequently used to introduce the nitrogen function into the asymmetric carbon atom.[5] Using carboxylic acid (**A**) with a tertiary asymmetric carbon at α position in systems satisfying the above requirements, it has been established that these rearrangements proceed with nearly 100% retention of configuration.[6]

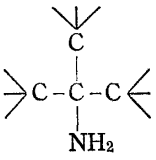
However, in carboxylic acids (**B**) which contain a quarternary asymmetric carbon atom at α position, investigations of the stereochemistry and optical degree of migration have never been done in a system which fulfills the above conditions. Several studies[7,8,9g] on rearrange-



A



B



C

1) Part III: S. Terashima, K.K. Lee, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 2533 (1969).
2) A part of this work was presented at the 85th Annual Meeting of the Pharmaceutical Society of Japan, October, 1964.
3) Part XI: S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2064 (1968).
4) Location: *Hongo, Bunkyo-ku, Tokyo.*
5) P.A.S. Smith, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N.Y. 1963, p. 528.
6) *a*) C.L. Arcus and J. Kenyon, *J. Chem. Soc.*, **1939**, 916; *b*) A. Campbell and J. Kenyon, *ibid.*, **1946**, 25.
7) S. Archer, *J. Am. Chem. Soc.*, **62**, 1872 (1940). An optically active alicyclic carboxylic acid amide, β-camphoramic acid (i), containing a four-substituted carboxamide group and a tri-substituted carboxyl group, gave aminodihydrocampholytic acid (ii) stereospecifically on Hofmann rearrangement. *cis*-Configuration of (ii) was confirmed by the fact that (ii) showed lactam (iii) formation. However, no accurate degree of configuration retention was reported.

ments of optically active carboxylic acid, type **B**, have been reported. These studies assume that rearrangements proceed with nearly complete configuration retention based only on results of examinations using optically active carboxylic acids of type **A**. The absolute configuration of the tertiary carbinamine skeleton (**C**), obtained from the Hofmann and Curtius rearrangement of carboxylic acid (**B**) derivatives, had never been clearly defined until our papers were published.[9]

In a previous report,[1] the absolute configuration of (+)-2-cyano-2-methyl-3-phenylpropionic acid ((+)-Ia), a carboxylic acid possessing very simple structure and carrying only one asymmetric quarternary carbon atom at α-position, was established as (*S*)-series by chemical correlation. We undertook Hofmann and Curtius rearrangements of optically active Ia to study the stereochemistry of these reactions.

Results and Discussions

Hofmann Rearrangement

When the Hofmann rearrangement is examined using Ia, two routes are possible as shown in Chart 1. One of these is through 2-cyano-2-methyl-3-phenylpropionamide (II) prepared

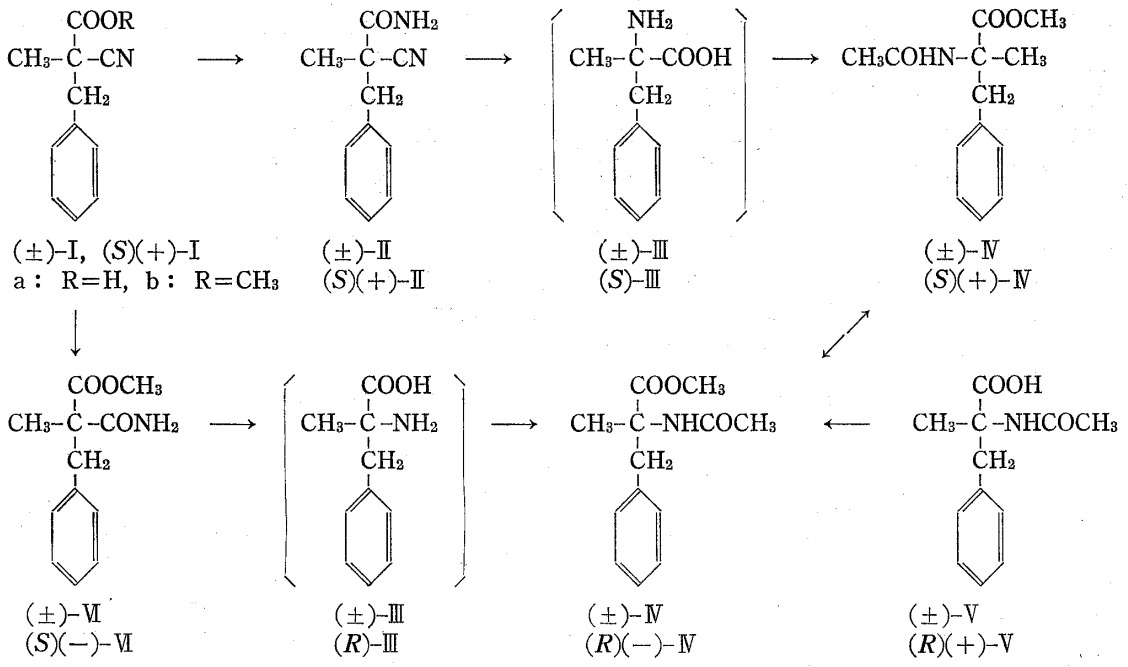
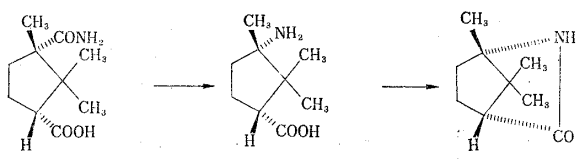


Chart 1



8) *a*) C.L. Arcus, J. Kenyon, and S. Levin, *J. Chem. Soc.*, **1951**, 407; *b*) Farbwerke Hoechst A.G., *Neth. Appl.*, **6**, 508, 882 (*C.A.*, **64**, 15982h (1966)); *c*) D.J. Cram and J.S. Bradshaw, *J. Am. Chem. Soc.*, **85**, 1108 (1963).

9) *a*) S. Yamada and K. Achiwa, *Chem. Pharm. Bull.* (Tokyo), **12**, 1525 (1964); *b*) S. Yamada, S. Terashima, and K. Achiwa, *ibid.*, **13**, 227 (1965); *c*) K. Achiwa and S. Yamada, *ibid.*, **14**, 537 (1966); *d*) S. Terashima, K. Achiwa, and S. Yamada, *ibid.*, **14**, 572 (1966); *e*) *Idem*, *ibid.*, **14**, 579 (1966); *f*) *Idem*, *ibid.*, **14**, 1138 (1966); *g*) H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *ibid.*, **15**, 1749 (1967); *h*) N. Takamura, S. Terashima, K. Achiwa, and S. Yamada, *ibid.*, **15**, 1776 (1967).

by amidation of Ia. The other is through methyl 2-carbamoyl-2-methyl-3-phenylpropionate (VI) obtained by hydrolysis of the cyano group of Ia. Since these rearrangements proceed under the same stereochemical course, products with opposite configuration should be prepared from (*S*)(+)-Ia by way of optically active II and VI.

First, rearrangement by way of II was undertaken. As shown in Chart 1, the acid chloride prepared by treatment of 100% optically pure (*S*)(+)-Ia, $[\alpha]_D^{21}$ +27.4° ($CHCl_3$)[1] with phosphorus pentachloride in hexane, was mixed with conc. aqueous ammonia solution to give (*S*)(+)-II, $[\alpha]_D^{21.5}$+55.1° ($CHCl_3$) in a 75% yield from (*S*)(+)-Ia. The (*S*)(+)-II obtained was added to an aqueous sodium hypobromide solution[10] cooled in an ice-salt bath. Rearrangement was performed by heating the reaction mixture at 85—90° for 30 min. The reaction product[11] was hydrolyzed, without isolation, by refluxing it with an excess amount of sodium hydroxide for 10 hr. This was followed by the usual treatment using an ion exchange column which give crude optically active α-methylphenylalanine (III). Crude III was acetylated with a mixture of pyridine and acetic anhydride,[9f] then submitted to esterification using diazomethane. The crude product was chromatographed with a silica gel column affording pure (+)-methyl 2-acetamido-2-methyl-3-phenylpropionate ((+)-IV), $[\alpha]_D^{25}$ +59.2° ($CHCl_3$) in a 12% yield based on (*S*)(+)-II.

Esterification of optically pure (*R*)(+)-N-acetyl-α-methylphenylalanine ((*R*)(+)-V), $[\alpha]_D^{24}$ +78.1° (CH_3OH) whose absolute configuration was demonstrated in our laboratory,[9f] with diazomethane afforded optically pure (*R*)(−)-IV, $[\alpha]_D^{23.5}$−60.1° ($CHCl_3$).

Dextrorotatory IV, obtained from this rearrangement and authentic (*R*)(−)-IV showed the same *Rf* values on thin layer chromatograms, identical infrared and NMR spectra, and opposite optical rotations. It was then evident that (+)-IV prepared from (*S*)(+)-II belonged to (*S*)-series and its optical purity was shown to be 99%. Thus, it was established that rearrangement of (*S*)(+)-II proceeded with 99% retention of configuration.

Rearrangement of (*S*)(+)-II was attempted two more times using 77% optically pure (*S*)(+)-Ia, $[\alpha]_D^{28.5}$+21.1° ($CHCl_3$). Results are summarized in Table 1. The average percent for configuration retention is shown to be 100%.

Table I. Hofmann and Curtius Rearrangements of (*S*)(+)-Ia

Type of reaction	(*S*)(+)-Ia used $[\alpha]_D$ ($CHCl_3$)	Optical purity (%)[a]	Substrate of rearrangement $[\alpha]_D$ ($CHCl_3$)	Isolated products (IV) $[\alpha]_D$ ($CHCl_3$)	Optical purity (%)[b]	Total yield from substrate (%)	Retention of configuration (%) Observed	Average
Hofmann rearrangement by way of (*S*)(+)-II	+27.4°	100	+55.1°	+59.2°	99	12	99	
	+21.1°	77	+40.3°	+48.6°	81	20	105	100
	+21.1°	77	+40.3°	+44.8°	75	18	97	
Hofmann rearrangement by way of (*S*)(−)-VI	+27.4°	100	− 9.0°	−55.6°	93	38	93	
	+21.1°	77	− 4.8°	−44.0°	74	24	95	97
	+21.1°	77	− 4.8°	−47.8°	80	19	103	
Curtius rearrangement of (*S*)(+)-Ia	+27.4°	100		+57.0°	95	18[c]	95	
	+21.1°	77		+45.7°	76	11[c]	99	98
	+21.1°	77		+45.9°	76	10[c]	99	

a) (*S*)(+)-Ia showing $[\alpha]_D^{21}$ +27.4° (*c*=2.556, $CHCl_3$) was assumed to be 100% optically pure.
b) (*R*)(−)-IV showing $[\alpha]_D^{23.5}$ −60.1° (*c*=1.970, $CHCl_3$) was assumed to be 100% optically pure.
c) Based on (*S*)(+)-Ia used.

10) I. Hori, M. Igarashi, and H. Midorikawa, *J. Org. Chem.*, **26**, 4511 (1961).
11) In preliminary experiments using racemic compounds, the reaction mixture was made acidic by adding 10% aqueous hydrochloric acid solution after the rearrangement was finished. This gave (±)-5-benzyl-5-methylhydantoin in a 95% yield based on (±)-II. To prevent preferential recrystallization of optically active hydantoin, hydantoin isolation was omitted when the optically active compound was rearranged (see Experimental).

Next, a Hofmann rearrangement of Ia was attempted through VI after the cyano group of Ia was converted to the carboxamide group. (*S*)(+)-Methyl 2-cyano-2-methyl-3-phenylpropionate ((*S*)(+)-Ib), $\alpha_D^{23.5}$ +2.751° (*l*=0.1, neat), prepared from optically pure (*S*)(+)-Ia[1] as reported previously,[1] was hydrolyzed with conc. sulfuric acid[10] to give (*S*)(−)-VI, $[\alpha]_D^{23}$ −9.0° ($CHCl_3$) in a 63% yield based on (*S*)(+)-Ib. Treatment of (*S*)(−)-VI similar to that of (*S*)(+)-II afforded the rearranged product.[12] This was hydrolyzed by refluxing it with 10% aqueous hydrochloric acid, followed by the same isolation procedure using an ion exchanger column to give crude optically active III. Crude III was converted to (−)-IV, $[\alpha]_D^{27.5}$ −55.6° ($CHCl_3$), by identical treatment with that used in the rearrangement of (*S*)(+)-II. The yield of (−)-IV was 38% based on (*S*)(−)-VI. This (−)-IV was identified with authentic (*R*)(−)-IV by mixed melting point measurement, thin-layer chromatography, and infrared spectra. Comparison of the optical rotations of (−)-IV and the authentic (*R*)(−)-IV, showed that (−)-IV prepared from (*S*)(−)-VI possessed (*R*)-configuration and that the percent of optical purity of (−)-IV; *i.e.* the percent of configuration retention, was 93%.

This rearrangement was also reexamined twice. Results are summarized in Table 1. The average percent of configuration retention is 97%.

Because nearly complete configuration retention was observed for rearrangements of (*S*)(+)-II and (*S*)(−)-VI, respectively, having a cyano and a methoxycarbonyl group at asymmetric carbons, it is obvious that these functional groups have no influence on the rearrangement mechanism. That enantiomeric (*S*)(+)-IV and (*R*)(−)-IV could be prepared from (*S*)(+)-Ia with nearly 100% configuration retention is interesting from the point of synthesizing optically active α-alkyl-α-amino acid.

Curtius Rearrangement

Chart 2 shows the acid chloride ((*S*)-VII), prepared from (*S*)(+)-Ia by the treatment with thionyl chloride, reacted with sodium azide in aqueous acetone to afford acyl azide ((*S*)-VIII). The azide was immediately rearranged by refluxing in toluene for 2 hr. Hydrobromic

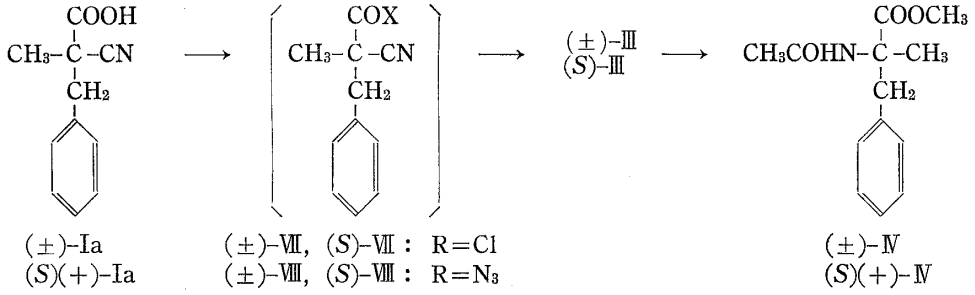


Chart 2

acid (47%) was added to the reaction mixture[13] and the whole was refluxed for 7 hr. The residue,[14] obtained by evaporation of the acidic solution, was further hydrolyzed using 20% aqueous sodium hydroxide solution. This was followed by the same treatment as in Hofmann rearrangement, to give crude optically active III. Crude III was treated in the same manner as described above to afford (*S*)(+)-IV, $[\alpha]_D^{23}$ +57.0° ($CHCl_3$) in a 18% yield based on (*S*)(+)-Ia. The rearrangement of (*S*)-VIII proceeded with 99% retention of configuration.

12) Isolation of the rearranged product was not attempted in this case.
13) When the racemic compound was examined, its residue from the evaporation of toluene solution, showed the presence of an isocyanato group on infrared spectrum measurement (see Experimental).
14) The residue obtained by evaporation of the 47% HBr solution was identified as (±)-5-benzyl-5-methylhydantoin by comparison of infrared spectra, when rearrangement using the racemic compound was carried out (see Experimental).

As in the Hofmann rearrangement, two more examinations were made on this rearrangement using 77% optically pure (*S*)(+)-Ia. Results are shown in Table 1. The average percent of configuration retention was 98%.

In summary these results establish that Hofmann and Curtius rearrangements of optically active carboxylic acid having an asymmetric quaternary carbon at α-position proceeded with nearly 100% retention of configuration as did optically active carboxylic acid which contains an asymmetric tertiary carbon at α position. This suggests that the mechanism for these rearrangements do not change whether the migrating group is tertiary or quaternary.[15]

Before optically active compounds were examined, all experiments were performed using racemic compounds in order to ascertain the working conditions. These are described in detail in the experimental section.

Experimental[17]

(±)-2-Cyano-2-methyl-3-phenylpropionamide ((±)-II)——PCl_5 (2.0 g, 0.010 mole) was added to a suspension of (±)-Ia[1] (2.0 g, 0.010 mole) in hexane (50 ml). The whole was stirred at room temperature for 3 hr. The hexane solution was cooled in an ice bath, then added dropwise to conc. NH_4OH (50 ml) cooled at −5° under stirring. The reaction mixture was stirred in an ice bath for 2 more hr. Filtration of the precipitated white crystals gave (±)-II (2.0 g, 100%), mp 114—116°. The mother liquor of this filtration was extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated *in vacuo* and gave no yield of (±)-II. Pure (±)-II was obtained by several recrystallizations from iso-Pr_2O. mp 114—115°. *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.02; H, 6.46; N, 15.18. IR ν_{max}^{KBr} cm^{-1}: 3446, 3380, 3356, 3206 (NH); 2245 (CN); 1660, 1613 ($CONH_2$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 3400 (NH); 2235 (CN); 1700, 1595 ($CONH_2$). NMR (in $CDCl_3$ solution): 8.40 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{CH_3}$); 6.95 τ (2H, quartet, $Ph-\underline{CH_2}-\underset{|}{\overset{|}{C}}-$, $J=13.0$ cps); 3.80 τ (2H, broad singlet, $CO\underline{NH_2}$); 2.75 τ (5H, singlet, benzene ring protons).

(*S*)(+)-2-Cyano-2-methyl-3-phenylpropionamide ((*S*)(+)-II)——The same treatment used for (*S*)(+)-Ia (mp 87.5—89°, $[\alpha]_D^{21}$ +27.4° ($c=2.556$, $CHCl_3$), optical purity 100%)[1] as for (±)-Ia gave (*S*)(+)-II (1.5 g, 75%), mp 97—98°, $[\alpha]_D^{26}$ +54.3° ($c=0.938$, $CHCl_3$). Several recrystallizations from iso-Pr_2O afforded pure (*S*)(+)-II as colorless needles, mp 100—101°, $[\alpha]_D^{21.5}$ +55.1° ($c=2.036$, $CHCl_3$). *Anal.* Calcd. for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.02; H, 6.46; N, 15.18. IR ν_{max}^{KBr} cm^{-1}: 3435, 3410, 3308 (NH); 2250 (CN); 1693, 1621 ($CONH_2$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470, 3426 (NH); 2240 (CN); 1700, 1595 ($CONH_2$). The infrared spectrum of (*S*)(+)-II was different from that of (±)-II in the solid state, but in $CHCl_3$ solution it was superimposable with that of (±)-II in the same state.

Partially resolved (*S*)(+)-Ia (mp 82—83°, $[\alpha]_D^{23.5}$ +21.1° ($c=2.168$, $CHCl_3$), optical purity 77%)[1] was treated the same as above. Filtration of precipitated crystals gave (*S*)(+)-II, which showed a mp of 90—91°, $[\alpha]_D^{26}$ +40.3° ($c=0.938$, $CHCl_3$). Extraction of the mother liquor with $CHCl_3$, followed by evaporation *in vacuo*, gave no (*S*)(+)-II. Accordingly, no preferential recrystallization of (*S*)(+)-II from the reaction mixture was expected in this procedure. The infrared spectrum of this sample was identical with that of (±)-II in $CHCl_3$ solution. This sample was used immediately for the following rearrangement.

(±)-Methyl 2-Carbamoyl-2-methyl-3-phenylpropionate ((±)-VI)——To conc. H_2SO_4 (9 ml) was added (±)-Ib[1] (8.0 g, 0.040 mole) under ice cooling. The whole was heated on a water bath at 90° for 30 min.[10] After cooling, the reaction mixture was poured onto crushed ice, and the white crystals which precipitated were extracted with $CHCl_3$ (50 ml ×3). The combined $CHCl_3$ extracts were washed with H_2O (20 ml ×3), and dried over anhyd. Na_2SO_4. Filtration and evaporation afforded white crystals, which were recrystallized from iso-Pr_2O to give pure (±)-VI (6.7 g, 75%) as colorless plates, mp 126—127° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.89; H, 6.86; N, 6.19. IR ν_{max}^{KBr} cm^{-1}: 3410, 3350, 3306, 3246 (NH); 1725 ($COOCH_3$); 1670, 1633 ($CONH_2$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3466, 3406, 3386 (NH);

15) Two possible mechanisms have been proposed for Hofmann and Curtius rearrangements (see ref. 5). One through concerted bond migration, the other is through an acyl nitrene intermediate. However, Lwowski, *et al.*,[16] recently established that the Curtius rearrangement proceeded by the concerted mechanism.

16) S. Linke, G.T. Tisue, and W. Lwowski, *J. Am. Chem. Soc.*, **89**, 6308 (1967).

17) All melting points are uncorrected. IR spectra measurement was performed with Spectrometers, Model DS-301 and Model IR-S, Japan Spectroscopic Co., Ltd. NMR spectra were measured using TMS as the internal standard with a Spectrometer, Model 3H-60 (60 Mc), Japan Electron Optics Lab. Optical activities were determined with a Yanagimoto Photo Directed Reading Polarimeter, Model OR-20.

1725 ($COOCH_3$); 1680, 1590 ($CONH_2$). NMR (in $CDCl_3$ solution): 8.59 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{CH_3}$), 6.74 τ (2H, quartet, $Ph-\underline{CH_2}-\underset{|}{\overset{|}{C}}-$, $J=13.2$ cps), 6.29 τ (3H, singlet, $COO\underline{CH_3}$), 3.85 τ (2H, broad singlet, $CO\underline{NH_2}$), 2.85 τ (5 H, singlet, benzene ring protons).

(*S*)(−)-Methyl 2-Carbamoyl-2-methyl-3-phenylpropionate ((*S*)(−)-VI)——Treatment of (*S*)(+)-Ib[1] (bp 138—148° (5 mmHg), $\alpha_D^{23.5}$ +2.751° ($l=0.1$, neat), optical purity 100%) (1.76 g, 0.0087 mole) similar to (±)-Ib, followed by evaporation of the $CHCl_3$ extracts, afforded (*S*)(−)-VI (1.2 g, 63%) as a colorless solid, mp 110—111°, $[\alpha]_D^{25}$ −8.1° ($c=1.550$, $CHCl_3$). Several recrystallizations from iso-Pr_2O gave pure (*S*)(−)-VI as colorless scales, mp 111—112° (decomp.), $[\alpha]_D^{23}$ −9.0° ($c=1.576$, $CHCl_3$). *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.15; H, 6.69; N, 6.57. IR ν_{max}^{KBr} cm^{-1}: 3430, 3406, 3330, 3290, 3200 (NH); 1735 ($COOCH_3$); 1665, 1608 ($CONH_2$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3406, 3386 (NH); 1725 ($COOCH_3$); 1680, 1585 ($CONH_2$). The infrared spectrum of (*S*)(−)-VI was different from that of (±)-VI in a solid state, but it was identical with that of (±)-VI in $CHCl_3$ solution.

The same treatment of (*S*)(+)-Ib (bp 125—128° (1—2 mmHg), $\alpha_D^{27.5}$ +2.150 ($l=0.1$, neat)), prepared from partially resolved (*S*)(+)-Ia (77% optically pure), gave (*S*)(−)-VI, (mp 107—108° (decomp.), $[\alpha]_D^{26.5}$ −4.8° ($c=2.724$, $CHCl_3$)). The infrared spectrum of this sample in $CHCl_3$ solution was superimposable on that of (±)-VI in the same state. This sample was immediately submitted to rearrangement without recrystallization from iso-Pr_2O.

(±)-Methyl 2-Acetamido-2-methyl-3-phenylpropionate ((±)-IV)——To a methanolic solution (5 ml) of (±)-V[9f] (1.0 g, 0.0045 mole) was added an ether diazomethane solution (20 ml) prepared from nitrosomethylurea (1.0 g, 0.01 mole). After the yellow color of diazomethane stabilized, an excess of diazomethane was decomposed by adding formic acid. The whole was evaporated *in vacuo*. Ether (10 ml) was added to the residue to crystallize (±)-IV (0.85 g, 80%), mp 115—116°. Several recrystallizations of (±)-IV from iso-Pr_2O afforded pure (±)-IV as colorless plates, mp 118—119°.[18] *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.41; H, 7.29; N, 6.20. IR ν_{max}^{KBr} cm^{-1}: 3290, 3078 (NH), 1740 ($COOCH_3$), 1642, 1565 ($CONH_2$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3385 (NH), 1740 ($COOCH_3$), 1673, 1505 ($CONH_2$). NMR (in $CDCl_3$ solution): 8.37 τ (3H, singlet, $-\underset{|}{\overset{|}{C}}-\underline{CH_3}$), 8.06 τ (3H, singlet, $-NHCO\underline{CH_3}$), 6.64 τ (2H, quartet, $Ph-\underline{CH_2}-\underset{|}{\overset{|}{C}}-$, $J=13.5$ cps), 6.25 τ (3H, singlet, $COO\underline{CH_3}$), 3.87 τ (1H, broad singlet, $\underline{NH}$), 3.10—2.60 τ (5H, broad singlet, benzene ring protons).

(*R*)(−)-Methyl 2-Acetamido-2-methyl-3-phenylpropionate ((*R*)(−)-IV)——(*R*)(+)-V[9f] (mp 201—202.5°, $[\alpha]_D^{24}$ +78.1° ($c=0.840$, MeOH), optical purity 100%) (0.50 g, 0.0023 mole) was treated the same as (±)-V. The residue after evaporation of the reaction mixture was purified using a silica gel column (30 g, solvent $CHCl_3$). Fractions containing (*R*)(−)-IV were collected and evaporated *in vacuo* giving a semisolid (0.40 g, 77%), to which was added petr. ether (10 ml). The whole was triturated to yield a white powder. This was recrystallized several times from petr. ether to give pure (*R*)(−)-IV (0.20 g), mp 81—82°, $[\alpha]_D^{23.5}$ −60.1° ($c=1.970$, $CHCl_3$). *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.30; H, 7.30; N, 6.17. IR ν_{max}^{KBr} cm^{-1}: 3320, 3075 (NH), 1735 ($COOCH_3$), 1640, 1550 ($NHCOCH_3$). Its infrared spectrum was different from that of (±)-IV in the same state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1740 ($COOCH_3$), 1670, 1505 ($NHCOCH_3$). This spectrum was superimposable with that of (±)-IV in the same state. The NMR spectrum (in $CDCl_3$ solution) of this sample was identical with that of (±)-IV as measured in the same solvent.

(±)-5-Benzyl-5-methylhydantoin——A mixture of (±)-α-methylphenylalanine hydrochloride[9f] (0.43 g, 0.0020 mole) and potassium cyanate (0.81 g, 0.010 mole) in H_2O (5 ml) was refluxed for 2 hr. After cooling, conc. HCl was added to the reaction mixture and the whole was refluxed for an additional 30 min. (±)-5-Benzyl-5-methylhydantoin (0.16 g, 39%) was crystallized when the reaction mixture was cooled in an ice bath. mp 223—224°. Recrystallization from aqueous EtOH gave pure colorless prisms, mp 225° (lit.[19,20] mp 227—228°). IR ν_{max}^{KBr} cm^{-1}: 3315, 3200 (NH), 1769, 1735, 1714 ($NHCONHCO-\underset{|}{\overset{|}{C}}-$).

Hofmann Rearrangement of (±)- and (*S*)(+)-2-Cyano-2-methyl-3-phenylpropionic Acid ((±)-Ia and (*S*)(+)-Ia) by Way of (±)- and (*S*)(+)-2-Cyano-2-methyl-3-phenylpropionamide ((±)-II and (*S*)(+)-II)——a) The rearrangement by way of (±)-II: Br_2 (1.9 g, 0.012 mole) was added to an aqueous NaOH solution (NaOH (4.0 g, 0.10 mole) in H_2O (40 ml)), which was cooled at −4° in an ice–salt bath. (±)-II (1.9 g, 0.010 mole) was added to the sodium hypobromide solution prepared above, and the whole was stirred at the same temperature for 30 min.

18) Gas chromatographic analysis of (±)-IV (Yanagimoto Gas Chromatograph, Model GCG–550T, 30% SE–30 on diasolid L, 2.25m, 222°) showed two peaks, whose retention times were 2.4 min and 5.5 min. The former peak was identified with the authentic (±)-5-benzyl-2,4-dimethyloxazolin-5-one.[9f] This suggests that (±)-IV was cyclized to oxazolin-5-one derivatives under the release of MeOH by heating.
19) R.M. Herbest and J.B. Johnson, *J. Am. Chem. Soc.*, **54**, 2463 (1932).
20) K.T. Potts, *J. Chem. Soc.*, **1955**, 1632.

The reaction mixture was, then, heated at 85—90° for 30 min. After cooling in an ice bath, the whole was made acidic (pH=1) by adding 10% HCl solution. Precipitated crystals were extracted with $CHCl_3$ (30 ml ×3) and the combined $CHCl_3$ layers were washed with H_2O, and dried over anhyd. Na_2SO_4. Filtration and evaporation gave (±)-5-benzyl-5-methylhydantoin (1.9 g, 95%) as a white solid, mp 226—228°. This was recrystallized from EtOH (5 ml) to afford a pure sample, mp 226—227°. Mixed melting point measurement of this with an authentic sample, prepared independently, showed no depression. Its infrared spectrum was also identical with the authentic sample in the same state.

A part of the hydantoin derivative (0.80 g, 0.004 mole) obtained above was dissolved in a 20% aqueous NaOH solution (16 ml), and the whole was refluxed for 10 hr. After being made acidic (pH=1) by the addition of 10% aqueous HCl solution, the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in conc. HCl (20 ml), and undissolved matter was filtered out. The acidic filtrate was evaporated to dryness *in vacuo*. Addition of H_2O (50 ml) to the residue and evaporation of the aqueous solution were repeated several times to give a brown powder. This was dissolved in H_2O (50 ml). The solution was poured through an ion exchange column (Amberlite IR-120, H^+ form, 100 ml). The column was washed with H_2O until the eluate became neutral. It was then eluted with diluted NH_4OH until the ninhydrin test became negative. Combined eluates were evaporated to dryness giving crude (±)-III (0.50 g, 71% from 5-benzyl-5-methylhydantoin) as a white powder. The infrared spectrum of this crude sample was identical with that of the authentic (±)-III[9f] in a solid state.

Crude (±)-III (0.50 g, 0.003 mole) was dissolved in a mixture of pyridine (3 ml) and Ac_2O (3 ml) by heating. The mixture was kept overnight at room temperature. The whole was poured onto crushed ice (*ca.* 50 g). The solution was evaporated *in vacuo* after addition of H_2O (*ca.* 50 ml). After this procedure was repeated several times, the residue was treated the same as (±)-V to afford crude (±)-IV (0.50 g), which was purified using a silica gel column (30 g, solvent $CHCl_3$), which gave (±)-IV (0.20 g, 32% based on (±)-III), mp 115—116°. Thin layer chromatography[21] of this sample showed a single spot, whose *Rf* value (0.3) was identical with that of the authentic (±)-IV. One recrystallization from iso-Pr_2O gave pure (±)-IV as colorless needles, mp 118—119°. Mixed melting point measurement of this sample with the authentic (±)-IV (mp 118—119°) showed no depression (mp 117°). Infrared spectra of this sample were identical with those of authentic (±)-IV in a solid state and in $CHCl_3$ solution.

b) Rearrangement by way of (*S*)(+)-II: (*S*)(+)-II (mp 100—101°, $[\alpha]_D^{21.5}$ +55.1° (c=2.036, $CHCl_3$)) (0.94 g, 0.0050 mole) was added to sodium hypobromide solution, prepared from NaOH (8.0 g, 0.20 mole) and Br_2 (1.0 g, 0.0062 mole) in H_2O (20 ml). The reaction mixture was treated the same as (±)-II and gave (+)-IV (0.143 g, 12% from (*S*)(+)-II). In this case, the alkaline reaction mixture was refluxed immediately for 10 hr without isolation of the hydantoin derivative. This sample showed a mp of 80—81°, and $[\alpha]_D^{25}$ +59.2° (c=1.768, $CHCl_3$). Thin layer chromatography[21] of the (+)-IV showed a single spot whose *Rf* value (0.3) was identical with that of the authentic (*R*)(−)-IV. Infrared spectra of this sample were superimposable with those of authentic (*R*)(−)-IV in a solid state and in $CHCl_3$ solution. The optical purity of the (+)-IV was calculated as 99% based on the assumption that (*R*)(−)-IV showing $[\alpha]_D^{23.5}$ −60.1° (c=1.970, $CHCl_3$) was optically pure. The rearrangement of (*S*)(+)-II obviously proceeded with 99% configuration retention. The same rearrangement was performed twice more using (*S*)(+)-II (mp 90—91°, $[\alpha]_D^{26}$ +40.3° (c=0.938, $CHCl_3$)). Two lots of (+)-IV (mp 79—80°, $[\alpha]_D^{21}$ +48.6° (c=2.058, $CHCl_3$), and mp 78—79°, $[\alpha]_D^{21}$ +44.8° (c=2.038, $CHCl_3$)) were obtained in 20% and 18% yields, respectively, from (*S*)(+)-II. These samples were identified with (+)-IV prepared previously by thin layer chromatography,[21] infrared spectra and mixed melting point measurements.

Hofmann Rearrangement of (±)- and (*S*)(+)-2-cyano-2-methyl-3-phenylpropionic Acid ((±)- and (*S*)(+)-Ia) by Way of (±)- and (*S*)(−)-2-Methyl 2-Carbomoyl-2-methyl-3-phenylpropionat ((±)- and (*S*)(−)-VI) ——a) Rearrangement by way of (±)-VI: To a sodium hypobromide solution (30 ml), prepared from NaOH (4.0 g, 0.10 mole) and Br_2 (2.0 g, 0.013 mole), (±)-VI (2.20 g, 0.010 mole) was added at −5°. After stirring at the same temperature for 30 min, the whole was heated at *ca.* 93° for 30 min, in a water bath. After cooling, the reaction mixture was made acidic (pH=3) by adding 10% HCl, followed by evaporation *in vacuo*. The residue was extracted with conc. HCl (50 ml). The conc. HCl extract was diluted with H_2O (25 ml) and refluxed for 17 hr. Evaporation *in vacuo* and addition of H_2O to the residue were repeated, alternately several times. The residue was dissolved in H_2O (50 ml). This solution was treated using an ion exchange column (Amberlite IR-120, H^+ form, 100 ml), as in the case of (±)-II, to afford crude (±)-III. The same treatment of crude (±)-III, as in the case of (±)-II, gave (±)-IV (0.80 g, 34% from (±)-VI), mp 116—117°. Pure (±)-IV was prepared by recrystallization from iso-Pr_2O, mp 118—119°. This sample was identified with the authentic (±)-IV using mixed melting point measurements.

b) Rearrangement by way of (*S*)(−)-VI: Treatment of (*S*)(−)-VI (mp 110—111°, $[\alpha]_D^{23}$ −9.0° (c=1.576, $CHCl_3$)) (1.1 g, 0.0050 mole) the same as that of (±)-VI afforded (−)-IV (mp 76—77°, $[\alpha]_D^{21.5}$ −55.6° (c=2.544, $CHCl_3$)) (0.46 g, 38%), which was identified with authentic (*R*)(−)-IV by thin layer chromatography and infrared spectra. This sample showed no depression (mp 79—80°) in mixed melting point

21) Silica gel (Kiesel gel G F_{254} nach Stahl), solvent $CHCl_3$.

measurement with authentic (*R*)(−)-IV (mp 81—82°). As this sample was 93% optically pure, it is evident that rearrangement of (*S*)(−)-VI proceeded with 93% retention of configuration.

This rearrangement was carried out twice more using (*S*)(−)-VI (mp 107—108°, $[\alpha]_D^{26.5}$ −4.8° (*c*=2.724, $CHCl_3$)) prepared from partially resolved (*S*)(+)-Ia (77% optically pure). (−)-IV, obtained in 24% and 19% yields, based on (*S*)(−)-VI; respectively, showed mp 78—79°, $[\alpha]_D^{31}$ −44.0° (*c*=2.530, $CHCl_3$) and mp 77—78°, $[\alpha]_D^{26}$ −47.8° (*c*=2.376, $CHCl_3$). These samples were confirmed by thin layer chromatography,[21] infrared spectra and mixed melting point measurements.

Curtius Rearrangement of (±)- and (*S*)(+)-2-Cyano-2-methyl-3-phenylpropionic acid ((±)- And (*S*)(+)-Ia) ——a) The Rearrangement of (±)-Ia: A mixture of (±)-Ia (18.9 g, 0.100 mole) and PCl_5 (22.0 g, 0.110 mole) in hexane (400 ml) was stirred at room temperature for 2 hrs. The $POCl_3$ produced and its solvent were evaporated on a water bath. The residue was submitted to fractional distillation under reduced pressure to give an acid chloride ((±)-VII) (20.4 g, 98%) as a pale yellow oil, bp 132—134° (7 mmHg). IR ν_{max}^{cap} cm^{-1}: 2275 (CN), 1780 (COCl).

Part of the acid chloride (2.1 g, 0.010 mole) was dissolved in acetone (20 ml). This was added dropwise to an aqueous solution (H_2O, 6 ml) of NaN_3 (0.93 g, 0.014 mole). Stirring was continued for 1 hr and the solvent was evaporated at room temperature under reduced pressure. A residual oil was extracted with benzene (20 ml×3). The benzene layer was dried over anhyd. $CaCl_2$. Evaporation of the benzene solution gave an oil, which showed absorptions at 2230 cm (CN) and 2190 cm (N_3) in its infrared spectrum.

This oil was dissolved in toluene (40 ml), and the whole was refluxed for 2 hr. Evaporation of toluene left an yellow oil, whose infrared spectrum showed an intense absorption at 2280 cm^{-1}. This oil seems to be (±)-2-cyano-2-isocyanato-1-phenylpropane. To this oil 47% hydrobromic acid (20 ml) was added, and the mixture was refluxed for 7 hr. After evaporation to dryness *in vacuo*, H_2O (50 ml) was added to the residue. Precipitated crystals showed an identical infrared spectrum with (±)-5-benzyl-5-methylhydantoin. The aqueous solution was evaporated *in vacuo*, and 20% NaOH solution was added to the residue. The alkaline solution was refluxed for 20 hr, followed by the same treatment as in the Hofmann rearrangement to give (±)-IV (0.70 g, 30% based on (±)-VII), mp 113—114°. Recrystallization from iso-Pr_2O gave pure (±)-IV, mp 118—119°. This sample was identified with authentic (±)-IV using thin-layer chromatography,[21] infrared spectra and mixed melting point measurement.

b) The rearrangement of (*S*)(+)-Ia: Treatment of (*S*)(+)-Ia (mp 87.5—89°, $[\alpha]_D^{21}$ +27.4° (*c*=2.556, $CHCl_3$), 100% optically pure) the same as that of (±)-Ia afforded (*S*)-VII in a 91% yield, bp 124—128° (5 mmHg). (*S*)-VII was also prepared by refluxing (*S*)(+)-Ia with $SOCl_2$ in benzene solution. (*S*)-VII, prepared from (*S*)(+)-Ia (2.0 g, 0.011 mole) using $SOCl_2$ (8.0 g, 0.090 mole) and benzene (40 ml), was treated as was (±)-VII to afford (+)-IV (0.46 g, 18% based on (*S*)(+)-Ia), mp 78—79°, $[\alpha]_D^{23}$ +57.0° (*c*=2.050, $CHCl_3$). Infrared spectra of this sample were identical with those of authentic (*R*)(−)-IV in the solid state and in $CHCl_3$ solution. This sample was further confirmed using thin layer chromatography.[21] These results, showed that (+)-IV obtained from this rearrangement was 95% optically pure. This established that Curtius rearrangement of (*S*)(+)-Ia proceeded with 95% retention of configuration.

The same rearrangements were made twice more using partially active (*S*)(+)-Ia (mp 78—79°, $[\alpha]_D^{25.5}$ +21.1° (*c*=2.168, $CHCl_3$) to give (+)-IV in 13% and 10% yields, respectively. These samples showed mp 78—79°, $[\alpha]_D^{25.5}$ +45.7° (*c*=2.010, $CHCl_3$), and mp 78—79°, $[\alpha]_D^{25.5}$ +45.9° (*c*=1.876, $CHCl_3$), and were confirmed by comparison of infrared spectra and by thin layer chromatography.[21]

Acknowledgement The authors are indebted to members of the Central Analysis Room of this Faculty for elemental analyses and spectral measurements.