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Stereochemical Studies. III.[1] Chemical Correlation of Absolute Configuration of 2-Cyano-2-methyl-3-phenylpropionic Acid to α-Methyl-α-isopropylsuccinic Acid

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The absolute configuration of (+)-2-cyano-2-methyl-3-phenylpropionic acid (Ia), an important compound for the investigation of reaction mechanisms, was elucidated as (*S*)-series by chemical correlation with (*S*)(+)-α-methyl-α-isopropylsuccinic acid ((*S*)(+)-III), whose absolute configuration is already established. During the correlation, (+)-2-isopropyl-2-methyl-3-phenylpropionic acid ((+)-VII) was also confirmed as belonging to (*R*) series.

Preliminary experiments on racemic compounds are described in detail in the experimental section.

2-Cyano-2-methyl-3-phenylpropionic acid (Ia), carrying a cyano group on the optically active quarternary carbon at α position to the carboxyl group, is considered to of value for the preparation of various compounds having an optically active quarternary carbon, when investigations on reaction mechanisms are examined; since the carboxyl and/or the cyano groups of Ia can be easily converted to other functional groups, *i.e.* ester, amide, hydroxymethyl *etc.* However, it has been assumed by Cram, *et al.*[3] that the absolute configuration of Ia showing $[\alpha]_D^{25}$ +25.7° (c=2.4, $CHCl_3$) is (*S*)-configuration, by speculation on the reaction mechanisms of the decarboxylation reaction of optically active Ia, itself and base-induced elimination reaction of optically active 2-benzyl-3-hydroxy-2,3-dimethylbutyronitrile (II) prepared from Ia.

In the course of our studies on reaction mechanisms, using several optically active compounds having only one asymmetric carbon,[4] it became nessessary to clearly establish the absolute configuration of Ia, in order to study the reaction mechanisms of several rearrangement reactions using optically active Ia and its derivatives.[5]

Establishment of the absolute configuration of Ia was undertaken by its chemical correlation to optically active α-methyl-α-isopropylsuccinic acid (III), whose absolute configuration has been already determined by the quasi-racemate technique[6] and the X-ray diffraction method.[7]

The chemical scheme which we employed is shown in Chart 1.

1) Part II: S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968).
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) *a*) D.J. Cram and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 2363 (1961); *b*) D.J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York and London, 1965, p. 142.
4) *a*) S. Yamada, S. Terashima, and H. Mizuno, *Chem. Commun.*, **1967**, 1058; *b*) S. Yamada and S. Terashima, *Chem. Pharm. Bull.* (Tokyo), **16**, 1816 (1968); *c*) S. Terashima and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1953 (1968); *d*) S. Yamada and S. Terashima, *Chem. Commun.*, **1969** 511
5) K. Achiwa, Kong Ko Lee, S. Terashima, and S. Yamada, 85th Annual Meeting of the Pharmaceutical Society of Japan, October, 1964.
6) J. Porath, *Arkiv. Kemi.*, **1**, 385 (1949).
7) M.R. Cox, H.P. Koch, and W.B. Whalley, *Chemun. Commum.*, **1967**, 212.

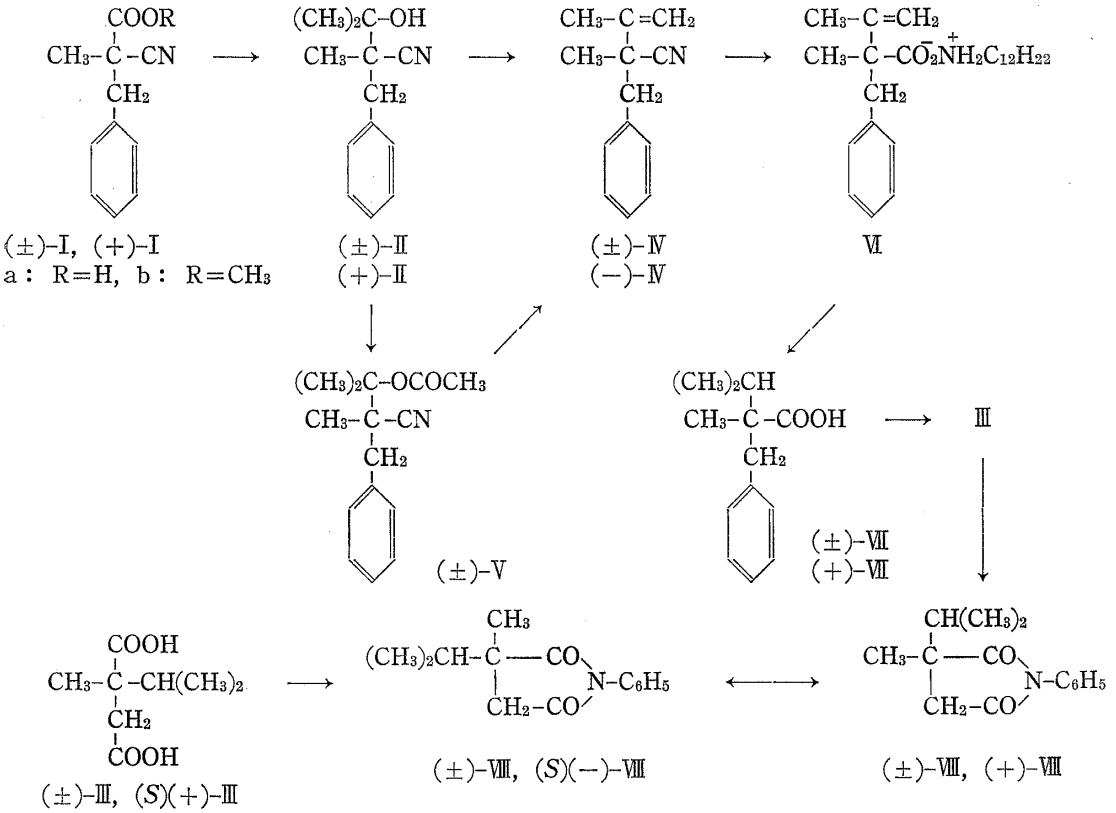

Chart 1

Esterification of (+)-Ia, $[\alpha]_D$ +19.7° ($CHCl_3$), prepared by the resolution of (±)-Ia according to the method of Kenyon, *et al.*,[8] gave (+)-methyl ester ((+)-Ib), $\alpha_D^{23.5}$ +2.188° (l=0.1, neat), which was treated with an excess amount of methyl magnesium iodide to afford (+)-II, $[\alpha]_D^{23}$+17.2° ($CHCl_3$), in a 75% yield from (+)-Ib. A pyridine solution containing (+)-II, thus obtained, and thionyl chloride[9] were stirred for 40 hr at room temperature, followed by purification using silica gel column chromatography, then fractional distillation under reduced pressure, to give (−)-2-benzyl-2,3-dimethyl-3-butenonitrile ((−)-IV), $[\alpha]_D^{23}$ −11.1° ($CHCl_3$), as a colorless oil in a 40% yield based on (+)-II.

In preliminary studies on reaction conditions using racemic compounds, (±)-IV was prepared in a 37% yield by the same treatment of (±)-II as in the case of the optically active compound. It was also obtainable in an 86% yield on the reflux of (±)-3-acetoxy-2-benzyl-2,3-dimethylbutyronitrile ((±)-V), prepared from (±)-II, with a catalytic amount of *p*-toluenesulfonic acid in xylene. (±)-IV obtained from (±)-II directly and (±)-V were identified by infrared spectra and gas chromatography.

Hydrolysis of the cyano group of (−)-IV was accomplished by stirring and heating at 130—140° in diethylene glycol with 10 equivalent potassium hydroxide.[10] The resulting carboxylic acid was isolated as dicyclohexylamine salt (VI) from the acidic extracts in a 64% yield. Crude VI was hydrogenated without purification using 5% Pd on charcoal at standard temperature and pressure, followed by decomposition of the hydrogenated salt with potassium hydroxide, to afford (+)-2-isopropyl-2-methyl-3-phenylpropionic acid ((+)-VII), $[\alpha]_D^{22}$+58.0° ($CHCl_3$). Yield from the hydrogenation and the decomposition of the salt with alkali were 94% and 84%, respectively. (+)-VII was treated with ozone, then with aqueous 30% hydrogen peroxide yielding crude III. Reflux of crude III with aniline for 1 hr, followed by puri-

8) J. Kenyon and W.A. Ross, *J. Chem. Soc.*, **1951**, 3407.
9) D.H.R. Barton, P. deMayo, and M. Safig, *J. Chem. Soc.*, **1958**, 3314.
10) H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1749 (1967).

fication with a silica gel column, afforded (+)-N-phenyl-α-methyl-α-isopropylsuccinimide ((+)-VIII), mp 91.5—92.5°, $[\alpha]_D^{25}$ +51.3° (EtOH), in a 40% yield based on (+)-VII.

On the other hand, the same treatment of (*S*)(+)-III, $[\alpha]_D^{18}$ +17.6° (EtOH), whose absolute configuration has already been established, as in the case of above, gave (*S*)(−)-VIII, mp 91.5—93°, $[\alpha]_D^{22}$ −56.3° (EtOH) in a 71% yield.

(+)-VIII prepared from (+)-VII and (*S*)(−)-VIII from (*S*)(+)-III showed identical infrared spectra in the solid state and in chloroform solution, but opposite signs for optical activity and optical rotatory dispersion curve measurements, so it is evident that (+)-VIII, obtained from (+)-Ia, had (*R*)-configuration.[11]

These results, as shown in Chart 2, establish unequivocally that the (+)-Ia used in this correlation has (*S*)-configuration as Cram has suggested.

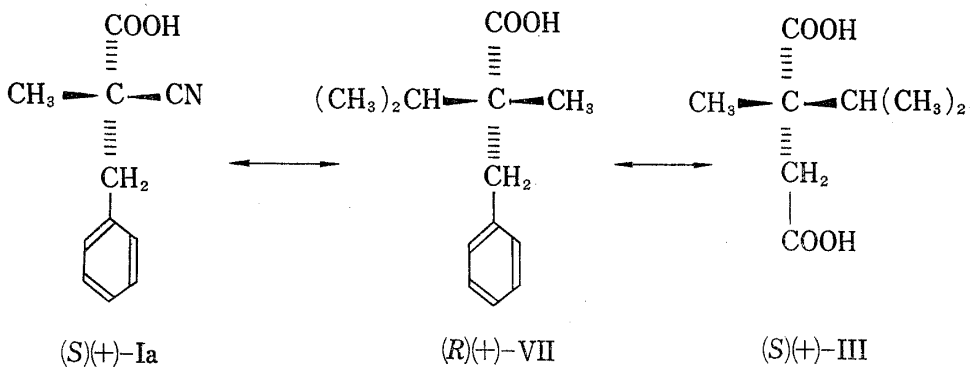

Chart 2

During chemical correlation, (+)-VIII, containing an asymmetric quarternary carbon at α position to the carboxyl group, was also determined to be (*R*)-series. This compound also seems to be valuable for investigations on reaction mechanisms.

Preliminary experiments with racemic compounds, and product identification using infrared and nuclear magnetic resonance spectra are described in detail in the experimental section.

Experimental[12]

(±)- and (*S*)(+)-2-Cyano-2-methyl-3-phenylpropionic Acid ((±)-Ia and (*S*)(+)-Ia)——(±)-Ia was prepared from benzaldehyde and ethyl cyanoacetate *via* ethyl α-cyanocinnamate (mp 51—52.5°) (lit.,[13] mp 51°; lit.,[14] mp 52°), (±)-ethyl α-cyanohydrocinnamate (bp 151—154° (6 mmHg)) (lit.,[15] bp 176—183° (21 mmHg); lit.,[16] bp 172—174° (11 mmHg)), and (±)-ethyl 2-cyano-2-methyl-3-phenylpropionate (bp 149—151° (9.5 mmHg)) (lit.,[8] bp 162—165° (14 mmHg)). (±)-Ia, recrystallized from ligroin as colorless crystals, showed a mp of 94—95° (lit.,[8] mp 94—95°). (±)-Ia obtained above was resolved according to the method of Kenyon, *et al.*,[8] affording (+)-Ia as colorless plates (recrystallized from ligroin), mp 87.5—

11) Mixed melting point measurement of (+)-VIII and (*S*)(−)-VIII showed mp 71.5—76°, which was close to that of (±)-VIII (mp 73.5—74.5°).

12) All melting points are uncorrected. IR spectra were measured using Spectrometers, Model DS-402 and Model IR-S, Japan Spectroscopic Co., Ltd. NMR spectra measurements were performed 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 Direct Reading Polarimeter, Model OR-20. ORD measurements were carried out with a Spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Gas chromatographic analyses were performed using Yanagimoto Gas Chromatographs, Model GCG-3D(**A**) and Model GCG-550T (**B**).

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16) E. Testa, A. Botani, G. Pagani, and E. Gatti, *Ann.*, **647**, 92 (1961).

89°, $[\alpha]_D^{21}$ +27.4° (c=2.556, $CHCl_3$) (lit.,[8] mp 87.5—88.5°, $[\alpha]_D^{19}$ +25.1° (c=2.43, $CHCl_3$); lit.,[3a] mp 88—89°, $[\alpha]_D^{25}$ +25.7° (c=2.4, $CHCl_3$)).

(±)-Methyl 2-Cyano-2-methyl-3-phenylpropionate ((±)-Ib)——A ether solution of (±)-Ia was treated with diazomethane as usual[3a] giving (±)-Ib as a colorless oil, bp 140—141° (8 mmHg). IR $\nu_{max}^{Cap.}$ cm^{-1}: 2230 (CN), 1743 ($COOCH_3$). NMR (in CCl_4 solution): 8.51 τ (3H, singlet, $-\underset{\underset{CH_3}{|}}{C}-$), 6.98 τ (2H, quartet, J=13.2 cps, $C_6H_5-C\underline{H}_2-$), 6.41 τ (3H, singlet, $COOC\underline{H}_3$), 2.84 τ (5H, singlet, benzene ring protons). *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.30; N, 6.80.

(+)-Methyl 2-cyano-2-methyl-3-phenylpropionate ((+)-Ib)——The same treatment for (+)-Ia ($[\alpha]_D$ +19.7° ($CHCl_3$))[17] (22.2 g, 0.017 mole) as that of (±)-Ia afforded (+)-Ib as a colorless oil, which showed bp 131—132° (4 mmHg), $\alpha_D^{23.5}$ +2.188° (l=0.1, neat) (lit.,[3a] α_D^{27} +26.72° (l=1, neat)). The IR spectrum of (+)-Ib thus obtained was identical with that of (±)-Ib in the same state.

(±)-2-Benzyl-3-hydroxy-2,3-dimethylbutyronitrile ((±)-II)——Grignard's solution prepared from Mg (4.0 g, 0.16 atom) and methyl iodide (24.0 g, 0.17 mole) in ether (160 ml) was added to an ether solution (40 ml) of (±)-Ib (8.0 g, 0.039 mole), for 10 min under ice cooling. Stirring was continued for 30 min in an ice bath and the complex prepared was decomposed with NH_4Cl solution, as usual. The upper ether layer was washed with satd. NaCl solution, diluted AcOH solution and satd. NaCl solution, then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a pale yellow oil (7.9 g), which solidified on trituration. Recrystallization of this solid with a mixture of benzene (20 ml) and hexane (100 ml) afforded crude (±)-II (4.4 g) as colorless crystals, mp 75.5—79.5°. Mother liquor of the recrystallization was evaporated to dryness *in vacuo*, and the resulting yellow oil was purified with column chromatography using silica gel (solvent $CHCl_3$), followed by recrystallization from benzene–hexane which afforded more crude (±)-II (1.0 g) as colorless crystals, mp 77.5—82.5°. Total yield of (±)-II was 68%. Pure (±)-II was obtained as colorless crystals, mp 81.5—82.5°, by several recrystallizations from benzene–hexane. *Anal.* Calcd. for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.23; H, 8.50; N, 6.99. IR ν_{max}^{KBr} cm^{-1}: 3495 (OH), 2230 (CN), 1210, 1195 (OH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3480 (OH), 2230 (CN). NMR (in $CDCl_3$ solution): 8.83 τ (3H, singlet, $-\underset{\underset{CH_3}{|}}{C}-$), 8.57 τ (6H, singlet, $-\underset{|}{C}-(C\underline{H}_3)_2$), 7.67 τ (1H, singlet, O$\underline{H}$), 7.10 τ (2H, quartet, J=13.2 cps, $C_6H_5-C\underline{H}_2-$), 2.74 τ (5H, singlet, benzene ring protons). A signal of 7.67 τ disappeared after treatment with D_2O.

(+)-2-Benzyl-3-hydroxy-2,3-dimethylbutyronitrile ((+)-II)——The same treatment for (+)-Ib (bp 131—132° (4 mmHg), $\alpha_D^{23.5}$ +2.188° (l=0.1, neat)) (22.3 g, 0.110 mole) as that of (±)-Ib gave a colorless solid (24.3 g), mp 82—98°, after evaporation of the ether extract. This was recrystallized from a mixture of benzene–hexane (1:3, 60 ml) to afford crude (+)-II (16.6 g, 75%) as colorless crystals, mp 94—105°, $[\alpha]_D^{24.5}$ +19.4° (c=2.706, $CHCl_3$). Four recrystallizations of crude (+)-II from the same solvent system gave pure (+)-II as colorless plates, mp 109—110°, $[\alpha]_D^{23}$ +17.2° (c=1.616, $CHCl_3$) (lit.,[3a] mp 108—109°, $[\alpha]_D^{26}$ +22.33° (c=10, $CHCl_3$)). IR spectra of (+)-II were superimposable with those of (±)-II in the solid state and in $CHCl_3$ solution.

(±)-3-Acetoxy-2-benzyl-2,3-dimethylbutyronitrile ((±)-V)——A mixture of (±)-II (7.3 g, 0.036 mole) and Et_3N (4.0 g, 0.040 mole) in acetic anhydride (73 ml) was refluxed for 5 hr. The whole was evaporated to dryness *in vacuo* giving a brown oil. H_2O (40 ml) was added to the oil, and extracted with ether (50 ml, ×2). The combined ether extracts were washed with H_2O (40 ml, ×1), diluted aq. $NaHCO_3$ (40 ml, ×1), then H_2O (40 ml, ×1), and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a reddish brown oil, which was submitted to column chromatography using silica gel (150 g, solvent $CHCl_3$). Fractions containing (±)-V were combined and evaporated to dryness *in vacuo* affording a yellow oil (5.5 g), which was recrystallized from hexane (25 ml) giving crude (±)-V (4.1 g, 47%) as pale yellow crystals, mp 69—70°. Pure (±)-V was obtained as colorless prisms by the two recrystallizations from the same solvent, mp 70.5—71°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.69; H, 7.72; N, 5.43. IR ν_{max}^{KBr} cm^{-1}: 2225 (CN), 1742 (CH_3COO-), NMR (in $CDCl_3$ solution): 8.78 τ (3H, singlet, $-\underset{\underset{CH_3}{|}}{C}-$), 8.27 τ (6H, singlet, $(C\underline{H}_3)_2\underset{|}{C}-$), 7.95 τ (3H, singlet, $C\underline{H}_3COO-$), 7.08 τ (2H, quartet, J=13.2 cps, $C_6H_5C\underline{H}_2-$), 2.68 τ (5H, singlet, benzene ring protons).

(±)-2-Benzyl-2,3-dimethyl-3-butenonitrile ((±)-IV)——a) (±)-IV from (±)-V: A xylene solution (120 ml) of (±)-V (8.3 g, 0.034 mole) and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 8 hr using Cope's apparatus. The brown solution prepared was washed with satd. aq. $NaHCO_3$ (50 ml,

17) Six lots of (+)-Ia shown below were cautiously mixed and used. The optical rotation of (+)-Ia used was calculated to be $[\alpha]_D$ +19.7° ($CHCl_3$). $[\alpha]_D^{19}$ +22.2° (c=2.374, $CHCl_3$) (0.5 g); $[\alpha]_D^{20}$ +20.2° (c=2.052, $CHCl_3$) (8.9 g); $[\alpha]_D^{21}$ +18.9° (c=2.014, $CHCl_3$) (0.9 g); $[\alpha]_D^{23}$ +18.4° (c=2.066, $CHCl_3$) (4.6 g); $[\alpha]_D^{23}$ +21.0° (c=2.342, $CHCl_3$) (1.3 g); $[\alpha]_D^{23}$ +19.7° (c=2.776, $CHCl_3$) (6.0 g).

×1), and satd. aq. NaCl (50 ml, ×2), then dried over anhyd. Na_2SO_4. A brown oil, obtained by filtration and evaporation of the above solution, was submitted to fractional distillation giving (±)-IV as a colorless oil (5.4 g, 86%), bp 115—115.5° (4 mmHg). Purification of crude (±)-IV with column chromatography by silica gel (solvent $CHCl_3$), then distillation under reduced pressure afforded pure (±)-IV as a colorless oil, bp 110° (5 mmHg) (bath temperature 135°). *Anal.* Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.45; H, 8.30; N, 7.52. IR $\nu_{max}^{Cap.}$ cm^{-1}: 2225 (CN), 1645, 906 ($-\overset{|}{C}=CH_2$). NMR (in $CDCl_3$ solution): 9.10 τ (3H, singlet, $-\overset{CH_3}{\overset{|}{C}}-$), 8.14 τ (3H, doublet, J=1.5 cps, $-\overset{CH_3}{\overset{|}{C}}=CH_2$), 7.09 τ (2H, quartet, J=13.8 cps, $C_6H_5-\underline{CH_2}-$), 5.04 τ (1H, multiplet, J=1.5 cps, $-\overset{CH_3}{\overset{|}{C}}=C\langle\overset{H}{\underline{H}}$), 4.94 τ (1H, singlet, $-\overset{CH_3}{\overset{|}{C}}=C\langle\overset{H}{\underline{H}}$), 2.76 τ (5H, singlet, benzene ring protons). Gas chromatographic analysis (5% SE-30 on diasolid L, 3 m, 167°, (A)) of this sample showed a single peak (retention time, 17.4 min).

b) (±)-IV from (±)-II: $SOCl_2$ (8.8 g, 0.074 mole) was added to a pyridine solution (30 ml) of (±)-II (3.0 g, 0.015 mole) for 5 min under stirring and ice cooling (10—20°). After the addition of $SOCl_2$ was finished, the ice bath was removed and stirring was continued for 40 hr at room temperature giving a dark colored solution, which was then poured onto H_2O (60 ml) under ice cooling. The whole was extracted with ether (100 ml, 50 ml), and the combined ether layers were washed successively with H_2O (50 ml, ×1), 10% aq. AcOH (50 ml, ×2), H_2O (50 ml, ×1), satd. aq. $NaHCO_3$ (50 ml, ×1), and H_2O (50 ml, ×2), then dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave an orange oil (2.5 g), which was purified with column chromatography using silica gel (100 g, solvent $CHCl_3$). Fractions containing (±)-IV were combined, and evaporated *in vacuo* yielding yellow oil. Fractional distillation of the oil afforded (±)-IV (1.0 g, 37%) as a colorless oil, bp 122—123° (7 mmHg). Refractionation of the (±)-IV obtained above gave pure (±)-IV as a colorless oil, bp 114—115° (4 mmHg). The IR spectrum of this sample, measured in capillary, was identical with that of the (±)-IV prepared in **a**). Gas chromatographic analysis (5% SE-30 on diasolid L, 3 m, 167°, (A)) showed a single peak whose retention time (17.2 min) was identical with that of (±)-IV obtained in a).

(−)-2-Benzyl-2,3-dimethyl-3-butenonitrile ((−)-IV)——(+)-II (mp 94—105,° $[\alpha]_D^{24.5}$ +19.4° (c=2.706, $CHCl_3$)) (15.6 g, 0.0768 mole) was treated the same as (±)-II affording crude (−)-IV (5.7 g, 40%) as a colorless oil bp 117.7—122° (5.5 mmHg), α_D^{22} −1.013° (l=0.1, neat), $[\alpha]_D^{23}$ −10.6° (c=5.308, $CHCl_3$). Crude (−)-IV was further purified with column chromatography using silica gel, followed by fractional distillation under reduced pressure to give pure (−)-IV as a colorless oil, bp 118° (5 mmHg), $[\alpha]_D^{23}$ −11.1° (c=0.450, $CHCl_3$).[18] *Anal.* Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.07; H, 8.09; N, 7.62. The IR spectrum of this sample was identical with that of (±)-IV in a capillary. Gas chromatographic analysis (5% SE-30 on diasolid L, 3 m, 167°, (A)) showed a single peak whose retention time (16.2 min) was identical with that of (±)-IV. ORD: $[M]^{23}$ (c=0.450, $CHCl_3$) (mμ): −14.8° (700), −20.6° (589), −23.0° (500). −57.5° (400), −86.5° (350), −154° (300).

(±)-2-Isopropyl-2-methyl-3-phenylpropionic Acid ((±)-VII)——A mixture of (±)-IV (4.5 g, 0.024 mole) and KOH (13.6 g, 0.243 mole) in diethylene glycol (40 ml) was stirred for 15 hr at 130—140°. H_2O (50 ml) was added to the reaction mixture, and the whole was extracted with ether (50 ml, ×2). The aqueous layer was made acidic (pH<1) with concd. HCl, and extracted with ether (50 ml, 30 ml, ×2). Combined ether layers were washed with H_2O (50 ml, ×2) and dried over anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave a brown oil (4.9 g), to which was added dicyclohexylamine (4.5 g, 0.025 mole) in ether (10 ml). The brown solid obtained by trituration was filtered and thoroughly washed with ether. (±)-2-methyl-2-(2-propenyl)-3-phenylpropionic acid dicyclohexylamine salt ((±)-VI) prepared as a brown powder (6.8 g, 72%) showed a mp 159.5—161°. Recrystallization of this brown powder from EtOH (50 ml) gave crude (±)-VI as pale yellow needles, mp 161.5—163.5°. IR ν_{max}^{KBr} cm^{-1}: 1623, 1542 ($COO^- \overset{+}{N}H_2\langle$), 899 ($-\overset{|}{C}=CH_2$).

A part of the crude (±)-VI (0.47 g, 0.0012 mole) prepared above was hydrogenated in EtOH (30 ml) using 5% Pd/C (0.20 g) as catalyst, until H_2 absorption ceased. Filtration and evaporation gave (±)-VII dicyclohexylamine salt (0.41 g, 88% based on (±)-VI) as a white solid, mp 148.5°. Two recrystallizations of the crude salt from aq. EtOH afforded a pure sample as colorless needles, mp 148.5—150°. *Anal.* Calcd. for $C_{25}H_{41}O_2N$: C, 77.47; H, 10.67; N, 3.61. Found: C, 77.45; H, 10.44; N, 4.25. IR ν_{max}^{KBr} cm^{-1}: 1623, 1538 ($COO^- \overset{+}{N}H_2\langle$). This IR spectrum showed no absorption at 900 cm^{-1}.

A 50% aqueous ethanolic solution (10 ml) containing crude (±)-VII dicyclohexylamine salt (0.22 g, 0.00057 mole) and KOH (1.0 g, 0.018 mole) was refluxed for 1 hr and concentrated under reduced pressure to *ca.* 1/2 volume. After addition of H_2O (4 ml), the whole was extracted with ether (10 ml, ×3). The aqueous layer was made acidic (pH<1) using 10% HCl, and the oil separated was extracted with ether (10 ml, ×2). The combined ether layers were washed with satd. NaCl (10 ml, ×2) and dried with anhyd. Na_2SO_4. Filtration and evaporation *in vacuo* gave crude (±)-VII (0.11 g, 92%) as a pale yellow solid, mp 93.5—94.5°.

18) This optical rotation value was calculated from the ORD chart.

The analytical sample was prepared as colorless prisms by several recrystallizations from hexane, mp 94.5—96.5°. *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.85; H, 8.77. IR ν_{max}^{KBr} cm^{-1}: 1707, 1682 (COOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (COOH). NMR (in $CDCl_3$ solution): 9.05 τ (3H, singlet, $-\underset{\underset{CH_3}{|}}{C}-$), 9.04, 9.00 τ (6H, 2 doublets, $J=6.6$ cps, $(\underline{CH_3})_2CH-$), 7.88 τ (1H, septet, $(CH_3)_2\underline{CH}-$), 7.13 τ (2H, quartet, $J=13.2$ cps, $C_6H_5-\underline{CH_2}-$), 2.85 τ (5H, singlet, benzene ring protons), −1.26 τ (1H, broad singlet, COO<u>H</u>). A signal which appeared at −1.26 τ disappeared after treatment with D_2O.

(+)-2-Isopropyl-2-methyl-3-phenylpropionic Acid ((+)-VII)——(−)-IV (bp 117.5—122° (5.5 mmHg), $[\alpha]_D^{23}$ −10.6° ($c=5.308$, $CHCl_3$)) (4.5 g, 0.024 mole) was treated the same as (±)-IV giving optically active VI (4.9 g) as brown powder, mp 147.5—150.5°, which was recrystallized from H_2O–EtOH (1:1) (60ml) affording a crude sample (4.5 g) as brown needles, mp 149.5—151.5°. A yellow oil (1.4 g), obtained by evaporating the first ether extracts, was treated with KOH (3.4 g, 0.061 mole) in diethylene glycol (10 ml) the same as (±)-IV affording more optically active VI (1.1 g) as a brown powder, mp 147.5—150.5°. Total yield of optically active VI was 64%. Recrystallization of the salt obtained above, from EtOH–H_2O (1:1, 15 ml), gave a crude optically active salt (VI) as pale brown needles (0.9 g), mp 150—152°. IR ν_{max}^{KBr} cm^{-1}: 1621, 1541 ($COO^- \overset{+}{N}H_2\langle$), 883 ($-\underset{|}{C}=CH_2$). This IR spectrum was nearly identical with that of (±)-VI in its solid state.

Treating part of the crude salt (VI) (0.85 g, 0.0022 mole) the same as (±)-VI gave optically active VII dicyclohexylamine salt as a nearly colorless solid (0.80 g, 94%), mp 149.5—151°. The IR spectrum of this solid was superimposable on that of the racemic salt in the same state.

Crude optically active VII dicyclohexylamine salt (mp 149.5—151°) (0.80 g, 0.0021 mole) was treated with KOH in a similar manner to the racemic compound giving crude (+)-VII (0.36 g, 84%) as a pale yellow solid, mp 87—88.5°, $[\alpha]_D^{26}$ +55.0° ($c=0.506$, $CHCl_3$). Several recrystallizations of the crude sample with hexane gave pure (+)-VII as colorless prisms, mp 89.5—90.5°, $[\alpha]_D^{22}$ +58.0° ($c=0.500$, $CHCl_3$). *Anal.* Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.83; H, 8.71. IR ν_{max}^{KBr} cm^{-1}: 1729, 1682 (COOH). This IR spectrum was different from that of (±)-VII in the same state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (COOH). This spectrum was identical with that of (±)-VII in $CHCl_3$ solution.

(±)- and (*S*)(+)-α-Methyl-α-isopropylsuccinic Acid ((±)- and (*S*)(+)-III)——According to the procedure reported by Porath,[6] (±)-III was prepared as colorless prisms, mp 147.5—148.5° (preheated to 130°) (lit.,[6] mp 148—149°). IR ν_{max}^{KBr} cm^{-1}: 1712, 1700 (COOH). NMR (in CF_3COOH solution): 9.01 τ (6H, doublet, $J=7.2$ cps, $(\underline{CH_3})_2CH-$), 8.68 τ (3H, singlet, $\underline{CH_3}-\underset{\underset{CH_3}{|}}{C}-$), 8.01 τ (1H, quartet, $J=7.2$ cps, $(CH_3)_2\underline{CH}-$), 7.15 τ (2H, quartet, $J=16.8$ cps, $-\underline{CH_2}-$).

(±)-III was resolved with cinchonidine by the method of Porath.[6] (*S*)(+)-III obtained as colorless prisms showed a mp of 130.5—131.5°, $[\alpha]_D^{18}$ +17.6° ($c=1.624$, EtOH), $[\alpha]_D^{18.5}$ +16.0° ($c=1.900$, MeOH), after recrystallization from H_2O, (lit.,[6] mp 126.5—127°, $[\alpha]_D^{25}$ +19.1° ($c=1.572$, EtOH), $[\alpha]_D^{25}$ +12.5° ($c=1.866$, H_2O); lit.,[19] $[\alpha]_D^{17}$ +16.1° (MeOH), $[\alpha]_D^{19}$ −0.64° ($CHCl_3$); lit.,[20] mp 133—134°, $[\alpha]_D^{21}$ +16° ($c=2.9$, 95% EtOH); lit.,[21] mp 136—137°, $[\alpha]_D^{30}$ +15.0° ($c=1.050$, EtOH)). IR ν_{max}^{KBr} cm^{-1}: 1704 (COOH). This IR spectrum was different from that of (±)-III, but the NMR spectrum of this sample was identical with that of (±)-III in CF_3COOH solution.

(±)-N-Phenyl-α-methyl-α-isopropylsuccinimide ((±)-VIII)——a) (±)-VIII from (±)-III: A mixture of (±)-III (0.50 g, 0.0029 mole) and aniline (1.5 ml) was refluxed for 1 hr in an oil bath. After cooling, H_2O (12 ml) was added and the reaction mixture acidified to pH<2 with 10% HCl. The whole was extracted with ether (20 ml, ×1), and the ether extract was washed with satd. aq. NaCl (20 ml, ×1), diluted aq. $NaHCO_3$ (20 ml, ×1), and satd. aq. NaCl (20 ml, ×1), then dried over anhyd. Na_2SO_4. Filtration and evaporation gave a red oil, which solidified on standing. This solid was purified by column chromatography using silica gel (20 g, solvent $CHCl_3$) to afford crude (±)-VIII (0.51 g, 77%) as a pale yellow solid, mp 72—74°. Several recrystallizations of the crude (±)-VIII from aq. EtOH gave pure (±)-VIII as colorless powder-like crystals, mp 73.5—74.5°. *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.96; H, 7.19; N, 6.08. IR ν_{max}^{KBr} cm^{-1}: 1777, 1704 (acid imide). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1776, 1714 (acid imide). NMR (in CCl_4 solution): 9.12, 9.08 τ (6H, 2 doublets, $J=7.2$ cps, $(\underline{CH_3})_2CH-$), 8.72 τ (3H, singlet, $\underline{CH_3}-\underset{\underset{CH_3}{|}}{C}-$), 7.97 τ (1H, septet $(CH_3)_2\underline{CH}-$), 7.58 τ (2H, quartet, $J=18$ cps, $-\underline{CH_2}-$), 2.90—2.50 τ (5H, multiplet, benzene ring protons). Gas chromatographic analysis (30% SE-30 on diasolid L, 2.25 m., 222°, (**B**)) of pure (±)-VIII showed a single peak (retention time 8.0 min).

b) (±)-VIII from (±)-VII: AcOH (10 ml) solution of (±)-VII (0.20 g, 0.0010 mole) was bubbled through O_3 gas for 3 hr at room temperature. 30% aq. H_2O_2 (0.3 ml) was added to the reaction mixture, and the whole was kept standing for 2 hr at room temperature. After excess H_2O_2 was decomposed with Pt, as usual, the AcOH solution was evaporated to dryness *in vacuo* giving a yellow oil, which was treated

19) W.B. Whalley, private communication.
20) E.H. Massey, H.E. Smith, and A.W. Gordon, *J. Org. Chem.*, **31**, 684 (1966).
21) J.D. Edwards, Jr. and N. Ichikawa, *J. Org. Chem.*, **29**, 503 (1964).

with aniline yielding a red oil (0.15 g). This oil was submitted to column chromatography using silica gel (15 g, solvent $CHCl_3$) to afford crude (±)-VIII (0.06 g, 26%) as a reddish orange solid, mp 68—70.5°. After treatment with charcoal, crude (±)-VIII was recrystallized twice from hexane and once from aq. EtOH to give pure (±)-VIII as colorless powderlike crystals, mp 73.5—74.5°. This sample showed no depression of the mixed melting point measurement with the authentic (±)-VIII obtained above. IR spectra of this sample in the solid state and in $CHCl_3$ solution were identical with those of the authentic one. Gas chromatographic analysis (30% SE-30 on diasolid L, 2.25 m., 222°, (**B**)) showed a single peak, whose retention time was identical with that of the authentic sample (retention time 8.5 min).

(*S*)(−)-N-Phenyl-α-methyl-α-isopropylsuccinimide ((*S*)(−)-VIII)——(*S*)(+)-III (mp 130.5—131.5°, $[\alpha]_D^{18}$ +17.6° (c=1.624, EtOH)) (0.70 g, 0.040 mole) was treated the same as(±)-III to give a brown solid (0.80 g) which, in this case, without purification using column chromatography, was recrystallized from EtOH (14 ml) and H_2O (2 ml) after treatment with charcoal. Crude (*S*)(−)-VIII (0.66 g, 71%) obtained as faint violet pillars showed a mp of 90.5—92°, $[\alpha]_D^{23.5}$ −54.1° (c=0.810, EtOH). Several recrystallizations of crude (*S*)(−)-VIII from aq. EtOH gave pure (*S*)(−)-VIII as colorless pillars, mp 91.5—93°, $[\alpha]_D^{22}$ −56.3° (c=0.622, EtOH). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.92; H, 7.51; N, 6.05. IR ν_{max}^{KBr} cm^{-1}: 1776, 1703 (acid imide), 752, 697, 690 (monosubstituted benzene). This IR spectrum was different from that of (±)-VIII in the solid state. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778, 1709 (acid imide). This spectrum was identical with that of (±)-VIII in the same state. ORD: $[M]^{22}$ (c=0.202, EtOH) (mμ): −91.5° (700), −130° (589), −192° (500), −342° (400), −536° (350), −910° (300), −3320° (250). Gas chromatographic analysis (30% SE-30 on diasolid L, 2.25 m., 222° (**B**)) showed a single peak whose retention time (8.8 min) was identical with that of the authentic sample.

(+)-N-Phenyl-α-methyl-α-isopropylsuccinimide ((+)-VIII)——(+)-VII ($[\alpha]_D$ +55.6 ($CHCl_3$)[22]) (0.54 g, 0.026 mole) was treated the same as (±)-VII to afford a red oil (0.45 g), which was purified with column chromatography using silica gel (30 g, solvent $CHCl_3$) giving crude (+)-VIII (0.25 g, 40%) as an orange solid, mp 85—89°, $[\alpha]_D^{24}$ +45.7° (c=0.778, EtOH). After treatment with charcoal, this solid was recrystallized four times from hexane and twice from aq. EtOH to give pure (+)-VIII as colorless pillars, mp 91.5—92.5°, $[\alpha]_D^{25}$ +51.3° (c=0.456, EtOH). *Anal.* Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.95; H, 7.55; N, 6.34. IR spectra of this sample were superimposable on those of (*S*)(−)-VIII in the solid state and in $CHCl_3$ solution. The mixed melting point of (+)-VIII with (*S*)(−)-VIII showed a mp of 71.5—76°, which was close to that of (±)-VIII. ORD: $[M]^{24}$ (c=0.124, EtOH) (mμ): +85.6° (700), +119° (589), +190° (500), +340° (400), +534° (350), +913° (300), +2980° (250). Gas chromatographic analysis (30% SE-30 on diasolid L, 2.25 m., 222°, (**B**)) showed a single peak whose retention time (8.5 min) was the same as that for (*S*)(−)-VIII.

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22) Three lots of (+)-VII were mixed and used. Optical rotation of the (+)-VII used was calculated to be $[\alpha]_D$ +55.6° ($CHCl_3$): $[\alpha]_D^{26}$ +55.0° (c=0.506, $CHCl_3$) (0.36 g), $[\alpha]_D^{26.5}$ +57.0° (c=0.474, $CHCl_3$) (0.15 g), $[\alpha]_D^{22}$ +58.0° (c=0.500, $CHCl_3$) (0.03 g).