SYNTHESIS AND RESOLUTION OF SUBSTITUTED PIPECOLIC ACIDS

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Abstract—A new general method for the preparation of 2-alkyl-pipecolic acids has been developed. The syntheses of 2-methyl-, 2-benzyl- and cis-6-methylpipecolic acids are described. (-)S- and (+)R-2-methylpipecolic acids were resolved by fractional crystallization of the quinine salt of their N-carbobenzoxy derivatives. Isolation of (-)S-cis-6-methylpipecolic acid required the use of 4-phenylbenzoxy carbonyl as protecting group to achieve selective crystallization of the quinine salt. The absolute configurations of these compounds were determined by circular dichroism.

INTRODUCTION
For some time we have been involved in the study of substituent effects on the polymerization of cyclic imino acids and of the conformational behaviour of the corresponding polypeptides [2-6]. This paper deals with the syntheses of 2-methyl-, 2-benzyl- and cis-6-methylpipecolic acids (2MPA, 2BPA and c6MPA, respectively) and with the resolution of 2-methyl- and cis-6-methylpipecolic acids. The following papers in this series will describe the dimerizations [7] and report on the conformations of some diketopiperazines derived from 2MPA and c6MPA [7] and report on the conformations of some diketopiperazines derived from 2MPA and t6MPA in solution and in the solid state [8].

EXPERIMENTAL
All melting points were determined in open capillary tubes on a Thomas Hoover Capillary Melting Point Apparatus and were uncorrected. Elemental analyses were performed by Spang Laboratories, Inc., Knoxville, Tennessee. Specific rotations at the sodium D line were measured by a Polarimeter using 0.1-1.0 mm cells. I.R. spectra were recorded on a Perkin-Elmer 241 MC and Rudolf polarimeter. Circular dichroism spectra were recorded on a JASCO J-40A spectropolarimeter using 0.1-1.0 mm cells. I.R. spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were recorded on a Varian T-60 spectrophotometer.

Ethyl 1-methyl-2-oxocyclopentanecarboxylate (2b)

Compound 2b was prepared according to the method of Claisen as modified by Barco, Benetti and Pollini [14]. Vigorous stirring of a mixture of K$_2$CO$_3$ (351.6 g, 2.54 mol), acetone (500 ml), ethyl 2-oxocyclopentanecarboxylate (99.4 g, 0.636 mol) and iodomethane (180.5 g, 1.27 mol), produced ethyl 1-methyl-2-oxocyclopentanecarboxylate (106.0 g, 0.62 mol) in 97.5% yield; b.p. 117-118°/20 mmHg (lit. 147/155 mmHg).

NMR (CDCl$_3$) $\delta$: 1.23 (3H, t, J = 7 Hz), 4.1 (2H$_x$, q, J = 7 Hz), 1.27 (3H$_y$, S), 1.80-2.40 (6H, m).

I.R. (neat): 2890-2990, 1760, 1730, 1465, 1455, 1440, 1410, 1380, 1320, 1275, 1240, 1200, 1160, 1070, 985 and 945 cm$^{-1}$.

Methyl 1-methyl-2-oxocyclopentanecarboxylate (2a)
The same procedure used for the preparation of 2b was employed here. The scale was three times that of the above example; yield 87-97%; b.p. 96°/11 mmHg, (lit. 102°C/13 mmHg).

NMR (CDCl$_3$) $\delta$: Methyl ester, 3.6 (3H, s); methylene group, 1.8-2.3 (6H, m); z-methyl, 1.25 (3H, s).

I.R. (neat): 2890-2990, 1760, 1730, 1465, 1455, 1440, 1410, 1380, 1320, 1275, 1240, 1200, 1160, 1070, 985 and 945 cm$^{-1}$.

Ethyl 2-methyl-6-oxopiperazol (3b)
The procedure of Plostnieks [13] was modified in the following manner. In a 2 l, 3-necked flask equipped with mechanical stirrer, pressure equalizing funnel, thermometer, and gas outlet were placed a dry solution of hydrazoic acid in chloroform (700 ml/0.45 N, 0.315 mol) and 2b (34 g, 0.2 mol). The solution was stirred and cooled to $-10^\circ$. Conc. sulphuric acid (70 ml) was added dropwise (2 hr), keeping the temperature below $-5^\circ$. About 5.51 of N$_2$ were evolved. Stirring was continued at room temperature for one additional hour and the excess of hydrazoic acid evolved was trapped in aqueous NaOH. The chloroform layer was decanted from the H$_2$SO$_4$ layer which contained most of the product. The H$_2$SO$_4$ layer was poured over ice (500 g) with stirring and external cooling, neutralized (Na$_2$CO$_3$), and extracted with methylene chloride. The chloroform layer was combined with the methylene chloride extract and dried over Na$_2$SO$_4$. The solvent was removed by distillation. The resulting solid was recrystallized from CHCl$_3$ with ethyl acetate as solvent. Yellow crystals, m.p. 105-110°, were obtained.

Analysis. Calculated for C$_9$H$_{11}$NO$_3$: C, 58.35; H, 8.11; N, 7.57. Found: C, 58.38; H, 8.05; N, 7.65.

NMR (CDCl$_3$) $\delta$: Amide, 7.4 (1H, s); methyl ester (A$_x$), 3.6 (3H, s); methyl ester (A$_y$), 3.3 (3H, s); ethyl ester (A$_Z$), 3.5 (2H, q, J = 7 Hz); x-methyl, 1.4 (3H, s); z-methyl, 1.35 (3H, s); aromatic group, 6.9-8.0 (3H).
from neutralizing the H₂SO₄, was filtered before extraction. The yellow solid product was triturated with diethyl ether to remove impurities and colour. Crystallization from 1,2-dimethoxyethane raised the melting point from 98–99 to 98.5–99.5 °C and gave pure colourless crystals (128.0 g, yield 75%).

**Analysis.** Calculated for C₁₆H₂₃NO₂; C, 56.13; H, 7.65; N, 8.18. Found: C, 56.20; H, 7.56; N, 8.27.

NMR (CDCl₃) δ: Amide, 7.60 (1H, s); methyl ester, 3.75 (3H, s); methyl group, 1.6–2.5 (6H, m); z-methyl, 1.45 (3H, s).


**Ethyl 2-methylpipicolate (6b)**

The procedure of Borch [15] for the reduction of secondary amides was used. Triethylxonium tetrafluoroborate [16] (6.64 g, 35 mmol), 3b (6.0 g, 32.4 mmol), methylene chloride (25 ml), absolute ethanol (30 ml) and sodium borohydride (3.0 g, 79 mmol) were used to give ethyl 2-methylpipicolate (3.75 g, 21.9 mmol) in 67.6% yield; b.p. 78°C/98 mmHg. The yellow solid product was triturated with diethyl ether to remove impurities and colour. Crystallization from (+)-N-carbobenzoxy-2-methyl-4-pipecolic acid (21) was used. Triethyloxonium tetrafluoroborate [16] (6.64 g, 35 mmol), 3b (6.0 g, 32.4 mmol), methylene chloride (25 ml), absolute ethanol (30 ml) and benzyl chloroformate (50 ml 4 N, 0.20 mol) were dissolved in hot acetone (2.5 l). The hot mixture was stirred and cooled for one additional hour, and the excess benzyl chloroformate was extracted with ether.

About 1 litre of water was added to the reaction mixture and brought to boiling. The heterogeneous mixture turned homogeneous after 2.5 hr was subsequently cooled and acidified to pH 4. The resultant milky solution was left at 0 ° overnight. Crystalline solid was formed, filtered, dried and recrystallized from chloroform/petroleum ether. Colourless crystals were obtained (35.7 g, 68% yield); m.p. 119.5–120.5 °C.

**Analysis.** Calculated for C₁₅H₂₇NO₂; C, 64.19; H, 9.61; N, 5.05. Found: C, 64.94; H, 6.85; N, 4.88.

NMR (d₆-acetone) δ: Carboxylic, 9.20 (1H, s), aromatic, 7.5–7.3 (5H, m), 5.10 (2H, s), (CH₂)₅: 4.05–0.65 (6H, m), α-CH₃, 1.7 (3H, s).

I.R. (KBr): 3300–3100, 2945, 2875, 1755, 1670, 1505, 1480, 1425, 1360, 1280, 1240, 1185, 1145, 1090, 1035, 990, 915, 885, 780, 750 and 710 cm⁻¹.

**(+)-N-carbobenzoxy-2-methyl-5-piperidinonic acid (16)**

Compound 17 (28 g, 0.10 mol) and quinine (32.4 g, 0.10 mol) were dissolved in hot acetone (2.5 l). The hot solution was filtered and allowed to stand at 5 ° overnight. White fluffy crystals were collected and the filtrate saved for the preparation of 21. After four recrystallizations from acetone the [(+)-A]·[−B] salt was obtained: 17.0 g, 56% yield, m.p. 164–165 °C; [α]₂⁰锺 = −93.3 ° (MeOH, c = 1.5 g/dl).

The same values were obtained after two additional recrystallizations. This salt was dissolved in 100 ml chloroform and 100 ml aqueous NaOH (1 N) were added dropwise with stirring. The chloroform was evaporated under vacuum, quinine precipitated and removed from the aqueous layer by filtration. The filtrate was brought to pH 4 with 2 N HCl, the precipitated solid was extracted with chloroform. After drying and removing the solvent, white crystals were obtained and recrystallized from chloroform/hexane to give white needles: 7.6 g, 54% overall yield; m.p. 136.5–138.5 °C; [α]₂⁰锺 = +25.4 ° (MeOH, c = 5 g/dl).

**Analysis.** Calculated for C₁₆H₂₃NO₄·H₂O; C, 52.16; H, 9.38; N, 8.69. Found: C, 52.21; H, 9.36; N, 8.72.

Mass spectrum (m/e, abundance): (144, 0.04), (128, 1.0), (99, 5.4), (98, 100), (82, 5.9), (70, 16.0); (69, 3.5), (59, 9.0), (42, 18.0), (41, 10.8), (39, 5.7), (30, 7.2), (28, 14.0).

NMR (D₂O) δ: (CH₃)₅: 3.3–3.6 (2H, m), (CH₂)₅: 1.8–2.7 (6H, m), α-CH₃: 1.7 (3H, s).


**2-Methylpipicolic acid monohydrate (7)**

Compound 6a (200 g, 1.27 mol) and water (2000 ml) were refluxed for 1 hr (the ethyl ester needed a longer reaction time, 10 hr). The reaction mixture was evaporated to dryness and the white residue was crystallized from an ethanol–water mixture (70:30 by vol.). White crystalline needles of 7 (193.0 g) were obtained in 94% yield; m.p. 340 with sublimation.
Synthesis and resolution of substituted pipecolic acids

(—)-2-Methyl-S-pipecolic acid (20)

(a) Hydrogen bromide method. A solution of HBr in acetic acid (10 ml) was added dropwise to 18 (2.0 g, 7.2 mmol) with stirring. The mixture was allowed to react for 30 min at room temperature. The reaction mixture was evaporated to dryness and the residue triturated with ethyl ether. The product precipitated as fine white crystals and was recrystallized from a methanol–ethyl ether mixture to give (—)-2-methyl-S-pipecolic acid hydrobromide salt (19) (1.5 g, 93% yield); m.p. 262–263 °C; [α]D = −5.25 (MeOH, c = 2 g/dl).

(b) Catalytic hydrogenation method. A solution of 18 (1.0 g, 3.6 mmol) in methanol (50 ml) and catalytic amounts of platinum oxide was hydrogenated at 45 psi. When hydrogen uptake ceased (8 hr) the solution was filtered, the filtrate cooled to 70 ° and acidified (1 N HCl) with stirring using MgSO4. The mixture was evaporated to dryness and the residue crystallized from methanol–ethyl ether to give free amino acid 20 (0.80 g, 85% yield); m.p. 350 ° (sublimation).

(-)-S-isomer 20.

Analysis. Calculated for C7H13NO2: C, 58.72; H, 9.82; N, 9.82.

IR: 3450, 3110, 3030, 2970, 2930, 2860, 2500–2400, 1615, 1595, 1450, 1425, 1390, 1345, 1330, 1310, 1280, 1190, 1185, 1150, 1100, 870, 750 and 710 cm−1.

(-)-2-Methyl-R-pipecolic acid (23)

Compound 23 was prepared in the same fashion as described for the l-rotatory isomer. (—)-2-Methyl-R-pipecolic acid hydrobromide (22) possessed the following properties: m.p. 261–263 °C; [α]D = +5.1 (MeOH, c = 2 g/dl).

Free amino acid 23 had the following properties: m.p. 350 ° (sublimation), [α]D = −3.7 (H2O, c = 2 g/dl).

Ethyl cis-6-methylpipecolate (11)

Analysis. Calculated for C7H13NO2: C, 68.00; H, 6.93; N, 5.69.

IR: 3445, 3115, 3035, 2970, 2930, 2860, 2500–2400, 1615, 1585, 1450, 1425, 1390, 1345, 1330, 1310, 1280, 1235, 1185, 1100, 870, 750 and 710 cm−1.

6-Methylpicolinic acid (9)

The method of Black, Deppe and Corson [18] was used for the partial oxidation of 2,6-lutidine.

Ethyl 6-methylcyclohexylacetate (10)

A solution of 9 (200 g, 1.46 mol) in absolute ethanol (1000 ml) was saturated with HCl gas, and allowed to reflux for 2 hr. The solvent was evaporated, the residue was washed with cold aqueous potassium carbonate, and extracted with ether. The extracts were dried (MgSO4), filtered, evaporated, and the ester was distilled under vacuum, yielding 217 g (90%) of pure colourless liquid; b.p. 125/20 mmHg (lit. [17] 79–81/0.25 mmHg).

Analysis. Calculated for C7H13NO2: C, 63.56; H, 6.00; N, 9.24.

IR: 3445, 3115, 3035, 2970, 2930, 2860, 2500–2400, 1615, 1585, 1450, 1425, 1390, 1345, 1330, 1310, 1280, 1235, 1185, 1100, 870, 750 and 710 cm−1.

Methyl 6-hydroxycyclohexylacetate (12)

The esterification procedure described above was not successful, instead the methyl ester was obtained in 46% yield when thionyl chloride [17] was used; b.p. 62/10 mm.

Analysis. Calculated for C7H12O2: C, 65.26; H, 6.00; N, 6.27.

IR: 3445, 3115, 3035, 2970, 2930, 2860, 2500–2400, 1615, 1585, 1450, 1425, 1390, 1345, 1330, 1310, 1280, 1235, 1185, 1100, 870, 750 and 710 cm−1.

Ethyl cis-6-hydroxycyclohexylacetate (11)

The catalytic hydrogenation of 10 was carried out according to the literature [17]; b.p. 58–60/10 mmHg (lit. [17] 99–100/13 mm). The product was analyzed by gas chromatography with three different columns (Chrom W deg, Propak P, and Chrom AW-DMCS); it was found that the ethyl ester is pure cis isomer.

Analysis. Calculated for C7H12O2: C, 65.26; H, 6.00; N, 6.27.

IR: 3445, 3115, 3035, 2970, 2930, 2860, 2500–2400, 1615, 1585, 1450, 1425, 1390, 1345, 1330, 1310, 1280, 1235, 1185, 1100, 870, 750 and 710 cm−1.
Methyl 6-methylpipicoleates (13, 14)

Compound 12 (28 g, 0.185 mol), 400 ml methanol (containing 2.5% HCl gas), and platinum oxide (2.5 g) were mixed and hydrogenated at 40 psi at room temperature for 12 hr. The purification was carried out as described in the previous example. A mixture of methyl cis- and trans-6-methyl pipicoleate was obtained (16 g, 35% yield); b.p. 47/10 mmHg. The composition of this mixture was found by gas chromatography (using Chrom W OF-1) to be 87% cis and 13% trans with retention times of 1'30" and 2'20", respectively.

Analysis. Calculated for C14H25NO3: C, 61.51; H, 9.03; N, 8.97. Found: C, 61.42; H, 9.06; N, 8.94.

NMR (neat) δ: Methyl ester 3.00 (3H, s), (CH2)2: 2.20 (6H, m), (CH3): 1.20 (3H, d, J = 6 Hz). 1H, m; (CH2)2: 1.90-0.90 (6H, m), (CH3): 1.00 (cis, J = 6 Hz), 0.98 (trans, J = 6 Hz).

Cis-6-methylpipicoleic acid hydrochloride (16)

A solution of 11 (20 g, 0.117 mol) in 100 ml 2 N HCl solution was refluxed for 2 hr. The solvent was evaporated to dryness and the residue was crystallized from methanol–ether (14 g, yield 56%), m.p. 262°.

Analysis. Calculated for C14H21ClNO3: C, 58.68; H, 7.85; N, 7.80. Found: C, 58.74; H, 7.77; N, 7.82.

NMR (D2O) δ: (CH3): 3.9 (1H, m), (CH2): 2.3-1.3 (6H, m), (CH2): 1.32 (3H, d, J = 6 Hz).


NMR (D2O) δ: (CH3): 3.9 (1H, m), (CH2): 2.3-1.3 (6H, m), (CH2): 1.32 (3H, d, J = 6 Hz). I.R. (KBr): 3450-2500, 1610, 1480, 1400, 1380, 1160, 970, 580 cm⁻¹.

Cis-6-methylpipicoleic acid (15)

Compound 11 (150 g, 0.88 mol) was suspended in water (1000 ml) and refluxed for 6 hr. Water was evaporated and the dry residue was crystallized from ethanol–ether, yielding 110 g (88%), m.p. 252-253° (dec).


NMR (D2O) δ: (CH3): 3.9 (1H, m), (CH2): 2.3-1.3 (6H, m), (CH2): 1.32 (3H, d, J = 6 Hz).


Cis-6-methyl-pipecolic acid hydrochloride (24)

A solution of 15 (10.0 g, 0.07 mol) in 17.5 ml 4N NaOH was mixed with 200 ml of dioxane-water (50:50 by vol.). The solution of 15 (26.0 g, 0.180 mol) in 45 ml 4N NaOH was mixed with 200 ml of dioxane-water (50:50 by vol.). The mixture was cooled to 0°; 45 ml 4 N NaOH and a solution of 47.0 g (0.19 mol) of crude 25 in 60 ml dioxane were added alternately to the cooled reaction mixture with vigorous stirring. When the addition was completed (0.5 hr) the reaction mixture was stirred for an additional 3 hr, keeping the temperature between 0 and 5°. The suspension was extracted 3 times with ethyl ether and once with ethyl acetate to remove the unreacted chloroformate derivative, dioxane and di-(4-phenylbenzyl)-carbonate formed as a side product. The aqueous layer was acidified with 5 N HCl to pH 4.0 and extracted with chloroform. The organic extracts were dried (MgSO4); filtration and evaporation of the solvent afforded 47.5 g (97%) of a 6.5% oil. Several attempts to crystallize the oily product were not successful. The compound was used directly in the following step, since its NMR indicated high purity.

NMR (CDCl3) δ: COOH 11.0 (1H, s); aromatic 7.7-7.2 (9H, m); ArCH2: 5.2 (2H, s); CH2: 4.9 (1H, m), CH: 4.4 (1H, m); (CH2): 2.3-1.4 (6H, m); CH3: 1.20 (3H, d, J = 6 Hz).

(—)-N-(4-Phenylbenzoyloxy-carbonyl)-cis-6-methyl-S-pipericolic acid (27)

Compound 26 (48.0 g, 0.133 mol) and quinine (43.2 g, 0.333 mol) were dissolved in 300 ml methanol and refluxed for 30 min. Solvent was evaporated under aspirator pressure and the residue was dissolved in hot toluene (450 ml). The clear solution was slowly cooled to −5° and allowed to crystallize for 24 hr. A white crystalline salt (40.0 g) was collected by filtration and recrystallized seven times from a mixture of acetone-water (90:10, by volume). The quinine salt of the L-rotatory salt was thus obtained (12.0 g, 27% yield; m.p. 163-164°, [a]D = −110.7° (MeOH, c = 2 g/dl).


An aqueous solution of NH3 (100 ml 2N) was added dropwise to a chloroform solution of the above quinine salt (11.0 g, 16 mmol in 100 ml CHCl3) with cooling and stirring. The chloroform was evaporated; the aqueous solution was extracted with ether to remove the free quinine, acidified to a pH of 4.0 with 2 N HCl, and extracted with chloroform. The chloroform layer was dried (MgSO4) and the solvent was evaporated. The foamy residue was crystallized by slow evaporation of chloroform–hexane solution to give 5.2 g (94%) of white crystals, m.p. 99-100°, [a]D = −31.9° (MeOH, c = 2 g/dl).

Analysis. Calculated for C19H17NO4: C, 71.37; H, 6.67; N, 3.88.

The NMR spectrum was identical to that of the racemic compound.

I.R. (KBr): 3140, 3095, 3060, 3030, 2980, 2950, 1735, 1665, 1490, 1450, 1430, 1410, 1385, 1360, 1345, 1335, 1290, 1210, 1160, 1135, 1110, 1080, 1045, 1010, 970, 950, 870, 830, 800, 780, 760 and 700 cm⁻¹.

(--)cis-6-methyl-S-pipericolic acid (28)

Compound 27 (1.1 g, 3.1 mmol) in 20 ml methanol was hydrogenated by a procedure similar to that for the preparation of 2-methyl-S-pipericolic acid. The free amino acid was crystallized from ethanol–ether, yielding 0.4 g (90%); m.p. 150-152° (dec), [α]D = −16° (MeOH, c = 2 g/dl).

Analysis. Calculated for C17H19N306: C, 72.65; H, 6.99; N, 6.20. Found: C, 72.65; H, 6.96; N, 5.94.

RESULTS AND DISCUSSION

Syntheses of 2- benzyl- and 2-methylpiperic acids

(--)S-piperic acid is a naturally occurring amino acid present in the fruit of beans and other legumes

Piperic acid was shown to be formed from lysine by plants and subsequently was implicated in lysine metabolism by mammals

Various methods for its synthesis are detailed by Greenstein and Winitz. Katchalski and others for its synthesis are detailed by Greenstein and Winitz. 

Katchalski et al. have reported on the properties of poly-S-piperic acid.

The only 2-alkylpiperic acid reported previously is piperic acid. A convenient and general
Synthesis and resolution of substituted pipecolic acids

**Scheme 1**

\[
\begin{align*}
&\text{Scheme 1} \\
&\text{Synthesis of 2-alkylpipecolic acids}
\end{align*}
\]

**Synthesis of cis-6-methylpipecolic acid**

6-Methylpipecolic acid has previously been synthesized but no indication was given about its stereochemistry [17]. 2,6-Lutidine was partially oxidized (see Scheme 2) to give 6-methylpicolinic acid (9) according to the literature [18]. Ethyl 6-methylpipeco-
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Scheme 2

1060

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} & \quad \text{CH}_3 \\
\xrightarrow{\text{KMnO}_4/\text{H}_2\text{O}} & \quad \text{CH}_3 & \quad \text{N} & \quad \text{COOH} \\
60-70^\circ & \text{C} & \quad \text{C}_2\text{H}_5\text{OH} & \text{HCl} \\
\text{or CH}_3\text{OH} & \text{-SOCl}_2 & \xrightarrow{\text{H}_2/\text{PtO}_2} & \text{HCl-C}_2\text{H}_5\text{OH} \\
\text{CH}_3 & \quad \text{COOC}_2\text{H}_5 & \xrightarrow{100\%} & \text{C}_2\text{H}_5\text{OH} \\
\text{II} & \xrightarrow{13\%} & \text{H}_2\text{O} & \text{reflux} \\
\text{11} & \xrightarrow{13\%} & \text{H}_2\text{O} & \text{reflux} \\
\text{12} & \text{H}_2\text{O} & \text{reflux} & \text{15}
\end{align*}
\]

The methyl ester 12 was obtained by reaction with thionyl chloride [17]. Catalytic hydrogenation of compounds 10 and 12 with platinum oxide in ethanol, saturated with hydrogen chloride [17], proceeded quantitatively. Reduction of the ethyl ester 10 gave pure ethyl 6-cis-methylpipecolate (11), whereas the methyl ester 12 upon hydrogenation afforded a mixture of 87% cis isomer 13 and 13% trans isomer 14, as determined by NMR and gas chromatography. Hydrolysis of 11 yielded pure cis-6-methylpipecolic acid (15) upon heating with water at reflux (80% yield). Acidic hydrolysis of 11 gave the hydrochloride salt of 15 in 56% yield.

Resolution of 2-methylpipecolic acid (2MPA)

The resolution of pipecolic acid was achieved by Mende [19] in 1896 through fractional crystallization of its salt with l and d-tartaric acid. This method was not successful for 2-methylpipecolic acid. However, fractional recrystallization of the quinine salt of the N-carbobenzoxy derivative [3] proved successful. Reaction of 2MPA with an excess of benzyl chloroformate yielded N-carbobenzoxy-2-methylpipecolic acid (17) in addition to the corresponding acid anhydride (approx. 1:1). Consequently, the reaction mixture was allowed to reflux with water in order to hydrolyze the anhydride, resulting in a 68% yield of pure 17. Resolution then proceeded according to Scheme 3. The quinine salt of 17 was prepared and crystallized from acetone at +5°. The less soluble salt [(+)-A·(-)Q] was crystallized and purified further by three recrystallizations from acetone at +5°. The free acid was liberated by treatment with ammonia with subsequent acidification. (+)-S-N-carbobenzoxy-2-methylpipecolic acid (18) was obtained in 54% overall yield, based on one enantiomer, [α]_D^20 = +25.4° (MeOH). The carbobenzoxy group was removed either by catalytic hydrogenation or by acidic cleavage with hydrogen bromide. (-)-S-2-methylpipecolic acid hydrobromide (19) and the free amino acid were obtained with [α]_D^20 = -5.25° (MeOH) and -3.7° (H_2O), respectively. The filtrate of the initial crystallization of the diastereomeric salts was determined to be enriched with the [(−)-A·(−)Q] salt. It was evaporated to dryness and recrystallized six times at −5° from acetone. Dissociation of this salt with ammonia followed by acidification produced (−)-R-N-carbobenzoxy-2-methylpipecolic acid (21) in 41% of the theoretical yield for one enantiomer; [α]_D^20 = -25.5° (MeOH). (+)-R-2-methylpipecolic acid hydrobromide (22) and the free amino acid (23) had [α]_D^20 = +5.1° (MeOH) and 5 ± 2° (H_2O), respectively. The specific rotations of all enantiomeric compounds in Scheme 3 are of comparable values with opposite signs of rotation, indicating high efficiency of the resolution.

Resolution of cis-6-methylpipecolic acid

We have made several attempts to resolve 6-methylpipecolic acid or its ethyl ester by means of fractional crystallization of the corresponding di-
astereomeric salts but none of these attempts were successful. Several diastereoisomeric salts were prepared by treating N-carbobenzoxy-cis-6-methyl-pipecolic acid with an optically active resolving agent such as tyrosine hydrazide, ephedrine, quinine or brucine. Several solvents or solvent combinations with variable polarities were used in an attempt to crystallize these salts, but unfortunately not one of these was crystallizable. In most cases the salt separated from it solution as an oil upon cooling.

Eventually, we decided on 4-phenylbenzyloxy-carbonyl as protecting group, due to its enhanced proclivity towards crystallization. 4-Phenylbenzyl chloroformate (25) was prepared in 92% yield from the reaction of phosgene with 4-biphenylmethanol by a procedure similar to that for the preparation of benzyl chloroformate [20]. Compound 25 was reacted with c6MPA in a dioxane-water (1:1) mixture. Dioxane was used as co-solvent in order to dissolve the solid chloroformate derivative 23. N-(4-phenylbenzyloxy carbonyl)-cis-6-methyl-pipecolic acid (26) was obtained as a viscous oil in 74% yield.

The quinine salt of compound 26 was formed in methanol (Scheme 4). It could be fractionally crystallized from toluene at -5°. The crystals were re-crystallized seven times from a mixture of acetone-water (9:1, v/v) at -5°, to give the quinine salt of the L-rotatory acid [(+)A,(-)Q] in 27% yield based on one enantiomer, \([\alpha]_D^25 = -110.7^\circ\) (MeOH). Treating this salt with ammonia followed by acidification gave the L-rotatory acid (27) in 94% yield, \([\alpha]_D^25 = -12.5^\circ\) (MeOH). The removal of the protecting group by catalytic hydrogenation afforded (-)-cis-6-methyl-S-pipecolic acid (28) in 90% yield, \([\alpha]_D^25 = -14.9^\circ\) (H₂O).

The filtrate retained from the first crystallization in toluene was evaporated to dryness. The residue contained the quinine salts of the D-rotatory acid and
Scheme 4

\[ \text{(±) PZ} \rightarrow \text{Filtrate} \rightarrow \text{Crystallization} \]

7 crystallizations
acetone-water
(70-30%) - 5°C

Oil rich in 
\[ \text{[(+)-A (-)Q} \]

5% \[\text{[(+)-A (-)Q} \]
\[\alpha\] = -110.5° (MeOH)

\[ \text{1. NH₃} \]
\[ \text{2. HCl} \]

\[ \text{CH₃} \]
\[ \text{N} \]
\[ \text{PZ} \]
\[ \text{COOH} \]

27

94% (-) \[\alpha\] = -12.5° (MeOH)

\[ \text{H₂/Pt} \]

\[ \text{CH₃} \]
\[ \text{N} \]
\[ \text{COOH} \]

28

90% (-) \[\alpha\] = -14.9° (H₂O)

Scheme 5

\[ 7 + \text{C}_6\text{H}_5\text{CH}_2\text{OOCO}_2 + 4\text{N-NaOH} \rightarrow \text{N-NO}_2 \text{ I oC ' O OH} + \]

\[ \text{CBZ}_{\text{O}} \text{O} \]

H₂O/reflux
HCl

\[ \text{CH₃} \]
\[ \text{N} \]
\[ \text{COOH} \]

17
Synthesis and resolution of substituted pipecolic acids

Scheme 6

\[
\begin{align*}
\text{Scheme 6} & \\
\text{(a) } & \\
\text{(b) } & \\
\text{(c) } & \\
\text{(d) } & \\
\text{(e) } & \\
\text{(f) } & \\
\text{Wavelength } \lambda \text{ (nm)} & \\
\end{align*}
\]

some of the l-rotatory acid. An attempt to crystallize
this residue from a mixture of acetone-water
(7:3, v/v) gave only the minor isomer as a crystalline
salt in 5% yield. The quinine salt of the d-rotatory
acid separated as an oil from the hot acetone-water
solution upon cooling to room temperature. No
further attempt was made to purify the d-rotatory
acid.

Absolute configurations

Optical rotatory dispersion (ORD) and circular
dichroism (CD) can be used for a rapid assignment
of the absolute configuration of \( \alpha \)-amino acids
[2, 21–23]. All naturally-occurring and most synthetic
\( \alpha \)-amino acids show positive Cotton effects around
200 nm in water and 208–210 in acid.

Figure 1 shows the CD spectra of \((-\)\(S\)-pipecolic
acid) \((-\)\(S\)-PA) \((-\)\(c\)6MPA, \((-\)\(2\)MPA, \((-\)\(S\)-proline
(S-P) and \((-\)\(2\)-methyl-\(S\)-proline (2M-S-P) in water
and in acid. The CD data are given in Table 1 as
measured from Fig. 1. S-PA and \((-\)\(c\)6MPA each
exhibits a single positive Cotton effect in water and
in acid around 207–208 nm. The similarity of their
CD curves suggests that both compounds possess the
S configuration. The CD spectrum of (-)2MPA in water shows three Cotton effects, a negative one at 195 nm, a positive one at 212 nm and another negative one at 230 nm, whereas the CD spectrum in acid shows only negative and positive Cotton effects at 202 and 231 nm.

Two Cotton effects have been observed in water for S-azetidine-2-carboxylic acid, S-proline and 4-methyl-S-proline [23] and three Cotton effects were reported for the CD spectrum of S-proline methyl ester [24]. More than one Cotton effect may arise from different conformations of the molecules [25], from different states of solvation [26], from the existence of "allowed" and "forbidden" transitions of closely similar energy levels [27], or from a combination of these factors [23]. Craig and Pereira [24] suggest that the three Cotton effects observed for proline methyl ester may be due to an optically active n→σ* transition of the nitrogen for the positive CD band at 202 nm, n→π transition of the ester carbonyl group for the positive CD band at 209 nm, and an interaction through space between the non-bonding orbital of the nitrogen atom and the chromophoric transition of the carbonyl group for the negative weak CD band at 232 nm. However, only one Cotton effect was observed in the CD spectra of the above compounds in acidic solutions around 208-212 nm [23, 24].

The S-configuration can be assigned to (-)2MPA based on the similarity of its CD spectra in water with that of proline and other related amino acids [23]. However, we have as yet no satisfactory explanation for the abnormal CD spectrum in acid of (-)2MPA.

The sector rule of Jorgensen [28], which relates the sign and amplitude of the Cotton effect to the conformation and absolute configuration of α-amino acids, can be applied here. His sector diagram is being referred to in the following discussion. The sector rule predicts a single positive Cotton effect with higher amplitude than that of S-PA because of the presence of an α-methyl group in or nearby the positive sector. The experimental result does not agree with the prediction of the sector rule. Perhaps this deviation is due to a change in the conformation of the molecules by substitution at the 2-position and/or a change in the curvatures of the sectors. We are currently attempting to determine the absolute configurations of (-)2MPA and (-)2MP by chemical means in order to resolve this problem.

At present we are inclined to assign the S-configuration for the l-rotatory amino acids based on the above results and on the CD curves of their cyclic dimers [8] or polymer [3].

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Dedication—The senior author (C. G. Overberger) dedicates this paper to Professor Oto Wichterle for his enormous contribution to macromolecular science, and in honour of his 70th birthday.

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