A Facile Method of Preparing L-α-Methyl DOPA
(L-3-(3,4-Dihydroxyphenyl)-2-methylalanine)

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To develop a practical method for production of L-α-methyl DOPA, the optical resolution of its precursor, DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine, was studied. The mono-
hydrochloride of DL-3-(3,4-methylenedioxyphenyl)-2-methylalanine was resolved by a preferen-
crystallization procedure. Optically pure L-α-methyl DOPA was obtained in good yield.

Industrial production of L-α-methyl DOPA by the present simple method is considered to be
very promising.

The importance of L-3-(3,4-dihydroxy-
phenyl)-2-methylalanine (L-α-methyl DOPA)
as an antihypertensive agent is well recognized. DL-α-Methyl DOPA can be synthesized from
3,4-methylenedioxyphenylacetone (MDPA) via
dL-3-(3,4-methylenedioxyphenyl)-2-methyl-
anine (DL-MDPMA)." In this case, it
is most desirable that an intermediate in the
chemical synthetic process, namely, DL-
MDPMA, is resolved into the optical
antipodes, because the undesired D-isomer can
be easily degraded to MDPA and it can be
reused for a starting material.5) Therefore, the
optical resolution of DL-MDPMA has been
investigated by the preferential crystallization
procedure which is considered one of the most
practical methods for industrial application.

In our previous reports4,5) it was shown
that both the p-phenolsulfonic acid salt of DL-
MDPMA and the hydrazine salt of N-acetyl-
DL-MDPMA are resolved by this simple reso-
lution method. In those days, the salt of
DL-MDPMA with hydrochloric acid was also
tested but could not be selected as a resolvable
salt. As a result of further detailed experi-
ments, however, the monohydrochloride of DL-
MDPMA (DL-MDPMA·HCl) has now been
found to crystallize as a racemic mixture from
a dilute solution of hydrochloric acid and to
be easily resolved into each of the antipodes by

EXPERIMENTAL6)

Preparation of L-, D-, and DL-MDPMA·HCl. Water
(210 ml) and 12 N HCl (100 ml, 1.2 mole) were added to
DL-MDPMA7) (223.2 g, 1 mole). The mixture was
heated, treated with charcoal, and allowed to stand in a
refrigerator overnight. The resulting precipitate was
collected, washed with cold water and dried in vacuo.
The initial crop of DL-MDPMA·HCl (173.5 g) was
obtained, mp 230 ~ 232°C (dec), and further crops were
obtained by successive concentrations of the combined
filtrates. The total yield was 233.2 g (89.8%). The products were almost pure and could be used for optical resolution without further purification. Crystallization from 0.25 N HCl gave a racemic mixture, colorless prisms, mp 233–234°C (dec). Anal. Caled for C11H14NO4Cl: C, 50.87; H, 5.43; N, 5.39; Cl, 13.65. Found: C, 50.99; H, 5.50; N, 5.30; Cl, 13.77. Solubility in 0.25 N HCl (g/100 ml): 26.7 (15°C), 28.9 (25°C), 43.9 (40°C).

The optically active L- and D-MDPMA.HCl were prepared from L- and D-MDPMA respectively in the same way as described above. The L-isomer: colorless prisms, [α]D0 +0.9° (c=1, 1 N HCl), [α]150 +21.8° (c=1, 1 N HCl); mp 244–245°C. Anal. Found: C, 50.98; H, 5.51; N, 5.30; Cl, 13.94. Solubility in 0.25 N HCl (g/100 ml): 19.5 (15°C), 22.9 (25°C), 29.8 (40°C). The D-isomer: [α]D0 −0.9° (c=1, 1 N HCl), [α]150 −21.8° (c=1, 1 N HCl); mp 244–245°C. The infrared spectra of L-, D-, and DL-MDPMA·HCl in KBr were identical. IR ν, cm⁻¹: 3150, 2950–2850, 2550, 1720–1670, 1600, 1500, 1260, 1240, 1190, 1115, 1095, 1035, 930, 880, 810.

When DL-MDPMA·HCl (2.0 g) was dissolved in water (4 ml) at elevated temperature and the solution was cooled to room temperature, DL-MDPMA·1/2HCl (0.4 g) crystallized as colorless prisms, mp 245–246°C (dec). Anal. Caled for C11H13NO4.1/2HCl: C, 54.72; H, 5.64; N, 5.80; Cl, 7.34. Found: C, 54.68; H, 5.62; N, 5.53; Cl, 7.34. IR ν, cm⁻¹: 3150, 2950–2850, 2550, 1720–1670, 1600, 1500, 1260, 1240, 1190, 1115, 1095, 1035, 930, 880, 810. On the other hand, recrystallization of optically active MDPMA·HCl from water gave the monohydrochloride, and the hemihydrochloride of optically active isomers was not obtained.

Optical resolution of DL-MDPMA·HCl. In a typical experiment, DL-MDPMA·HCl (28.00 g) and L-MDPMA·HCl (2.00 g) were dissolved in 0.25 N HCl (50 ml) at elevated temperature. The solution was cooled to 25°C, seeded with fine pulverized crystals of L-MDPMA·HCl (0.05 g) and stirred for 50 min at the same temperature. The precipitated crystals were collected by filtration, washed with a small amount of cold water (1 ml) and dried to give L-MDPMA·HCl (4.66 g),
Preparation of L-α-Methyl DOPA

**TABLE I. SUCCESSIVE RESOLUTIONS OF DL-MDPMA•HCl**

<table>
<thead>
<tr>
<th>Expt</th>
<th>Amount of addition</th>
<th>Composition of solution</th>
<th>Separated crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>DL-Form (g)</td>
<td>Active form (g)</td>
</tr>
<tr>
<td>1 (L)</td>
<td>28.00</td>
<td>2.00</td>
<td>28.00</td>
</tr>
<tr>
<td>2 (D)</td>
<td>4.75</td>
<td>—</td>
<td>28.00</td>
</tr>
<tr>
<td>3 (L)</td>
<td>4.78</td>
<td>—</td>
<td>28.00</td>
</tr>
<tr>
<td>4 (D)</td>
<td>4.70</td>
<td>—</td>
<td>28.00</td>
</tr>
<tr>
<td>mean</td>
<td>4.74</td>
<td>—</td>
<td>28.00</td>
</tr>
</tbody>
</table>


a) Resolutions were carried out at 25°C on a 50 ml scale. Crystallization time was 50 min in every case.

b) The optical purity was calculated based on the maximum rotation \([\alpha]_D^{25} +21.8°\) (\(c=1, 1\, \text{N HCl}\)).

c) Values calculated theoretically from analysis of separated crystals and mother liquors.

\([\alpha]_D^{25} +20.3°\) (\(c=1, 1\, \text{N HCl}\)). Its optical purity was 93.1%, based on the maximum rotation \([\alpha]_D^{25} +21.8°\) (\(c=1, 1\, \text{N HCl}\)). After the separation of the L-isomer, DL-MDPMA•HCl (4.75 g) and a small amount of 0.25 N HCl were added to the mother liquor in order to prepare the supersaturated solution of almost the same composition as in the previous resolution except that the D-isomer predominated. The solution thus obtained was cooled to 25°C, seeded with D-MDPMA•HCl (0.05 g) and stirred. After 50 min, the precipitated crystals were treated in the same manner as described above to yield D-MDPMA•HCl (4.67 g), \([\alpha]_D^{25} -20.6°\) (\(c=1, 1\, \text{N HCl}\)), optical purity 94.5%. By repeating these procedures, L- and D-isomers were successively obtained. The examples of the several runs are shown in Table I.

**Purification of optically impure MDPMA•HCl.** The optically impure L-MDPMA•HCl (16.00 g, optical purity 87.5%) obtained by the above procedure was recrystallized from 2 N HCl (125 ml). The precipitated crystals were filtered off, washed with water and dried to give optically pure L-MDPMA•HCl (11.50 g), \([\alpha]_D^{25} +21.8°\) (\(c=1, 1\, \text{N HCl}\)), mp 244-245°C (dec). Their mp and specific rotation did not change on further recrystallization. The L-MDPMA•HCl (3.00 g) obtained above was dissolved in hot water (10.5 ml) and adjusted to pH 6 with 5 N ammonium hydroxide. The precipitate was collected, washed with cold water and air-dried at 60°C to give L-α-methyl DOPA•3/2H2O, 8.6 g (72.3%). Recrystallization from a diluted sulfuric acid solution (0.5%) gave a white powder of L-α-methyl DOPA•3/2H2O and drying of the sesquihydrate in vacuo at 100°C gave the anhydrous form \([\alpha]_D^{25} -5.2°\), \([\alpha]_D^{25} -5.5°\) (\(c=2, 0.1\, \text{N HCl}\)), mp 306-307°C (dec). [lit.\(^4\) \([\alpha]_D^{25} +4°\) (\(c=2, 0.1\, \text{N HCl}\)), and \([\alpha]_D^{25} +5.5°\) (\(c=2, 0.1\, \text{N HCl}\)) for D-α-methyl DOPA). Anal. Calcd for C10H13N04: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.65; H, 6.23; N, 6.56.

**REFERENCES AND NOTES**


6) All the experimental methods and the instruments were identical to those described in the previous report\(^5\) unless otherwise noted.

7) The authors are grateful to Dr. M. Miyoshi and Dr. K. Matsumoto for a donation of this compound.

8) Resolved in the previous report.\(^6\)

9) A good spectrum was not obtained in KBr.