
On the other hand, a distillate from the steam distillation was extracted with Et2O (3~20 cc.) and CHCl3 (3~20 cc.), the combined organic layers were dried and evaporated in vacuo below 30° (bath temp.), giving a white solid, m.p. 42~42.5°, [α]D +12.0° (c=1.66, EtOH), 0.60 g. (63.8%), which was identical with l-menthol on mixed m.p. test and infrared spectrum comparison.

3-(3,4-Methylenedioxyphenyl)-D-alanine (D-V) — In the same way as that of (L-V), 1.0 g. (68.0%) of the HCl salt was obtained. Adjustment with 10% NH4OH to pH 5.8, gave 0.45 g. of (D-V) and from the filtrate an additional amount of 0.15 g. was obtained. Yield, 0.60 g. (48.0%). The crude (D-V) was purified from H2O to colorless needles, m.p. 239~240° (decomp.), [α]D +12.0° (c=1.66, N HCl). Anal. Calcd. for C10H11O4N: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.42; H, 5.13; N, 6.52.


l-Menthol was recovered in 56.4% yield (0.53 g.) as white crystals of m.p. 39~42, [α]D +48.0° (c=4.62, EtOH).

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Summary

Asymmetric hydrogenation of l-menthyl α-acetamido-3,4-methylenedioxyacinnamate was carried out by two methods: i) 10% palladium-carbon in ethanol, ii) 10% palladium-carbon in benzene. Hydrogenation products were separated by fractional crystallization, and were converted to optically active 3-(3,4-methylenedioxyphenyl)alanines by transesterification followed by acid hydrolysis.

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In 1913 Torquati*3 isolated from the velvet bean (Vicia faba) 3-(3,4-dihydroxyphenyl)-l-alanine (l-Dopa), whose identification and absolute configuration were later established by Guggenheim,*3 and other investigators.*3 It is now known that Dopa plays an important role in mammalian metabolism of tyrosine*4 and also in the hypothetical biogenesis of some alkaloids.*5

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*3 Part II: This Bulletin, 10, 688 (1962).
*2 Hongo, Tokyo (渋谷東京, 竹治長津).
1) T. Torquati: Arch. farm. sper., 15, 213, 308 (1913). (C.A., 7, 2774 (1913)).
Since the first synthesis of DL-Dopa in 1911\(^6\) many synthetic methods have been group reported.\(^7\) However, many of them are tedious and often give an impure product.

For the preparation of the optically active Dopa, the following four methods have been reported; namely, isolation from natural sources,\(^8\) introduction of a second OH L-tyrosine\(^3a\) or D-tyrosine,\(^3b\) resolution of the intermediate N-acyl derivative by brucine\(^9\) or cinchonine followed by hydrolysis of the N-acyl and O-methyl groups.\(^10\) The first two methods give only one optical isomer, whereas the last two furnish both D- and L-isomers.

In the preceding paper,\(^11\) the authors reported the preparation of 3-(3,4-methylene-dioxyphenyl)-D-, and -L-alanine (D- and L-(I)) and their N-acetylated derivatives (D- and L-(II)). The processes involved are synthesis of N-acetyl-3-(3,4-methylene dioxyphenyl)-DL-alanine (DL-II) by means of an acetamidomalonic synthesis, chemical or enzymatic resolution of the racemic N-acetyl derivative (DL-(II)) by cinchonine or Takadiastase, and hydrolysis of D- and L-(II). The preparation of N-acetyl-3-(3,4-methylene dioxyphenyl)-D-, and -L-alanine 1-menthyl ester (IIIa and IIIb) by an asymmetric reduction of 1-menthyl \(\alpha\)-acetamido-3,4-methylenedioxy cinnamate was also reported by the present authors.\(^12\) However, the experimental proofs for the absolute configurations of these compounds were not described in those papers.

Now the preparations of D- and L-Dopa from these compounds were attempted as shown in Chart 1, so that the absolute configurations of the starting materials might also be established.

![Chart 1](image_url)

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As a preliminary experiment, it was attempted to hydrolyze the racemic compounds (DL-(I) and DL-(II)) with acids such as conc. HCl, HBr, and HI in a stream of nitrogen or carbon dioxide. In spite of every effort, however, it was difficult to obtain DL-Dopa in a pure state in all cases tried. On the other hand, when the condition used in the hydrolysis of N-methyl-3-(3-methoxy-4-hydroxyphenyl)alanine\(^{13}\) was applied, the hydrolysis proceeded very smoothly. The hydrochloride of DL-(I) was heated under reflux with red phosphorus and a mixture (1:1) of HI (d=1.7) and acetic anhydride to afford after the isolation procedure colorless prisms of DL-Dopa in a yield of 55%. Similar hydrolysis of the racemic N-acetyl derivative (DL-(II)) gave DL-Dopa in a yield of 55%. In the next place, the same condition as in the case of the racemate was applied to the optical isomers. Thus, 3-(3,4-methylenedioxyphenyl)-L-alanine (L-(I)), obtained by the asymmetric hydrolysis of DL-(II) with Takadiastase,\(^{11}\) gave L-Dopa in a yield of 80%. One recrystallization from water furnished an analytically pure sample (m.p. 276\(^\circ\)C\(\text{~}\)278\(^\circ\)C\(\text{~}\text{decomp.})\), \(\left[\alpha\right]_D^{13}=+13.1\) (N HCl)), which was shown to be identical with a sample of natural L-Dopa, isolated from Vicia faba L. by Nagasawa,\(^{14}\) by direct comparison of their physical properties (ultraviolet and infrared absorption spectra, Rf values, \(\left[\alpha\right]_D\) values, and color reactions). Now the absolute configuration of the starting amino acid (L-(I)) was simultaneously established. On being subjected to the same condition as above, the N-acetyl-D-amino acid (D-(II)), obtained by the asymmetric hydrolysis of DL-(II) with Takadiastase,\(^{11}\) gave D-Dopa, m.p. 276\(^\circ\)C\(\text{~}\)278\(^\circ\)C\(\text{~}\text{decomp.})\), \(\left[\alpha\right]_D^{11}=+13.0\) (N HCl), in a yield of 72%.

It is reported that DL-Dopa is more soluble in water than the optical isomer.\(^{10}\) For the preparation of D- and L-Dopa, therefore, it seemed unnecessary to start with an optically pure sample of D- and L-(II). Thus, when the crude N-acetyl amino acids (D- and L-(II)), derived from the corresponding crude cinchonine salts,\(^{11}\) were hydrolyzed under the same condition as above, D- and L-Dopa were obtained in 71% and 63% yield, respectively. The overall yields based on DL-(II) used were ca. 60% and ca. 50%, respectively.

The hydrolysis of the l-menthyl esters (IIa and IIb)\(^{12}\) was also effected by refluxing them for 4~5 hours with the same reagents as in the case of (II) to afford D- and L-Dopa, respectively, in each 42% yield.

Judging from their \(\left[\alpha\right]_D\) values the optically active samples obtained by the above methods seem to be practically pure, although a biological method of evaluation\(^{15}\) has not been applied to them. An attempt to detect the contamination of a sample of optically active Dopa with the racemate by measuring its infrared absorption spectrum, was of no use, because both authentic samples of L-Dopa and DL-Dopa gave superimposable infrared absorption spectra in KBr discs.

The methods mentioned above would serve as a new and advantageous way for the preparation of DL-, D-, and L-Dopa, when combined with the preparation of the intermediates (I), (II) and (III).\(^{11,12}\)

**Experimental**

3-(3,4-Dihydroxyphenyl)-DL-alanine (DL-Dopa) — i) From 3-(3,4-methylenedioxyphenyl)-DL-alanine (DL-(I)): The amino acid hydrochloride (DL-(I)·\(\frac{1}{2}\) HCl: 2.50 g.),\(^{11}\) red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac₂O (15 cc.) were heated under reflux in a stream of CO₂ for 3 hr.

\(^{13}\) All m.p.s are uncorrected. The UV and IR absorption spectra were respectively measured with a Cary Model 11, and with a Koken Model DS-301 spectrophotometer equipped with NaCl optics. A "Zeiss Kreis polarimeter" was used for the measurement of optical rotation.

After cooling the remaining red phosphorus was filtered with suction and washed with 50% AcOH (20 cc.). The nearly colorless filtrate was combined with the washings, treated with a small amount of red phosphorus, and then evaporated in vacuo at 60–65°C in a stream of H₂, leaving a slightly yellowish syrup. The syrup was dissolved in H₂O (20 cc.) and then Et₂O, giving 550 mg. of Dl-Dopa, m.p. 270–272° (decomp.) with sintering at 250°. The combined solution of the filtrate and the washings was concentrated to ca. 10 cc. in vacuo at 50°C in a stream of H₂, and kept standing, in the same way as above, for 3 days. The colorless crystals separated were treated as above, giving an additional 660 mg. of Dl-Dopa. The IR absorption spectra of both crystals were identical. Total yield, 1.21 g. (55.2%). For purification 450 mg. of the product was dissolved in boiling H₂O (10 cc.), treated with a small amount of charcoal, and filtered. The resulting colorless solution was kept standing under a layer of hexane in a refrigerator for a day. The colorless prisms separated were collected, washed with H₂O, EtOH, and then Et₂O, giving 260 mg. of a pure sample, m.p. 270–272° (decomp.). For analysis it was dried at 70°C in vacuo (2 mm. Hg) over P₂O₅ for 5 hr. Anal. Calcd. for C₉H₁₁O₄N: N, 7.10. Found: N, 7.07. Rf 0.18.*⁴ IR ν_max cm⁻¹: 3450–3260 (OH), 3060, 2580 (NH₃⁻), 1660 (NH₃⁺), 276–278° (decomp.), ¹¹D +13.0° (c=5.273, NHCl, l=1).

The IR absorption spectrum of this sample in KBr disc was superimposable with that of an authentic sample of Dl- as well as L-Dopa. It reduced Tollens reagent immediately, and gave a slightly bluish green coloration with FeCl₃ in an aqueous solution. These properties agreed with those of Dl-Dopa.

ii) From N-acetyl-3-(3,4-methylenedioxyphenyl)-dl-alanine (dl-(I)): The N-acetyl derivative (dl- (II)): red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac₂O (15 cc.) were allowed to react and worked up in the same manner as described in (i). Dl-Dopa was obtained as colorless prisms, m.p. 270° (decomp.) with sintering at 250°. Yield, 1.09 g. (55.3%). Recrystallization of the crystals (800 mg.) from H₂O (20 cc.) (SO₂-treated charcoal) gave 510 mg. of pure Dl-Dopa. Anal. Calcd. for C₉H₁₁O₄N: N, 7.10. Found: N, 6.77. Rf 0.18.*⁴ This sample agreed in all properties including the IR absorption spectrum with an authentic Dl-Dopa.

3-(3,4-Dihydroxyphenyl)-dl-alanine (D-Dopa) i) From N-acetyl-3-(3,4-methylenedioxyphenyl)-dl-alanine (dl- (I)): The N-acetyl-β-amino acid (dl- (I), [α]₂₀° +52.4°; 2.51 g.⁴¹) obtained by the asymmetric hydrolysis of dl- (I) with Takadiastase, was hydrolyzed in the same way as in the case of dl- (II) described above. D-Dopa was obtained as colorless needles, m.p. 275–276° (decomp.) with sintering at 255°, in a yield of 1.42 g. (72.1%). One gram of the crystals was recrystallized from H₂O (40 cc.) (SO₂-treated charcoal) to give 650 mg. of colorless needles (D-Dopa). It was dried at 70°C in vacuo (2 mm. Hg) over P₂O₅ for 5 hr.; m.p. 276–278° (decomp.), [α]₂₀° +13.0° (c=5.273, NHCl, l=1). Anal. Calcd. for C₉H₁₁O₄N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.64; H, 5.54; N, 6.89. Rf 0.18.*⁴ The IR absorption spectrum of this sample in KBr disc was superimposable with that of a sample of natural D-Dopa.

ii) From the crude N-acetyl-β-amino acid (ν- (II)): The crude N-acetyl-β-amino acid (ν- (II), [α]₂₀° -51.0° (c=2.072, EtOH, l=1) was obtained via the crude less soluble chinchonine salt by the resolution of ν- (II) in an over-all yield of 84.2% based on ν- (II) used. The procedure was given in the preceding report.¹¹ The crude N-acetyl-β-amino acid (ν- (II), 3.52 g.), red phosphorus (8.4 g.) and a mixture of HI (d=1.7; 22 cc.) and Ac₂O (22 cc.) were heated and worked up as in the case of ν- (I), when ν-Dopa was obtained as colorless needles, m.p. 275–276° (decomp.) with sintering at 255°. Yield, 1.96 g. (71%). 1.00 g. of the crystals was recrystallized from H₂O (40 cc.) (SO₂-treated charcoal) to afford 700 mg. of D-Dopa as colorless needles, m.p. 275–276° (decomp.) with sintering at 255°. Yield, 1.00 g. (71%). 1.00 g. of the crystals was recrystallized from H₂O (40 cc.) (SO₂-treated charcoal) to afford 700 mg. of D-Dopa as colorless needles, m.p. 275–276° (decomp.). It was dried at 70°C in vacuo (2 mm. Hg) over P₂O₅ for 5 hr.; m.p. 276–278° (decomp.), [α]₂₀° +13.0° (c=5.273, NHCl, l=1). Anal. Calcd. for C₉H₁₁O₄N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.64; H, 5.54; N, 6.89. Rf 0.18.*⁴ The IR absorption spectrum of this sample in KBr disc was superimposable with that of a sample of natural D-Dopa.

iii) From the l-menthyl ester (IIIa): The l-menthyl ester (IIIa, m.p. 85–87°C, [α]₂₀° -55.2° (c=1.50, benzene, l=1): 3.80 g.⁴¹) red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac₂O (15 cc.) were heated under reflux for 5 hr. in the same manner as in (i) and worked up also in the same way as in (i) to furnish 830 mg. (42.1%) of colorless needles, m.p. 266–267° (decomp.). One part of it was recrystallized from 40 parts of H₂O containing a few drops of aqueous SO₂ (charcoal), giving ν-
Dopa as colorless needles, m.p. 278 (decomp.), (α)D +13.3 (c=1.53, NHCl, l=1). Anal. Calcd. for C9H11O4N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.61; H, 5.69; N, 6.94. Ref 0.18.*4 The IR spectrum of this sample in KBr disc was superimposable with that of a sample of natural L-Dopa.

3-(3,4-Dihydroxyphenyl)-L-alanine (L-Dopa) —— i) From 3-(3,4-methylenedioxyphenyl)-L-alanine (L-(1)): 3-(3,4-methylenedioxyphenyl)-L-alanine (L-(1), (α)D -13.6 (NHCl); 1.00 g.)11) derived from the asymmetric hydrolysis of DL-(1) with Takadiastase, red phosphorus (3.0 g.) and a mixture of HI (d=1.7; 7.5 cc.) and Ac2O (7.5 cc.) were heated and worked up as in the case of DL-(1), when 730 mg. (77.5%) of colorless needles (L-Dopa), m.p. 275–276 (decomp.) with sintering at 255°, were obtained. The needles (500 mg.) were recrystallized from H2O (20 cc.) (SO2-treated charcoal) to give L-Dopa as colorless needles (350 mg.), m.p. 276–278 (decomp.), (α)D -13.1 (c=5.122, N HCl, l=1). Anal. Calcd. for C9H11O4N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.90; H, 5.61; N, 7.24. Rf 0.18.*4 UV λmax (0.001 NHCl) λ (log ε): 220.5 (3.79), 280 (3.42); UV λmin (0.001 NHCl) λ (log ε): 217 (3.78), 250 (2.33). IR νmax (cm⁻¹): 3450–3260 (OH), 3060, 2580 (NH3+), 1660 (NH3+), 1573 (COO-).

The UV and IR absorption spectra of this sample were respectively superimposable with those of a sample (m.p. 276–278 (decomp.), (α)D -13.2 (c=4.184, N HCl, l=1), Rf 0.18*4) of natural L-Dopa isolated from Vicia faba L. by Nagasawa.14)

ii) From the crude N-acetyl-L-amino acid (L-(II)): The crude N-acetyl-L-amino acid (L-(II), (α)D +46.5 (c=2.347, EtOH, l=1)) was obtained via the crude easily soluble cinchonine salt by the resolution of DL-(II), according to the procedure reported previously,11) in an over-all yield of 76.2% based on DL-(II) used. When 3.52 g. of the crude acid (L-(II)) was treated in the same manner as in the case of the crude D-isomer, L-Dopa was obtained as colorless, m.p. 275–276 (decomp.) with sintering at 255°. Yield, 1.74 g. (68%). Recrystallization of the crystals (1.00 g.) from H2O (40 cc.) (SO2-treated charcoal) gave 620 mg. of colorless needles, m.p. 276–278 (decomp.), (α)D -12.3 (c=5.097, N HCl, l=1). Anal. Calcd. for C9H11O4N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.97; H, 5.32; N, 7.08. Rf 0.18.*4 The IR absorption spectrum of this sample in KBr disc was superimposable with that of a sample of natural L-Dopa.

iii) From the l-menthyl ester (IIIb): The l-menthyl ester (IIIb, m.p. 150–151°, (α)D -3.8 (c=1.52, benzene, l=1); 3.90 g.),12) red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac2O (15 cc.) were heated under reflux for 4 hr. and worked up in the same manner as in (i), when 830 mg. (42.1%) of colorless needles, m.p. 276–278 (decomp.), (α)D -13.1 (c=1.53, N HCl, l=1). Anal. Calcd. for C9H11O4N: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.69; H, 5.44; N, 6.82. Ref 0.18.*4 This sample was also identified by comparison of the IR spectrum with a sample of natural L-Dopa.

The samples of D- and L-Dopa, which were obtained by the method described above, gave the same color reactions with FeCl3, Tollens reagent and ninhydrin as natural D- and L-Dopa.

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Summary

Hydrolyses of the racemate and the optical isomers of 3,4-methylenedioxyphenylalanine (I), and of their N-acetyl derivatives (DL-, D-, and L-(II)) including the l-menthyl esters (IIIa and IIIb) were smoothly effected by using a mixture of HI, Ac2O and red phosphorus to furnish the corresponding racemate and optical isomers of 3-(3,4-dihydroxyphenyl)alanine (Dopa) in fair yields.

This method would be a new and advantageous way for the preparation of DL-, D-, and L-Dopa, when combined with the previously reported preparation11,12) of the racemic and optically active intermediates. The absolute configurations of the optical isomers of (I), of their N-acetyl derivatives (D- and L-(II)), and of the l-menthyl esters (IIIa and IIIb) were simultaneously established by the above hydrolyses.

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