HCl salt : colorless needles (from H_2O), m.p. 250～250.5°(decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_4N \cdot HCl$: Cl, 14.42. Found : Cl, 14.16.

On the other hand, a distillate from the steam distillation was extracted with Et_2O (3×20 cc.) and $CHCl_3$ (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°, $[\alpha]_D^{19}$ −49.3°(c=3.06, 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% NH_4OH 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 H_2O to colorless needles, m.p. 239～240°(decomp.), $[\alpha]_D^8$ +12.0°(c=1.66, *N* HCl). *Anal.* Calcd. for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found : C, 57.42; H, 5.13; N, 6.52.

HCl salt : colorless needles (from H_2O), m.p. 250～250.5°(decomp.). *Anal.* Calcd. for $C_{10}H_{11}O_4N \cdot HCl$: Cl, 14.42. Found : Cl, 14.49. *l*-Menthol was recovered in 56.4% yield (0.53 g.) as white crystals of m.p. 39～42°, $[\alpha]_D^{15}$ −48.0° (c=4.62, EtOH).

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Summary

Asymmetric hydrogenation of *l*-menthyl α-acetamido-3,4-methylenedioxycinnamate 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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111. Shun-ichi Yamada, Tozo Fujii, and Takayuki Shioiri : Studies on Optically Active Amino Acids. III.*1 Preparation of 3-(3,4-Dihydroxyphenyl)-DL-, -D-, and -L-alanine.

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In 1913 Torquati[1] 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,[2] and other investigators.[3] It is now known that Dopa plays an important part in mammalian metabolism of tyrosine[4] and also in the hypothetical biogenesis of some alkaloids.[5]

*1 Part II : This Bulletin, **10**, 688 (1962).

*2 Hongo, Tokyo (山田俊一, 藤井澄三, 塩入孝之).

1) T. Torquati : Arch. farm. sper., **15**, 213, 308 (1913). (C. A., **7**, 2774 (1913)).

2) M. Guggenheim : Z. physiol. Chem., **88**, 276 (1913).

3) *a*) E. Waser, M. Lewandowski : Helv. Chim. Acta, **4**, 657 (1921). *b*) S. Goldschmidt, G. Freyss : Ber., **66**, 784 (1933). *c*) P. A. Levene, S. Mardashew : J. Biol. Chem., **117**, 179 (1937). *d*) E. Waser, E. Brauchli : Helv. Chim. Acta, **7**, 740 (1924). *e*) R. S. Coffey, M. Green, G. W. Kenner : J. Chem. Soc., **1959**, 4100. *f*) O. Lutz, B. Jirgensons : Ber., **64**, 1221 (1931). *g*) R. R. Sealock : J. Biol. Chem., **166**, 1 (1946).

4) C. E. Dalgliesh : "Advances in Protein Chemistry," Vol. 10, 65 (1955). Academic Press, Inc., New York.

5) *a*) *Idem* : *Ibid.*, Vol. 10, 117 (1955). *b*) R. Robinson : "The Structural Relations of Natural Products," (1955). Clarendon Press, Oxford.

Since the first synthesis of DL-Dopa in 1911[6] many synthetic methods have been group toreported.[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,[3g] 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-methylenedioxyphenyl)-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-methylenedioxyphenyl)-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-methylenedioxyphenyl)-D-, and -L-alanine *l*-menthyl ester (IIIa and IIIb) by an asymmetric reduction of *l*-menthyl α-acetamido-3,4-methylenedioxycinnamate was also reported by the present authors.[12] However, the experimental proofs for the absolute configrations of these compounds were not described in those paper.

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.

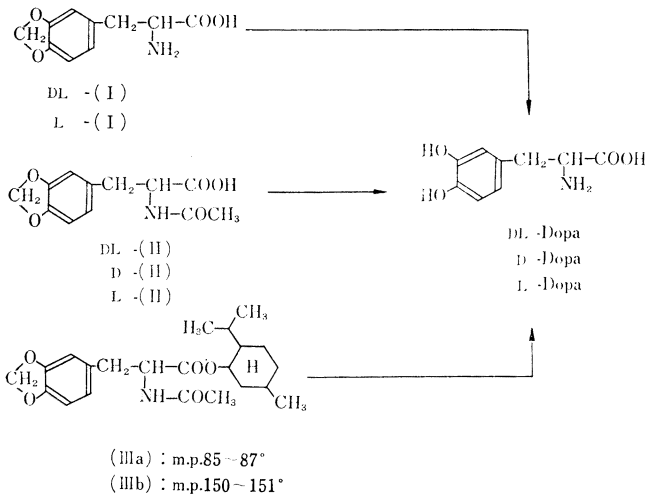

Chart 1.

6) C. Funk : J. Chem. Soc., **99**, 554 (1911).
7) *a*) K. Fromherz, L. Hermanns : Z. physiol. Chem., **91**, 221 (1914). *b*) H. Stephen, C. Weizmann : J. Chem. Soc., **105**, 1152 (1914). *c*) K. Hirai : Biochem. Z., **114**, 67 (1921). *d*) Y. Sugii : Yakugaku Zasshi, **41**, 130 (1921). *e*) C. R. Harington, W. McCartney : Biochem. J., **21**, 852 (1927); C. R. Harington : *Ibid.*, **22**, 407 (1928). *f*) V. Deulofeu, G. Mendivelzua : Z. physiol. Chem., **219**, 233 (1933). *g*) R. H. Barry, A. M. Mattocks, W. H. Hartung : J. Am. Chem. Soc., **70**, 693 (1948). *h*) Y. Matsuda, I. Matsumoto : Yakugaku Kenkyu, **29**, 508 (1957). *i*) *Idem* : Japan, 916 (1960), Feb. 18. (C. A., **54**, 19520 (1960)). *j*) K. Mori : Nippon Kagaku Zasshi, **81**, 464 (1960).
8) Biochem. Preparations, **1**, 25 (1949).
9) C. R. Harington, S. S. Randall : Biochem. J., **25**, 1028 (1931).
10) K. Vogler, H. Baumgartner : Helv. Chim. Acta, **35**, 1776 (1952).
11) Part I. S. Yamada, T. Fujii, T. Shioiri : This Bulletin, **10**, 680 (1962).
12) Part II. S. Yamada, T. Shioiri, T. Fujii : *Ibid.*, **10**, 688 (1962).

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 Inspite 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 ~278°(decomp.), $[\alpha]_D^3$ −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, $[\alpha]_D$ 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. 276~278°(decomp.), $[\alpha]_D^{11}$ +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 (IIIa and IIIb)[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 $[\alpha]_D$ 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-(3,4-Dihydroxyphenyl)-DL-alanine (DL-Dopa)——i) From 3-(3,4-methylenedioxyphenyl)-DL-alanine (DL-(I)) : The amino acid hydrochloride (DL-(I)·½ HCl : 2.50 g.),[11] red phosphorus (6.0 g.) and a mixture of HI (*d*=1.7; 15 cc.) and Ac_2O (15 cc.) were heated under reflux in a stream of CO_2 for 3 hr.

*3 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.

13) R.D.H. Heard : Biochem. J., **27**, 54 (1933); T.H. Guerrero, V. Deulofeu : Ber., **70**, 947 (1937).
14) T. Nagasawa : Nippon Nogei-Kagaku Kaishi, **34**, 233 (1960).
15) A. Meister, L. Levintow, R.B. Kingsley, J.P. Greenstein : J. Biol. Chem., **192**, 535 (1951); J.P. Greenstein, S.M. Birnbaum, M.C. Otey : *Ibid.*, **204**, 307 (1953).

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° in a stream of H_2, leaving a slightly yellowish syrup. The syrup was dissolved in H_2O (20 cc.) and again evaporated *in vacuo* in the same way as described above. The resulting syrup was again dissolved in H_2O (20 cc.) and filtered. To the slightly yellowish clear filtrate thus obtained was added 10% NH_4OH under cooling and stirring until Congo red paper no longer turned blue (pH ca. 4.4), and the solution was kept standing under a layer of hexane in a refrigerator for a day. The colorless prisms separated were filtered, washed with H_2O, EtOH, and then Et_2O, 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° in a stream of H_2, 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 H_2O (10 cc.), treated with a small amount of charcoal, which was pretreated with aqueous SO_2, and filtered. The resulting colorless solution was kept standing in a refrigerator for 2 days and the colorless prisms separated were collected, washed with H_2O, EtOH, and then Et_2O, giving 260 mg. of a pure sample, m.p. 270~272° (decomp.). For analysis it was dried at 70° *in vacuo* (2 mm. Hg) over P_2O_5 for 5 hr. *Anal.* Calcd. for $C_9H_{11}O_4N$: N, 7.10. Found : N, 7.07. Rf 0.18.*4 IR ν_{max}^{KBr} cm^{-1} : 3450~3260 (OH), 3060, 2580 (NH_3^+), 1660 (NH_3^+), 1573 (COO^-).

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 $FeCl_3$ in an aqueous solution. These properties agreed with those of DL-Dopa.

ii) From N-acetyl-3-(3,4-methylenedioxyphenyl)-DL-alanine (DL-(II)) : The N-acetyl derivative (DL-(II); 2.51 g.), red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac_2O (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 (900 mg.) from H_2O (20 cc.) (SO_2-treated charcoal) gave 510 mg. of pure DL-Dopa. *Anal.* Calcd. for $C_9H_{11}O_4N$: 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)-D-alanine (D-Dopa)——i) From N-acetyl-3-(3,4-methylenedioxyphenyl)-D-alanine (D-(II)) : The N-acetyl-D-amino acid (D-(II), $[\alpha]_D^{23}$ −52.4°; 2.51 g.)[11] obtained by the asymmetric hydrolysis of DL-(II) with Takadiastase, was hydrolyzed in the same way as in the case of DL-(II) described above. D-Dopa was obtainedne 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 H_2O (40 cc.) (SO_2-treated charcoal) to give 650 mg. of colorless needles (D-Dopa). It was dried at 70° *in vacuo* (2 mm. Hg) over P_2O_5 for 5 hr.; m.p. 276~278° (decomp.), $[\alpha]_D^{11}$ +13.0° (c=5.273, NHCl, l=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: 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 L-Dopa.

ii) From the crude N-acetyl-D-amino acid (D-(II)) : The crude N-acetyl-D-amino acid (D-(II), $[\alpha]_D^{13}$ −51.0° (c=2.072, EtOH, l=1) was obtained via the crude less soluble chinchonine salt by the resolution of DL-(II) in an over-all yield of 84.2% based on DL-(II) used. The procedure was given in the preceding report.[11] The crude N-acetyl-D-amino acid (D-(II); 3.52 g.), red phosphorus (8.4 g.) and a mixture of HI (d=1.7; 22 cc.) and Ac_2O (22 cc.) were heated and worked up as in the case of DL-(I), when D-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 H_2O (40 cc.) (SO_2-treated charcoal) to afford 700 mg. of D-Dopa as colorless needles, m.p. 276~278° (decomp.), $[\alpha]_D^{12}$ +13.2° (c=5.165, N HCl, l=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: N, 7.10. Found : N, 6.95. Rf 0.18.*4 The IR absorption spectrum of this sample in KBr disc was identical with that of a sample of natural L-Dopa.

iii) From the l-menthyl ester (IIIa) : The l-menthyl ester (IIIa, m.p. 85~87°, $[\alpha]_D^{12}$ −55.2° (c=1.50, benzene, l=1) : 3.90 g.),[12] red phosphorus (6.0 g.) and a mixture of HI (d=1.7; 15 cc.) and Ac_2O (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 H_2O containing a few drops of aqueous SO_2 (charcoal), giving D-

*4 The samples were applied on Toyo Roshi No. 50 filter paper and run ascendingly for 17 hr. with a solvent system of BuOH-AcOH-H_2O (4:1:1). Spots were detected by spraying with 5% solution of ninhydrin in acetone as usual. Rf values in this report represent the values under this condition, unless otherwise stated.

Dopa as colorless needles, m.p. 278 (decomp.), $[\alpha]_D^{10}$ +13.1° (c=1.53, *N*HCl, *l*=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.10. Found : C, 54.61; H, 5.69; N, 6.94. Rf 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-(I)) : 3-(3,4-methylenedioxyphenyl)-L-alanine (L-(I), $[\alpha]_D^{20}$ −13.6° (*N*HCl); 1.00 g.)[11] derived from the asymmetric hydrolysis of DL-(II) with Takadiastase, red phosphorus (3.0 g.) and a mixture of HI (*d*=1.7; 7.5 cc.) and Ac_2O (7.5 cc.) were heated and worked up as in the case of DL-(I), 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 H_2O (20 cc.) (SO_2-treated charcoal) to give L-Dopa as colorless needles (350 mg.), m.p. 276~278° (decomp.), $[\alpha]_D^{13}$ −13.1° (c=5.122, *N* HCl, *l*=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.10. Found : C, 54.90; H, 5.61; N, 7.24. Rf 0.18.*4 UV $\lambda_{max}^{0.001\,N\,HCl}$ mμ (log ε) : 220.5 (3.79), 280 (3.42); UV $\lambda_{min}^{0.001\,N\,HCl}$ mμ (log ε) : 217 (3.78), 250 (2.33). IR ν_{max}^{KBr} cm^{-1} : 3450~3260 (OH), 3060, 2580 (NH_3^+), 1660 (NH_3^+), 1573 (COO^-).

The UV and IR absorption spectra of this sample were respectively superimposable with those of a sample (m.p. 276~278 (decomp.), $[\alpha]_D^{12}$ −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), $[\alpha]_D^{12}$ +46.5° (c=2.347, EtOH, *l*=1)) was obtained via the crude easily soluble cinchonine salt byt he 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. (63%). Over-all yield from DL-(II), 48%. Recrystallization of the crystals (1.00 g.) from H_2O (40 cc.) (SO_2-treated charcoal) gave 620 mg. of colorless needles, m.p. 276~278° (decomp.), $[\alpha]_D^{11}$ −12.3° (c=5.097, *N* HCl, *l*=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: 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°, $[\alpha]_D^{13}$ −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 Ac_2O (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. 267° (decomp.), were obtained. One part of it was recrystallized from 40 parts of H_2O containing a few drops of aqueous SO_2 (charcoal), giving L-Dopa as colorless needles, m.p. 278° decomp.), $[\alpha]_D^{10}$ −13.1° (c=1.53, *N* HCl, *l*=1). *Anal.* Calcd. for $C_9H_{11}O_4N$: C, 54.82; H, 5.62; N, 7.10. Found : C, 54.60; H, 5.44; N, 6.82. Rf 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 $FeCl_3$, 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, Ac_2O 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 preparation[11,12] 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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