

Stereochemical Studies on Aromatic Amino-acids. Part 4.† Absolute Configuration of 3-Amino-2-phenylpropionic Acid¹

By Juan A. Garbarino * and Oswaldo Nuñez, Department of Chemistry, Universidad Simón Bolívar, Caracas, Venezuela

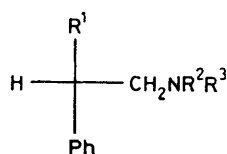
(+)-3-Amino-2-phenylpropionic acid (1) was assigned the (*S*)-configuration by chemical correlation with (+)-(*S*)-1-amino-2-phenylbutane (2). O.r.d. and molecular rotation data for this amino-acid and various derivatives are reported and discussed in the light of well known rules which have been applied to α -amino-acids previously.

As part of our programme of studies on the stereochemistry of aromatic amino-acids,²⁻⁴ we have examined the chemical correlation between (+)-3-amino-2-phenylpropionic acid (1) and (+)-(*S*)-1-amino-2-phenylbutane (2) in view of the biological importance of this amino-acid. Derivatives of (1) show important neurophysiological control properties;⁵ moreover it is present in the antibiotic betacine which displays a broad spectrum of antibacterial activity.⁶

The amino-acid (1) was obtained from atropic acid and hydroxylamine in the presence of sodium,⁷ and resolved with (+)-camphor-10-sulphonic acid.⁶ Subsequent basic hydrolysis yielded the (+)-amino-acid (1) with $[\alpha]_D^{21} +95^\circ$. Reaction of the (+)-amino-acid (1) with phthalic anhydride gave (+)-2-phenyl-3-phthalimidopropionic acid (3) which was then converted into (+)-2-phenyl-3-phthalimidopropionyl chloride (4) and (+)-

chloric and acetic acids gave (+)-1-amino-2-phenylbutane (2), $[\alpha]_D^{21} +9.2^\circ$. The agreement of specific rotation between (2) thus obtained and that of (2) obtained earlier⁸ from (+)-(*S*)-2-phenylbutane, $[\alpha]_D^{21} +9.8^\circ$, indicates that the conversion (+)-(1) \longrightarrow (+)-(2) was effected without significant racemisation (94% optical purity).

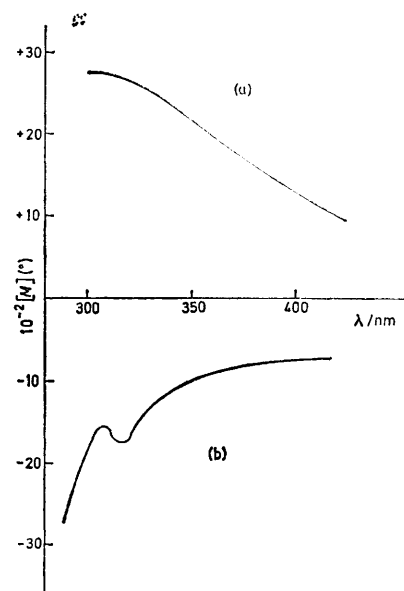
This evidence for the proposed configuration of (+)-(1) exemplifies the use of optical rotatory dispersion curves



- (1) $\text{R}^1 = \text{COOH}$, $\text{R}^2 = \text{R}^3 = \text{H}$
- (2) $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{R}^3 = \text{H}$
- (3) $\text{R}^1 = \text{COOH}$, $\text{R}^2\text{R}^3 = \text{Pht}$
- (4) $\text{R}^1 = \text{COCl}$, $\text{R}^2\text{R}^3 = \text{Pht}$
- (5) $\text{R}^1 = \text{COCHN}_3$, $\text{R}^2\text{R}^3 = \text{Pht}$
- (6) $\text{R}^1 = \text{COMe}$, $\text{R}^2\text{R}^3 = \text{Pht}$
- (7) $\text{R}^1 = \text{C}(\text{SCH}_2)_2\text{Me}$, $\text{R}^2\text{R}^3 = \text{Pht}$
- (8) $\text{R}^1 = \text{Et}$, $\text{R}^2\text{R}^3 = \text{Pht}$

Pht = $o\text{-C}_6\text{H}_4(\text{CO})_2$

1-diazo-3-phenyl-4-phthalimidobutan-2-one (5). This diazoketone showed no racemisation after heating in organic solvents or standing in the solid state at room temperature. Its conversion into the corresponding methyl ketone was effected with hydriodic acid in chloroform. The resulting (+)-2-phenyl-1-phthalimidobutan-3-one (6) reacted with ethanedithiol and boron trifluoride-ether giving the (+)-dithioacetal (7), $[\alpha]_D^{21} +64.7^\circ$. Desulphurisation of (7) by heating under reflux with Raney nickel (W-1) catalyst in acetone yielded (+)-2-phenyl-1-phthalimidobutane (8), which upon removal of the protecting group by reflux with a mixture of hydro-



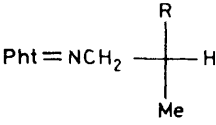
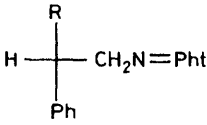
O.r.d. curves of (a) compound (3) and (b) phthalylphenylalanine

and molecular rotation data in comparisons between α - and β -amino-acids. Both (+)-2-phenyl-3-phthalimidopropionic acid (3) and the (–)-L-phenylalanine *N*-phthaloylate derivative⁹ show plain dispersion curves, (+)-(3) showing a positive curve while the L-phenylalanine derivative showing a negative one (Figure). Thus the stereochemical configurations are opposite.

Finally, we applied the stereochemical rotation shift rules to our case. Use of Freudenberg's displacement rule¹⁰ involved comparison of the molecular optical rotations of (–)-(*R*)-1-amino-2-methylpropionic acid and its derivatives¹¹ with those of (+)-3-amino-2-

† Part 3 is ref. 3.

phenylpropionic acid (Table). The value for (+)-2-phenyl-1-phthalimidobutan-3-one (6) is the only exception in this comparison. The observations of Clough¹² and Lutz and Jirgensons¹³ confirmed the broad application of their rule to stereochemical determinations of

| Molecular rotations | | |
|---|---|-----------|
|  |  | |
| | R | |
| -186.6° | COCHN ₂ | +1 280.0° |
| -56.8° | COOH | +395.3° |
| +22.5° | COMe | +714.9° |
| +42.9° | C(SCH ₃) ₂ Me | +238.7° |
| +52.1° | Et | +123.8° |

synthetic amino-acids.^{2,3} Thus the absolute configuration of (+)-3-amino-2-phenylpropionic acid (1) has been proved to be that of the *S*-series.

EXPERIMENTAL

M.p.s were determined with a Fischer-Johns apparatus. Spectra were recorded with a Perkin-Elmer model 567 spectrophotometer, a Cary 15 spectrophotometer, and a Varian T-60A n.m.r. spectrometer (tetramethylsilane as internal reference). Optical rotations were measured in a 0.1 dm quartz cell using a Perkin-Elmer 241 MC automatic polarimeter. Analyses were performed at the micro-analytical laboratory of Dr. F. Pascher, Bonn, Germany. T.l.c. was carried out on silica gel (Merck G60) in the following solvent systems: (1) ethyl acetate–light petroleum (1 : 1 v/v) and (2) ethyl acetate–light petroleum (1 : 4 v/v).

Resolution of (±)-3-Amino-2-phenylpropionic Acid (1).—The acid (1) was obtained in 24% yield from atropic acid by the method of McKenzie and his co-workers,¹⁴ m.p. 222–224 °C (from H₂O–EtOH) (lit.,⁷ 222–224 °C). The (±)-acid (14 g, 85 mmol) and (+)-camphor-10-sulphonic acid (20 g, 85 mmol), [α]_D²⁰ +20° (c, 2 in H₂O), were dissolved in ethanol (183 ml), refluxed for 1 h, and then kept in a refrigerator overnight.⁶ The precipitate was filtered off to give crude camphorsulphonate salt of (+)-3-amino-2-phenylpropionic acid (8.5 g, 54%), m.p. 186–188 °C, [α]_D²¹ +64° (c 0.5 in H₂O) {lit.,⁶ m.p. 190–192 °C, [α]_D²¹ +63° (c, 0.5 in H₂O)}.

A solution of the above salt (8.5 g) in hot water (20 ml) was brought to pH 5 by addition of aqueous sodium hydroxide (10%; 11 ml). After 12 h in a refrigerator the precipitate was filtered off. Recrystallisation from ethanol gave (+)-3-amino-2-phenylpropionic acid (3 g, 42%), m.p. 224–225 °C, [α]_D²¹ +95°, [M]_D²⁰ +156.7° (c, 0.2 in H₂O), [α]_D²¹ +125°, [M]_D²⁰ +206.2° (c, 0.2 in 1N-HCl) {lit.,⁶ m.p. 223–226 °C, [α]_D²¹ +85° (c, 0.2 in H₂O)}. The i.r. spectrum was identical with that of the racemic form.

(+)-2-Phenyl-3-phthalimidopropionic Acid (3).—A suspension of (+)-3-amino-2-phenylpropionic acid (4.3 g, 26 mmol) and phthalic anhydride (3.9 g, 35.5 mmol) in toluene (40 ml) and triethylamine (0.7 ml) was refluxed for 5 h in a Dean-Stark apparatus. Toluene was evaporated off *in vacuo* leaving an oil, which on trituration with water (80 ml) and aqueous hydrochloric acid (15 ml; 6N) gave white crystals. Recrystallisation from ethanol–water (1 : 4 v/v)

afforded (+)-2-phenyl-3-phthalimidopropionic acid (3) (6.5 g, 85%), m.p. 172–173 °C, [α]_D²¹ +134°, [M]_D²⁰ +395.3° (c, 1.0 in CHCl₃), [α]_D²¹ +165°, [M]_D²⁰ +486.7°, [α]₄₂₀²¹ +400°, [M]₄₂₀²¹ +1 181°, [α]₄₀₀²¹ +463°, [M]₄₀₀²¹ +1 367°, [α]₃₅₀²¹ +743°, [M]₃₅₀²¹ +2 194°, [α]₃₄₀²¹ +855°, [M]₃₄₀²¹ +2 525°, [α]₃₂₀²¹ +756°, [M]₃₂₀²¹ +2 232°, [α]₃₁₀²¹ +751°, [M]₃₁₀²¹ +2 217° (c, 1.0 in MeOH); λ_{\max} (MeOH) 260 and 292 nm (log ϵ 2.82 and 3.17); ν_{\max} (KBr) 3 060, 1 780, 1 740, 1 710, and 1 600 cm⁻¹; δ (DMSO) 4.00 (3 H, s, 2-H and 3-CH₂), 7.21 (5 H, s, Ph), and 7.65 (4 H, s, ArH) (Found: C, 69.4; H, 4.5; N, 4.75. C₁₇H₁₃NO₄ requires C, 69.1; H, 4.4; N, 4.7%).

(+)-2-Phenyl-3-phthalimidopropionyl Chloride (4).—(+)-Phthalimido acid (3) (6.2 g, 21 mmol) and thionyl chloride (27 ml) were refluxed for 5 h (oil-bath, 75 °C). The excess of thionyl chloride was evaporated off under reduced pressure, the last traces being removed by dissolving the residue in benzene and evaporating to dryness. The crude product was recrystallised from benzene–light petroleum (1 : 4 v/v) to give (+)-2-phenyl-3-phthalimidopropionyl chloride (4) (6.4 g, 97%), m.p. 127–128°, [α]_D²¹ +204°, [M]_D²⁰ +639.3° (c, 1.0 in CHCl₃), [α]_D²¹ +206.9°, [M]_D²⁰ +649.0° (c 0.58 in benzene); ν_{\max} (KBr) 1 780, 1 760, 1 710, and 1 500 cm⁻¹; δ (CDCl₃) 4.30 (2 H, s, 3-CH₂), 4.81 (1 H, q, *J* 7 Hz, 2-H), 7.44 (5 H, s, Ph) and 7.64 (4 H, s, ArH) (Found: C, 65.0; H, 3.9; N, 4.4; Cl, 11.2. C₁₇H₁₂NO₃Cl requires C, 65.1; H, 3.9; N, 4.6; Cl, 11.3%).

(+)-1-Diazo-3-phenyl-4-phthalimidobutan-2-one (5).—A solution of the chloride (4) (6.2 g, 19 mmol) in benzene (50 ml) was added to an ethereal solution of diazomethane [from *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide¹⁵ (18 g)] at 0 °C. After standing for 12 h at 20 °C the solution was evaporated to dryness *in vacuo*. The oily residue was dissolved in ethyl acetate (30 ml) and light petroleum (65 ml) was added to give (+)-1-diazo-3-phenyl-4-phthalimidobutan-2-one (5.7 g, 90%), m.p. 129–130 °C, [α]_D²¹ +327.6°, [M]_D²⁰ +1 046° (c, 0.76 in CHCl₃), [α]_D²¹ +401.3°, [M]_D²⁰ +1 280° (c, 0.56 in AcOEt); ν_{\max} (KBr) 3 080, 2 100, 1 780, and 1 720 cm⁻¹; δ (CDCl₃) 1.60 (1 H, s, CHN₂), 4.32 (2 H, s, 3-CH₂), 5.27 (1 H, s, 2-H), 7.23 (5 H, s, Ph), and 7.74 (4 H, s, ArH) (Found: C, 67.6; H, 4.1; N, 12.8. C₁₈H₁₃N₃O₃ requires C, 67.7; H, 4.1; N, 13.2%).

(+)-2-Phenyl-1-phthalimidobutan-3-one (6).—To a solution of (+)-1-diazo-3-phenyl-4-phthalimidobutan-2-one (5.4 g, 17 mmol) in chloroform (60 ml) at 0 °C, hydriodic acid (18 ml, 67%) was added with stirring. After standing for 20 min at -5 °C, t.l.c. indicated that no starting material remained. The reaction mixture was diluted with cold water (60 ml) and cold chloroform (40 ml). To the separated chloroform layer were added cold water (20 ml) and mercury (15 ml), and the mixture was shaken until the chloroform layer became colourless. The chloroform solution was treated with a small quantity of charcoal, filtered, dried (Na₂SO₄), and evaporated under reduced pressure. The crystalline recrystallisation from benzene–light petroleum (1 : 4 v/v) afforded (+)-2-phenyl-1-phthalimidobutan-3-one (4.2 g, 85%), m.p. 138–139 °C, [α]_D²¹ +244.3°, [M]_D²⁰ +714.9° (c, 0.44 in CHCl₃), δ (CDCl₃) 2.00 (3 H, s, CH₃), 4.01–4.23 (3 H, m, 2-H and 3-CH₂N), 7.38 (5 H, s, Ph), and 7.73 (4 H, s, ArH) (Found: C, 73.5; H, 5.3; N, 4.8. C₁₈H₁₅NO₃ requires C, 73.7; H, 5.15; N, 4.8%).

(+)-3,3-Ethylenedithio-2-phenyl-1-phthalimidobutane (7).—(+)-2-Phenyl-1-phthalimidobutan-3-one (3.7 g, 10

mmol) was dissolved at -10°C in ethane-1,2-dithiol-ether (70 ml; 3 : 4 v/v), and a solution of boron trifluoride-ether (10 ml) in ether (50 ml) was added at -10°C . The mixture was kept at -10°C for 1 h and then for 3 days at room temperature. T.l.c. after this time showed no starting material. The ethereal solution was then washed with water and evaporated to dryness. Traces of ethanedithiol were removed by drying at 1–2 mmHg for 1 day (oil bath, 60°C). The residual oil was dissolved in benzene (20 ml) and light petroleum (50 ml) was added to give colourless crystals which after recrystallisation from benzene–light petroleum ether (1 : 4 v/v) yielded the *dithioacetal* (7) (3.0 g, 81%), m.p. $94\text{--}95^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{21} + 64.7^{\circ}$, $[M]_{\text{D}} + 238.7^{\circ}$ (*c*, 0.34 in CHCl_3), R_{F} (2) 0.6; ν_{max} (KBr) 1760, 1480, 710, and 600 cm^{-1} ; $\delta(\text{CDCl}_3)$ 1.81 (3 H, s, 4-CH_3), 3.42 (4 H, s, $-\text{S}[\text{CH}_2]_2\text{S}-$), 3.97 (1 H, q, J 6 Hz, 2-H), 4.81–4.22 (2 H, m, 1- CH_2), 7.50–7.27 (5 H, s, Ph), and 7.71–7.69 (4 H, s, ArH) (Found: C, 65.1; H, 5.1; N, 3.7. $\text{C}_{20}\text{H}_{19}\text{NO}_2\text{S}_2$ requires C, 65.0; H, 5.2; N, 3.8%).

(+)-2-Phenyl-1-phthalimidobutane (8).—A solution of the foregoing dithioacetal (7) (2.5 g, 6.8 mmol) in acetone (60 ml) was heated under reflux with Raney nickel catalyst¹⁸ (8 g, W-1 activity) with stirring for 6 h, and cooled. The catalyst was filtered off and washed with acetone (150 ml), and the combined acetone filtrates were evaporated under reduced pressure. The residual oil was dissolved in chloroform (60 ml), dried (Na_2SO_4), and evaporated *in vacuo* to give a pale yellow oil which crystallised after 2 days at room temperature. Recrystallisation from chloroform–light petroleum (1 : 1 v/v) yielded the *phthalimidobutane* (8) (1.8 g, 85%), m.p. $57\text{--}58^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{21} + 39.3^{\circ}$, $[M]_{\text{D}} + 123.8^{\circ}$ (*c*, 0.28 in CHCl_3), R_{F} (2) 0.7; ν_{max} (KBr) 3080, 3060, 3040, 1780, and 1715 cm^{-1} ; $\delta(\text{CDCl}_3)$ 0.82 (3 H, t, 4-CH_3), 1.65 (2 H, q, J 3 Hz, 3- CH_2), 3.87 (2 H, d, J 7 Hz, 1- CH_2), 7.45 (5 H, s, Ph) and 7.91–7.57 (4 H, m, ArH) (Found: C, 77.1; H, 6.1; N, 5.0. $\text{C}_{18}\text{H}_{17}\text{NO}_2$ requires C, 77.4; H, 6.1; N, 5.0%).

(+)-1-Amino-2-phenylbutane (2).—A solution of (+)-2-phenyl-1-phthalimidobutane (8) (0.5 g, 1.7 mmol) in glacial acetic acid (8 ml) and concentrated hydrochloric acid (8 ml) was refluxed for 6 h; the glacial acetic and hydrochloric acids were removed under reduced pressure. The residue was dissolved in NaOH solution (10%; 30 ml) and extracted

with ether. The organic layer was washed with NaCl solution (5%; 35 ml), dried (K_2CO_3), and evaporated under reduced pressure. An oily residue (0.25 g) was obtained which t.l.c. indicated to be a mixture of starting materials and products. This mixture was dissolved in ether and extracted with hydrochloric acid (10%; 25 ml); the acid solution was then basified with aqueous NaOH (25%; 15 ml) and extracted with ether (30 ml). After drying (K_2CO_3) and evaporation an oily product was isolated. Distillation afforded (+)-1-amino-2-phenylbutane (2) (0.15 g, 65%), b.p. $70\text{--}75^{\circ}\text{C}$ 8 at 2 mmHg (lit.,⁸ 69°C at 1.5 mmHg), n_{D}^{25} 1.5575, $[\alpha]_{\text{D}}^{21} + 9.2^{\circ}$, $[M]_{\text{D}} + 17.5^{\circ}$ (*c*, 1.0 in ether) {lit.,¹⁷ $[\alpha]_{\text{D}}^{21} + 9.8^{\circ}$ (in ether)}, $[\alpha]_{\text{D}}^{21} + 35^{\circ}$, $[M]_{\text{D}} + 47.2^{\circ}$ (*c* 0.12 in MeOH), $[\alpha]_{\text{D}}^{21} + 12.1^{\circ}$, $[M]_{\text{D}} + 16.3^{\circ}$ (*c* 0.19 in CHCl_3), $[\alpha]_{\text{D}}^{21} + 13.0^{\circ}$, $[M]_{\text{D}} + 17.5^{\circ}$ (*c* 0.33 in EtOH), R_{F} (2) 0.9; ν_{max} (film) 3430, 3080, 3060, and 1600 cm^{-1} .

[0/792 Received, 28th May, 1980]

REFERENCES

- ¹ Presented at the 8th Latinoamerican Seminar of Chemistry, Buenos Aires, Argentina, November, 1979.
- ² H. Dahn, J. A. Garbarino, and C. O'Murchu, *Helv. Chim. Acta*, 1970, **53**, 1370.
- ³ J. A. Garbarino, J. Sierra, and R. Tapia, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1866.
- ⁴ D. Dodsworth, J. A. Garbarino, and R. Requiz, 12th Latinoamerican Congress of Chemistry, Quito, Ecuador, September, 1976.
- ⁵ F. Leonard, A. Wajngot, M. Klein, and C. Smith, *J. Org. Chem.*, 1961, **26**, 4062.
- ⁶ E. Testa, G. Gignarella, G. Pifferi, S. Furesz, M. Timbal, P. Schiatti, and G. Maffi, *Il Farmaco (Sci. Ed.)*, 1964, **19**, 895.
- ⁷ A. McKenzie and R. Strathern, *J. Chem. Soc.*, 1925, **127**, 82.
- ⁸ W. Kirmse and W. Gruber, *Chem. Ber.*, 1971, **104**, 1795.
- ⁹ C. Djerassi, E. Lund, E. Bunnenberg, and J. Sheehan, *J. Org. Chem.*, 1961, **26**, 4509.
- ¹⁰ K. Freudenberg, F. Brauns, and H. Siegel, *Ber.*, 1923, **56**, 193.
- ¹¹ K. Balenovic and N. Bregant, *Tetrahedron*, 1959, **5**, 44.
- ¹² G. W. Clough, *J. Chem. Soc.*, 1918, **113**, 526.
- ¹³ O. Lutz and B. Jirgensons, *Ber.*, 1930, **63**, 448; 1931, **64**, 1221.
- ¹⁴ A. McKenzie and K. Wood, *J. Chem. Soc.*, 1919, **115**, 828.
- ¹⁵ T. de Boer and H. Backer, *Org. Synth.*, Coll. Vol. 4, J. Wiley and Sons, New York, 1963, p. 250.
- ¹⁶ L. Cornert and H. Adkins, *J. Am. Chem. Soc.*, 1932, **54**, 4116.
- ¹⁷ P. Levene, L. Mikeska, and K. Passoth, *J. Biol. Chem.*, 1930, **88**, 27.