Stereochemical Studies on Aromatic α-Alkyl-α-amino-acids. Part III.† Absolute Configuration of 2-Amino-2-phenylbutyric Acid [1]

By **Juan A. Garbarino,* Jorge Sierra,** and **Ricardo Tapia,** Institute of Chemistry, Catholic University of Chile, Santiago, Chile

(+)-2-Formamido-2-phenylbutyric acid has been converted into (−)-2-phenyl-2-*p*-tolylsulphonylaminobutane, which was also obtained by tosylation of (−)-(*S*)-2-amino-2-phenylbutane. This correlation proves the *S*-configuration of (+)-2-amino-2-phenylbutyric acid. Application of stereochemical optical rotation shift rules confirms this assignment.

THE stereochemistry of several compounds related to aromatic α-alkyl-α-amino-acids has been reported.[2,3] We now report the absolute configuration of (+)-2-amino-2-phenylbutyric acid (I). Derivatives of this

† Part II is reference 3.

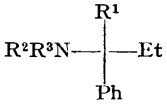
[1] Presented in part at the 11th Latinoamerican Congress of Chemistry, Santiago, Chile, January 1972.

[2] J. A. Garbarino, *Ann. Chim.* (*Italy*), 1969, **59**, 841.

[3] L. Contreras and J. A. Garbarino, *Rev. Latinoam. Quim.*, 1971, **2**, 15.

acid show important vasodilatation and antiarrhythmic properties.[4,5]

The (+)-acid (I) was first correlated chemically with (−)-(*S*)-2-amino-2-phenylbutane (VII) (whose stereochemistry has been reported by Cram and Bradshaw [6]) through (−)-2-phenyl-2-*p*-tolylsulphonylaminobutane (VI). By Strecker's method,[7] (±)-2-amino-2-phenyl-



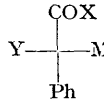
(I) $R^1 = CO_2H$, $R^2 = R^3 = H$
(II) $R^1 = CO_2H$, $R^2 = H$, $R^3 = CHO$
(III) $R^1 = CO_2Et$, $R^2 = R^3 = H$
(IV) $R^1 = CH_2{\cdot}OH$, $R^2 = R^3 = H$
(V) $R^1 = CH_2{\cdot}OTs$, $R^2 = H$, $R^3 = Ts$
(VI) $R^1 = Me$, $R^2 = H$, $R^3 = Ts$
(VII) $R^1 = Me$, $R^2 = R_3 = H$
(VIII) $R^1 = CO_2H$, $R^2 = R^3 = Me$
(IX) $R^1 = CO_2Me$, $R^2 = R^3 = Me$
(X) $R^1 = CO_2Me$, $R^2 = R^3 = H$
(XI) $R^1 = CO_2Et$, $R^2 = H$, $R^3 = COMe$
$Ts = SO_2{\cdot}C_6H_4Me\text{-}p$

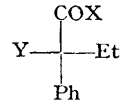
butyric acid, prepared from propiophenone, was converted into (±)-2-formamido-2-phenylbutyric acid (II), which was resolved with cinchonidine and hydrolysed with hydrobromic acid to give the (+)-acid (I). Attempts to achieve this resolution with quinine, as reported by Sobotka *et al.*,[8] were unsuccessful. The (+)-amino-acid (I) was esterified in ethanolic hydrogen chloride to give the expected (+)-amino-ester (III), identified by i.r. spectroscopy and elemental analysis. Reduction of the (+)-ester with sodium borohydride [9] gave the expected (+)-amino-alcohol as an oil which solidified. This reaction was checked with racemic (III), using both lithium aluminium hydride and sodium borohydride as reducing agents; the latter method gave higher yields. The (+)-amino-alcohol (IV) was tosylated with toluene-*p*-sulphonyl chloride in the usual manner to give the (+)-*NO*-ditosyl derivative of 2-amino-2-phenylbutan-1-ol (V). This was reduced with lithium aluminium hydride in refluxing ether–benzene, affording (−)-2-phenyl-2-*p*-tolylsulphonylaminobutane (VI), $[\alpha]_D$ −21·1°.

The (−)-sulphonamide was then chemically correlated with (−)-(*S*)-2-amino-2-phenylbutane (VII). The amine (VII) was resolved through the tartrate salt; the product obtained after alkaline hydrolysis showed $[\alpha]_D$ −16·2°, implying that (VII) was 89% optically pure (the value $[\alpha]_D$ −18·2° given by Cram and Bradshaw [6] was taken as the specific rotation of the pure amine). This compound (VII), treated with toluene-*p*-sulphonyl chloride, afforded the (−)-sulphonamide (VI), $[\alpha]_D$ −21·7°, identical with that obtained from the (+)-acid (I) (mixed m.p., i.r. spectra, and t.l.c.). Specific rotation values of the two samples were in good agreement, indicating that the conversion (+)-(II) ⟶ (−)-(VI) was effected without significant racemisation.

Further evidence for the proposed configuration of (+)-(I) arises from the application of stereochemical rotation shift rules. Use of Freudenberg's displacement rule [10] involved comparison of the molecular optical rotations of (+)-(*S*)-2-amino-2-phenylpropionic acid and its derivatives [11] with those of (+)-2-amino-2-phenylbutyric acid (see Table). The value for (+)-ethyl

Molecular rotations



X	Y	
OH	NH·CHO	+134
OH	NH_2	+63
OEt	NH_2	+30
OEt	NHAc	+50
OMe	NH_2	+19
OMe	NMe_2	+21

2-acetamido-2-phenylbutyrate (XI) is the only exception in this comparison.

Finally, one can apply the Clough–Lutz–Jirgensons rule,[12,13] which has been shown to be applicable to aryl-substituted (*S*)-α-alkyl-α-amino-acids.[14,15] A positive shift in rotation in going from neutral to acidic solution was observed for both the amino-acids (+)-(I) and (−)-(VIII), agreeing with an *S*-configuration for each compound.

Thus the absolute configuration of (+)-2-amino-2-phenylbutyric acid (I) has been proved to be *S*. As a consequence of our experiments, the proposal of Cram and Bradshaw [6] about the stereochemistry of (−)-(VII) has been shown to be correct.

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer 137 spectrophotometer. Specific rotations were measured on a Hilger and Watts M412 polarimeter (0·5 dm tubes). M.p.s were determined with a Kofler hot-stage apparatus.

Resolution of (±)-2-*Formamido*-2-*phenylbutyric Acid* (II). —The acid (II) was obtained (83%) from (±)-2-amino-2-phenylbutyric acid [7] by the method of Cram and his co-workers; [16] m.p. 197—198° (from water) (lit.,[8] 193°). The (±)-acid (20·3 g) and (−)-cinchonidine (28·8 g), $[\alpha]_D^{20}$ −127·5° (*c* 5·0 in EtOH) were dissolved in boiling water

[4] J. A. Garbarino, F. Huidobro, J. Lewin, and J. P. Huidobro, *Acta Physiol. Latinoam.*, 1968, **18**, 368.
[5] F. Huidobro, J. Lewin, J. P. Huidobro, J. A. Garbarino, and E. Samaniego, *Arch. Internat. Pharmacodyn.*, 1969, **182**, 49.
[6] D. J. Cram and J. S. Bradshaw, *J. Amer. Chem. Soc.*, 1963, **85**, 1108.
[7] R. E. Steiger, *Org. Synth.*, 1955, Coll. Vol. III, p. 88.
[8] H. Sobotka, M. F. Holzman, and J. Kahn, *J. Amer. Chem. Soc.*, 1932, **54**, 4697.
[9] H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 995.
[10] K. Freudenberg, F. Brauns, and H. Siegel, *Ber.*, 1923, **56**, 193.
[11] H. Dahn, J. A. Garbarino, and C. O'Murchu, *Helv. Chim. Acta*, 1970, **53**, 1370.
[12] G. W. Clough, *J. Chem. Soc.*, 1918, **113**, 526.
[13] O. Lutz and B. Jirgensons, *Ber.*, 1930, **63**, 448; 1931, **64**, 1221.
[14] E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *J. Org. Chem.*, 1964, **29**, 2053.
[15] K. Achiwa, S. Terashima, H. Mizuno, N. Takamura, T. Kitagawa, K. Ishikawa, and S. Yamada, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 61.
[16] D. J. Cram, L. K. Gaston, and H. Jager, *J. Amer. Chem. Soc.*, 1961, **83**, 2183.

(900 ml) and kept in a refrigerator overnight. The precipitate was filtered off to give crude (−)-2-*formamido*-2-*phenylbutyrate cinchonidine salt* (23·1 g), $[\alpha]_D^{21}$ −57·3° (*c* 1·11 in EtOH). Two recrystallisations from water gave crystals (19·2 g, 76%) of m.p. 196—197°, $[\alpha]_D^{20}$ −65·2° (*c* 1·01 in EtOH) (Found: C, 71·8; H, 7·1. $C_{30}H_{35}N_3O_4$ requires C, 71·8; H, 7·0%). A suspension of the (−)-cinchonidine salt in aqueous sodium carbonate (15% w/v; 300 ml) was stirred at room temperature, and free cinchonidine was extracted into chloroform. The aqueous layer was acidified with dilute hydrochloric acid, evaporated to 100 ml, and kept at 0° for 24 h. The (+)-formamido-acid was filtered off (11·3 g); two recrystallisations from water produced white crystals (9·6 g, 73%), m.p. 202—203°, $[\alpha]_D^{26}$ +64·6°, $[M]_D$ +134° (*c* 1·07 in EtOH) {lit.,[8] m.p. 212°, $[\alpha]_D^{26}$ +126° (*c* 1·00 in aq. alkali)}. The i.r. spectrum was identical with that of the racemic form.

(+)-2-*Amino*-2-*phenylbutyric Acid* (I).—(+)-2-Formamido-2-phenylbutyric acid (9 g) was warmed with hydrobromic acid (N; 70 ml) until a clear solution resulted. Evaporation to dryness gave a pale yellow solid. The crude (+)-amino-acid hydrobromide was dissolved at 0° in dry ethanol (25 ml) saturated with dry ammonia gas. After a further 4 days at 0° the solution was filtered and solid was recrystallised from aqueous ethanol giving the (+)-amino-acid (I) (5 g, 64%), m.p. 255—265° (decomp.), $[\alpha]_D^{20}$ +34·4°, $[M]_D$ +63° (*c* 1·63 in H_2O), $[\alpha]_D^{27}$ +75·8°, $[M]_D$ +136° (*c* 0·99 in 6N-HCl) {lit.,[8] $[\alpha]_D$ +41° (*c* 1·01 in aq. alkali)}; the i.r. spectrum was identical with that of the racemic amino-acid.

(+)-*Ethyl* 2-*Amino*-2-*phenylbutyrate* (III).—A solution of the (+)-amino-acid (I) (5 g) in absolute ethanol (35 ml) was saturated with dry hydrogen chloride at 0° and then was refluxed for 6 h. After cooling, benzene (50 ml) was added and the solution was distilled up to a temperature of 78°. The residue was basified with dilute ammonium hydroxide and the free ester was extracted into ether (3 × 20 ml). After washing with water (2 × 15 ml), the extract was dried (Na_2SO_4) and the solvent removed. Distillation of the residual oil gave the (+)-amino-ester (III) as an oil (4·5 g, 78%), b.p. 90—91° at 3 mmHg, n_D^{20} 1·5100, $[\alpha]_D^{20}$ +14·6°, $[M]_D$ +30° (*c* 1·08 in EtOH) {lit.,[8] b.p. 270° (decomp.), $[\alpha]_D$ +36° (*c* 0·76 in H_2O)}, $\nu_{max.}$ 3380, 3230, and 1724 cm^{-1} (Found: C, 69·2; H, 8·3. Calc. for $C_{12}H_{17}NO_2$: C, 69·5; H, 8·3%).

(+)-2-*Amino*-2-*phenylbutan*-1-*ol* (IV).—The (+)-amino-ester (4·6 g) in dry ethanol (45 ml) was treated with sodium borohydride (5·2 g) in dry ethanol (150 ml). The solution was heated under reflux for 2 h and the solvent removed *in vacuo*. Water (30 ml) was added to the residue, which was then extracted with ethyl acetate (3 × 20 ml). The extract was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residual oil was distilled, affording the liquid (+)-*amino-alcohol* (IV) (2·5 g, 69%), b.p. 116—117° at 4 mmHg, m.p. 51—52°, $[\alpha]_D^{18}$ +25·6° (*c* 1·95 in EtOH), $\nu_{max.}$ 3390, 3125, and 1064 cm^{-1} (Found: C, 72·8; H, 9·1. $C_{10}H_{15}NO$ requires C, 72·7; H, 9·15%).

(+)-2-*Phenyl*-2-(p-*tolylsulphonyl*)*aminobutyl Toluene*-p-*sulphonate* (V).—(+)-2-Amino-2-phenylbutan-1-ol (2 g) in dry pyridine (15 ml) was cooled to −5°. Toluene-*p*-sulphonyl chloride (8 g) was added slowly and the resulting paste was stirred for 1 h. After 7 days in the refrigerator, the mixture was poured into ice–water (50 ml) and extracted with ether (2 × 30 ml). The combined ether layers were extracted with dilute hydrochloric acid, washed with water, dried (Na_2SO_4), and evaporated to give the crude NO-*ditosylate*, (+)-(V) (1·6 g, 28%), m.p. 122·5—123·5° (from methanol–water), $[\alpha]_D^{18}$ +25·4° (*c* 1·08 in EtOH), $\nu_{max.}$ 3390, 1605, 1351, 1172, and 810 cm^{-1} (Found: C, 60·65; H, 5·8; S, 13·6. $C_{24}H_{27}NO_5S_2$ requires C, 60·9; H, 5·75; S, 13·6%).

(−)-2-*Phenyl*-2-p-*tolylsulphonylaminobutane* (VI).—The (+)-ditosylate (V) (0·5 g) in dry benzene (5 ml) was added slowly to lithium aluminium hydride (0·25 g) in dry ether (25 ml). After 18 h under reflux, the mixture was left overnight and then decomposed with a slight excess of dilute hydrochloric acid. The aqueous layer was extracted with ether (2 × 20 ml) and the combined extracts were washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was taken up in methanol and drops of water were added, precipitating plates of the (−)-N-p-*tolylsulphonyl derivative* (0·2 g, 62%), m.p. 126—127°, $[\alpha]_D^{25}$ −21·1° (*c* 1·2 in dioxan), $\nu_{max.}$ 3280, 1587, 1315, 1155, and 813 cm^{-1} (Found: C, 67·2; H, 7·0; S, 10·8. $C_{17}H_{21}NO_2S$ requires C, 67·3; H, 7·0; S, 10·55%).

Resolution of (±)-2-*Amino*-2-*phenylbutane* (VII).—This amine, prepared by the procedure of Cram and Knight,[17] was kept as its hydrochloride salt, m.p. 247·5° (from ethanol–ether) (lit.,[18] 242°), $\nu_{max.}$ 2925 and 1610 cm^{-1} (Found: C, 64·8; H, 8·5; N, 7·5. Calc. for $C_{10}H_{16}ClN$: C, 64·4; H, 8·7; N, 7·5%). The (±)-amine (13·9 g) and (+)-tartaric acid (14 g), $[\alpha]_D^{20}$ +12° (*c* 10 in H_2O) were dissolved in hot ethanol (140 ml); the solution was filtered hot and the (−)-*amine* (+)-*hydrogen tartrate* (10·2 g), $[\alpha]_D^{20}$ +17·3° (*c* 1·07 in H_2O) was collected after cooling for 12 h. Three recrystallisations from ethanol gave the (+)-salt as crystals (8·4 g, 60%), m.p. 168—170°, $[\alpha]_D^{20}$ +24·4° (*c* 1·27 in H_2O), $\nu_{max.}$ 3390 and 3040 cm^{-1} (Found: C, 55·9; H, 7·0. $C_{14}H_{21}NO_6$ requires C, 56·2; H, 7·1%).

A solution of (+)-salt (1·3 g) in water (7 ml) was added to aqueous sodium hydroxide (10N; 1 ml) and stirred for 1 h at room temperature. Free amine was extracted with ether (2 × 10 ml); the combined ether layers were washed, dried (Na_2SO_4), and evaporated. Distillation of the residual oil afforded the (−)-*amine* (VII) (0·4 g, 57%), b.p. 70—72° at 5 mmHg, n_D^{25} 1·5152, $[\alpha]_D^{20}$ −16·2° (neat) {lit.,[6] b.p. 50—52° at 2 mmHg, n_D^{25} 1·5148, $[\alpha]_D^{20}$ −18·2° (neat)}, $\nu_{max.}$ 3560 and 1615 cm^{-1}.

(−)-2-*Phenyl*-2-p-*tolylsulphonylaminobutane* (VI).—The (−)-amine (VII) (0·2 g) in dry pyridine (4 ml) was shaken with toluene-*p*-sulphonyl chloride (0·25 g) in dry pyridine (2 ml) for 2 h at 0°. After 3 days in a refrigerator, the solution was worked up in the usual way, affording the (−)-*sulphonamide* (0·24 g, 59%), which twice recrystallised from aqueous methanol, had m.p. 126—127°, $[\alpha]_D^{25}$ −21·7° (*c* 1·54 in dioxan), and was identical (mixed m.p. and i.r. spectrum) with (−)-(VI) obtained from the reduction of (+)-(V). Both samples showed a single spot on t.l.c. [R_F 0·75 on silica gel G, developed by ethyl acetate–petroleum (50% v/v)].

(−)-2-*Dimethylamino*-2-*phenylbutyric Acid* (VIII).—The (+)-formamido-acid (II) (1 g) in concentrated formic acid (2·7 g) and formaldehyde (38%; 1·2 g) was warmed at 90° for 5 h. No solid was deposited so the solution was evaporated *in vacuo* leaving an oil, which on trituration with acetone gave white crystals of the (−)-*dimethylamino-acid* (VIII) (0·35 g, 34%), m.p. 206—207°, $[\alpha]_D^{25}$ −16·6°, $[M]_D$

[17] D. J. Cram and J. D. Knight, *J. Amer. Chem. Soc.*, 1954, **74**, 5835.

[18] D. J. Cram, C. A. Kingsbury, and A. Langemann, *J. Amer. Chem. Soc.*, 1959, **81**, 5785.

$-34°$ (*c* 2·4 in H_2O), $[\alpha]_D^{23}$ $+16·9°$, $[M]_D$ $+35°$ (*c* 1·03 in 6N-HCl), $\nu_{max.}$ 2350 and 1760 cm^{-1} (Found: C, 69·8; H, 8·1. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3%).

(+)-*Methyl 2-Dimethylamino-2-phenylbutyrate* (IX).—A suspension of the (−)-acid (VIII) (0·3 g) in dry methanol (15 ml) was treated with an excess of diazomethane in ether (25 ml) [prepared from nitrosomethylurea (0·7 g)] and left overnight at room temperature. The solvent was evaporated off *in vacuo* and the residual oily (+)-*dimethylamino-ester* (IX) was distilled (0·25 g, 77%), b.p. 90° at 0·5 mmHg, n_D^{16} 1·5158, $[\alpha]_D^{26}$ $+9·5°$, $[M]_D$ $+21°$ (*c* 0·11 in petroleum), $\nu_{max.}$ 2875, 2830, 2780, and 1715 cm^{-1} (Found: C, 70·4; H, 8·6. $C_{13}H_{19}NO_2$ requires C, 70·55; H, 8·6%).

(+)-*Methyl 2-Amino-2-phenylbutyrate* (X).—A suspension of the (+)-amino-acid (I) (0·6 g) in dry methanol (25 ml) was added to an excess of diazomethane in ether (40 ml) [prepared from nitrosomethylurea (1·4 g)] and left overnight at room temperature. The mixture was then concentrated *in vacuo* and the resulting oil distilled affording the (+)-*amino-ester* (X) (0·2 g, 32%), b.p. 85—87° at 1·5 mmHg, n_D^{27} 1·5141, $[\alpha]_D^{26}$ $+10°$, $[M]_D$ $+19°$ (*c* 1·02 in EtOH), $\nu_{max.}$ 3450, 3380, and 1725 cm^{-1} (Found: C, 68·4; H, 8·0. $C_{11}H_{15}NO_2$ requires C, 68·4; H, 7·8%).

(+)-*Ethyl 2-Acetamido-2-phenylbutyrate* (XI).—The (+)-amino-ester (III) (0·1 g) in dry ether (5 ml) was cooled to 0° and acetic anhydride (1 ml) was added slowly. After 3 h at room temperature, the solution was heated under reflux for 0·5 h and then all volatile material was removed *in vacuo*. The residue was dissolved in chloroform (15 ml) and washed with sodium hydroxide solution (N; 10 ml). The organic layer was washed with water (15 ml), dried (Na_2SO_4), and evaporated. The residue was taken up in petroleum (b.p. 40—60°), affording the (+)-*acetamido-ester* (XI) (0·1 g, 83%), m.p. 101°, $[\alpha]_D^{24}$ $+20°$, $[M]_D$ $+50°$ (*c* 1·24 in EtOH), $\nu_{max.}$ 1730 and 1650 cm^{-1} (Found: C, 67·7; H, 7·8. $C_{14}H_{19}NO_3$ requires C, 67·4; H, 7·7%).

This research was supported by a Grant from FORGE. We thank Professor G. B. Marini-Bettólo, Institute of Chemistry of the Catholic University of Rome, for elemental analyses.

[3/338 *Received*, 14*th February*, 1973]