Synthesis of Peptides containing 1,2,3,4-Tetrahydroquinoline-2-carboxylic Acid. Part 1. Absolute Configurations of 1,2,3,4-Tetrahydroquinoline-2-carboxylic Acids and 2-Substituted 1,2,3,4-Tetrahydroquinolines

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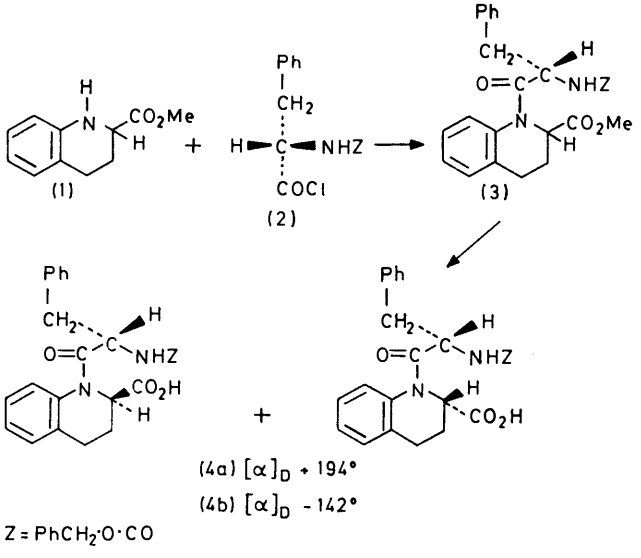
(−)-1,2,3,4-Tetrahydroquinoline-2-carboxylic acid was isolated by oxidation of the racemic amino-acid with D-amino-acid oxidase; (+)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, obtained from hydrolysis of the dipeptide (+)-*N*-benzyloxycarbonyl-(*S*)-phenylalanyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid, was chemically correlated with (−)-1,2,3,4-tetrahydro-2-methylquinoline through (−)-(*R*)-β-anilinobutyric acid, the configuration of which was also established. The absolute configuration of (−)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid and (−)-1,2,3,4-tetrahydro-2-methylquinoline is shown to be *S*.

CYCLIZATIONS of small protected peptides containing proline have been described;[1] azacyclols and acylpiperazinediones were obtained from activated linear tripeptides. In view of these results it seemed of interest to examine the cyclization reactions of peptides containing 1,2,3,4-tetrahydroquinoline-2-carboxylic acid instead of proline. This cyclic amino-acid has been little used so far and only its racemic mixture is known.[2] We report here the determination of the absolute configurations of the 1,2,3,4-tetrahydroquinoline-2-carboxylic acids and stereochemical correlations that allowed the absolute configurations of some 2-substituted tetrahydroquinolines to be assigned.

The resolution of 1,2,3,4-tetrahydroquinoline-2-carboxylic acid was performed by fractional crystallisation of the mixture of the two diastereoisomeric *N*-benzyloxycarbonyl-(*S*)-phenylalanyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acids (4a and b) obtained by basic hydrolysis of the corresponding dipeptide esters (3), formed in turn by the reaction between the acid chloride of *N*-benzyloxycarbonyl-(*S*)-phenylalanine (2) and (*RS*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1). The dipeptide acids (4a and b) showed $[\alpha]_D$ +194° and −142°, respectively. Compound (4a) was hydrolysed under mild acidic conditions and the product yielded methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1a) with $[\alpha]_D$ −44° on esterification with methanolic sulphuric acid.

There is only one report concerning the absolute configuration of a 2-substituted 1,2,3,4-tetrahydroquinoline, in which the *S*-configuration is attributed to (+)-1,2,3,4-tetrahydro-2-methylquinoline, by comparing the g.l.c. behaviour of 2-[*N*-trifluoroacetyl-(*S*)-prolyl]-1,2,3,4-tetrahydroquinolines with that of *N*-trifluoroacetyl-(*S*)-prolyl derivatives of asymmetric cyclic amines.[3] Thus, it seemed appropriate to correlate methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate with 1,2,3,4-tetrahydro-2-methylquinoline by chemical transformation. Nevertheless our first aim was to verify the configurational assignment of (+)-1,2,3,4-tetrahydro-2-methylquinoline by a chemical correlation, as follows.

β-Anilinopropionic and butyric acids are known to undergo cyclization yielding 2,3-dihydroquinolin-4(1*H*)-one derivatives.[4] Thus a β-anilinobutyric acid with known configuration was required to yield, by cyclization, a 2,3-dihydro-2-methylquinolin-4(1*H*)-one which



SCHEME 1

could be easily reduced to a 1,2,3,4-tetrahydro-2-methylquinoline with known configuration. The absolute configuration of β-anilinobutyric acid was not known.

The resolution of β-anilinobutyric acid was carried out by fractional crystallisation of its quinine salts. A β-anilinobutyric acid with $[\alpha]_D$ −24° was isolated and related to (+)-(*R*)-α-anilinopropionic acid, whose configuration had been determined by Portoghese.[5] (+)-(*R*)-α-Anilinopropionic acid was not transformed into β-anilinobutyric acid by the classical Arndt–Eistert method, since the acid chloride and the carbene formed by decomposition of the intermediate diazo-ketone underwent secondary cyclization reactions. We therefore chose the following two series of reactions (Scheme 2),

[1] G. Lucente and A. Romeo, *Chem. Comm.*, 1971, 1605; G. Lucente and P. Frattesi, *Tetrahedron Letters*, 1972, 4283; G. Lucente, A. Romeo, and G. Zanotti, *Gazzetta*, 1972, **102**, 941; F. Conti, G. Lucente, A. Romeo, and G. Zanotti, *Internat. J. Peptide Protein Res.*, 1973, **5**, 353.

[2] H. Wieland, O. Hettche, and T. Hoschimo, *Ber.*, 1928, **61**, 2341.

[3] J. W. Westley and B. Halpern, 'Gas-Chromatography,' Copenhagen, 1968, p. 119.

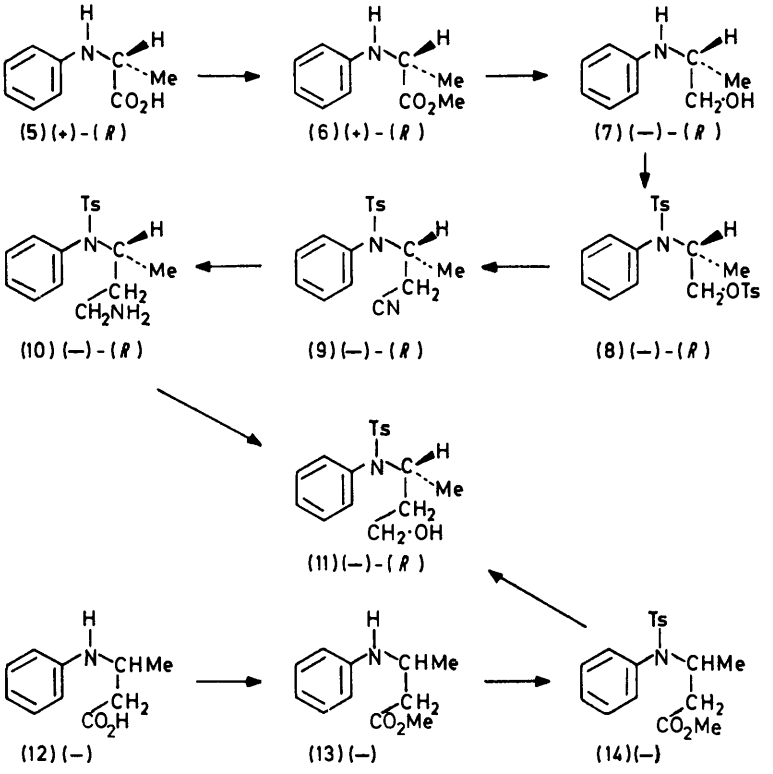
[4] (*a*) R. C. Elderfield and A. Maggiolo, *J. Amer. Chem. Soc.*, 1949, **71**, 1906; (*b*) J. Koo, *J. Org. Chem.*, 1963, **28**, 1134.

[5] P. S. Portoghese, *J. Pharm. Sci.*, 1964, **53** (2), 228.

both of which yielded 3-(*N*-tosylanilino)butan-1-ol, from (+)-(*R*)-α-anilinopropionic acid and (−)-β-anilinobutyric acid, respectively.

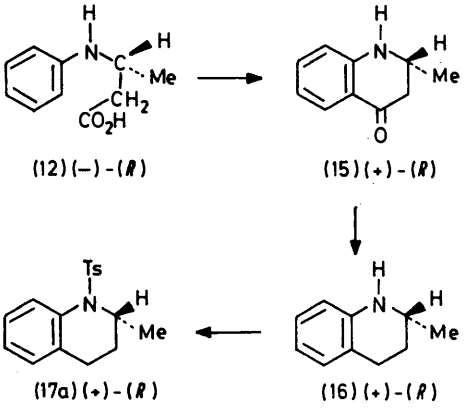
(+)-(*R*)-α-Anilinopropionic acid (5), the reference compound throughout this work, was esterified with methanolic sulphuric acid. The methyl ester (6) was reduced to the amino-alcohol (7), and the derived ditosylate (8) was treated with potassium cyanide in dimethyl sulphoxide at *ca.* 30 °C, to give the nitrile (9). The amine (10), prepared by reduction ($LiAlH_4$) was treated with sodium nitrite in aqueous acetic acid yielding the tosyl alcohol (11) with $[\alpha]_D$ −108°. In the other series of reactions (−)-β-anilinobutyric acid (12) was esterified with methanolic sulphuric acid and the ester (13) transformed into the tosyl ester (14). Reduction ($LiAlH_4$) gave the tosyl alcohol (11) with $[\alpha]_D$ −100°. Thus the two sets of reactions led to the same (−)-3-(*N*-tosylanilino)butan-1-ol: as a consequence the *R*-configuration was assigned to (−)-β-anilinobutyric acid, which was then employed to yield a 1,2,3,4-tetrahydro-2-methylquinoline of known configuration.

(−)-(*R*)-β-Anilinobutyric acid (12) was cyclized by heating with polyphosphoric acid at 125—130 °C yielding (+)-1,2-dihydroquinolin-4(3*H*)-one (15). This was then reduced with aluminium chlorohydride to 1,2,3,4-tetrahydro-2-methylquinoline (16) with $[\alpha]_D$ +85°. The tosylate (17a) of (16) showed $[\alpha]_D$ +130°. Since we had thus carried out a synthesis not involving the chiral centre, the *R*-configuration was ascribed to the (+)-1,2,3,4-tetrahydro-2-methylquinoline obtained from (−)-(*R*)-β-anilinobutyric acid. This result corrects the previously reported assignment of the *S*-configuration to (+)-tetrahydro-2-methylquinoline and allowed us to set up a new chemical correlation to ascertain the stereochemistry of (−)-methyl tetrahydroquinoline-2-carboxylate (1a).



SCHEME 2

The ester (1a) was reduced ($LiAlH_4$) to 1,2,3,4-tetrahydroquinolin-2-ylmethanol (18), which was then transformed into the ditosyl derivative (19). Reduction of

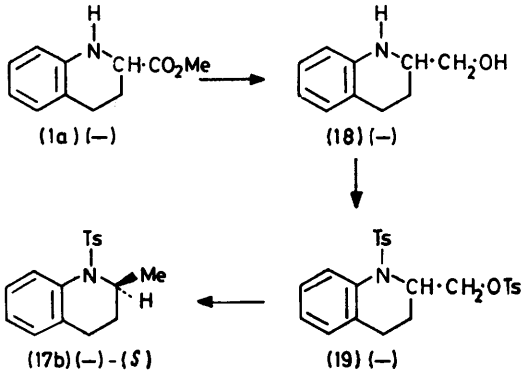


SCHEME 3

(19) ($LiAlH_4$) gave 1,2,3,4-tetrahydro-2-methyl-1-tosylquinoline (17b) with $[\alpha]_D$ −133°; the tosylate of (−)-tetrahydro-2-methylquinoline is reported to exhibit $[\alpha]_D$ −134°.[6] This result showed that no racemization

[6] W. J. Pope and T. F. Winmill, *J. Chem. Soc.*, 1912, **101**, 2309.

had occurred during the chosen sequence of reactions, and allowed us to conclude that the 1,2,3,4-tetrahydroquinoline-2-carboxylic acid obtained from hydrolysis of the dipeptide (4a) was of high optical purity.



SCHEME 4

As is apparent from Scheme 4, the *R*-configuration is to be attributed to (−)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1a) (note the change in priority sequence of substituents about the asymmetric centre).

It was then found that quinoline-2-carboxylic acid and (−)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid were obtained by the action of D-amino-acid oxidase (DAO) on (±)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid. The cyclic amino-acid was isolated as the hydrochloride and showed $[\alpha]_D$ −18° in 0.5N-HCl; the methyl ester showed $[\alpha]_D$ +41°. These data agreed with the stereospecificity previously observed in oxidations with DAO of α-amino-acids, even when these are cyclic, *e.g.* proline [7] and pipecolic acid,[8] furthermore confirmed the *S*-configuration of (+)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate and (−)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid.

EXPERIMENTAL

M.p.s were determined with a Büchi oil-bath apparatus; optical rotations were taken at 20 °C with a Schmidt-Haensch polarimeter (1 dm cell). I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer (KBr discs or CCl_4 solutions). N.m.r. spectra were measured for solutions in $CDCl_3$ (Me_4Si as internal standard) with a JEOL C-60 HL spectrometer. Woelm alumina was used for column chromatography; preparative layer chromatography (p.l.c.) was carried out with Merck HF_{254} silica gel (layers 0.5 mm thick). Light petroleum refers to the fraction with b.p. 30—50 °C.

N-Benzyloxycarbonyl-(S)-phenylalanyl-(R)-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid (4a).—A mixture of *N*-benzyloxycarbonyl-(*S*)-phenylalanine (6.72 g) and phosphorus pentachloride (4.11 g) in dry ether (150 ml) was stirred at 0 °C for 15 min and then added to a solution of (±)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1) (2.88 g) in anydrous pyridine (15 ml). The mixture was left at room temperature for 2 h, then poured into ice–water and extracted with ether; the ether layers were washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The residue (5 g) was chromatographed on alumina (Brockmann IV; 200 g); elution with light petroleum–ether (7 : 3) gave an oil (3.8 g) which was homogeneous on t.l.c. [silica; benzene–ethyl acetate (9 : 1); R_F 0.4]; $\nu_{max.}$ (CCl_4) 3 425, 1 737, 1 720, and 1 655 cm^{-1}. This oil (3.5 g), consisting probably of a mixture of two diastereoisomeric dipeptide methyl esters (3), was dissolved in methanolic 5% sodium hydroxide (14 ml) and left at room temperature for 4 h. After evaporation of methanol under reduced pressure, water and ethyl acetate were added, and the aqueous phase was acidified with concentrated hydrochloric acid and extracted with ether. The ether layers were washed with water to neutrality, dried (Na_2SO_4), and evaporated. The residue (3.2 g), after fractional crystallisation from ether, afforded the *dipeptide acid* (4a) (1.4 g), m.p. 92—96°, $[\alpha]_D$ +194° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (KBr) 3 520, 3 380, 3 290, 1 715, 1 680, and 1 630 cm^{-1}, δ 1.5 and 2.3 (4 H, 2m, $CH_2{\cdot}CH_2$), 2.74 (2 H, AB part of ABX system, $PhCH_2{\cdot}CH$), 4.78 (1 H, m, $CH{\cdot}CO_2H$), 5.11 (2 H, s, $PhCH_2{\cdot}O{\cdot}CO$), 5.33 (1 H, X part of ABX system, $PhCH_2{\cdot}CH$), and 6.6—7.4 (14 H, m, aromatic) [absorptions at 5.8 (NH, CO_2H, and H_2O) were removed in D_2O] (Found: C, 67.9; H, 5.85; N, 5.9. $C_{27}H_{26}N_2O_5$, H_2O requires C, 68.05; H, 5.9; N, 5.9%). Further fractional crystallisation of material from the mother liquors gave the more soluble *isomer* (4b), m.p. 151—153°, $[\alpha]_D$ −142° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (KBr) 3 290, 1 745, 1 680, and 1 620 cm^{-1} (Found: C, 70.65; H, 5.8; N, 6.0. $C_{27}H_{26}N_2O_5$ requires C, 70.75; H, 5.7; N, 6.1%).

Acid-catalysed Hydrolysis of the Dipeptide (4a).—A solution of the dipeptide (4a) (1 g) in concentrated hydrochloric acid–acetic acid (2 : 1; 45 ml) was stirred at 50 °C for 2 days and then evaporated to dryness under vacuum. The residue was dissolved in methanol (20 ml) and concentrated sulphuric acid was added (0.5 ml). The mixture was refluxed for 5 h and then the solvent removed under reduced pressure. Partition between aqueous sodium hydrogen carbonate and ethyl acetate gave, after evaporation of the dried (Na_2SO_4) organic layers, a residue (0.6 g) which was chromatographed on silica (60 g). Elution with ether–light petroleum (4 : 6; 100 ml) yielded (−)-(R)-*methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate* (1a) as an oil, $[\alpha]_D$ −44° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 410, 1 735, and 1 205 cm^{-1}, δ 1.7—2.9 (4 H, 2m, $CH_2{\cdot}CH_2$), 3.75 (3 H, s, CO_2CH_3), 4.01 [2 H, dd, CH superimposed on NH (broad signal)], and 6.42—7.15 (4 H, m, aromatic) (Found: C, 68.75; H, 6.8; N, 7.15. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.35%).

(+)-(R)-*Methyl α-Anilinopropionate* (6).—Resolution of (+)-(*R*)-α-anilinopropionic acid (5) was accomplished as described by Portoghese.[5] Acid-catalysed esterification of (5) in the usual way yielded (+)-(R)-*methyl α-anilinopropionate* (6) as an oil, $[\alpha]_D$ +60° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 400, 1 740, 1 157, and 688 cm^{-1}, δ 1.44 (3 H, d, *J* 6.8 Hz, CH_3), 3.66 (3 H, s, CO_2CH_3), 4.10 [2 H, q, *J* 6.8 Hz, CH superimposed on NH (broad signal)], and 6.37—7.25 (5 H, m, aromatic) (Found: C, 67.0; H, 7.3; N, 7.75. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%).

(−)-(R)-2-*Anilinopropan*-1-*ol* (7).—A solution of the ester (6) (2 g) in dry ether (20 ml) was added dropwise to lithium aluminium hydride (1.2 g) in dry ether (20 ml); the mixture was stirred at room temperature for 1 h. The usual work-up afforded a residue (1.53 g) which was nearly homogeneous on t.l.c. Chromatography on silica (p.l.c.) with benzene–ethyl acetate (7 : 3) as eluant yielded pure

[7] D. Wellner and H. Scannone, *Biochemistry*, 1964, **3**, 1746.

[8] K. E. Cooksey and D. M. Greenberg, *Arch. Biochem. Biophys.*, 1965, **112**, 238.

(−)-(R)-2-*anilinopropan*-1-*ol* (7) as an oil, $[\alpha]_D$ −37° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 625, 3 400, and 687 cm^{-1}, δ 1.11 (3 H, d, *J* 6 Hz), 2.83 (2 H, s, NH and OH), 3.3—3.8 (3 H, m, CH and CH_2·O), and 6.4—7.3 (5 H, m, aromatic) (Found: C, 71.35; H, 8.65; N, 9.15. $C_9H_{13}NO$ requires C, 71.5; H, 8.65; N, 9.25%).

(−)-(R)-2-(N-*Tosylanilino*)*propyl Tosylate* (8).—Tosylation of the alcohol (7) with tosyl chloride in pyridine, at room temperature, overnight, afforded, after conventional work-up, the (−)-(R)-*tosylate* (8), m.p. 79—80° (from ether–light petroleum), $[\alpha]_D$ −2° (*c* 3.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 1 180—1 150, 690, 660, and 570 cm^{-1}, δ 1.08 (1 H, d, *J* 6.8 Hz), 2.42 and 2.47 (6 H, 2s, aromatic CH_3), 3.8 (2 H, AB part of ABX system, CH_2·CH), 4.7 (1 H, m, CH), and 6.8—7.8 (12 H, m, aromatic) (Found: C, 59.9; H, 5.45; N, 2.95; S, 14.05. $C_{23}H_{25}NO_5S_2$ requires C, 60.1; H, 5.5; N, 3.05; S, 13.95%).

(−)-(R)-3-(N-*Tosylanilino*)*butyronitrile* (9).—A mixture of the tosylate (8) (2 g) and potassium cyanide (0.85 g) in dimethyl sulphoxide was stirred at 25—30 °C for 6 days, then poured into water and extracted with ethyl acetate. The organic layers were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. The residue (1.9 g) was chromatographed on silica (p.l.c.) [elution with benzene–ethyl acetate (9 : 1)] giving starting material (1.04 g) and a more polar fraction (0.38 g) which was then dissolved in ether. The solution was washed (N-NaOH and water), dried, and evaporated to yield finally the pure (−)-R-*nitrile* (9) (0.27 g), m.p. 94—95° (from diethyl ether–di-isopropyl ether), $[\alpha]_D$ −18° (*c* 2.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 2 240, 1 165, 692, 653, and 575 cm^{-1}, δ 1.22 (3 H, d, *J* 6.7 Hz, aliphatic CH_3), 2.34—2.56 [5 H, aromatic CH_3 (at 2.40) superimposed on CH_2,m], 4.72 (1 H, pseudo-q, CH), and 6.9—7.7 (9 H, m, aromatic) (Found: C, 64.85; H, 5.8; N, 8.85; S, 10.3. $C_{17}H_{18}N_2O_2S$ requires C, 64.95; H, 5.75; N, 8.9; S, 10.2%).

(−)-(R)-3-(N-*Tosylanilino*)*butylamine* (10) *Hydrochloride*.—A solution of the nitrile (9) (0.24 g) in dry ether was added dropwise to lithium aluminium hydride (0.15 g) in dry ether (3 ml). The resulting mixture was stirred at room temperature for 1 h. After the usual work-up the ethereal solution was extracted with 2N-hydrochloric acid and the aqueous layer afforded, after concentration under vacuum and cooling at 5 °C, the (−)-(R)-*amine* (10) *hydrochloride* as needles (0.13 g), m.p. 152—154°, $[\alpha]_D$ −80° (*c* 1.0 in acetic acid), $\nu_{max.}$ (KBr) 3 600, 3 380, 3 020—2 800br, 650, and 576 cm^{-1} (Found: C, 55.2; H, 6.85; Cl, 9.55; N, 7.5; S, 8.7. $C_{17}H_{23}ClN_2O_2S,H_2O$ requires C, 54.75; H, 6.75; Cl, 9.5; N, 7.5; S, 8.6%).

(−)-(R)-β-*Anilinobutyric Acid* (12).—(±)-β-Anilinobutyric acid was prepared as described previously for β-(*p*-chloroanilino)butyric acid,[4a] by heating to reflux a solution of aniline (9.6 g) and crotonic acid (8.6 g) in benzene (50 ml) for 16 h. Conventional work-up yielded an *oil* (14.7 g) which did not crystallise;[9] $\nu_{max.}$ (CCl_4) 3 520w, 3 400w, 1 700, and 688 cm^{-1}, δ 1.29 (3 H, d, *J* 6.6 Hz, CH_3), 2.6 (2 H, AB part of ABX system, CH_2·CH), 3.91 (1 H, m, CH), and 6.5—7.5 (7 H, m, aromatic, NH and OH) (Found: C, 66.9; H, 7.35; N, 7.7. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%).

Equimolar amounts of (±)-amino-acid and quinine gave a *salt* which was crystallised four times from acetone to constant m.p. and specific rotation: m.p. 148—149°, $[\alpha]_D$ −130° (*c* 1.0 in MeOH) (Found: C, 71.5; H, 7.4; N, 8.3. $C_{30}H_{37}N_2O_4$ requires C, 71.55; H, 7.4; N, 8.35%).

Treatment of the salt with aqueous N-sodium hydroxide, followed by extraction with chloroform and acidification of the aqueous solution to pH 4, afforded the (−)-(*R*)-amino-acid (12) as an oil, $[\alpha]_D$ −24° (*c* 3.0 in MeOH), identical in i.r. spectrum with racemic β-anilinobutyric acid.

(−)-(R)-*Methyl* β-*Anilinobutyrate* (13).—Acid-catalysed esterification in methanol of the acid (12) gave the *ester* (13) as an oil, $[\alpha]_D$ −7° (*c* 2.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 400, 1 730, 1 190—1 140, and 683 cm^{-1}, δ 1.26 (3 H, d, *J* 6.5 Hz, CH_3), 2.5 (2 H, AB part of ABX system, CH_2·CH), 3.5br (1 H, s, NH), 3.62 (3 H, s, CO_2CH_3), 3.9 (1 H, m, CH), and 6.4—7.3 (5 H, m, aromatic) (Found: C, 68.25; H, 7.65; N, 7.15. $C_{11}H_{15}NO_2$ requires C, 68.35; H, 7.8; N, 7.25%).

(−)-(R)-*Methyl* β-(N-*Tosylanilino*)*butyrate* (14).—Tosylation of the ester (13) with tosyl chloride in pyridine, at room temperature, overnight, gave the N-*tosyl derivative* (14) as an oil, homogeneous on t.l.c., $[\alpha]_D$ −35° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 1 735, 1 160, 692, 650, and 572 cm^{-1}, δ 1.12 (3 H, d, *J* 6.5 Hz, aliphatic CH_3), 1.98—2.75 (5 H, m, aromatic CH_3; s at 2.38 superimposed on AB part of ABX system, CH_2·CH), 3.63 (3 H, s, CO_2CH_3), 4.85 (1 H, pseudo-q, CH), and 6.8—7.7 (5 H, m, aromatic) (Found: C, 62.2; H, 6.1; N, 4.1; S, 9.15. $C_{18}H_{21}NO_4S$ requires C, 62.2; H, 6.1; N, 4.05; S, 9.25%).

(−)-(R)-3-(N-*Tosylanilino*)*butan*-1-*ol* (11).—(*a*) To lithium aluminium hydride (42 mg) in dry ether (2 ml) was added a solution of the ester (14) (0.125 g) in dry ether (3 ml). After the usual work-up, the ethereal solution was washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and evaporated to afford the crude (−)-(R)-*alcohol* (11) (105 mg), m.p. 90—91° (from di-isopropyl ether), $[\alpha]_D$ −100° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 540, 1 155, 690, 650, and 570 cm^{-1}, δ 0.94 (3 H, d, *J* 6.5 Hz, aliphatic CH_3), 1.5 (2 H, m, CH_2·CH), 2.4 (3 H, s, aromatic CH_3), 2.72br (1 H, s, OH), 3.8 (2 H, m, CH_2OH), 4.56 (1 H, m, CH), and 6.8—7.7 (9 H, m, aromatic) (Found: C, 63.85; H, 6.55; N, 4.4; S, 10.05. $C_{17}H_{21}NO_3S$ requires C, 63.9; H, 6.65; N, 4.4; S, 10.05%).

(*b*) Sodium nitrite (0.4 g) in acetic acid–water (1 : 1; 3 ml) was added dropwise to a solution of the amine (10) (0.185 g) in acetic acid–water (1 : 1; 3 ml). The mixture was set aside with occasional shaking at room temperature for 1 h, and then evaporated under vacuum to dryness. Ethyl acetate and 2N-hydrochloric acid were added and the organic phase was separated, washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield an oil (0.155 g). Chromatography on silica (p.l.c.) [benzene–ethyl acetate (7 : 3) as eluant] gave the (−)-(R)-alcohol (11) (0.072 g), m.p. 90—91° (from di-isopropyl ether), $[\alpha]_D$ −108° (*c* 1.0 in $CHCl_3$), identical in i.r. spectrum (CCl_4) with the compound obtained from the ester (14).

(+)-(R)-2,3-*Dihydro*-2-*methylquinolin*-4(1H)-*one* (15).—The (−)-(*R*)-acid (12) was cyclized as reported [4b] for some 2-anilinopropionic acids. A mixture of the acid (12) (1.8 g) and polyphosphoric acid (35 g) was heated on a hot plate at 125—130 °C for 30 min with stirring. After cooling to 80 °C the deep red mixture was poured into ice (100 g) and neutralized with ammonia to complete dissolution, and then extracted with ether. The ether layers were dried (Na_2SO_4) and evaporated, and the residue (0.85 g) was chromatographed on silica (p.l.c.). Elution with benzene–ethyl acetate (8 : 2) gave the (+)-(R)-*quinoline* (15) as yellow needles (0.53 g), m.p. 69—70° (from ether–light petroleum), $[\alpha]_D$ +220° (*c* 1.0 in benzene), $\nu_{max.}$ (KBr) 3 350—3 330, 1 650, 1 610, and 750 cm^{-1}, δ 1.33 (3 H, d, *J* 6.4 Hz, CH_3),

[9] R. Stoermer and E. Robert, *Ber.*, 1922, **55**, 1030.

2.6 (2 H, AB part of ABX system, CH_2·CH), 3.8 (1 H, m, CH), 4.4br (1 H, s, NH), and 6.5—8 (4 H, aromatic) (Found: C, 74.35; H, 6.95; N, 8.55. $C_{10}H_{11}NO$ requires C, 74.5; H, 6.9; N, 8.7%).

(+)-(R)-1,2,3,4-*Tetrahydro-2-methylquinoline* (16).—A solution of the quinolone (15) (0.3 g) in dry ether (10 ml) was added dropwise to a stirred solution previously prepared by slowly adding aluminium chloride (0.6 g) in dry ether (5 ml) to lithium aluminium hydride (0.17 g) in dry ether (5 ml). The mixture was stirred at room temperature for 1 h. The usual work-up, followed by chromatography of the residue (0.26 g) on silica (p.l.c.) (benzene as eluant), yielded the (+)-(*R*)-quinoline (16) (0.15 g), $[\alpha]_D$ +85° (*c* 2.0 in benzene) {lit.,[10] $[\alpha]_D$ −88.6° (*c* 2.6 in benzene) for the enantiomer}.

(+)-(R)-1,2,3,4-*Tetrahydro-2-methyl-1-tosylquinoline* (17a).—Tosylation of the quinoline (16) in pyridine with tosyl chloride at room temperature overnight gave the (+)-(*R*)-*N*-tosyl derivative (17a), m.p. 109—110°, $[\alpha]_D$ +130° (*c* 1.0 in benzene) {lit.,[6] m.p. 109°, $[\alpha]_D$ −134° (*c* 1.0 in benzene) for the enantiomer}.

(−)-(S)-1,2,3,4-*Tetrahydroquinolin-2-ylmethanol* (18).—To a stirred suspension of lithium aluminium hydride (0.29 g) in dry ether (5 ml) was added a solution of (−)-(*R*)-methyl 1,2,3,4-tetrahydroquinoline-2-carboxylate (1a) (0.49 g) in dry ether (10 ml). After stirring at room temperature for 1 h the excess of the reagent was decomposed with water. The ethereal solution was separated by filtration and the solid residue washed with ether. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated. Chromatography of the residue (0.46 g) on silica (p.l.c.) [elution with benzene–ether (6 : 4)] gave the (−)-(*S*)-alcohol (18) as an oil (0.36 g), $[\alpha]_D$ −66° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 3 620 and 3 400 cm^{-1}, δ 1.82 and 2.76 (4 H, 2m, CH_2·CH_2), 3.07—3.86 (5 H, m, CH_2·OH, CH, and NH), and 6.37—7.20 (4 H, m, aromatic).

(−)-(S)-1,2,3,4-*Tetrahydro-1-tosyl-2-tosyloxymethylquinoline* (19).—To a cooled solution of the alcohol (18) (0.32 g) in pyridine (4 ml) was added toluene-*p*-sulphonyl chloride (1.48 g); the mixture was left at room temperature overnight and then cold water (5 ml) was added. The mixture was stirred at room temperature for 1 h and then extracted with ethyl acetate. The organic layers were washed with 2N-hydrochloric acid and water, dried (Na_2SO_4), and evaporated. The residue (0.91 g), homogeneous on t.l.c., was crystallised from ether–light petroleum to afford the (−)-(S)-*ditosyl derivative* (19), m.p. 81—83°, $[\alpha]_D$ −76° (*c* 1.0 in $CHCl_3$), $\nu_{max.}$ (CCl_4) 1 365, 1 170, 655, and 570 cm^{-1}, δ 1.25—2.28 (4 H, m, CH_2·CH_2), 2.36 and 2.45 (6 H, 2s, aromatic CH_3), 3.86—4.50 (3 H, m, CH and CH_2·OTs), and 6.80—7.88 (12 H, m, aromatic) (Found: C, 61.0; H, 5.4; N, 2.85; S, 13.55. $C_{24}H_{25}NO_5S_2$ requires C, 61.1; H, 5.35; N, 2.95; S, 13.6%).

(−)-(S)-1,2,3,4-*Tetrahydro-2-methyl-1-tosylquinoline* (17b).—A mixture of the ditosyl derivative (19) (0.55 g) and lithium aluminium hydride (0.16 g) in dry ether (10 ml) was refluxed for 1 h. After cooling, the usual work-up gave the (−)-(*S*)-*N*-tosyl compound (17b) (0.285 g), m.p. 108—109° (from ethanol), $[\alpha]_D$ −133° (*c* 1.0 in benzene) {lit.,[6] m.p. 109°, $[\alpha]_D$ −134° (*c* 1.0 in benzene)}.

Oxidation of (RS)-1,2,3,4-*Tetrahydroquinoline-2-carboxylic Acid by* D-*Amino-acid Oxidase*.—A solution of the (±)-acid hydrochloride (1 g, 4.68 mmol) in water (12 ml) was adjusted to pH 8 with N-lithium hydroxide. After the addition of D-amino-acid oxidase (25 mg) (Boehringer; crystalline suspension in 1.8M-ammonium sulphate), catalase (3 mg), and pyrophosphate buffer (0.1M; pH 8; 5 ml), the mixture, maintained at pH 8, was stirred at 35 °C for 48 h. After cooling the mixture was acidified to pH 5 with N-hydrochloric acid and the protein removed by filtration through a DIAFLO membrane (XM 50) and washed with water (3 × 40 ml). The filtrate was concentrated under vacuum and desalted on a column of Dowex 50W-X 8 resin (H^+; 200—400 mesh; 170 ml). Washing with water was continued until the eluate was neutral, and the amino-acid, together with its oxidation product, was then eluted with N-ammonium hydroxide (160 ml). The alkaline solution was concentrated under vacuum, decolourised with charcoal, and then made strongly acidic with concentrated hydrochloric acid. Further concentration and cooling to 0 °C resulted in separation of crystals of quinoline-2-carboxylic acid hydrochloride (0.34 g), identical with an authentic sample [i.r. spectrum (KBr disc)]. The mother liquors were evaporated to dryness and the residue [0.35 g, $[\alpha]_D$ −11° (*c* 1.0 in 0.5N-HCl)] was extracted with hot ethyl acetate. Cooling gave crystalline (−)-(S)-1,2,3,4-*tetrahydroquinoline-2-carboxylic acid hydrochloride*, m.p. 170—175°, $[\alpha]_D$ −18° (*c* 1.0 in 0.5N-HCl) (Found: C, 56.1; H, 5.65; N, 6.5 $C_{10}H_{12}ClNO_2$ requires C, 56.2; H, 5.65; N, 6.55%).

Acid-catalysed esterification of the amino-acid in methanol under reflux for 4 h yielded, after the usual work-up (+)-(S)-*methyl* 1,2,3,4-*tetrahydroquinoline-2-carboxylate*, as an oil, $[\alpha]_D$ +41° (*c* 1.0 in $CHCl_3$). The i.r. spectrum (CCl_4) was identical with that of the enantiomeric amino-ester (1a) (Found: C, 68.6; H, 6.35; N, 6.95. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.35%).

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[10] W. J. Pope and S. J. Peachey, *J. Chem. Soc.*, 1899, **75**, 1066.