3 H), 1.97–2.16 (m, 1 H), 2.26–2.56 (m, 2 H), 2.77–2.92 (m, 2 H), 3.10–3.21 (m, 2 H), 3.21–3.30 (m, 1 H), and 5.06–5.23 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 22.54 (q), 22.71 (t), 28.49 (t), 28.80 (t), 29.03 (t), 36.78 (d), 40.27 (d), 44.28 (t), 53.60 (d), 117.92 (d), 136.14 (s), 172.49 (s), 173.44 (s), and 174.50 (s); IR (KBr) 2960, 1850, 1750, 1640, 1420, 1250, and 910 cm^{-1}; mass spectrum, m/z (relative intensity) 277 (2, P), 204 (12), 146 (20), 91 (41), 77 (46), 65 (20), 56 (63), 55 (65), 54 (50), 43 (100, B), 41 (70), and 39 (59). Anal. Calcd for $C_{15}H_{19}NO_4$: 277.1315. Found: 277.1307 (±1.4 mmu).

(b) With Ethyl Acrylate in Toluene. Reaction of 0.500 g (2.79 mmol) of **10** and 0.279 g (2.79 mmol) of ethyl acrylate for 130 h gave after chromatography (ether/silica gel, R_f 0.17) 0.560 g (2.00 mmol, 72%) of 6-carbethoxy-3-methyl-1-(1,3,4,5,6,7-hexahydro-2*H*-azepin-1-yl)-2-cyclohexene (**27**) as a clear oil: ^{1}H NMR ($CDCl_3$) δ [*Z*] 1.22 (t, 3 H), 1.71 (s, 3 H), 1.49–1.82 (m, 8 H), 1.87–1.99 (m, 2 H), 2.44 (t, 2 H), 2.63–2.82 (m, 1 H), 3.32 (t, 2 H), 4.08 (q, 2 H), 5.22 (s, 1 H), and 5.39 (s, 1 H); ^{1}H NMR ($CDCl_3$) δ [*E*] 1.20 (t, 3 H), 1.64 (s, 3 H), 1.54–1.76 (m, 8 H), 2.28–2.43 (m, 1 H), 2.53 (t, 2 H), 3.21 (t, 2 H), 4.09 (q, 2 H), 5.06 (s, 1 H), and 5.43 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.00 (q), 21.36 (q), 23.17 (t), 23.57 (t), 28.80 (t), 28.94 (t), 29.82 (t), 37.57 (t), 43.46 (d), 45.59 (t), 49.17 (d), 60.29 (t), 119.27 (d), 139.49 (s), 173.69 (s), and 175.06 (s); IR (neat) 2970, 1720, 1630, 1290, 1190, and 860 cm^{-1}; mass spectrum, m/z (relative intensity) 279 (2, P), 251 924), 208 (38), 121 (43), 113 (29), 96 (44), 93 (96), 91 (72), 84 (26), 79 (44), 77 (58), 55 (91), 41 (100, B), and 39 (52). Anal. Calcd for $C_{16}H_{25}NO_3$: 279.1836. Found: 279.1827 (±1.4 mmu).

(c) With Ethyl Acrylate in 50% Aqueous Ethanol. Reaction of 0.200 g (1.12 mmol) of **10** with 0.112 g (1.12 mmol) of ethyl acrylate for 84 h gave after chromatography as in b 0.284 g (1.02 mmol, 91%) **27**. GC/MS analysis showed the *Z*:*E* ratio to be 60:40.

Acknowledgment. We thank Smith/Kline and French and the UCONN Research Foundation for funding this work. C.A.Z. thanks Smith/Kline and French for their support as a SKF fellow.

Registry No. **2**, 112682-86-7; **6**, 112682-88-9; **7**, 112682-87-8; **8**, 112682-83-4; **9**, 112682-84-5; **10**, 112682-85-6; (*E*,*E*)-**11**, 112682-89-0; (*E*,*Z*)-**11**, 112682-90-3; (*E*,*E*)-**12**, 112682-91-4; (*E*,*Z*)-**12**, 112682-92-5; **13**, 112682-96-9; **14**, 112682-97-0; **15**, 112682-98-1; (*E*)-**16**, 112682-99-2; (*Z*)-**16**, 112683-00-8; **18a**, 112683-03-1; **18b**, 112683-04-2; **18c**, 112683-05-3; **18d**, 112683-06-4; **19a**, 112683-15-5; **19b**, 112683-18-8; **19c**, 112683-17-7; **19d**, 112683-16-6; **20**, 112682-93-6; **21**, 112682-94-7; **22**, 112682-95-8; (*E*)-**23**, 112683-01-9; (*Z*)-**23**, 112683-02-0; (*E*)-**24**, 112683-07-5; (*Z*)-**24**, 112683-08-6; (*E*)-**25**, 112683-09-7; (*Z*)-**25**, 112683-10-0; (*E*)-**26**, 112683-11-1; (*Z*)-**26**, 112683-12-2; (*E*)-**27**, 112683-13-3; (*Z*)-**27**, 112683-14-4; 2-pyrrolidinone, 616-45-5; crotonaldehyde, 4170-30-3; (*E*)-2-pentenal, 1576-87-0; (*E*)-2-octenal, 2548-87-0; 3-methyl-2-butenal, 107-86-8; 2-piperidone, 675-20-7; hexahydro-2*H*-azepin-2-one, 105-60-2; maleic anhydride, 108-31-6; ethyl acrylate, 140-88-5.

Absolute Configuration of the Enantiomers of 7-Chloro-4-[[4-(diethylamino)-1-methylbutyl]amino]quinoline (Chloroquine)

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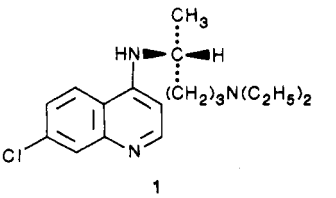
(*R*)-(−)-4-[[4-(Diethylamino)-1-methylbutyl]amino]-7-chloroquinoline [(*R*)-(−)-chloroquine] was prepared in a 10-step synthesis starting from L-glutamic acid via *N*,*N*-phthaloyl-L-glutamic acid, N^{γ},N^{γ}-diethyl-N^{α},N^{α}-phthaloyl-L-glutamine, and *N*,*N*-diethyl-L-glutamine. Reductive conversion of the α-carboxyl group to a methyl group led to *R*-(−)-4-amino-1-(diethylamino)pentane of >90% optical purity, which on condensation with 4,7-dichloroquinoline gave (*R*)-(−)-chloroquine.

Drugs possessing asymmetric centers generally exhibit marked differences in the biological activities of their optical isomers. One isomer may be preferentially metabolized by stereospecific enzymes, or there may be differences in the interactions of the enantiomers with the putative receptor. The report[1] that resolved enantiomers of chloroquine of equal and opposite rotation had identical activity against *Plasmodium lophurae* in mice[2] was therefore unexpected. Recently the two enantiomers of chloroquine, obtained from resolved[3] 4-amino-1-(diethylamino)pentane, have been found to possess specific rotations of about 9 times the magnitude reported earlier,[1] and to differ significantly in their activities on both *Plasmodium berghei*[4] and *P. vinckei*[5] in mice, and also in their binding affinity to DNA.[5] In order to carry out studies on the putative receptor, a knowledge of the absolute configuration of the two enantiomers of chloroquine was needed. This was accomplished by condensing *R*-(−)-4-amino-1-(diethylamino)pentane (**6c**), obtained from L-glutamic acid, with 4,7-dichloroquinoline to give *R*-(−)-chloroquine (**1**) of known absolute configuration.



1

Diethyl *N*-(2-carboxybenzoyl)-L-glutamate,[6] prepared from diethyl-L-glutamate,[7] was converted to diethyl *N*,*N*-

(1) Riegel, B., Sherwood, I. T. *J. Am. Chem. Soc.* **1949**, *71*, 1129.
(2) Berliner, R.; Butler, T. In *Survey of Antimalarial Drugs. 1941–1945*; Wiselogle, F. Y., Ed.; Edwards: Ann Arbor, MI, 1946; pp 221–390.
(3) Blaschke, G.; Kraft, H. P.; Schwanghart, A. D. *Chem. Ber.* **1978**, *111*, 2732.
(4) Haberkorn, A.; Kraft, H. P.; Blaschke, G. *Tropenmed. Parasitol.* **1979**, *30*, 308.
(5) Fink, E.; Minet, G.; Nickel, P. *Arzneim. Forsch.* **1979**, *29*, 163.
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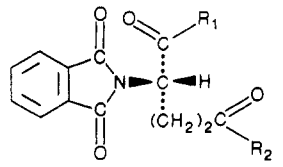
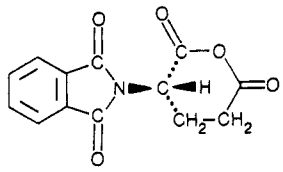
phthaloyl-L-glutamate (**2a**) in 66% yield by a modification of the published method,[6] by working in benzene solution and using a greatly reduced quantity of the dehydrating agent. Acid hydrolysis[6,8] of **2a**, followed by a new purification procedure, resulted in an improved quality and yield of *N*,*N*-phthaloyl-L-glutamic acid (**2b**). This was transformed into *N*,*N*-phthaloyl-L-glutamic 1,5-anhydride



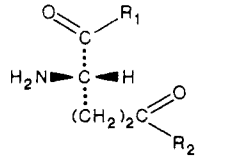
2a: $R_1 = R_2 = OC_2H_5$
b: $R_1 = R_2 = OH$
c: $R_1 = OH$, $R_2 = N(C_2H_5)_2$
d: $R_1 = N(C_2H_5)_2$, $R_2 = OH$



3

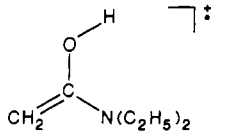
(**3**) by using acetic anhydride[6,9] with an added purification step, which increased the yield to 82%. The phthaloyl protecting group was chosen in preference to the carbobenzoxy moiety because ring opening of the appropriate L-glutamic anhydride with amines is known[10,11] to give γ-glutamyl derivatives with the former protecting group, while yielding α-glutamyl products with the latter. In agreement with this expectation, ring opening of the anhydride **3** with diethylamine, by a modification of the procedure reported by Friedman et al.[10] for DL-glutamic acid, gave N^{γ},N^{γ}-diethyl-N^{α},N^{α}-phthaloyl-L-glutamine (**2c**) in essentially quantitative yield. Alternative nucleophilic attack of diethylamine could have occurred on the α-carbonyl group of **3**, with the formation of the isomeric *N*,*N*-phthaloyl-L-glutamic acid α-(*N*,*N*-diethylamide) (**2d**). However, the action of ammonia on *N*,*N*-phthaloyl-DL-glutamic anhydride was reported to give only N^{α},N^{α}-phthaloyl-DL-glutamine,[11] and the product obtained from diethylamine by Friedman et al.[10] had been found on cleavage with hydrazine to yield N^{γ},N^{γ}-diethyl-DL-glutamine, identified as an α-amino acid by a positive ninhydrin reaction as well as appropriate carboxylate ion bands in the infrared spectrum.[10]

The phthaloyl derivative **2c** was hydrolyzed with hydrazine to give the hygroscopic N^{γ},N^{γ}-diethyl-L-glutamine hydrochloride (**4a**·HCl), which was converted to N^{γ},N^{γ}-diethyl-L-glutamine (**4a**) by ion-exchange chromatography.



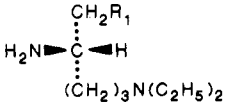
4a: $R_1 = OH$, $R_2 = N(C_2H_5)_2$
b: $R_1 = OCH_3$, $R_2 = N(C_2H_5)_2$
c: $R_1 = N(C_2H_5)_2$, $R_2 = OCH_3$

The hydrochloride **4a**·HCl has been reported[12] from (*S*)-N^{α}-(*tert*-butoxycarbonyl)-N^{γ},N^{γ}-diethylglutamine. Additional evidence for the structure **2c** was obtained by methylating N^{γ},N^{γ}-diethyl-L-glutamine hydrochloride (**4a**·HCl) with diazomethane. The product, N^{γ},N^{γ}-diethyl-L-glutamine methyl ester (**4b**), showed in its high-resolution mass spectrum an intense ion at *m*/*z* 115.0948 ($C_6H_{13}NO$), which represents the McLafferty rearrangement product **5** derived from the structure **4b**.



5

Lithium aluminum hydride reduction of N^{γ},N^{γ}-diethyl-L-glutamine hydrochloride by a modification of the reported method[12] gave (*S*)-2-amino-5-(diethylamino)-pentanol (**6a**), which was converted to the hydrochloride and treated with thionyl chloride to form (*S*)-2-amino-1-chloro-5-(diethylamino)pentane hydrochloride (**6b**).



6a: $R_1 = OH$
b: $R_1 = Cl$
c: $R_1 = H$

Without purification this was further reduced (lithium aluminum hydride) to the desired (*R*)-4-amino-1-(diethylamino)pentane (**6c**). In order to determine the enantiomeric composition (optical purity) of the product **6c**, we treated the diamine with the acid chloride of optically pure (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid[13] to give a mixture of diastereomeric amides, which were separated by capillary gas chromatography, showing the product **6c** to consist of 90.6% of the *R* isomer and 9.4% of the *S* isomer. Some slight racemization had therefore occurred in the seven-step reaction sequence from **2a** to **6c**.

When the enantiomeric diamines (**6c** and its mirror image) were obtained by resolution of the racemic diamine using (*R*)- and (*S*)-mandelic acid,[3] the corresponding optically active diamines were found to be 89.0% (*R*) and 89.3% (*S*) optically pure by using the same analytical method.[13] It was observed that the diamines not only showed strong concentration dependence of their optical rotation at all wavelengths but gave an inversion of the sign

Table I. Specific Rotations of (*S*)-(+)-4-Amino-1-(diethylamino)pentane[a,b]

wavelength, nm	specific rotation: [α], deg			
	c = 10.0[d]	*c* = 5.0[d]	*c* = 2.5[d]	neat
589	−0.21	−0.46	−0.53	+4.96
578	−0.24	−0.47	−0.67	+5.15
546	−0.30	−0.60	−0.74	+5.83
436	−0.89	−1.34	−1.50	+9.66
365	−2.20	−2.81	−3.12	+14.39[c]

[a] Obtained by resolution of racemic diamine by using (*R*)-(−)-mandelic acid.[3] [b] The enantiomeric diamine gave rotations of opposite sign agreeing within 5%. [c] In an apparent typographical error, the authors of ref 3 refer to $[\alpha]_D$ +15.2°/−15.3° (neat) rather than $[\alpha]_{365}$. [d] In ethanol.

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of rotation when measured as the neat liquids (Table I). Because of the much larger magnitude of the neat rotation, the enantiomers will be referred to as (*R*)-(−)-diamine **6c** (derived from L-glutamic acid) and (*S*)-(+)-diamine, with the sign of rotation of the neat liquids. Condensation of (*R*)-4-amino-1-(diethylamino)pentane (**6c**) with 4,7-dichloroquinoline was carried out via the 4-phenoxy derivative,[14] which avoids using an excess of the diamine, and gave crystalline (*R*)-(−)-4-[[4-(diethylamino)-1-methylbutyl]amino]-7-chloroquinoline (**1**), converted[15] into the (*R*)-(−)-diphosphate. Both (−)-chloroquine and its (−)-diphosphate showed melting point, mixed melting point, and rotation identical with those of the (−)-chloroquine and (−)-chloroquine diphosphate of unknown configuration made from the (−)-diamine obtained by resolution.[3]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were carried out by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley. Infrared spectra were determined on Beckman IR-8 and Perkin-Elmer Model 337 spectrophotometers using potassium bromide disks. Band positions were calibrated by using polystyrene. Proton magnetic resonance spectra were measured in deuteriochloroform unless otherwise indicated with tetramethylsilane as the internal standard, on Varian A-60-A (60 MHz) and JEOL JNM-4H-100 (100 MHz) spectrometers. Chemical shifts are reported in parts per million; coupling constants (*J* values) are given in cycles/second. Specific rotations were determined on a Bendix-NPL automatic polarimeter with a 5.002-mm cell or a Perkin-Elmer Model 141 polarimeter using a 10.002-cm cell. Gas chromatographic analyses were carried out with a Varian Model 2100 dual-column gas chromatograph equipped with flame-ionization detectors, using 6-ft, $^1/_8$-in. i.d. glass columns packed with 2% Carbowax 20 M + 2% KOH on 100/120 Gaschrom P at 55 °C, with helium as carrier gas and injector and detector temperature at 250 °C. Capillary gas chromatography was carried out by using a Hewlett-Packard Model 5890 A gas chromatograph equipped with an HP Model 3342A electronic integrator, employing a 15-m, 0.32-mm-i.d., 0.25-μm-thick DB-1701 fused silica capillary column with a flame-ionization detector. Initial column temperature was 130 °C. Following a 2-min hold, the column temperature was programmed at 3 °C rise/min to 200 °C. Mass spectral analyses were carried out on a Kratos MS-50 (EI high resolution) or an MS-9 (CI low resolution) instrument.

Diethyl *N*,*N*-Phthaloyl-L-glutamate (2a). Freshly distilled thionyl chloride (369 mL, 602 g, 5.06 mol) was slowly dropped at room temperature into a stirred suspension of diethyl *N*-(2-carboxybenzoyl)-L-glutamate[6] (590 g, 1.68 mol) (prepared from diethyl L-glutamate[6,7]) in dry benzene (1.5 L). After the addition was complete, stirring was continued at room temperature overnight and the solution evaporated in vacuo, followed by the addition and evaporation of dry benzene (350 mL). The residue was taken up in ether, washed with saturated aqueous sodium bicarbonate and with distilled water, and then dried over anhydrous sodium sulfate. Removal of solvent in vacuo left **2a** as a viscous oil (368 g, 66%) (lit.[6] no yield given.) High-resolution mass spectrum: calcd for $C_{17}H_{19}NO_6$ M^+ m/z 333.1212, found 333.1204.

***N*,*N*-Phthaloyl-L-glutamic Acid (2b).** A solution of diethyl *N*,*N*-phthaloyl-L-glutamate (**2c**) (329.2 g, 988 mmol) in glacial acetic acid (1471 mL) was treated with concentrated hydrochloric acid (359 mL) and the mixture stirred until a clear solution resulted. Hydrolysis was effected by refluxing (2 h) and the solution then concentrated to 720 mL in vacuo and left at 5 °C overnight. A crystalline precipitate of phthalic acid (126.4 g), mp and mixed mp 184–192 °C, was removed and the filtrate evaporated in vacuo. The residue was dissolved in saturated aqueous sodium bicarbonate (2.6 L) and extracted with ether. The bicarbonate layer was acidified to pH 1 with concentrated hydrochloric acid and extracted with ether. The combined ethereal extracts were decolorized (charcoal) and dried over anhydrous sodium sulfate. Removal of ether in vacuo left 191.5 g (70%) of **2b**, which after two crystallizations from ethyl acetate gave white crystals of **2b** (122 g): mp 158–161 °C (lit.[16] mp 160 °C); $[\alpha]^{33}_D$ −46.8° (*c* 3.13, dioxane) (lit.[9] $[\alpha]^{23}_D$ −48.3° (*c* 3, dioxane)).

***N*,*N*-Phthaloyl-L-glutamic 1,5-Anhydride (3).** A mixture of *N*,*N*-phthaloyl-L-glutamic acid (**2b**) (121.2 g, 437.4 mmol) and freshly distilled acetic anhydride (410 mL) was heated at 100 °C until solution was complete and then stirred for a further 10 min. The solution was cooled and concentrated in vacuo, and the crystalline solid was washed with cold acetic anhydride (90 mL) to remove a colored impurity and then with dry ether (100 mL), to give the anhydride **3** as white crystals: mp 194–197 °C (lit.[6] mp 195–200 °C); $[\alpha]^{33}_D$ −41.2 (*c* 3.32, dioxane) (lit.[9] $[\alpha]^{22}_D$ −43.1° (*c* 3, dioxane)); IR (KBr) 1840, 1800 (C=O of anhydride), 1730, 725 cm^{-1} (characteristic bands of phthalimido residue); ^{1}H NMR δ 2.51 (m, 4 H, CH_2), 5.13 (m, 1 H, CH), 8.03 (m, 4 H, aromatic CH). Yield: 82% (lit.[6] yield 67%).

***N*$^\gamma$,*N*$^\gamma$-Diethyl-*N*$^\alpha$,*N*$^\alpha$-phthaloyl-L-glutamine (2c).** A solution of the anhydride **3** (99.3 g, 364 mmol) in dry dioxane (770 mL) was treated with a solution of freshly distilled diethylamine (62.6 g, 88.6 mL, 857 mmol) in dry dioxane (100 mL) over 3 h with stirring at room temperature. After 12 of refluxing, volatile material was removed in vacuo and the residue dissolved in distilled water (500 mL) adjusted to pH 7. The aqueous solution was extracted with chloroform (neutral extract), then acidified to pH 1, and reextracted with chloroform. The *neutral* chloroform extract was dried (sodium sulfate) and evaporated in vacuo and the residue dissolved in dioxane (380 mL) and retreated with fresh diethylamine (35.4 g) by the method used above. Working up of the first acidic chloroform extract gave **2c** as an oil (67.1 g), with an additional 51.9 g of product **2c** from the working up of the second *acidic* chloroform extract. Combined yield of **2c** was 119 g (98.4%), crystallizing from 25% aqueous ethanol as white crystals: mp 136–138 °C; $[\alpha]^{23}_D$ −8.0° (*c* 2, EtOH); $[\alpha]^{23}_D$ −34.3° (*c* 2.75, dioxane); IR (KBr) 1790 (*O*=COH), 1620 (*O*=CNRR), 1730 and 720 cm^{-1} (phthalimido group); ^{1}H NMR δ 1.07 and 1.11 (2 overlapping t, J = 7.0 Hz, 6 H, CH_3), 2.48 (m, 4 H, CH_2), 3.27 and 3.35 (2 overlapping q, J = 7.0 Hz, 4 H, NCH_2CH_3), 4.95 (m, 1 H, CH), 7.83 (m, 4 H, aromatic CH), 9.85 (s, 1 H, COO*H*). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.02; N, 8.43. Found: C, 61.10; H, 6.06; N, 8.46.

***N*$^\gamma$,*N*$^\gamma$-Diethyl-L-glutamine (4a).** A. The phthaloyl derivative **2c** (4.4 g, 14.7 mmol) was dissolved in water (25 mL) containing sodium carbonate (1.3 g), hydrazine hydrate (50%, 1.5 g, 15 mmol) was added, and the mixture was set aside for 2 days. After addition of water (10 mL), the solution was neutralized with 2 N hydrochloric acid. Precipitated phthalhydrazide was filtered off, the filtrate stirred with silver carbonate (7.5 g) for 15 h and filtered, and the pH adjusted to 7. This solution was concentrated at 37 °C in vacuo, a little more phthalhydrazide removed by precipitation with alcohol, and the alcohol filtrate evaporated in vacuo. The residue was dissolved in water and subjected to ion-exchange chromatography on a column of Dowex-50, which had been activated with 5 N hydrochloric acid. Elution first with water (1 L) and then with 10% aqueous ammonia (250-mL portions) gave, on evaporation, a residue, which crystallized from ethanol/ether as white needles of **4a** (0.3 g, 10%): mp 170–172 °C (lit.[10] for DL compound: mp 167–168 °C); $[\alpha]^{23}_D$ −1.16° (*c* 1.25, ethanol); ^{1}H NMR [in D_2O, chemical shifts relative to DSS (sodium 2,2-dimethyl-2-silapentane-5-sulfonate)] δ 1.33 and 1.41 (2 overlapping t, J = 7.0 Hz, 6 H, NCH_2CH_3), 2.43 (t, J = 6.0 Hz, 2 H, CH_2), 2.85 (m, 2 H, CH_2), 3.60 and 3.63 (2 overlapping q, J = 7.0 Hz, 4 H, NCH_2), 4.03 (t, J = 6.0 Hz, 1 H, CH). Anal. Calcd for $C_9H_{18}N_2O_3 \cdot 0.25H_2O$: C, 52.28; H, 9.02; N, 13.55. Found: C, 52.52, 52.70; H, 8.86, 9.07; N, 13.85, 13.75.

B. The phthaloyl derivative **2c** (60 g, 181 mmol) was dissolved in water (300 mL) containing 16 g (190 mmol) of sodium bicarbonate, hydrazine (100%, 11.2 g, 350 mmol) was added, and

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the mixture was allowed to stand at room temperature for 2.5 days, after which it was acidified with 2 N hydrochloric acid till precipitation ceased. The precipitated phthalhydrazide was filtered, the filtrate evaporated in vacuo, and absolute alcohol added to precipitate sodium chloride, which was removed by filtration. Removal of solvent in vacuo gave **4a**·HCl as a hygroscopic solid (40 g, 92.8%): ^{1}H NMR (D_O chemical shifts relative to DSS) identical with that of the product **4a** obtained in section A (above) (lit.[12] reports **4a**·HCl as a deliquescent solid). Treatment of **4a**·HCl with diazomethane in methanol at 0 °C gave N^γ,N^γ-diethyl-L-glutamine methyl ester[17] (**4b**): IR (neat) 3600–3200 (br, NH_2), 1735 (O=$COCH_3$), 1635 [O=$CN(C_2H_5)_2$] cm^{-1}; ^{1}H NMR δ 1.12 and 1.20 (overlapping t, J = 7.5 Hz, 6 H, NCH_2CH_3), 2.15 (m, 6 H, CH_2 and NH_2), 3.33 (m, 5 H, NCH_2 and CH), 3.75 (s, 3 H, OCH_3); high-resolution mass spectrum calcd for $C_{10}H_{20}N_2O_3$ M^+ 216.1470, found 216.1467.

(*S*)-2-Amino-5-(diethylamino)pentanol (6a). A suspension of **4a**·HCl (3.34 g, 14 mmol) in dry tetrahydrofuran (100 mL) was treated at 0 °C with a suspension of lithium aluminum hydride (3.34 g, 88 mmol) in dry tetrahydrofuran (100 mL), and the mixture was then refluxed for 12 h. After decomposition of excess reagent by sodium sulfate decahydrate (6.04 g), 100 mL of alcohol was added, the mixture refluxed for 1 h and filtered, and the filtrate evaporated in vacuo. The residue on distillation gave the alcohol **6a** (1.91 g, 78.5%) as a light yellow oil: bp 100–108 °C (0.18 mm); $[\alpha]^{23}_D$ +5.77° (*c* 10.3, dioxane); $[\alpha]^{33}_D$ +6.91° (*c* 9.24, ethanol); IR (neat) 3200–3600 (OH), 2950 (CH), 1550 (NH_2), 1200 (NH) cm^{-1}; ^{1}H NMR δ 1.02 (t, J = 7.5 Hz, 6 H, CH_3), 1.50 (m, 4 H, CH_2), 2.45 (m, 8 H, $N(CH_2)$, $N(CH_2)_3$ and NH_2), 3.15 (br s, 1 H, OH, exchanged with D_2O), 3.60 (m, 3 H, CH_2OH and CH); ^{1}H NMR (CF_3COOH) δ 1.42 (t, J = 7.5 Hz, 6 H), 2.00 (br s, 4 H, CH_2), 3.25 (m, 7 H, $HN^+(CH_2)_3$), 4.35 (m, 4 H, CH_2OH and CH), 7.35 (br s, 3H, N^+H_3). Anal. Calcd for $C_9H_{22}N_2O$: C, 62.06; H, 12.64; N, 16.09. Found: C, 62.18; H, 12.64; N, 15.87. (Literature[12] reports **6a** as an air-sensitive liquid, no analysis or spectra recorded, prepared from N^γ,N^γ-diethyl-(*S*)-glutamine hydrochloride.)

(*R*)-4-Amino-1-(diethylamino)pentane (6c). A solution of (*S*)-2-amino-5-(diethylamino)pentanol (**6a**) (1.9 g, 11 mmol) in dry ether (100 mL) was treated at 0 °C with 1.75 N ethereal hydrogen chloride (13.0 mL) when a drop of the ether solution indicated a pH of 5 on a wet pH paper. Removal of solvent in vacuo left a residue, which was suspended in dry chloroform (100 mL), treated with thionyl chloride (8.16 g, 5 mL, 68.5 mmol) in chloroform (50 mL), and stirred and refluxed for 12 h. After removal of volatile material in vacuo, the residue was suspended in dry tetrahydrofuran (100 mL) and treated at 0 °C with a suspension of lithium aluminum hydride (2.55 g, 67.2 mmol) in tetrahydrofuran (100 mL). Refluxing for 12 h was followed by cooling to room temperature and addition of sodium sulfate decahydrate (4.5 g) and alcohol (100 mL). Refluxing for 1 h, filtration, and evaporation of the filtrate in vacuo gave a residue, which was taken up in dichloromethane, dried (sodium sulfate), and distilled in a Kugelrohr apparatus to give the diamine **6c** as a colorless liquid (0.36 g, 21% overall yield): bp (airbath) 98 °C (30 mm); $[\alpha]^{23}_D$ +0.30°; $[\alpha]^{23}_{365}$ +2.25° (*c* 10.2, EtOH); IR (neat) 3100–3600 (NH_2), 2950 (CH), 1600, 1475, and 1390 cm^{-1}; ^{1}H NMR δ 1.00 (t, J = 7.0 Hz, 6 H, CH_3), 1.06 (d, J = 6.0 Hz, 3 H, CH_3), 1.47 (m, 4 H, CH_2), 2.90 (q overlapping m, 8 H, CH_2 and NH_2), 3.66 (m, 1 H, CH). Anal. Calcd for $C_9H_{22}N_2$: 158.1783. Found by high-resolution electron-impact mass spectrometry: 158.1777. The compound gave a single peak on gas chromatography, t_R 5.0 min, identical in t_R with a sample of the racemic diamine. Derivatization of **6c** with optically pure (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, $[\alpha]^{23}_D$ -129° (*c* 5.6, CCl_4) (lit.[13] $[\alpha]_D$ -129.0° (*c* 5.2, CCl_4)), was carried out by the method of Dale et al.[13] with one exception: since the derivative contains a tertiary amine functionality, the acid wash must be eliminated. Capillary gas chromatography showed the product to consist of 90.6% of the *R* isomer (t_R 15.09 min) and 9.4% of the *S* isomer (t_R 15.75 min).

(*R*)-(-)-Chloroquine (1). A mixture of 4,7-dichloroquinoline (6 g, 30.3 mmol), phenol (5.72, 60.8 mmol), and (*R*)-4-amino-1-(diethylamino)pentane (**6c**) (4.8 g, 30.4 mmol) was stirred at 120–130 °C for 18 h, cooled to room temperature, and dissolved in chloroform (50 mL). The solution was extracted first with ice-cold 15% NaOH solution and then with 1 N hydrochloric acid (5 × 50 mL). The combined acid layers were washed with ether, basified to pH 11 with saturated sodium carbonate, and extracted with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to give (*R*)-(-)-chloroquine (6.24 g, 64%) as white crystals (from hexane): mp and mixed mp 65–67 °C (lit.[3] mp 68–69 °C); $[\alpha]^{20}_D$ -86.2° (*c* 1, EtOH) (lit.[3] $[\alpha]^{22}_D$ -108.0° (*c* 1, EtOH). The diphosphate, prepared by the published method,[15] had mp and mixed mp 202 °C (lit.[3] mp 202 °C) and $[\alpha]^{25}_D$ -68.95° (*c* 2.1, H_2O) (lit.[3] $[\alpha]^{22}_D$ -86.9° (*c* 2.1, H_2O)).

(17) Gas chromatographic analysis of the crude product showed the presence of an impurity (5–10%) identified as the α-N-methylated and α-N,N-dimethylated homologues of **4b** by mass spectrometry. These were readily removed by chromatography on alumina, from which they were eluted first, followed by pure **4b**.

Palladium-Catalyzed Coupling of 2-Bromoanilines with Vinylstannanes. A Regiocontrolled Synthesis of Substituted Indoles

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The palladium-catalyzed cross-coupling reaction of aryl halides and triflates with vinylstannane reagents has been used to produce a variety of substituted indoles. The mild reaction conditions and selectivity inherent in the coupling reaction have been utilized to produce regiochemically pure 4-, 5-, and 6-substituted indoles.

While 4-substituted indoles represent an important class of alkaloids that possess a wide range of biological activity,[1] the synthesis of these compounds is not straightforward. The method of choice, particularly for the 2,3-unsubstituted indoles,[2] relies on the Leimgruber–Batcho procedure[3] starting from the commercially available 2-methyl-3-nitrobenzoic acid, but these procedures generally do not tolerate sensitive functionality.

The synthesis of 4-bromoindoles by a Batcho–Leimgruber procedure from 6-bromo-2-nitroaniline provides an

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