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Stereoselective Synthesis and Relative and Absolute Configuration of α,1-Bis(4-chlorophenyl)isoindoline-1-ethanol[1]

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When 1-(4-chlorophenyl)-1-(4'-chlorophenacyl)-3-ethoxy-1*H*-isoindole (**2**) was reduced in the presence of diborane (α*RS*,1*RS*)-α,1-bis(4-chlorophenyl)isoindoline-1-ethanol (**3a**) was isolated in 88% yield. The crude reduction product also contained the second diastereoisomer **3b** in a ratio of **3a**/**3b** of 95:5. The relative and/or absolute configurations of the compounds **3a–f**, **4a,b**, **5a–c**, **6a–f**, and **8a–c** were assigned on the basis of the X-ray analysis of the (*S*)-(−)-2-pyrrolidone-5-carboxylic acid salt of the (α*S*,1*S*)-(+) enantiomer **3c**. The starting material **2** was prepared from 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1**) via alkylation with 4-chlorophenacyl bromide. When the carbocyclic ketone **11** was reduced in the presence of diborane, a mixture of diastereoisomeric alcohols **10** was obtained.

Earlier, we have described[2] the alkylation of 1-(4-chlorophenyl)-3-ethoxy-1*H*-isoindole (**1**) with a variety of alkylating agents. We now wish to report the reaction of **1** with 4-chlorophenacyl bromide to give the novel isoindole **2** in 82% yield (Scheme I). This compound underwent a highly stereoselective reduction to (α*RS*,1*RS*)-α,1-bis-(4-chlorophenyl)isoindoline-1-ethanol[3] (**3a**) in 88% yield of isolated material in the presence of diborane. High-pressure liquid chromatography on a Microporasil column of the crude reduction material revealed the presence of the second diastereoisomer **3b** (α*RS*,1*SR*; see below). The ratio of **3a** to **3b** was found to be 95:5 by integration.

The structural assignment of **3a** was based on analytical and spectral data. The stereochemistries of **3a** and of all the compounds described in this paper are based on X-ray analysis (see Experimental Section) of the chiral **3c**, obtained from **3a** with the aid of a chiral acid of known absolute stereochemistry (vide infra).

When the imino ester **2** was treated with $NaBH_4$ in ethanol at room temperature, only the keto group was reduced, and both diastereoisomers **4a** and **4b** were isolated in a ratio of 6:4, showing a marked decrease in the stereoselectivity as compared to that for the reduction in the presence of diborane. The higher melting isomer **4a** was reduced further with diborane to give **3a**. The lower melting isomer was reduced under similar conditions to give **3b** as an amorphous material which was fully characterized as the crystalline maleic acid addition salt.

The keto lactam **5a**, obtained from the imino ester **2** by mild acidic hydrolysis, also gave two diastereoisomers, **6a** and **6b**, in a ratio of 6:4 upon reduction with $NaBH_4$. Both compounds **6a** and **6b** could also be obtained from **4a** and **4b**, respectively, via acid hydrolysis.

The keto lactam **5a** was reduced in the presence of diborane to give the amino alcohol **3a** in 61% yield. The reduction of the hydroxy lactams **6a** and **6b** to **3a** and **3b**, respectively, will be discussed in more detail for the chiral compounds.

Due to difficulties encountered in the initial attempts to separate the enantiomers from the racemic amino alcohol **3a**, we searched for a viable alternative, possibly involving the separation of a racemic acid. With this in mind, the imino ester **7** was prepared from **1** and methyl bromoacetate (Scheme II). Hydrolysis of the crude **7** gave the acid **8a** in 86% overall yield. A Friedel–Crafts reaction between the acid chloride of **8a** and chlorobenzene in the presence of aluminum chloride at −40 °C gave the keto lactam **5a** in 55% yield.

The formation of a spiro lactam as the result of an intramolecular Friedel–Crafts reaction was not observed.

Chiral Compounds. Two approaches to the chiral amino alcohol **3c** were investigated. A direct separation of the racemic compound **3a** was accomplished with the

(1) Presented at the 172nd National Meeting of the American Chemical Society, San Francisco, CA, Sept 1976.
(2) M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970). M. K. Eberle, L. Brzechffa, and W. J. Houlihan, *J. Org. Chem.*, **42**, 894 (1977).
(3) Pharmacological results[1] will be published in *J. Med. Chem.*; M. K. Eberle, U.S. Patent 3 892 771 (1975).

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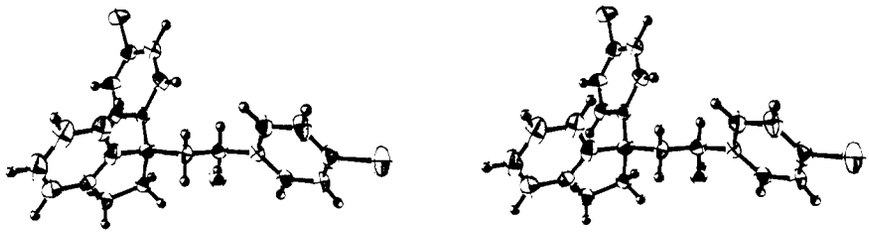
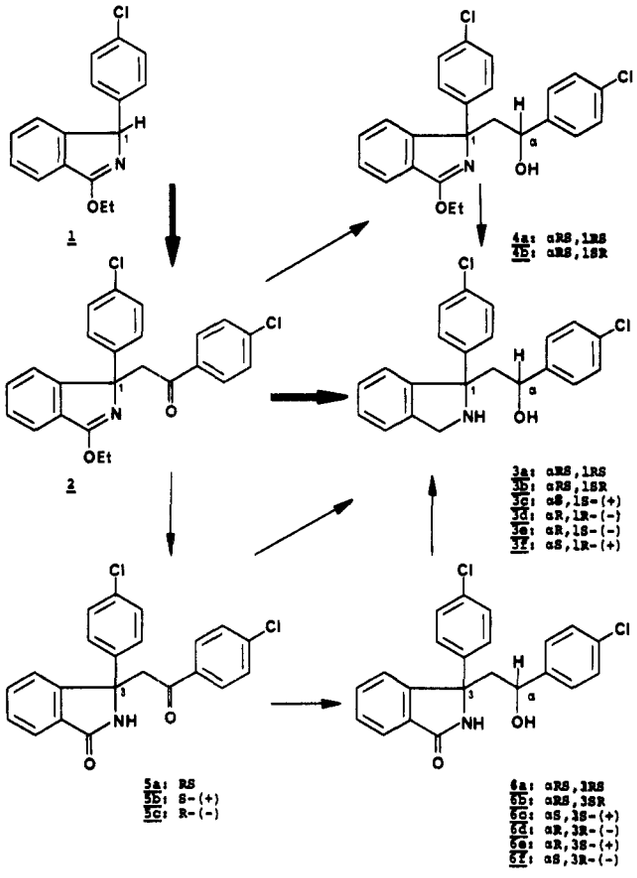
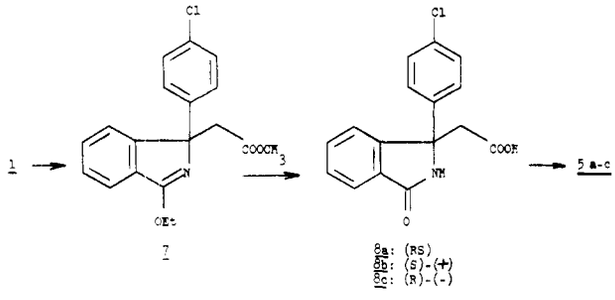


Figure 1. ORTEP stereoscopic drawing of **3c**; 50% ellipsoids were used for C, N, O, and Cl; the hydrogen atoms are shown as 0.15-Å radius spheres.

Scheme I

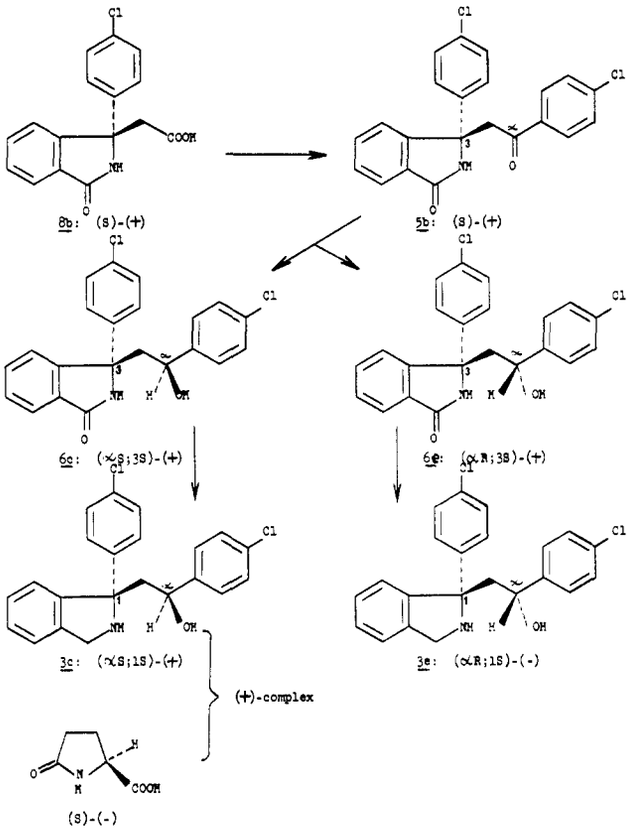


Scheme II



aid of commercial (*S*)-(−)-2-pyrrolidone-5-carboxylic acid.[4] The acid formed a crystalline (+) complex with the (*S*,*S*)-(+) enantiomer **3c** of the racemic amino alcohol. This compound was subjected to an X-ray analysis to determine the relative and absolute stereochemistries of the title compound, as shown in Figure 1. This also allowed the

Scheme III



assignment of the relative stereochemistry for the diastereomeric compounds described above. The absolute configuration for the compounds described so far follows from the sequence of reactions leading from the chiral acid **8b** to the chiral **3c**.

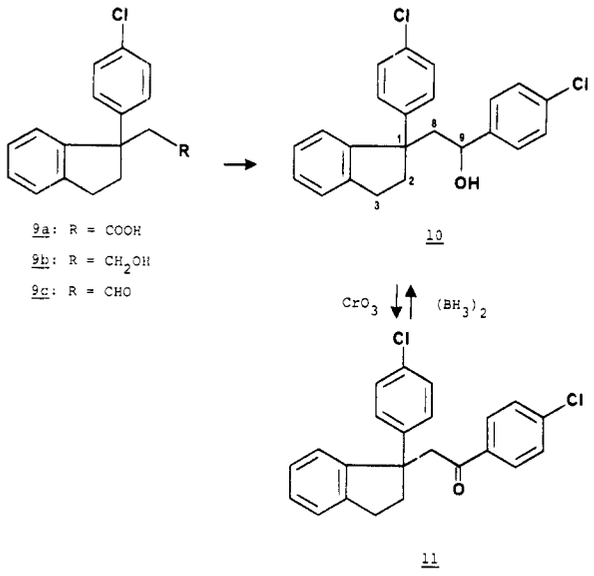
The racemic acid **8a** was readily separated into its enantiomers **8b** and **8c** via the brucine salts. The (*S*)-(+) acid **8b** formed a methanol-insoluble complex from which the acid was recovered by following the conventional procedures. From the methanolic solution the brucine complex of the (*R*)-(−) acid **8c** was obtained and decomposed without further purification to give the chiral acid.

(*S*)-(+) acid **8b** was converted to the (*S*)-(+)-keto lactam **5b** in 74% yield (Scheme III) via the acid chloride followed by a low-temperature Friedel–Crafts reaction developed for the racemic compound **5a**. [The sequence of reactions described for the (*S*)-(+) acid **8b** has also been carried out by starting with the (*R*)-(−) enantiomer **8c**.]

Reduction of **5b** in the presence of $NaBH_4$ gave the two chiral diastereoisomers **6c** and **6e** in a ratio of 1:3. The desired (αS,3*S*)-(+) isomer **6c** was then reduced further in the presence of diborane and under carefully controlled conditions to amorphous (αS,1*S*)-(+)-α,1-bis(4-chlorophenyl)isoindoline-1-ethanol (**3c**). This was characterized as the (*S*)-(−)-2-pyrrolidone-5-carboxylic acid salt and was

(4) A. Menozzi and G. Appiani, *Gazz. Chim. Ital.*, **22**, 106 (1892). See also: E. Hardegger and H. Ott, *Helv. Chim. Acta*, **38**, 312 (1955); W. H. Gray, *J. Chem. Soc.*, 1264 (1928).

Scheme IV



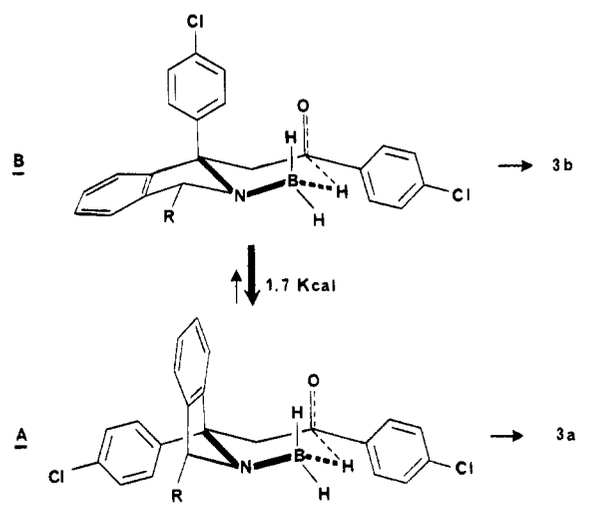
found to be identical in every respect with a sample obtained from the separation of the racemic amino alcohol **3a** with the aid of the same acid.

Since all four chiral compounds **3c–f** were amorphous substances, their enantiomeric excesses were individually estimated by using the chiral shift reagent Eu-Optishift I (tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato]europium(III)). For the compounds **3c** and **3d**, the enantiomeric excess was estimated to be >97%. The corresponding peaks for the compounds **3e** and **3f** were also shifted differently by equivalent amounts of chiral shift reagent, and the enantiomeric excess was estimated to be 90%.

Studies on the Mechanism of the Reduction with Diborane. On the basis of the high stereoselectivity observed for the reduction of **2** in the presence of diborane, it was suspected that the reduction of the carbonyl group might occur via an *intramolecular* hydride transfer in a complex between **2** and borane. The pivotal role played by the nitrogen of the imino ester during the reduction became obvious when the isosteric carbocyclic compound **11** was reduced in the presence of diborane (Scheme IV). A mixture of both diastereoisomers **10** in a ratio of 3:4 (^{13}C NMR data; see Experimental Section) was isolated, which is in sharp contrast to the high stereoselectivity observed for the reduction of **2**. The ketone **11** was prepared via Grignard reaction (with *p*-chlorophenylmagnesium bromide) from the aldehyde **9**, which resulted in the formation of a different mixture of the same diastereoisomers **10** in a ratio of 2:1 (^{13}C NMR), followed by oxidation. The aldehyde **9** in turn was prepared by following procedures described in the literature for the dechloro compound[5] of **9**.

The inference of a complex between the nitrogen of **2** and borane does not exclude an intermolecular reduction.[6] However, when **2** was treated[7] with tributylborane prior to the addition of diborane, a marked increase in the formation of the isomer **3b** could be observed. Under these conditions the ratio of **3a** to **3b** was found to be 57:43. This ratio was determined by high-pressure liquid chromatography. Since only about 5% of **3a** was formed in the absence of tributylborane this difference may be attributed to different mechanisms under the different reaction conditions.[7] Also, the product distribution of 95:5 should reflect a difference of the free energy of about 1.7 kcal in favor of transition state A (Scheme V).

Scheme V



In one experiment we added only 0.5 equiv of borane to **2** with the result that only 8% of **3a** could be isolated. This seems to indicate that the reduction of **2** is not of first order with respect to borane and that the imino ester group is reduced in a separate step. Cases of intramolecular reductions of carbon–carbon double bonds in complexes between aziridines[7] and borane, tertiary amines[8] and LAH, amino ketones[9] and LAH, amino ketones[10] and $NaBH_4$, and a hydroxy ketone[11] and $NaBH_4$ have been reported.

Evidence supporting a six-centered transition state involving phenylborane and diallylaniline has been published[12] since our experiments were carried out.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were not corrected. Proton NMR spectra were obtained on a Varian A-60 spectrometer and ^{13}C NMR spectra were recorded on a Varian XL-100 spectrometer and are recorded in parts per million, both relative to tetramethylsilane as internal standard. Infrared spectra were measured on a Perkin-Elmer spectrometer, Model 457. High-pressure liquid chromatography was carried out on a Waters Microporasil column in combination with a UV monitor. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel HF-254 (E. Merck AG). Mass spectra were measured on an LKB 9000 mass spectrometer. Optical rotations were measured in absolute ethanol in a tube of 5-cm length.

1-(4-Chlorophenyl)-1-(4′-chlorophenacyl)-3-ethoxy-1*H*-isoindole (2). To a suspension of 5.4 g (0.23 mol) of NaH in 100 mL of absolute DMF was added a solution of 54.5 g (0.2 mol) of the imino ester[2] **1** in 250 mL of DMF slowly from a dropping funnel. The mixture was stirred under an atmosphere of N_2 for 2 h. Then a solution of 47.0 g (0.205 mol) of commercial 4-chlorophenacyl bromide in 150 mL of DMF was added slowly. The mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure (high vacuum). The residue was dissolved in methylene chloride and worked up the usual way. The crude product was filtered through a short silica gel column (toluene) to give the crystalline product **2**: yield

(5) R. K. Hill and D. A. Cullison, *J. Am. Chem. Soc.*, **95**, 1229 (1973); J. H. Brewster and R. T. Prudence, *ibid.*, **95**, 1217 (1973).
(6) P. S. Anderson, *Tetrahedron Lett.*, 1141 (1976).
(7) R. Chaabouni, A. Laurent, and B. Marquet, *Tetrahedron Lett.*, 757 (1976).
(8) A. P. Marchand and R. W. Allen, *Tetrahedron Lett.*, 67 (1975).
(9) P. S. Portoghese and D. A. Williams, *Tetrahedron Lett.*, 6299 (1966).
(10) S. Yamada and K. Koga, *Tetrahedron Lett.*, 1711 (1967).
(11) P. T. Lansbury, J. F. Bieron, and M. Klein, *J. Am. Chem. Soc.*, 88, 1477 (1966).
(12) C. L. McCormick and G. B. Butler, *J. Org. Chem.*, 41, 2803 (1976).

69.3 g (82%); mp 99–101 °C; mass spectrum, *m/e* 423 (M^+); NMR ($CDCl_3$) δ 1.3 (t, 3, *J* = 7 Hz, CH_3), 3.78 (q, 2, *J* = 14 Hz, Δν = 9.7 Hz, CH_2CO), 4.0–4.6 (m, 2, CH_2O), 7.0–7.8 (m, 12, aromatic H); IR ($CHCl_3$) 1675 (C=O), 1620 (C=N), 1590, 1570 cm^{-1} (aromatic). Anal. Calcd for $C_{24}H_{19}Cl_2NO_2$ (mol wt 424.3): C, 67.9; H, 4.5; N, 3.3. Found: C, 67.9; H, 4.6; N, 3.3.

(αRS,1RS)-α,1-Bis(4-chlorophenyl)isoindoline-1-ethanol (3a). A solution of 183.0 g (0.43 mol) of the imino ester **2** in 700 mL of absolute THF in a 5-L flask equipped with stirrer under an inert atmosphere and cooled in an ice bath was treated with 870 mL (0.87 mol) of 1 M diborane solution in THF. The mixture was stirred at 4 °C overnight. The solvent was evaporated under reduced pressure, and the residue was dissolved in methylene chloride, basified with 180 mL of 2 N NaOH, and worked up the usual way. The crude product was recrystallized from CH_2Cl_2/hexane to give three crops of product: yield 140.6 g (85%); mp 163–164 °C. From the filtrates, which were treated with 15.0 g of maleic acid, an additional 5.4 g (3.3%) of the product was isolated via the maleic acid addition salt (7.0 g; mp 175–182 °C), thus raising the total yield to 88.3%: mass spectrum, *m/e* 383 (M^+); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.8–2.6 (m, 2, CH_2CHOH), 4.30 (s, 2, CH_2NH), 4.1–4.9 (m, 3, two exchangeable in D_2O, NH, CH_2CHOH), 7.0–7.8 (m, 12, 3 C_6H_4); IR (Nujol) 3310 (NH, OH), 1640 cm^{-1} (weak). Anal. Calcd for $C_{22}H_{19}Cl_2NO$ (mol wt 384.3): C, 68.8; H, 5.0; N, 3.6; Cl, 18.4. Found: C, 68.6; H, 5.2; N, 3.8; Cl, 18.6.

The maleic acid addition salt was recrystallized from methanol/ether; mp 191–193 °C. Anal. Calcd for $C_{22}H_{19}Cl_2NO{\cdot}C_4H_4O_4$ (mol wt 500.4): C, 62.4; H, 4.6; N, 2.8; Cl, 14.2. Found: C, 62.0; H, 4.3; N, 2.6; Cl, 14.0.

The same compound was obtained from **4a**, **5a**, and **6a** in 79, 61, and 53% yields, respectively, under conditions similar to those described above.

A solution of 2.1 g (0.005 mol) of **2** in 20 mL of THF was treated with 5 mL of a commercial 1 M solution of tributylborane in THF and kept at room temperature overnight. The mixture was cooled with an ice bath and treated with 20 mL of 1 M diborane solution. This solution was kept at room temperature overnight and then worked as described above to give 3.0 g of crude material. This was analyzed by high-pressure liquid chromatography (500 psi) on a Waters Microporasil column with the solvent system 1:69:30 MeOH–hexane–$CHCl_3$ and a flow rate of 2 mL/min to give a ratio of 43:57 for **3b** to **3a**. When the crude mixtures from reductions in the presence of diborane but in the absence of tributylborane were analyzed, the ratio of **3b** to **3a** was 5:95.

(αRS,1SR)-α,1-Bis(4-chlorophenyl)isoindoline-1-ethanol (3b). When 1.6 g (0.004 mol) of the imino ester **4b** was reduced in the presence of 5.5 mL of 1 M diborane in THF, the amino alcohol **3b** was isolated as a noncrystalline material and converted into the maleic acid salt: mp 119–120 °C; yield 0.6 g (20%); mass spectrum, *m/e* 383 (M^+); NMR ($CDCl_3$) δ 2.0–3.3 (m, 2, CH_2CHOH), 3.35 (s, 1, OH), 4.2–4.8 (m, 3, $NHCH_2$ and CHOH), 6.0 (s, 2, maleic acid), 7.1–7.7 (m, 12, 3 C_6H_4); IR (CH_2Cl_2) 3620, 1700 cm^{-1} (weak). Anal. Calcd for $C_{22}H_{19}Cl_2NO{\cdot}C_4H_4O_4$ (mol wt 500.4): C, 62.4; H, 4.6; N, 2.8; Cl, 14.2. Found: C, 62.0; H, 4.8; N, 2.7; Cl, 13.9.

(αS,1S)-(+)-α,1-Bis(4-chlorophenyl)isoindoline-1-ethanol (3c). (a) From 6c. A solution of 4.0 g (0.01 mol) of **6c** in 100 mL of absolute THF was kept at 0 °C for 48 h in the presence of 30 mL of 1 M diborane solution (THF) under an atmosphere of N_2. The solvent was evaporated under reduced pressure, and the residue was dissolved in methylene chloride and washed with carbonate solution. The residue (4.1 g) was chromatographed on a silica gel column. With chloroform, 2.55 g (66%) of a foamy product was obtained; $[\alpha]_D$ +65.1° (*c* 1.08). A solution of 1.9 g (0.005 mol) of this product in methanol was treated with 0.65 g (0.005 mol) of (*S*)-(−)-2-pyrrolidone-5-carboxylic acid[4] in methanol. The complex was precipitated by the addition of ether: yield 1.8 g (70%); mp 180–181 °C; $[\alpha]_D$ +6.65° (*c* 0.825); IR (Nujol) 3210 (NH), 1670 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{19}Cl_2NO{\cdot}C_5H_7NO_3$ (mol wt 513.45): C, 63.2; H, 5.1; N, 5.5; Cl, 13.8. Found: C, 63.4; H, 5.2; N, 5.5; Cl, 13.5. When the above complex was treated with 2 N NaOH solution, the free base **3c** could be recovered in 80% yield as a noncrystalline material: $[\alpha]_D$ +64.8° (*c* 1.22); NMR ($CDCl_3$) 1.7–2.7 (m, 2, $CHOHCH_2$), 4.24 (s, 2, CH_2N), 4.36 (br s, 2, NH and OH), 4.5–4.9 (m, 1, CHOH), 6.8–7.5 (m, 12, 3 C_6H_4).

(b) Isolation of the Enantiomers 3c and 3d via Separation of the Racemate 3a. A mixture of 75.0 g (0.195 mol) of racemic amino alcohol **3a** and 26.5 g (0.205 mol) of (*R*)-(+)-pyroglutamic[13] acid in 1 L of methanol was warmed on the water bath until an almost clear solution was obtained. The insoluble material was filtered off; 7.3 g, mp 163–166 °C (starting material). The filtrate was concentrated to approximately half the volume. Ether was added to precipitate 43.0 g of the complex, mp 177–179 °C. This substance was recrystallized from methanol/methylene chloride/ether to give 40.5 g (90%) of pure complex (acid with **3d**): mp 180–182 °C; $[\alpha]_D$ −9.5° (*c* 0.867). When a sample of the above complex was separated into its components as described above, the noncrystalline base **3d** was obtained; $[\alpha]_D$ −71.0° (*c* 1.03). The soluble complex from the separation above was separated into the components as described previously. From the basic aqueous solution the (*R*)-(+)-pyroglutamic acid was recovered by filtration through an ion-exchange column (Dowex 50W-X4).

A combined sample of 64.0 g (0.17 mol) of crude (+)-amino alcohol **3c** obtained from two separations of the (−) enantiomer was added to 24.5 g (0.19 mol) of (*S*)-(−)-pyroglutamic acid[4] in methanol. The complex precipitated from the solution, was filtered off, and was washed with methanol/ether: yield 58.0 g (66%); mp 180–182 °C; $[\alpha]_D$ +2.40° (*c* 1.03). The free base **3c** was prepared as usual.

(αR,1S)-(−)-α,1-Bis(4-chlorophenyl)isoindoline-1-ethanol (3e). A solution of 8.0 g (0.02 mol) of **6e** in 100 mL of THF was treated with 60 mL of a 1 M solution of diborane in THF (0.06 mol) while the mixture was cooled with an ice bath under an atmosphere of N_2. The mixture was kept at 4 °C for 2 days. The mixture was worked up as described above to give 7.0 g of **3e** (90%): mass spectrum, *m/e* 384 [$(M + 1)^+$]; $[\alpha]_D$ −59.6° (*c* 0.835); NMR ($CDCl_3$) 2.2–2.5 (m, 2, CH_2OH), 4.20 (s, 2, NCH_2), 4.3–4.6 (m, 1, CHOH), 6.9–7.5 (m, 12, 3 C_6H_4).

(αRS,1RS)-α,1-Bis(4-chlorophenyl)-3-ethoxy-1H-isoindole-1-ethanol (4a) and (αRS,1SR)-α,1-Bis(4-chlorophenyl)-3-ethoxy-1H-isoindole-1-ethanol (4b). To the suspension of 28.0 g (0.066 mol) of the imino ester **2** in 250 mL of absolute ethanol was added 8.0 g (0.21 mol) of $NaBH_4$ in small portions. The mixture was kept at room temperature overnight under an atmosphere of N_2. The solvent was evaporated under reduced pressure and the residue worked up in methylene chloride as usual. The mixture of diastereoisomers was separated via column chromatography on silica gel. With benzene as eluent, 16.1 g (58%) of the alcohol **4a** was separated. Continued elution yielded 11.4 g (42%) of the alcohol **4b**, recrystallized from ethanol.

4a: mp 148–150 °C; mass spectrum, *m/e* 425 (M^+); NMR ($CDCl_3$) δ 1.55 (t, 3, *J* = 7 Hz, CH_3), 1.74 (d, 1, *J* = 14 Hz, HCHCHOH), 2.80 (q, 1, *J* = 14 Hz, Δν = 2 Hz, HCHCHOH), 4.4–4.9 (m, 3, OCH_2CH_3 and CH_2CHOH), 6.04 (br s, 1, OH), 7.0–7.7 (m, 12, 3 C_6H_4); IR (CH_2Cl_2) 3300 (OH), 1630 (C=N), 1605 cm^{-1} (arom). Anal. Calcd for $C_{24}H_{21}Cl_2NO_2$ (mol wt 426.4): C, 67.6; H, 5.0; N, 3.3; Cl, 16.6. Found: C, 67.5; H, 5.1; N, 3.3; Cl, 16.8.

4b: mp 136–138 °C; mass spectrum, *m/e* 425 (M^+); NMR ($CDCl_3$) δ 1.52 (t, 3, *J* = 7 Hz, CH_3), 2.5–3.1 (m, 2, CH_2CHOH), 3.9–4.3 (m, 2, one exchangeable with D_2O, CHOH), 4.63 (q, 2, *J* = 7 Hz, OCH_2), 6.9–7.8 (m, 12, 3 C_6H_4); IR (CH_2Cl_2) 3430 (OH), 1620 (C=N), 1600 cm^{-1} (arom). Anal. Calcd for $C_{24}H_{21}Cl_2NO_2$ (mol wt 426.4): C, 67.6; H, 5.0; N, 3.3; Cl, 16.6. Found: C, 67.5; H, 5.0; N, 3.3; Cl, 16.9.

3-(4-Chlorophenyl)-3-(4′-chlorophenacyl)phthalimidine (5a). (a) From 2. A solution of 10.0 g (0.024 mol) of imino ester **2** in 50 mL of ethanol was heated to reflux in the presence of 3.5 mL of 2 N HCl solution for 2 h. The product was precipitated by the addition of water and recrystallized from methylene chloride/hexane: yield 7.2 g (76%); mp 192–194 °C; mass spectrum, *m/e* 395 (M^+); NMR ($CDCl_3$) δ 3.95 (q, 2, *J* = 18 Hz, Δν = 81 Hz, CH_2), 7.1–8.1 (m, 13, NH and 3 C_6H_4); IR (CH_2Cl_2) 3435 (NH), 1705, 1685 cm^{-1} (C=O). Anal. Calcd for $C_{22}H_{15}Cl_2NO_2$ (mol wt 396.3): C, 66.7; H, 3.8; N, 3.5; Cl, 17.9. Found: C, 66.4; H, 3.9; N, 3.8; Cl, 17.9.

(13) A. Menozzi and G. Appiani, *Gazz. Chim. Ital.*, **24**, 382 (1894). We have prepared this acid from (*R*)-(−)-glutamic acid following procedures from ref 4. Since then, this reaction has been described in the literature: U. Schmidt and R. Schölm, *Synthesis*, 752 (1978).

(b) From 8a. The suspension of 1.5 g (0.005 mol) of the racemic acid **8a** in 35 mL of dichloroethane was treated with 3 mL of thionyl chloride and 1 drop of absolute DMF. The mixture was heated to reflux for 20 min, and then the solvents were evaporated under reduced pressure. The crude acid chloride was dissolved in a mixture of 35 mL of dichloroethane and 8.0 g of chlorobenzene. The solution was cooled to −40 °C, and 3.0 g of $AlCl_3$ was added in small portions. After being kept at room temperature overnight, the mixture was poured on ice and worked up in CH_2Cl_2 as usual to yield 1.9 g crude product which was purified from benzene/ligroine: mp 188–190 °C; yield 1.1 g (55%).

(*S*)-(+)-3-(4-Chlorophenyl)-3-(4′-chlorophenacyl)phthalimidine (5b). To the suspension of 30.1 g (0.1 mol) of (*S*)-(+) acid **8b** in 300 mL of dichloroethane was added 60 mL (0.83 mol) of thionyl chloride slowly followed by 5 drops of DMF. The mixture was heated on a water bath for 30 min at 50–60 °C. A yellow solution was obtained. The solvent was evaporated under reduced pressure. An amorphous acid chloride was obtained which was used without further purification since it was found to be unstable. The acid chloride was dissolved in a mixture of 250 mL of dichloroethane and 98.0 g of chlorobenzene under an atmosphere of N_2. The mixture was chilled to −50 °C. To this was added 26.0 g (0.2 mol) of $AlCl_3$ in small portions. The low temperature was maintained for 2 h, and then the mixture was allowed to reach room temperature, where it was kept overnight. The mixture was poured on ice, and the product was extracted with methylene chloride, washed with water (500 mL), dried over K_2CO_3, and concentrated. The crude product was crystallized from CH_2Cl_2/hexane/ether to give 29.3 g (74%) of pure **5b**: mp 171–172 °C; mass spectrum, *m/e* 395 (M^+); $[\alpha]_D$ +334.0° (*c* 1.07); NMR ($CDCl_3$) δ 3.92 (q, 2, *J* = 18 Hz, Δν = 81 Hz, CH_2), 7.1–8.1 (m, 13, NH and 3 C_6H_4); IR (CH_2Cl_2) 3420 (NH), 1708 (amide), 1684 cm^{-1} (ketone). Anal. Calcd for $C_{22}H_{15}Cl_2NO_2$ (mol wt 396.3): C, 66.7; H, 3.8; N, 3.5; Cl, 17.9. Found: C, 66.3; H, 4.0; N, 3.4; Cl, 18.1.

(α*RS*,3*RS*)-α,3-Bis(4-chlorophenyl)phthalimidine-3-ethanol (6a) and (α*RS*,3*SR*)-α,3-Bis(4-chlorophenyl)-phthalimidine-3-ethanol (6b). When 2.0 g (0.005 mol) of the keto lactam **5a** was reduced in the presence of 0.4 g (0.010 mol) of $NaBH_4$ in absolute ethanol under conditions similar to those described above, the two diastereomeric hydroxy lactams **6a** and **6b** were isolated by column chromatography.

6a: yield 1.0 g (50%); mp 212–214 °C; mass spectrum, *m/e* 397 (M^+); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.8–3.1 (m, 2, CH_2), 4.4–4.9 (m, 1, CHOH), 5.41 (d, 1, *J* = 4 Hz, OH), 7.2–7.9 (m, 12, 3 C_6H_4), 8.33 (s, 1, NH); IR (CH_2Cl_2) 3590, 3400 (NH, OH), 1690 cm^{-1} (lactam). Anal. Calcd for $C_{22}H_{17}Cl_2NO_2$ (mol wt 398.3): C, 66.3; H, 4.3; N, 3.5; Cl, 17.8. Found: C, 66.7; H, 4.3; N, 3.5; Cl, 18.0. The same compound was isolated in 85% yield from the hydrolysis of the hydroxyimino ester **4a** in acidic medium.

6b: yield 0.7 g (35%); mp 115–117 °C; mass spectrum, *m/e* 397 (M^+); NMR ($CDCl_3$) δ 2.4–3.2 (m, 2, CH_2), 4.1–4.4 (br, 1, HCOH), 4.73 (d, 1, exchangeable in D_2O, *J* = 4 Hz, OH), 6.7–7.8 (m, 12, 3 C_6H_4), 8.54 (s, 1, exchangeable in D_2O, NH); IR (CH_2Cl_2) 3680, 3590, 3420 (NH, OH), 1690 cm^{-1} (lactam). Anal. Calcd for $C_{22}H_{17}Cl_2NO_2$ (mol wt 398.3): C, 66.3; H, 4.3; N, 3.5; Cl, 17.8. Found: C, 66.0; H, 4.5; N, 3.4; Cl, 17.8. The same compound was obtained from the hydrolysis of the hydroxyimino ester **4b** in acidic medium.

(α*S*,3*S*)-(+)-α,3-Bis(4-chlorophenyl)phthalimidine-3-ethanol (6c) and (α*R*,3*S*)-(+)-α,3-Bis(4-chlorophenyl)-phthalimidine-3-ethanol (6e). A suspension of 28.5 g (0.072 mol) of the (+) isomer **5b** in 500 mL of absolute ethanol was treated with 9.0 g (0.24 mol) of $NaBH_4$. The mixture was stirred overnight under an atmosphere of nitrogen at room temperature. The solvent was evaporated under reduced pressure, and the residue was worked up the usual way with methylene chloride. The crude material (32.0 g) was chromatographed on a silica gel column. After elution first with benzene, chloroform was added gradually and a crystalline material, **6c**, was obtained: yield 6.9 g (24%); mp 231–233 °C; $[\alpha]_D$ +182.4° (*c* 1.17); NMR ($CDCl_3$ + Me_2SO-d_6) δ 1.8–3.2 (m, 2, CH_2), 4.4–4.9 (m, 1, HCOH), 5.39 (d, 1, *J* = 4 Hz, exchangeable with D_2O, OH), 7.2–7.9 (m, 12, 3 C_6H_4), 8.34 (s, 1, exchangeable, NH); IR (CH_2Cl_2) identical with the IR spectrum (CH_2Cl_2) of racemic compound **6a**.

With $CHCl_3$/MeOH (98:2) as eluent, the second isomer, **6e**, was obtained as a noncrystalline material: yield 20.4 g (71%); TLC one component (no **6c**); mass spectrum, *m/e* 397 (M^+); $[\alpha]_D$ +65.2° (*c* 1.09); IR (CH_2Cl_2) identical with IR spectrum (CH_2Cl_2) of **6b**.

3-(4-Chlorophenyl)-3-phthalimidineacetic Acid (8a). To the suspension of 27.6 g (1.2 mol) of sodium hydride in 250 mL of absolute DMF which was placed in a 5-L flask equipped with a mechanical stirrer, a condenser, and a dropping funnel under an atmosphere of N_2 was added a solution of 272.5 (1.0 mol) of imino ester **1**[2] in 1 L of DMF dropwise. After the addition was completed, the mixture was stirred at room temperature for 2 h. A solution of 155.0 g (1.0 mol) of methyl bromoacetate in 200 mL of DMF was added slowly (exothermic reaction). The mixture was kept at room temperature overnight. Then the solvent was evaporated under reduced pressure (high vacuum), and a small sample of the crude imino ester **7** was filtered through a silica gel column to give pure **7** as a liquid: NMR ($DCCl_3$) δ 1.47 (t, 3, *J* = 7 Hz, CH_2CH_3), 3.27 (s, 2, CH_2COO), 3.43 (s, 3, OCH_3), 4.57 (q, 2, *J* = 7 Hz, OCH_2), 7.1–7.7 (m, 8, aromatic); IR (film) 1735 (C=O), 1625 cm^{-1} (C=N). The residue was heated to reflux in a mixture of 800 mL of 2 N NaOH/500 mL of ethanol for 3 h. The solvent was evaporated under reduced pressure (aspirator), and the residue was dissolved in water and filtered over Celite. The filtrate was acidified with 90 mL of concentrated HCl to precipitate the product which was collected by filtration; the crude product was recrystallized from absolute methanol: yield 222 g (74%); mp 226–228 °C; a second crop (36.5 g, 12%; mp 232–234 °C) was collected; total yield 258.5 g (86%); mass spectrum, *m/e* 301 (M^+); NMR ($CDCl_3$ + Me_2SO-d_6) δ 3.27 (q, 2, *J* = 16 Hz, Δν = 48.6 Hz, CH_2), 7.1–8.3 (m, 10, 8 arom H, NH, OH); IR (Nujol) 3240 (NH, COOH), 1665 cm^{-1} (br, C=O). Anal. Calcd for $C_{16}H_{12}ClNO_3$ (mol wt 301.7): C, 63.7; H, 4.0; N, 4.6; Cl, 11.7. Found: C, 63.3; H, 4.2; N, 4.6; Cl, 11.8.

(*S*)-(+)-3-(4-Chlorophenyl)-3-phthalimidineacetic Acid (8b). Separation of Racemic 8a. A solution of 222.0 g (0.74 mol) of the racemic acid **8a** in 2.5 L of hot methanol was treated with 295.0 g (0.75 mol) of brucine in 0.8 L of methanol. A solid formed immediately and was filtered from the cold solution, washed with methanol/ether, and dried to give 260 g of the complex. This was suspended in 500 mL of methanol and acidified with 160 mL of 2 N HCl solution. The mixture was cooled and the solid acid removed by filtration. The crude acid was dissolved in hot methanol and precipitated by the addition of 20 mL of concentrated HCl followed by the addition of 150 mL of water. The acid was recrystallized from hot methanol: yield 76.0 g (69%); mp 215–217 °C; mass spectrum, *m/e* 301 (M^+); $[\alpha]_D$ +236.5° (*c* 0.95); NMR (Me_2SO-d_6) δ 3.35 (q, 2, *J* = 16 Hz, Δν = 13.6 Hz, CH_2), 7.2–7.8 (m, 8, 2 C_6H_4); IR (Nujol) 3350, 3440 (NH, COOH), 1725, 1710 (COOH), 1665 cm^{-1} (lactam). Anal. Calcd for $C_{16}H_{12}ClNO_3$ (mol wt 301.7): C, 63.7; H, 4.0; N, 4.6; Cl, 11.7. Found: C, 63.3; H, 4.2; N, 4.6; Cl, 11.8.

(*R*)-(−)-3-(4-Chlorophenyl)-3-phthalimidineacetic Acid (8c). The filtrate containing the soluble brucine complex was evaporated to dryness, acidified with concentrated HCl, and diluted with water. The acid was collected by filtration and recrystallized from hot methanol: yield 49.5 g (44.6%); mp 215–216 °C; $[\alpha]_D$ −244.5° (*c* 0.89); second crop yield 20.5 g (18.5%); mp 213–215 °C; $[\alpha]_D$ −221.9° (*c* 0.92).

1-(4-Chlorophenyl)-2,3-dihydro-1*H*-indene-1-acetic acid (9a) was prepared in 84% yield by following the same procedures as for the dechloro compound:[5] mp 107–109 °C; mass spectrum, *m/e* 286 (M^+); NMR ($CDCl_3$) δ 2.2–3.2 (m, 6, 3 CH_2), 7.0–7.5 (m, 8, arom), 9.8 (br, 1, OH); IR (CH_2Cl_2) 3500 (OH), 1705 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClO_2$ (mol wt 286.8): C, 71.2; H, 5.3; Cl, 12.4. Found: C, 70.7; H, 5.5; Cl, 12.4.

1-(4-Chlorophenyl)-2,3-dihydro-1*H*-indene-1-ethanol (9b). The acid **9a** was reduced in the presence of diborane: yield 95%; mp 56–58 °C (methylene chloride/hexane); mass spectrum, *m/e* 272 (M^+); NMR ($CDCl_3$) δ 1.4 (br, 1, exchangeable in D_2O, OH), 2.1–2.5 (m, 4, 2 CH_2), 2.7–3.1 (m, 2, CH_2), 3.6 (t, 2, *J* = 7.5 Hz, CH_2OH), 7.0–7.4 (m, 8, arom); IR (CH_2Cl_2) 3620 (OH), 1600 (arom) cm^{-1}. Anal. Calcd for $C_{17}H_{17}ClO$ (mol wt 272.8): C, 74.9; H, 6.3; Cl, 13.0. Found: C, 75.1; H, 6.2; Cl, 13.3.

1-(4-Chlorophenyl)-2,3-dihydro-1*H*-indene-1-acetaldehyde (9c). Oxidation of **9b** in the presence of pyridine with chromic

acid gave a 60% yield of **9c**; mp 61–62 °C; mass spectrum, m/e 270 (M^+); NMR ($CDCl_3$) δ 2.1–2.9 (m, 4, 2 CH_2), 3.0 (d, 2, J = 2 Hz, CH_2CHO), 7.0–7.4 (m, 8, arom), 9.6 (t, 1, J = 2 Hz, CHO); ^{13}C NMR ($CDCl_3$) 202.0 (C-9), 53.3 (C-1), 52.7 (C-8), 41.8 (C-2), 30.3 (C-3), in addition to 10 signals for the aromatic carbons; IR (film) 1720 (C=O) cm^{-1}. Anal. Calcd for $C_{17}H_{15}ClO$ (mol wt 270.8): C, 75.4; H, 5.6; Cl, 13.1. Found: C, 75.0; H, 6.0; Cl, 13.0.

α,1-Bis(4-chlorophenyl)-2,3-dihydro-1*H*-indene-1-ethanol (10). A solution of 2.7 g (0.01 mol) of aldehyde **9c** in 20 mL of THF was added dropwise to a Grignard solution prepared from 3.8 g (0.02 mol) of *p*-chlorobromobenzene and 1.0 g (0.04 mol) of magnesium. The mixture was kept at room temperature overnight and then worked up the usual way with ether to yield 4.8 g of crude material. This was chromatographed on silica gel (chloroform) to give 3.1 g (81%) of **10** as a liquid: mass spectrum, m/e 364 ($M^+ - H_2O$); NMR ($CDCl_3$) δ 1.8 (br, 1, OH), 2.1–3.1 (m, 6, 3 CH_2), 4.4–4.8 (m, 1, CHOH), 7.0–7.5 (m, 12, arom); ^{13}C NMR ($CDCl_3$) 71.2 (C-9), 54.8 (C-1), 49.1 (C-8), 39.6 (C-2), 30.0 (C-3) (signals for the aliphatic carbons of the major isomer; for minor isomer see below; ratio 2:1); IR (film) 3600, 3450 (OH) cm^{-1}.

The reduction of 1.0 g (0.003 mol) of **11** in the presence of 10 mL of a 1 M solution of diborane in THF at room temperature for 1 h gave, after the usual workup followed by a filtration through silica gel (chloroform), a different mixture of the diastereoisomers of **10**: yield 0.9 g (90%); mass spectrum, m/e 364 ($M^+ - H_2O$); ^{13}C NMR ($CDCl_3$) 71.2 (C-9), 54.4 (C-1), 49.2 (C-8), 40.0 (C-2), 30.3 (C-3) (signals for the aliphatic carbons of the major isomer; for the minor isomer see above; ratio 4:3).

1-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)-2,3-dihydro-1*H*-inden-1-yl]ethanone (11). A solution of 1.1 g (0.003 mol) of **10** (from the Grignard reaction) in 20 mL of acetone was treated with an excess of Jones reagent. After 30 min at room temperature the product was extracted with ether and filtered through a silica gel column to give pure **11** as a liquid: yield 1.0 g (90%); NMR ($CDCl_3$) δ 2.3–3.1 (m, 4, CH_2CH_2), 3.7 (q, 2, J = 17 Hz, $\Delta\nu$ = 15.5 Hz, CH_2CO), 7.0–8.0 (m, 12, arom); ^{13}C NMR ($CDCl_3$) 196.5 (C-9), 53.9 (C-1), 47.7 (C-8), 41.3 (C-2), 30.6 (C-3), in addition to 13 signals for the aromatic carbons); IR (film) 1690 (C=O) cm^{-1}.

X-ray Analysis of 3c. Suitable crystals for X-ray diffraction were grown from an equimolar mixture of **3c** with (*S*)-(−)-2-pyrrolidone-5-carboxylic acid in methanol. The colorless prismatic crystals of elemental composition $C_{27}H_{26}N_2O_4Cl_2$, mol wt 513.4, belong to the orthorhombic space group $P2_12_12_1$ and have a = 10.692 (8) Å, b = 15.316 (9) Å, c = 15.545 (8) Å, and V = 2546 Å^3, with Z = 4 molecules per cell (d_{calcd} = 1.34 g cm^{-3}).

Diffraction data of a crystalline prism of size 0.2 × 0.3 × 0.5 mm were measured with Mo Kα radiation (graphite monochromator) on a CAD4 diffractometer, ω–2θ scan mode, variable scan angle $\delta\omega = 0.9° + 0.5 \tan\theta$, variable aperture $\delta A = 3.0 + 1.5 \tan\theta$ (mm), the scan speed adjusted to obtain a ratio $\sigma(I)/I = 0.02$ (maximum time 120 s/reflextion). A total of 2027 unique reflexions were measured within ($\sin\theta/\lambda < 0.55$ Å^{-1}). The stability of the crystal was monitored by frequent checks on control reflexions; no significant variation was detected.

The net intensity of a reflexion, I_h, was evaluated by means of Diamond's method of profile analysis.[14] The standard deviation was calculated as shown in eq 1, where i_n is the nth profile count

$$\sigma(I_h) = (\sum_n i_n)^{1/2} + CI_h \quad (1)$$

and C an experimental parameter set at 0.02. Of all reflexions, 1363 (=67%) had an intensity $I_h > 3\sigma(I_h)$ and were accepted as significant measurements.

The intensities were corrected for Lorentz–polarization effects but not for absorption and were scaled to absolute values, $|F_h|$, by Wilson's method.[15] The standard deviation of the structure factors was defined as shown in eq 2, where k is the scale factor

$$\sigma(F_h) = k\frac{\sigma(I_h)}{2|F_h|} \quad (2)$$

relating I_h and $|F_h|^2$ (significant reflexions only). The calculation of normalized structure factors $|E_h|_2$ yielded the averages $\langle|E|\rangle$ = 0.857, $\langle|E^2| - 1\rangle$ = 0.796, $\langle|E^2|\rangle$ = 1.010, with $\bar{B}$ = 4.2 Å^2 (from Wilson's method). The structure was solved by a multisolution procedure[16] and the positional and thermal atomic parameters refined by standard least-squares methods. The weighting scheme applied was $w_h = \sigma(F_h)^{-2}$ for significant and $w_h = 0$ for insignificant reflections. In an intermediate stage of refinement the positions of the hydrogen atoms were located from a difference electron density map. In the final structure factor calculation, based on 420 parameters (anisotropic for C, N, O, and Cl atoms, isotropic for H atoms, one scale factor), an R = 0.032 for the 1363 significant reflexions was obtained. The final positional standard deviations were, on average, σ(C, N, O) = 0.005 Å, σ(Cl) = 0.001 Å, and σ(H) = 0.05 Å. The crystallographic numbering of the atoms is shown in Figure 2 (supplementary material), a list of the positional and thermal parameters is given in Table I (supplementary material), and a stereoscopic view of **3c** is shown in Figure 1.

There are no unusual features in the molecular structure of both base and acid. However, an interesting network of hydrogen bonds, involving all potential acceptor and receptor atoms of the two molecules, is present in this crystal structure, of which details are given in Table II.

Table II. Hydrogen Bond Distances (Å) and Angles (Deg)

no.	A···H-D	d_{AD}	d_{DH}	$d_{H\cdots A}$	∢A-H-D
1	O(32)···H_A-N(1)	2.750	1.05	1.65	163
2	O(34)···H_B-N(1)	2.673	0.98	1.91	141
3	O(12)···H_B-N(1)	2.811	0.98	2.34	109
4	O(12)···H-N(27)	2.842	1.02	1.89	150
5	O(35)···H-O(12)	2.577	1.00	1.59	170

[a] Average values: $\sigma(d_{AD})$ = 0.007 Å, σ(DH, H···A) = 0.05 Å, σ(∢) = 5°. H bonds no. 1, 2, 4, and 5 are *intermolecular*; H bond no. 3 is *intramolecular*; H bonds no. 2 and 3 are bifurcated.

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Registry No. **1**, 55695-76-6; **2**, 74113-19-2; **3a**, 74164-78-6; **3a** maleic acid salt, 74164-79-7; **3b**, 74164-80-0; **3b** maleic acid salt, 74164-81-1; **3c**, 55516-88-6; **3c** (*S*)-(−)-2-pyrrolidone-5-carboxylic acid, 74127-88-1; **3d**, 55516-87-5; **3d** (*R*)-(+)-pyroglutamic acid, 74113-20-5; **3e**, 55516-85-3; **4a**, 74113-21-6; **4b**, 74113-22-7; **5a**, 74113-23-8; **5b**, 54089-77-9; **6a**, 74164-82-2; **6b**, 74164-83-3; **6c**, 55516-84-2; **6e**, 55516-81-9; **7**, 74113-24-9; **8a**, 54161-37-4; **8b**, 54089-75-7; **8b** acid chloride, 55695-77-7; **8b** brucine, 74219-16-2; **8c**, 54089-76-8; **9a**, 74113-25-0; **9b**, 74113-26-1; **9c**, 74113-27-2; **10** (isomer 1), 74113-28-3; **10** (isomer 2), 74113-29-4; **11**, 74113-30-7; 4-chlorophenacyl bromide, 536-38-9; maleic acid, 110-16-7; (*S*)-(−)-2-pyrrolidone-5-carboxylic acid, 98-79-3; (*R*)-(+)-pyroglutamic acid, 4042-36-8; brucine, 357-57-3.

Supplementary Material Available: Figure 2 (atomic numbering) and Table I (fractional coordinates and thermal parameters for **3c**) (4 pages). Ordering information is given on any current masthead page.

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