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The Absolute Stereochemistry at C1 and C2 of *Cis*-(+)-2-Hydroxy-2-phenylcyclohexanecarboxylic Acid (Cicloxilic Acid)

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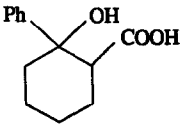
Abstract: A study of the C.D. spectrum of a derivative of *cis*-(+)-2-hydroxy-2-phenylcyclohexanecarboxylic acid has been achieved, providing a useful method for establishing the C1 and C2 absolute configuration of this compound.

A large portion of pharmaceutical substances from both natural and synthetic origin contains at least one stereogenic centre. Chirality gives rise to the problem of stereoisomerism : the main consequence of this is that the effects of the (+) enantiomer may be very different from those of the (-) enantiomer[1a,b]. Numerous and often dramatic examples of dangerous properties allied to a single enantiomer are known in the field of pharmacology[1a,b]. Therefore a complete stereochemical characterization is required for all chiral pharmaceutical substances.

Cis-2-hydroxy-2-phenylcyclohexanecarboxylic acid (cicloxilic acid) **1** is a choleretic agent[2-4] characterized by the property of reducing in the patients the cholesterol saturation of bile [5-7]. Furthermore compound **1** is the starting material to synthesize dialkylaminoethyl or aminocycloalkyl esters, a large series of spasmolitic agents: cicloxilic acid in fact constitutes the acyl portion of these classical antagonists of muscarinic M3 receptors[8,9].



1

The role of stereocomplementarity in the interaction between drugs and biological macromolecules[10] with the related hypothesis of three-points attachment for the binding sites of the receptors[11] and the frequently stressed relevance of "drug chirality", particularly when the stereogenic center is a moiety acting on the receptors[4], suggest the importance to consider the influence of the stereochemistry of cicloxilic acid on the interaction with its biological target. The first problem of this investigation is the determination of the absolute configuration of the enantiomers of cicloxilic acid, that can be nicely solved by circular dichroism (C.D.) spectroscopy, provided to suitably modify its structure.

Indeed **1** possesses a chromophore, the alkyl substituted benzene, the electronic transitions of which are well characterized[12]: in particular it shows an intense absorption band at about 180 nm, assigned to the electrically allowed degenerate $^1A_{1g} \rightarrow {}^1E_{1u}$ transition, the two components of which are polarized as described in chart 1.

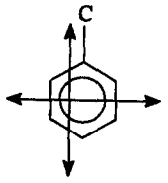
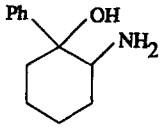


chart 1

By introducing in **1** a second chromophore having well defined electronically allowed transitions, exciton coupling effects could be observed by C.D. spectroscopy. As it is well known, the analysis of the exciton coupling affords a simple and reliable non-empirical method of assigning absolute configurations[13].

In the case of cicloxilic acid the carboxy group could be profitably used to introduce the second chromophore needed for the exciton coupling. The transformation of the COOH to the NH_2 group (Hofmann degradation of amides) affords the aminoalcohol **2**, which , in turn, can be transformed in the substituted amide **3**, having the same absolute stereochemistry since the Hofmann reaction takes place with complete retention of configuration[14].



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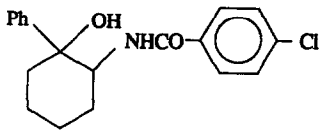


3

The simple benzamide chromophore shows[13] an electronically allowed transition at 225 nm (ε=11000), polarized along the C^*-N axis. This transition is well suited for stereochemical predictions: in fact (R,R) *trans*-1,2-dibenzamidecyclohexane shows[15] a negative couplet effect, in keeping with the Harada-Nakanishi chirality rule[13].

The *para*-chlorosubstitution should only affect the intensity of the absorption and cause a red-shift of the maximum, in analogy to the behaviour[13] of the para-substituted benzoates, without changing the polarization direction. Then the coupling between this amide transition and the $^1A_{1g} \rightarrow {}^1E_{1u}$ excitation of the substi-

tuted benzene chromophore, could afford the C.D. spectral feature suitable for the stereochemical assignment. In addition, to confirm the C.D. assignment, a X-ray crystallographic analysis of derivative **3** was performed by using the anomalous dispersion of the chlorine atom.

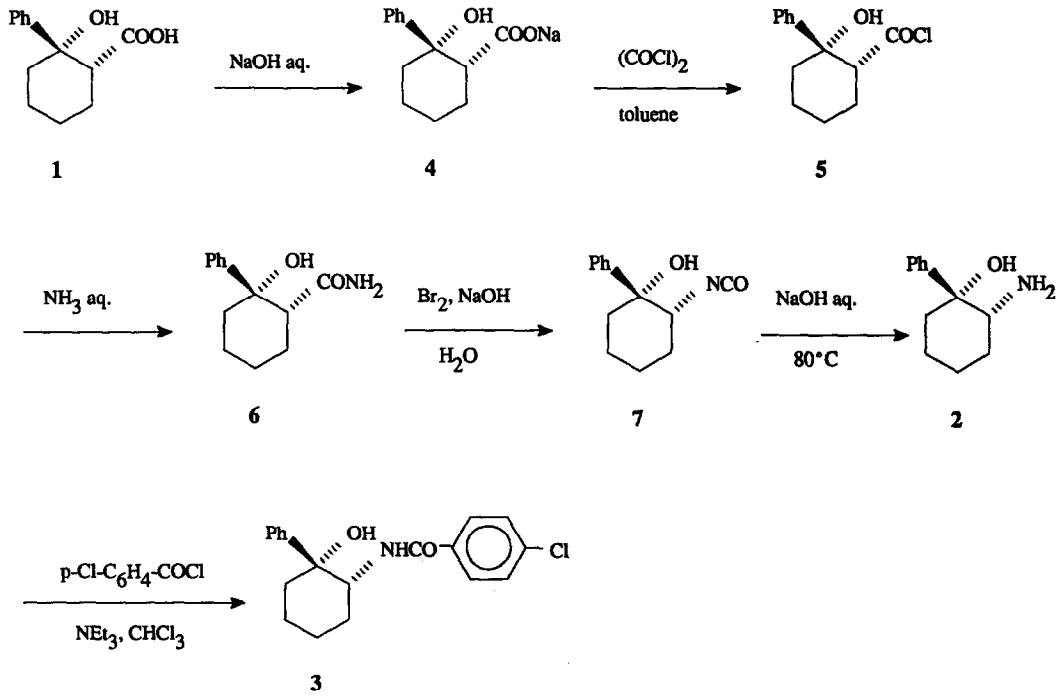
RESULTS AND DISCUSSION

Cicloxilic acid was prepared according to the Zimmerman et al.[16] procedure ; our results confirmed that only one of the two isomers (*cis* and *trans*) of **1** is isolated by this synthetic route even though GLC analysis showed the presence of a small amount (5%) of the contaminant (*trans*) isomer. The *cis* configuration of hydroxyl and carboxyl groups in **1** was established on the basis of its IR and NMR spectra in comparison with the spectra of its *trans* isomer and of their cyclohexyl analogues[17].

Racemic cicloxilic acid was then resolved by reaction with (-)-cinchonidine in ethanol: a solution of the resulting (-)-cinchonidine salt in water was acidified and extracted with ethyl acetate. After evaporation of the solvent from the organic layers, (-)-*cis*-**1** was obtained as white crystals with an e.e. of 98%. The (+)-isomer was obtained with an analogous procedure by treatment of the residue recovered from the mother liquors coming from the resolution of (-)-isomer, with (+)-quinine.

The derivative **3** was obtained by the synthetic sequence shown in the Scheme 1, where the reactions involved occur neither with racemization or with inversion of configuration of the stereogenic centers in the molecule.

Scheme 1



Cis-(+)-2-hydroxy-2-phenylcyclohexanecarboxylic acid **1**, was converted to the sodium salt **4** by adding a 0.1 N sodium hydroxide solution to a solution of **1** in absolute ethanol, to the pink coloration of phenolphtalein. The solution was concentrated to a white residue, which was dried over phosphorus pentoxide.

The dried sodium salt was treated with a stoichiometric amount of oxalyl chloride in dry toluene[18]. After filtration of the precipitated solid, the filtrate was concentrated yielding **5** as a white semisolid, which was used without further purification.

Compound **5** was then treated with an excess of NH_3 at 0°C: after the workup, the residue was purified by column chromatography to give **6**. The transformation of the amide group to amine was carried out by Hofmann reaction, which occurs with complete retention of the configuration at the stereogenic centre C1[14].

A solution of sodium hypobromite was added to amide **6**: after few minutes of warming at 80°C to effect the rearrangement, it was noted the formation of a white solid, wich was identified through its ^{1}H-NMR and MS spectra as isocyanide **7**. It is well known[4] infact that in the Hofmann reactions isocyanides are involved as intermediates, that easily decompose by warming in a basic aqueous solution yielding amine and CO_2.

On the contrary, compound **7** needed to be warmed at 80°C for a few hours in a NaOH solution in order to obtain the complete disappearence of the solid. After the work up of the reaction mixture, aminoalcohol **2** was obtained in 52 % yield.

Reaction of compound **2** with an equimolar amount of 4-chlorobenzoyl chloride and triethylamine in chloroform (24 hours at room temperature) yielded the derivative **3** as a white solid in 58% yield. The derivative **3**, not described in literature, was purified by thin-layer chromatography and by crystallization from CCl_4; structural assignments were carried out by ^{1}H-NMR spectroscopy and MS.

The U.V. spectrum of **3** (Figure 1) exhibits an absorption band between 200 and 300 nm, centered at 235 nm with an ε_{max}=12900 assignable, on the basis of the previous discussion, to the *para*-chlorobenzamide chromophore. In the corrisponding region, the C.D. spectrum (Figure 1) of **3** shows a negative Cotton effect with $\Delta\varepsilon$= -4,9; this effect may be attributable to the exciton coupling between the benzoate transition and the $^1A_{1g} \rightarrow {}^1E_u$ transition of the phenyl chromophore at C2.

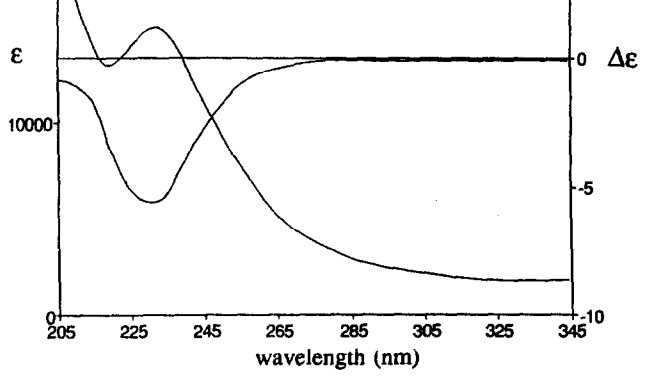


Figure 1. U.V. and C.D. spectra of N-*cis*-(2-phenyl-2-hydroxycyclohexyl)-4-chlorobenzamide **3**.

In order to carry out a spectrum-structure relationship, we assumed a *R,R* absolute configuration for the two strereogenic centers C1 and C2 of **3**. Assuming also that the cyclohexane ring adopt the more stable chair conformation with the bulkyest substituents (phenyl and the benzamide groups) both equatorial, then the relative position of the two chromophore can be reasonably described by the Newman projection in chart 2.

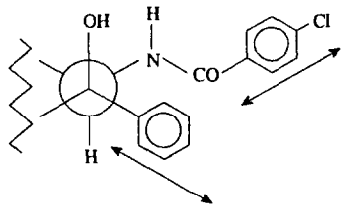


chart 2

The transoid disposition of H-C-N-H fragment is indicated in the ^{1}H-NMR analysis by the high value of the vicinal coupling constant[19] H-C1-N-H (~12 Hz) which corrisponds to a diedral angle of about 180°.

Thus, since the phenyl group can rapidly rotate around the C2-phenyl bond (as determined by the analysis of ^{13}C-NMR relaxation times), the only possible exciton coupling is that between the long axis transition of the phenyl group and the transition at 230 nm of the *para*-chlorobenzamide chromophore. The two transition moments constitute a negative exciton chirality which agree with the negative sign of the observed C.D. Cotton effect at 230 nm. Therefore the absolute configuration at the two stereogenic centers of derivative **3** is *R,R*: this configuration can be correlated to that of the (+) enantiomer of cicloxilic acid **1**, from which the derivative **3** was obtained[20] and the 1*R*, 2*S* configuration has to be assigned to the (+)-cicloxilic acid.

To confirm the above assignment a X -ray crystallographic analysis of the derivative **3** was performed. The asymmetric unit present in the structure of **3** consists of two molecules showing a slightly different conformation. The Figure 2 displays the two molecules, labelled as A and B, with the numbering of the atoms. The geometrical parameters are listed in Table 1.

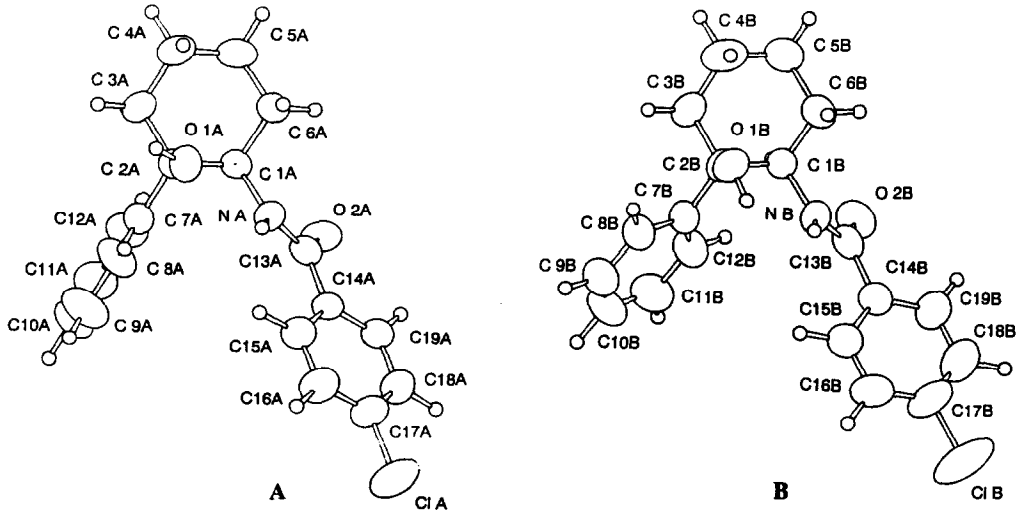


Figure 2. ORTEP view of the molecular structure of N-*cis*-(2-phenyl-2-hydroxycyclohexyl)-4-chlorobenzamide with atom numbering. The thermal ellipsoids are represented at 50% probability.

Table 1. Relevant structural parameters in N-*cis*-(+)-(2-phenyl-2-hydroxycyclohexyl)4-chlorobenzamide. Distances are in Å, angles in degrees. E's.d. are given in parentheses.

C 1A - C 2A	1.528(5)	C 1B - C 2B	1.533(5)
C 1A - C 6A	1.542(5)	C 1B - C 6B	1.529(6)
C 1A - N A	1.462(5)	C 1B - N B	1.458(5)
C 2A - C 3A	1.544(5)	C 2B - C 3B	1.535(6)
C 2A - O 1A	1.445(4)	C 2B - O 1B	1.438(4)
C 2A - C 7A	1.510(5)	C 2B - C 7B	1.524(5)
C 3A - C 4A	1.536(6)	C 3B - C 4B	1.536(7)
C 4A - C 5A	1.498(6)	C 4B - C 5B	1.501(8)
C 5A - C 6A	1.523(6)	C 5B - C 6B	1.544(7)
C 7A - C 8A	1.378(6)	C 7B - C 8B	1.385(6)
C 7A - C12A	1.392(6)	C 7B - C12B	1.390(6)
C 8A - C 9A	1.384(7)	C 8B - C 9B	1.381(7)
C 9A - C10A	1.372(10)	C 9B - C10B	1.344(8)
C10A - C11A	1.390(8)	C10B - C11B	1.382(8)
C11A - C12A	1.386(7)	C11B - C12B	1.393(7)
N A - C13A	1.321(5)	N B - C13B	1.331(5)
C13A - O 2A	1.235(4)	C13B - O 2B	1.245(5)
C13A - C14A	1.487(5)	C13B - C14B	1.491(5)
C14A - C15A	1.384(5)	C14B - C15B	1.385(6)
C14A - C19A	1.389(5)	C14B - C19B	1.387(6)
C15A - C16A	1.376(6)	C15B - C16B	1.384(6)
C16A - C17A	1.367(6)	C16B - C17B	1.379(8)
C17A - C18A	1.371(6)	C17B - C18B	1.346(8)
C17A - Cl A	1.744(4)	C17B - Cl B	1.728(6)
C18A - C19A	1.379(6)	C18B - C19B	1.382(8)

C 6A- C 1A- N A	110.1(3)	C 6B- C 1B- N B	110.5(3)
C 2A- C 1A- N A	107.9(3)	C 2B- C 1B- N B	111.7(3)
C 2A- C 1A- C 6A	113.6(3)	C 2B- C 1B- C 6B	111.7(3)
C 1A- C 2A- C 7A	110.4(3)	C 1B- C 2B- C 7B	113.9(3)
C 1A- C 2A- O 1A	103.9(3)	C 1B- C 2B- O 1B	109.9(3)
C 1A- C 2A- C 3A	110.1(3)	C 1B- C 2B- C 3B	108.4(3)
O 1A- C 2A- C 7A	111.1(3)	O 1B- C 2B- C 7B	109.6(3)
C 3A- C 2A- C 7A	111.1(3)	C 3B- C 2B- C 7B	109.0(3)
C 3A- C 2A- O 1A	110.0(3)	C 3B- C 2B- O 1B	105.7(3)
C 2A- C 3A- C 4A	112.9(3)	C 2B- C 3B- C 4B	111.5(4)
C 3A- C 4A- C 5A	111.2(4)	C 3B- C 4B- C 5B	112.3(4)
C 4A- C 5A- C 6A	112.0(4)	C 4B- C 5B- C 6B	110.7(4)
C 1A- C 6A- C 5A	110.1(3)	C 1B- C 6B- C 5B	110.2(4)
C 2A- C 7A- C12A	120.5(4)	C 2B- C 7B- C12B	124.0(3)
C 2A- C 7A- C 8A	121.4(4)	C 2B- C 7B- C 8B	118.3(4)
C 8A- C 7A- C12A	118.2(4)	C 8B- C 7B- C12B	117.7(4)
C 7A- C 8A- C 9A	120.8(5)	C 7B- C 8B- C 9B	121.5(4)
C 8A- C 9A- C10A	121.3(6)	C 8B- C 9B- C10B	120.8(5)
C 9A- C10A- C11A	118.5(5)	C 9B- C10B- C11B	119.5(5)
C10A- C11A- C12A	120.4(6)	C10B- C11B- C12B	120.6(5)
C 7A- C12A- C11A	120.9(4)	C 7B- C12B- C11B	120.1(4)
C 1A- N A - C13A	125.6(3)	C 1B- N B - C13B	123.8(3)
N A - C13A- C14A	118.0(3)	N B - C13B- C14B	115.9(3)
N A - C13A- O 2A	121.2(3)	N B - C13B- O 2B	123.0(4)
O 2A- C13A- C14A	120.7(3)	O 2B- C13B- C14B	121.1(3)
C13A- C14A- C19A	118.3(3)	C13B- C14B- C19B	120.1(4)
C13A- C14A- C15A	123.4(3)	C13B- C14B- C15B	121.8(4)
C15A- C14A- C19A	118.2(3)	C15B- C14B- C19B	118.1(4)
C14A- C15A- C16A	121.3(4)	C14B- C15B- C16B	121.1(4)
C15A- C16A- C17A	118.9(4)	C15B- C16B- C17B	118.6(5)
C16A- C17A- Cl A	118.6(4)	C16B- C17B- Cl B	117.8(5)
C16A- C17A- C18A	121.6(4)	C16B- C17B- C18B	121.5(5)
C18A- C17A- Cl A	119.8(3)	C18B- C17B- Cl B	120.8(5)
C17A- C18A- C19A	119.1(4)	C17B- C18B- C19B	119.8(5)
C14A- C19A- C18A	120.9(4)	C14B- C19B- C18B	120.8(5)

Both the molecules contain a chair conformed cyclohexane bearing the two bulkyest substituents in equatorial positions on C1 and C2 atoms, the hydroxyl group lying on C2 atom in axial position. The main differences among the molecules A and B are outlined in the Table 2, listing the angles between the more relevant molecular planes. Markedly different are the torsion angles O1-C2-C7-C8 and O2-C13-C14-C19, 6.7(5)° and 17.9(5)° in the molecule A and 38.1(5)° and 43.0(6)° in the molecule B respectively.

Table 2. Main molecular planes in **3**. Distances in Å from the plane are given in parentheses, the angles between the planes are listed on the right.

plane	atoms defining the plane	angles between the planes		
		2	3	4
1	C 1A(.010), C 2A(−.011), C 4A(.018), C 5A(−.021)	72.5(2)	31.5(2)	45.6(2)
2	C 7A(−.003), C 8A(.002), C 9A(−.002), C10A(.004), C11A(−.007), C12A(.007)		76.7(1)	65.5(2)
3	C14A(.005), C15A(−.007), C16A(−.003), C17A(.013), C18A(−.010), C19A(.000)			18.9(1)
4	N A(−.001), C13A(.005), O 2A(−.001), C14A(−.002)			
		6	7	8
5	C 1B(−.007), C 2B(.007), C 4B(−.019), C 5B(.017)	43.4(2)	62.3(1)	48.8(2)
6	C 7B(−.001), C 8B(.003), C 9B(−.003), C10B(−.001), C11B(.004), C12B(−.001)		73.1(1)	70.2(1)
7	C14B(.013), C15B(−.005), C16B(−.013), C17B(.021), C18B(−.002), C19B(−.019)			42.8(2)
8	N B(.000), C13B(−.001), O 2B(.000), C14B(.001)			

The molecules of **3** are held together in the structure through an extended hydrogen-bond system, involving the two oxygen atoms O1 and O2 and the nitrogen. The Figure 3 shows a projection of the crystal structure down *a* axis.

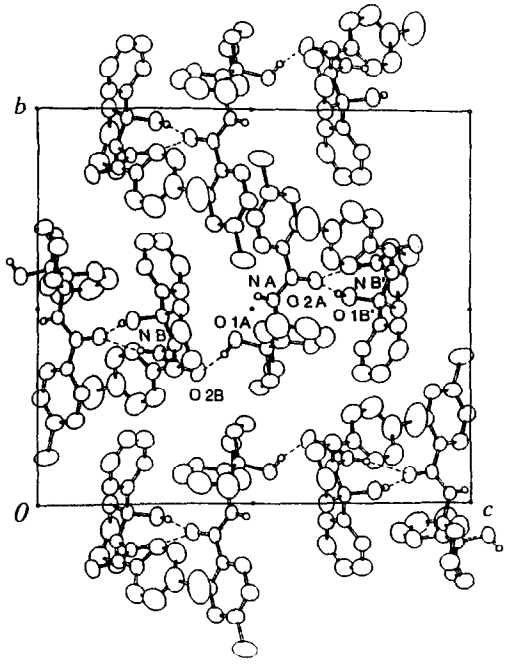


Figure 3. View of the crystal packing of N-*cis*-(2-phenyl-2-hydroxycyclohexyl)-4-chlorobenzamide down the *a* axis direction. The dashed lines represent the strongest hydrogen interactions: O2B···H OA 1.93(5) Å; O2B···O1A 2.764(4) Å; O2B···HOA-O1A 157(4)°; O2A···H OB' 1.91(5) Å; O2A···O' 2.785(4) Å; O2A···H OB'-O1B' 169(6)°; O2A···H NB' 2.04(3) Å; O2A···NB' 2.882(4) Å; O2A···H NB'-NB' 169(3)°; where '=1/2-*x*, 1-*y*, 1/2+*z*.

The molecules A and B are connected end-on to make sequences A···B···A···B···, that are infinity repeated by the screw operator parallel to the *c* axis. It is interesting to note that the hydrogen atoms connected to the oxygen and nitrogen atoms have been located on the difference Fourier map and their positions have been refined in the last least-squares cycles.

So the compound **3**, obtained from cicloxilic acid in a stereospecific manner, resulted a suitable compound for the absolute configuration assignment of the parent compound by C.D. spectroscopy. Applying the Nakanishi rule for the observed C.D. and taking into account the formal inversion of configuration at C2 due to introduction of the nitrogen atom of the amide, the 1*R*, 2*S* configuration is assigned to the starting sample of the acid showing a positive sign of the optical rotation at 589 nm. Once again the reliability of the C.D. method, even if applied to the coupling of two transition of different chromophore (phenyl and *para*-chlorobenzamide), has been demonstrated by carrying out a X-ray crystallographic analysis on the same derivative.

EXPERIMENTAL

Melting points are uncorrected. Proton magnetic resonance were measured at 200 MHz with a Varian Gemini 200 spectrometer. Signal positions are reported in ppm downfield from tetramethylsilane (δ scale) as an internal standard, and $CDCl_3$ as solvent; the number of protons, multiplicity and proton assignments are indicated in parentheses. Mass measurement were performed on a Double Focusing VG-70E instrument. EI spectra were taken with an electron energy of 70 eV by direct inlet of the sample in the source. FAB measurements were performed with an acceleration potential of 8 kV for the gun and using glycerol as matrix. Optical rotations were measured with a Perkin-Elmer Model 241 Polarimeter. Analytical GLC was performed on a Carlo Erba Mega Gas-Chromatograph. The enantiomeric excess (e.e.) was performed by chiral GLC methods using a Megadex 2 column (trimethyl β-cyclodextrin) at 150°C (He flow: 1.5 ml/min, split 1:100).

Cis-(-)-2-hydroxy-2-phenyl-cyclohexanecarboxylic acid **1**. A solution of 20.0 g (67.9 mmol) of (-)-cinchonidine in EtOH (235 mL) at 50°C was added to a stirred solution of 14.9 g (67.9 mmol) of cicloxilic acid, synthesized as reported in [16], in EtOH (235 mL) at 50°C. The resulting solution was allowed to cool to room temperature and to stand overnight, to provide a colorless precipitate. The product was filtered, by suction, redissolved in EtOH (400 mL) and allowed to crystallize at room temperature. Further recrystallization of this material did not change the optical rotation. The (-)-cinchonidine salt was filtered and dried in vacuo at 50°C to give 13.3 g of a white solid: m.p.248-250°; $[\alpha]_D$ -75.0 (C=0.5, EtOH). A solution of 13.3 g of this salt in water (100 mL) was added to EtOAc (80 mL) and the mixture acidified (pH 2), by dropwise addition of 10% aqueous sulphuric acid with stirring. The two layers were separated, the aqueous phase was extracted with EtOAc (30 mL) and the organic phases combined , washed with brine, dried over Na_2SO_4 , and concentrated at reduced pressure to give 55 g (74%) of *cis*-(-)-2-hydroxy-2-phenylcyclohexanecarboxylic acid as white crystals. m.p. 135-137°; $[\alpha]_D$ -12.7 (C=1; 0.5 N NaOH); chiral GLC analysis of the methyl ester (a sample was prepared by esterifying the acid with CH_2N_2) showed an e.e.=98%. ^{1}H-NMR δ: 7.55-7.10 (m, 5H, phenyl); 3.05 (dd, 1H, C1H); 2.15-1.75 (m, 5H, cyclohexane); 1.75-1.2 (m, 3H, cyclohexane). ^{13}C-NMR δ: 21.25 (C4); 24.95 (C5); 26.15 (C6); 40.05 (C3); 49.95 (C1); 73.21 (C2); 124.40 (C9, C11);

127.10 (C10); 128.26 (C8, C12); 147.45 (C7); 181.00 (C13). (Found: C, 70.95; H, 7.51. $C_{13}H_{16}O_3$ requires: C, 70.89; H, 7.32%.)

Cis-(+)-2-hydroxy-2-phenylcyclohexanecarboxylic acid **1**. Recovering of crude *cis*-(+)-**1** from the mother and crystallization liquors coming from the resolution of (-)-isomer, afforded a product with an [α]20 +7 (C=1; 0.5 N NaOH). A stirred solution of 8.0 g (36.4 mmol) of the crude (+)-isomer in 95% EtOH (35 mL) was added to 11.8 g (36.4 mmol) of (+)-quinine and heated at 50°C to obtain a clear solution. After cooling, the solution was seeded with previously prepared crystals of the wanted diastereoisomeric salt, and allowed to stand at room temperature for 3 hours, to provide a white solid. The product was collected and recrystallized three times from 95% EtOH (50; 30; 30 mL) to give 6.5 g of *cis*-(+)-2-hydroxy-2-phenylcyclohexanecarboxylic quinine salt, as a white solid. A suspension of this salt in 1N HCl (15 mL) and diethyl ether (30 mL) was stirred at room temperature; the two layers were separated, the organic phase was washed with water (5 mL) dried over Na_2SO_4 and evaporated to give 2.1g of the title compound as white crystals. m.p.135-137°C; $[\alpha]_D$ +12.88 (C=1; 0.5 N NaOH). Chiral GLC analysis of the methyl ester showed an e.e.=98%.

Cis-2-hydroxy-2-phenylcyclohexanecarboxyamide **6**. 114 mL of a 0.1 N NaOH solution were slowly added to a solution of 2.5 g (0.0114 mol) of ciclossilic acid **1** in 50 mL of absolute ethanol up to the pink coloration of phenolphtalein; it was then added a trace of acid to just cause the disappearence of the pink colour. The solution was concentrated in vacuo to a white residue which was dried on phosphorus pentoxide for three days at room temperature. 0.87 mL (0.0102 mol) of oxalyl chloride were then added under nitrogen to the grounded sodium salt **4** in 50 mL of dry toluene. The heterogeneous reaction mixture was stirred for five hours and after that it was filtered and concentrated in vacuo, yielding a white solid that was used without further purification. 30 mL of 25% aqueous ammonia were added to that residue at 0°C; the solution got a pink colour and the solid dissolved after about 30 minutes. After stirring for one night, the mixture was diluted with 50 mL of water and then extracted with diethyl ether. The organic phase dried over Na_2SO_4 was concentrated at reduced pressure, yielding a residue which was purified by chromatography (SiO_2; $CHCl_3$ as eluent) ; two fractions were obtained, the second of which containing 0,240 g of amide **6** as a white solid (10% yield with respect to **1**). m.p. 185-186°. ^{1}H-NMR δ: 7.6-7.1 (m, 5 H, phenyl); 5.5 and 5.8 (ds, 2 H, NH_2); 5,2 (bs, 1H, OH); 2.7-2.5 (m, 1H, C1-H); 2.1-1.1 (complex signal, 8 H, cyclohexane). EIMS (70 eV, direct inlet) m/z (rel. int.): 219 [M^+] (15), 202 (30), 174 (13), 158 (36), 129 (30), 105 (95), 91 (30), 77 (40), 55 (25), 43 (100). (Found: C, 71.36; H, 7.87; N, 6.43. $C_{13}H_{17}NO_2$ requires: C, 71.21; H, 7.81; N, 6.39%.)

Cis-2-amino-1-phenylcyclohexanol **2**. 0.2 g (0.91 mmol) of amide **6** and 5 mL of water were added to 2 mL of a sodium hypobromite solution, obtained by slowly adding 0.28 mL .0,054 mol) of bromine to a solution of 1.09 g (0.0272 mol) of NaOH in 10 mL of water, at 0°C. The mixture was stirred at room temperature for one hour and then at 80 °C for 30 minutes. After cooling to room temperature, the residue was filtered , dried in vacuo and characterized by ^{1}H-NMR and MS as compound **7**. This solid ,suspended in a solution of 0.22 g of NaOH in 5 mL of water, was warmed at 80°C for seven hours. After cooling again, the aqueous layer was extracted with ether and then the organic layers were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (SiO_2; $CHCl_3$ as eluent), obtaining 0.090 g

(52%) of **2** as a white solid. m.p. 74-76°. ^{1}H-NMR δ: 7.6-7.1 (m, 5 H, phenyl); 3.2 (dd, 1 H, C2-H); 2.7 (bs, 3 H exchangeable, NH_2 and OH); 2-1.3 (complex signal, 8 H, cyclohexane). EIMS (70 eV, direct inlet) m/z (rel. int.): 191 [M^+] (70); 174 (19), 157 (10), 146 (20), 133 (32), 120 (30), 105 (85), 86 (53), 77 (84), 69 (95), 56 (100), 43 (85). (Found: C, 75.56; H, 8.87; N, 7.35. $C_{12}H_{17}NO$ requires: C, 75.35; H, 8.96; N, 7.32%.)

N-cis-(2-phenyl-2-hydroxycyclohexyl)4-chlorobenzamide **3**. 14.6 μL (0.105 mmol) of triethylamine and 13.3 μL (0.0105 mmol) of 4-chlorobenzoyl chloride were added to 0,02 g (0.0105 mmol) of **2** in 3 mL of $CHCl_3$. The mixture was stirred at room temperature for 24 hours , then it was diluted with $CHCl_3$ and washed with a 10% aqueous solution of $NaHCO_3$ and then with water. The dried organic layer was evaporated and the residue was purified by preparative TLC (SiO_2; $CHCl_3$ as eluent), obtaining 0.02 g (58%) of derivative **3** as a white solid, which was crystallized from CCl_4. m.p. 173-174°. ^{1}H-NMR δ: 7.6-7.1 (m, 9 H, phenyl); 6.5-6.3 (d, 1 H, NH); 4.4 (m, 1 H, C1-H); 4 (m, 1 H, C6-H); 2.5 (s, 1 H, OH); 2-1 (complex signal, 8 H, cyclohexane). FAB MS m/z : 330 M + 1. (Found: C, 69.62; H, 5.94; N, 4.31; Cl, 10.91. $C_{19}H_{19}NO_2Cl$ requires: C, 69.40; H, 5.82; N, 4.26; Cl, 10.78%.)

X-ray crystallography of derivative **3**. Colourless prismatic crystals of N-*cis*-(2-phenyl-2-hydroxycyclohexyl)4-chlorobenzamide, obtained from a CCl_4 solution, were glued at the end of glass fibers and studied through Weissenberg diffraction patterns. The crystal producing the sharpest spots on the film was used for the following intensity data collection, which was performed through a single-crystal four-circle diffractometer by using the experimental conditions summarized in Table 3.

The periodic rescan of the reflections 0 4 0 and 2 0 5, used as a standard, allowed to exclude any measurable decay of the specimen. After correction of the collected data for Lorentz and polarization effects, the intensities of equivalent reflections were merged, obtaining a total of 3620 intensity data. The absorption correction was applied lately by using the method of Walker and Stuart[21].

The positions of the main part of non-hydrogen atoms were determined by the direct phasing method included in the TREF routine of SHELX 86 program[22] and the atom search was completed by standard Fourier synthesis contained in SHELX 76 program[23]. The atomic positions were refined by full-matrix least-squares methods. The positional parameters of hydrogen atoms could in part be determined on the difference Fourier map and in par calculated by imposing an ideal geometry. Their thermal parameters has been let to vary in the refinement. In the final cycles the non-hydrogen atoms were refined with anisotropic thermal parameters. The final reliability factor *R* was 0.044, refining 467 parameters on 3620 observed independent reflections.

At the end of the refinement the positional parameters of all the atoms have been inverted with respect to the origin, obtaining the enantiomeric structure. This one, refined with the same number of parameters, gave $R = 0.054$, indicating that the previous one was the correct configuration of the compound in study.

Atomic scattering factors and anomalous scattering coefficients were taken from the literature[24], ORTEP II[25] and PARST[26] programs were also used. The calculations were carried out on a computer IBM 3081 of the 'Centro Nazionale Universitario di Calcolo Elettronico, C.N.U.C.E.' (Pisa). The final atomic coordinates with anisotropic thermal parameters have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Rd., Cambridge, CB2 1EW, UK.

Table 3. Experimental data for the crystallographic analysis of N-*cis*-(+)-(2-phenyl-2-hydroxycyclohexyl)4-chlorobenzamide.

Formula		$C_{19}H_{20}ClNO_2$
Molecular weight		329.83
Space group		$P2_12_12_1$
a/Å		9.920(2)
b/Å		17.988(3)
c/Å		19.761(4)
U/Å^3		3526(1)
Z		8
d_{calc}/Mg m^{-3}		1.243
Reflections for Lattice parameters	number	24
	θ range / °	12.0 + 14.5
Radiation		CuK_α
λ /Å		1.54178
F(000)		1392
T/K		296
Crystal size/mm		0.28×0.40×0.55
Diffractometer		Philips PW1100
μ /mm^{-1}		1.99
Absorption corrections (min., max.)		0.86, 1.18
Scan speed/ °s^{-1}		0.025
Scan width/ °		1.2
θ-range/ °		3.3 + 55.0
h-range		−10 + 10
k-range		0 + 18
l-range		0 + 20
Standard reflections		0 4 0 + 2 0 5
Scan mode		θ/2θ
Condition for observed reflections		$I>2\sigma(I)$
No. of unique measured reflections		3620
No. of reflections used in the refinement		3620
Anisotropic least-squares on *F*		full-matrix
Max. least-squares shift-to-error ratio		0.052
Min.,Max. height in final Fourier map, ρ /e Å^{-3}		−0.48, 0.30
No. of refined parameters		467
$R=\Sigma\lvert\Delta F\rvert/\Sigma\lvert F_o\rvert$		0.044
$R'=[\Sigma w(\Delta F)^2/\Sigma wF_o^2]^{1/2}$		0.065
$S=[\Sigma w(\Delta F)^2/(N-P)]^{1/2}$ [a]		0.603
k, g ($w=k/[s^2(F_o)+gF_o^2]$)		1.0, 9.91×10^{-3}

[a] *P* = number of parameters, *N* = number of observations.

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