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The diastereoisomers 2-[(*S*/*R*)-2-chloro-3-quinolyl]-2-[(*R*)-1-(4-methoxyphenyl)ethylamino]acetonitrile at 100 K

Souheila Ladraa,[a] Abdelmalek Bouraiou,[a] Sofiane Bouacida,[b]* Thierry Roisnel[c] and Ali Belfaitah[a]

[a]Laboratoire des Produits Naturels d'Origine Végétale et de Synthèse Organique, PHYSYNOR, Université Mentouri-Constantine, 25000 Constantine, Algeria, [b]Unité de Recherche de Chimie de l'Environnement et Moléculaire Structurale, CHEMS, Université Mentouri-Constantine, 25000 Constantine, Algeria, and [c]Centre de Diffractométrie X, UMR 6226 CNRS Unité Sciences Chimiques de Rennes, Université de Rennes I, 263 Avenue du Général Leclerc, 35042 Rennes, France
Correspondence e-mail: bouacida_sofiane@yahoo.fr

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In the structures of the two enantiopure diastereoisomers of the title compound, $C_{20}H_{18}ClN_3O$, which crystallize in different space groups, the molecules are very similar as far as bond distances and angles are concerned, but more substantial differences are observed in some torsion angles. The crystal structures of both molecules can be described as zigzag layers along the *c* axis. The packing is stabilized by hydrogen-bond interactions of N—H···O, C—H···Cl and C—H···π types for 2-[(*R*)-2-chloro-3-quinolyl]-2-[(*R*)-1-(4-methoxyphenyl)ethylamino]acetonitrile, and of N—H···N, C—H···O and C—H···π types for 2-[(*S*)-2-chloro-3-quinolyl]-2-[(*R*)-1-(4-methoxyphenyl)ethylamino]acetonitrile, resulting in the formation of two- and three-dimensional networks.

Comment

Quinolines and their annulated derivatives are important compounds due to their presence in numerous natural products, along with their wide-ranging applications as drugs, pharmaceuticals and agrochemicals (Jones, 1996; Jackson & Meth-Cohn, 1995; Kansagra *et al.*, 2000). Amino acid derivatives are broadly useful chiral building blocks, with especially important applications in complex natural-product and combinatorial syntheses (Burk *et al.*, 1998; Williams, 1989). In recent years, we have developed a programme devoted to the synthesis and biological evaluation of quinolyl derivatives (Benzerka *et al.*, 2008; Bouraiou *et al.*, 2007, 2008). In previous work, we have reported the synthesis and stereostructure determination of 2-[(*S*)-2-chloro-3-quinolyl]-2-[(*S*)-α-methylbenzylamino]acetonitrile (Belfaitah *et al.*, 2006). We report here the synthesis and structure determinations of two diastereoisomers of the title compound at 100 K.

The Strecker reaction is one of the oldest and best known routes to racemic amino acids (Shuichi *et al.*, 2004; Boesten *et al.*, 2001). The use of optically active α-methylbenzylamine-derived aldimines has a significant role in the diastereoselective Strecker synthesis (Bhanu-Prasad *et al.*, 2004). The title diastereoisomers were synthesized from (*R*,*E*)-*N*-[(2-chloro-3-quinolyl)methylene]-1-(4-methoxyphenyl)ethanamine in the presence of *tert*-$BuMe_2SiCN$. A 45:55 ratio of the (*R*,*R*) and (*S*,*R*) diastereoisomers was observed by NMR spectroscopy. Since separation of the isomers by standard chromatographic methods failed, an attempt was made to crystallize the mixture directly by fractional crystallization from a CH_2Cl_2–petroleum ether (1:9) solution at 298 K.

Initially, microsphere crystals were obtained from the first crystallization and these were separated by hand, while after several recrystallizations good crystals were obtained in the form of long thin needles. The material of these needles was shown by NMR spectroscopy to be the minor component of the mixture. The different crystals obtained were analysed by single-crystal diffractometry, and it was be found that the long needles represent the (*R*,*R*) diastereoisomer, (I) (Fig. 1), while the microsphere crystals correspond to the (*S*,*R*) diastereoisomer, (II) (Fig. 2). Diastereoisomers (I) and (II) crystallize in different crystal systems, both in noncentrosymmetric space groups ($P2_12_12_1$ and $P2_1$). The structures were further elucidated by detailed NMR studies (see *Experimental*). It is clear that the difference between the isomers is the disposition of

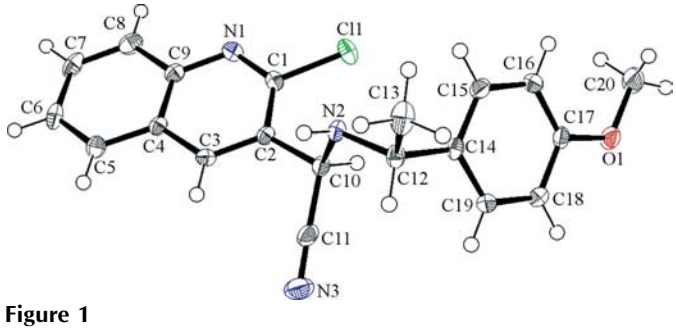

Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

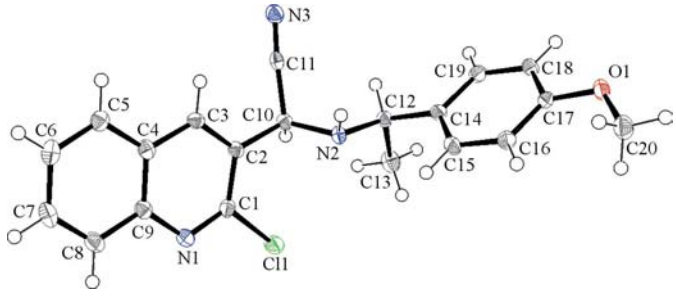

Figure 2
The molecular structure of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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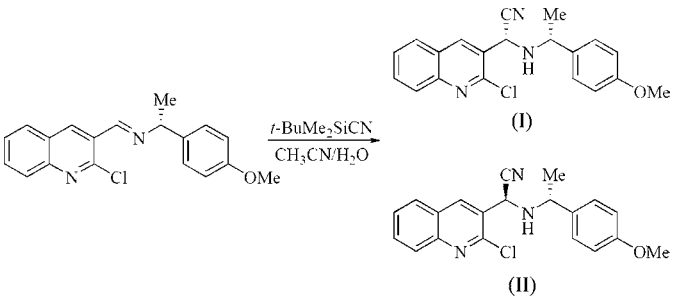
the H atom at the stereogenic centre at C10, which is confirmed by the torsion angles (Table 1).



Chemically equivalent bond distances in diastereoisomers (I) and (II) do not differ by more than 2 s.u.'s from their mean values, while equivalent angles in some cases reach this limit. The largest difference is seen for N2—C10—C2 [109.65 (12) and 112.50 (15)° for (I) and (II), respectively]. The differences in the torsion angles are sometimes greater than 90°, in particular around the bonds C12—C14, C10—N2, C10—C2 and N2—C12. The maximum difference of 93.4° is seen for the torsion angle C14—C12—N2—C10 [63.88 (17) and 158.18 (14)° for (I) and (II), respectively] (Table 1). The planar quinolyl unit are planar and form dihedral angles of 0.78 (5) and 1.65 (4)° for (I) and (II), respectively; this unit forms dihedral angles of 81.68 (5) and 53.51 (4)° with the plane of the benzene ring for (I) and (II), respectively.

In the packing of (I), a weak classical intermolecular N—H···O hydrogen bond (*PLATON*; Spek, 2009) creates extended chains which run parallel to the [001] direction, and C—H···Cl interactions link these chains together to form an undulating two-dimensional network which lies parallel to the (010) plane. An interlayer C—H···π interaction involving the C4–C9 benzene ring of the quinoline group (ring centroid *Cg*1) helps to stabilize the layers (Table 2 and Fig. 3).

In the packing of (II), an intermolecular C—H···O interaction forms zigzag chains along the [011] and [0$\bar{1}$1] directions (Fig. 4*a*). Intermolecular N—H···N and C—H···π(C14–C19) (ring centroid *Cg*2) interactions involving the same pair of donor and acceptor molecules connect these chains together, resulting in the formation of a two-dimensional network parallel to the (100) plane and reinforcing the cohesion of the structure (Table 3 and Fig. 4*b*).

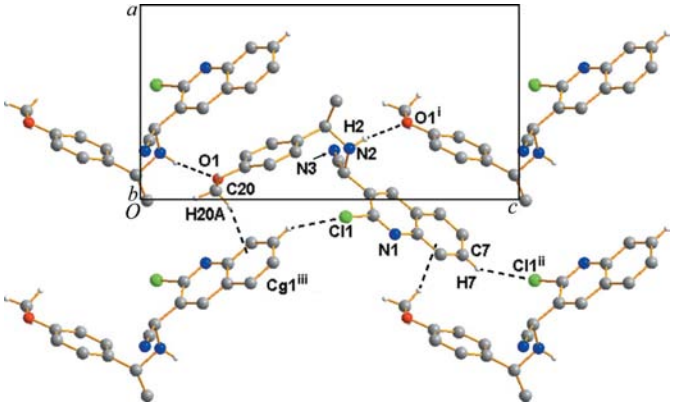


Figure 3
Part of the crystal packing of (I), showing classical hydrogen bonds and other interactions as dashed lines in the layers. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $-x+\frac{1}{2}, -y+1, z+\frac{1}{2}$; (ii) $-x-\frac{1}{2}, -y+1, z+\frac{1}{2}$; (iii) $-x-\frac{1}{2}, -y+1, z-\frac{1}{2}$.]

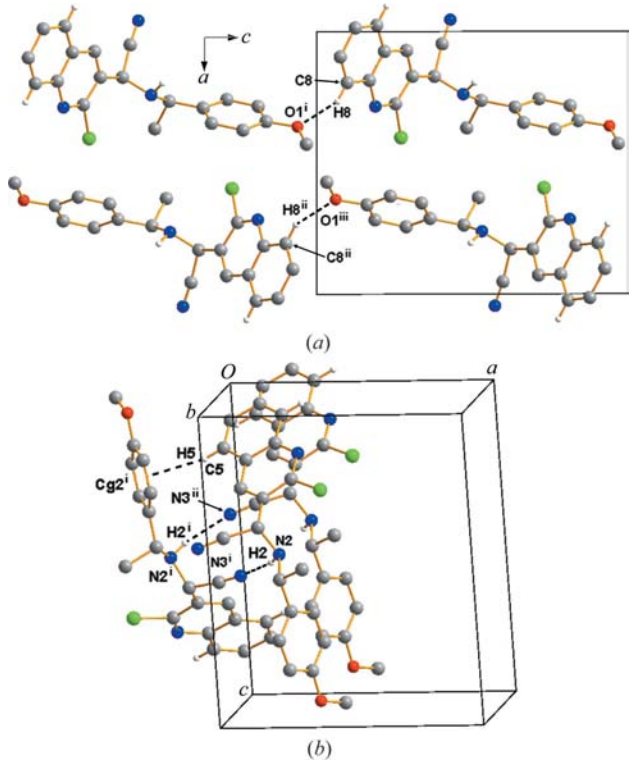


Figure 4
(*a*) Chains of C—H···O interactions (dashed lines) in the crystal packing of (II). [Symmetry codes: (i) $x, y-1, -1+z$; (ii) $1-x, \frac{1}{2}+y, -z$; (iii) $1-x, -\frac{1}{2}+y, 1-z$.] (*b*) Part of the crystal packing of (II), showing the N—H···N and C—H···π interactions (dashed lines) between chains. H atoms not involved in hydrogen bonding have been omitted for clarity. [Symmetry codes: (i) $-x, -\frac{1}{2}+y, 1-z$; (ii) $x, -1+y, z$.]

Experimental

Reaction of (*R*,*E*)-*N*-[(2-chloro-3-quinolyl)methylene]-1-(4-methoxyphenyl)ethanamine (1.0 g, 3.08 mmol), *tert*-butyldimethylsilyl cyanide (0.367 mg, 1.2 equivalents, 3.69 mmol) and a few drops of water in acetonitrile gave the title compound in a mixture of (*R*,*R*), (I), an (*S*,*R*), (II), diastereoisomers in a 45:55 ratio as a yellow solid in 91% yield. IR (KBr, ν, cm^{-1}): 2212 (CN). Crystals of each diastereoisomer were obtained by fractional crystallization from a CH_2Cl_2–petroleum ether (1:9 *v*/*v*) solution of the mixture.

Analysis for (I): white crystals, m.p. 421 K; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.43 (*s*, 1H, H_4, quinolyl), 8.04 (*dd*, J = 8.4 and 1.1 Hz, 1H, H_8, quinolyl), 7.88 (*dd*, J = 8.1 and 1.0 Hz, 1H, H_5, quinolyl), 7.80 (*ddd*, J = 8.1, 7.0 and 1.0 Hz, 1H, H_7, quinolyl), 7.63 (*ddd*, J = 8.1, 7.0 and 1.0 Hz, 1H, H_6, quinolyl), 7.43 (*dd*, J = 6.6 and 2.0 Hz, 2H, H_{arom}), 6.95 (*dd*, J = 6.6 and 2.0 Hz, 2H, H_{arom}), 4.78 (*br*, 1H, Hα), 4.25 (*q*, J = 6.5 Hz, 1H, Hα'), 3.85 (*s*, 3H, OCH_3), 1.86 (*br*, 1H, NH), 1.47 (*d*, J = 6.5 Hz, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.4 (C), 148.9 (C), 147.4 (C), 137.8 (CH), 133.7 (C), 131.4 (CH), 128.4 (2 × CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 127.2 (C), 126.7 (C), 117.9(CN), 114.0 (2 × CH), 56.5 (OCH_3), 55.2 (CH), 50.1 (CH), 24.5 (CH_3).

Analysis for (II): yellow crystals, m.p. 418 K; ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.27 (*s*, 1H, H_4, quinolyl), 8.05 (*dd*, *J* = 8.7 and 1.0 Hz, 1H, H_8, quinolyl), 7.95–7.75 (*m*, 2H, H7 and H_5, quinolyl), 7.62 (*ddd*, *J* = 8.2, 7.0 and 1.1 Hz, 1H, H_6, quinolyl), 7.25 (*dd*, *J* = 6.6 and 2.0 Hz, 2H, H_{arom}), 6.81 (*dd*, *J* = 6.6 and 2.0 Hz, 2H, H_{arom}), 5.24 (*br*, 1H, Hα), 4.08 (*q*, *J* = 6.4 Hz, 1H, Hα'), 3.74 (*s*, 3H, OCH_3), 2.04 (*br*, 1H, NH), 1.48 (*d*, *J* = 6.4 Hz, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 159.0 (C), 148.9 (C), 147.3 (C), 137.8 (CH), 135.5 (CH), 131.3 (CH), 128.3 (CH), 127.8 (2 × CH), 127.7 (CH), 126.9 (C), 126.6 (C), 117.7 (CN), 114.0 (2 × CH), 55.9 (OCH_3), 55.1 (CH), 49.9 (CH), 22.7 (CH_3).

Compound (I)

Crystal data

$C_{20}H_{18}ClN_3O$
M_r = 351.82
Orthorhombic, $P2_12_12_1$
a = 8.7606 (7) Å
b = 11.8494 (10) Å
c = 17.0002 (12) Å
V = 1764.8 (2) Å^3
Z = 4
Mo *K*α radiation
μ = 0.23 mm^{-1}
T = 100 K
0.59 × 0.50 × 0.37 mm

Data collection

Bruker APEXII diffractometer
15585 measured reflections
4051 independent reflections
3828 reflections with $I > 2\sigma(I)$
R_{int} = 0.048

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.079
S = 1.03
4051 reflections
229 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Absolute structure: Flack (1983), based on 1733 Friedel pairs
Flack parameter: 0.05 (5)

Compound (II)

Crystal data

$C_{20}H_{18}ClN_3O$
M_r = 351.82
Monoclinic, $P2_1$
a = 11.2728 (7) Å
b = 5.7612 (4) Å
c = 13.3573 (9) Å
β = 90.171 (4)°
V = 867.48 (10) Å^3
Z = 2
Mo *K*α radiation
μ = 0.23 mm^{-1}
T = 100 K
0.55 × 0.12 × 0.07 mm

Data collection

Bruker APEXII diffractometer
Absorption correction: multi-scan *SADABS* (Sheldrick, 2002)
T_{min} = 0.837, T_{max} = 0.984
13007 measured reflections
3868 independent reflections
3630 reflections with $I > 2\sigma(I)$
R_{int} = 0.049

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.036
$wR(F^2)$ = 0.087
S = 1.03
3868 reflections
231 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Absolute structure: Flack (1983), based on 1698 Friedel pairs
Flack parameter: 0.03 (5)

Atoms H2N atoms in both structures were located in a difference Fourier map and were refined isotropically. All remaining H atoms were located in difference Fourier maps but introduced in calculated positions, with C—H = 0.93, 0.96 and 0.98 Å for aromatic, methyl and tertiary H atoms, respectively, and refined using a riding model, with U_{iso}(H) = 1.5U_{eq}(C) for methyl H atoms or 1.2U_{eq}(C) otherwise. The absolute configurations of the two isomers presented here are based on the values of the Flack (1983) parameters of 0.05 (5) for (I) and 0.03 (5) for (II).

Table 1
Comparison of selected torsion angles (°) for (I) and (II).

	(I)	(II)
C3—C2—C10—N2	−99.63 (16)	110.05 (19)
C1—C2—C10—N2	77.27 (16)	−72.2 (2)
C3—C2—C10—C11	24.6 (2)	−14.7 (2)
N2—C10—C11—N3	−9 (2)	4 (2)
N2—C12—C14—C15	67.47 (18)	33.7 (2)
C13—C12—C14—C15	−53.51 (18)	−88.0 (2)
N2—C12—C14—C19	−113.54 (15)	−148.59 (16)
C13—C12—C14—C19	125.48 (16)	89.7 (2)
C11—C10—N2—C12	58.65 (17)	−68.00 (18)
C2—C10—N2—C12	−178.10 (12)	166.95 (14)
C14—C12—N2—C10	63.88 (17)	158.18 (14)
C13—C12—N2—C10	−172.08 (13)	−79.75 (18)
C18—C17—O1—C20	178.29 (15)	−175.64 (16)
C16—C17—O1—C20	−1.5 (2)	5.0 (3)
Cl1—C1—C2—C10	3.06 (18)	0.7 (2)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

*Cg*1 is the centroid of the C4–C9 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···O1^{i}	0.85 (2)	2.35 (2)	3.1767 (17)	163 (2)
C7—H7···Cl1^{ii}	0.93	2.73	3.5474 (18)	147
C20—H20*A*···*Cg*1^{iii}	0.96	2.94	3.7513 (13)	143

Symmetry codes: (i) $-x+\frac{1}{2}, -y+1, z+\frac{1}{2}$; (ii) $-x-\frac{1}{2}, -y+1, z+\frac{1}{2}$; (iii) $-x-\frac{1}{2}, -y+1, z-\frac{1}{2}$.

Table 3
Hydrogen-bond geometry (Å, °) for (II).

*Cg*2 is the centroid of the C14–C19 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N2—H2···N3^{i}	0.88 (3)	2.32 (3)	3.176 (2)	166 (2)
C8—H8···O1^{ii}	0.93	2.45	3.245 (2)	144
C5—H5···*Cg*2^{i}	0.93	2.76	3.646 (2)	159

Symmetry codes: (i) $-x, y-\frac{1}{2}, -z+1$; (ii) $x, y-1, z-1$.

For both compounds, data collection: *APEX2* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SIR2002* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *DIAMOND* (Brandenburg & Berndt, 2001); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3121). Services for accessing these data are described at the back of the journal.

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