Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(*R*)-3,5-Bis[(*E*)-benzylidene]-1-(1-phenylethyl)piperidin-4-one, 3,5-bis[(*E*)-4-chlorobenzylidene]-1-[(*R*)-1-phenylethyl]piperidin-4-one and 3,5-bis[(*E*)-2-chlorobenzylidene]-1-[(*R*)-1-phenylethyl]piperidin-4-one

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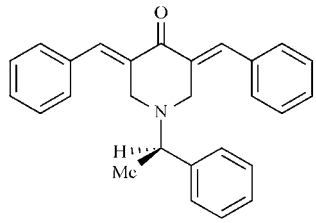
Received 1 March 2007
Accepted 12 March 2007
Online 28 April 2007

Polysubstituted piperidones, *viz*. the title compounds, $C_{27}H_{25}NO$, (I), $C_{27}H_{23}Cl_2NO$, (II), and $C_{27}H_{23}Cl_2NO$, (III), adopt sofa conformations. The molecular packing in (I) and (II) is a result of van der Waals interactions, whereas in (III), a C—H···O interaction is also found.

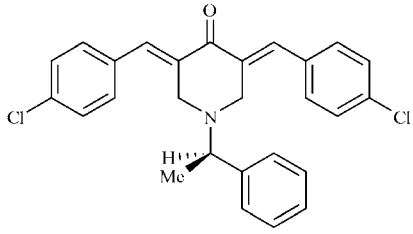
Comment

Piperidine ring systems are of great interest in the pharmaceutical industry as they exhibit a wide range of biological activities (Guengerich *et al.*, 1973; Puder *et al.*, 2000). A number of α,β-unsaturated ketones display cytotoxic and anticancer properties (Dimmock, Elias *et al.*, 1999; Dimmock, Kandepu *et al.*, 1999), and also serve as precursors for various complex heterocycles. (*R*)-1-Phenylethylamine is one of the most promising and less expensive chiral auxiliaries (Juaristi *et al.*, 1999). It is obvious that the design of a specific chiral environment utilizing chiral auxiliaries provides a useful protocol to prepare optically active substances. The three title substituted piperidones, (I)–(III), being enantiomerically pure, have enormous potential in the construction of more complex optically active compounds, and hence the structure determination of these compounds is of paramount importance.

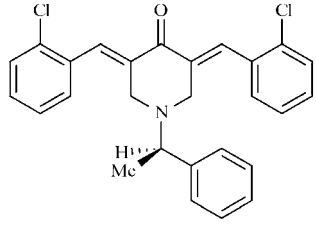
The piperidone rings in (I), (II) and (III) (Figs. 1–3) adopt sofa conformations. Atom N1 deviates from the mean plane passing through atoms C2–C6 by −0.731 (3) Å in (I), −0.774 (5) Å in (II) and −0.705 (4) Å in (III). The differences in the deviations are due to steric factors and the different substituents at the C3 and C5 positions of the piperidone ring. Both olefinic double bonds have an *E* configuration, and the aryl rings are not coplanar with either the adjacent olefinic double bonds or the planar portion of the piperidone ring in (I), (II) and (III). The aryl rings are rotated to move atoms



(I)



(II)



(III)

C53 and C37 from the plane of the other five atoms of the piperidone ring, in the opposite direction with respect to the displacement of atom N1. As a result, the torsion angles C5—C51—C52—C53 (θ_1) and C3—C31—C32—C37 (θ_2) have the values 40.7 (4) and −43.6 (5)° in (I), −26.0 (8) and 25.3 (7)° in (II), and 137.5 (4) and −135.3 (4)° in (III), respectively. This lack of coplanarity is caused by nonbonded interactions between one of the *ortho* H atoms in the aryl rings and the equatorial H atoms at the 2- and 6-positions of the piperidone ring (H53/H6*A* or H6*B*, and H37/H2*A* or H2*B*). These steric repulsions are reduced by the expansion of the bond angles

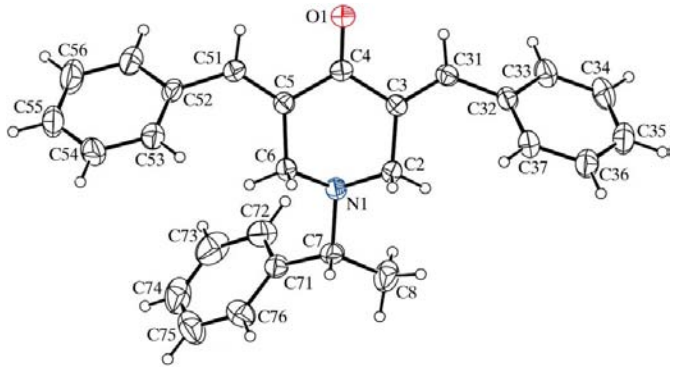


Figure 1
The molecular structure of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented as small spheres of arbitrary radii.

 DOI: 10.1107/S0108270107011626

C5—C51—C52 (ψ_1) and C3—C31—C32 (ψ_2) [129.0 (3) and 128.2 (3)° in (I), 129.5 (4) and 129.0 (4)° in (II), and 127.6 (4) and 126.8 (4)° in (III), respectively], which are otherwise 120°. Similar effects have been observed in related compounds (Ompraba *et al.*, 2003). The steric repulsion on the C71–C76 phenyl rings and methyl groups in (I), (II) and (III) could be understood in terms of the torsion angles C6—N1—C7—C71 and C2—N1—C7—C8 (Table 3). The dihedral angle between the N1/C7/C71 planes and the C71–C77 phenyl rings is 46.4 (2)° in (I), 51.6 (2)° in (II) and 64.2 (2)° in (III).

The data presented here are useful in the design of additional analogues. The replacement of the equatorial H atoms at the 2- and 6-positions, and the inclusion of substituents of varying sizes at atoms C33, C37, C53 and C57, are likely to alter the θ and ψ values. Correlations have been established between the θ values and bioactivity (Pandeya & Dimmock, 1997). In addition, the increased ψ values would lead to variations in the relative locations of the aryl rings, which could affect the alignment (or possibly cause nonalignment) of these rings at a binding site and hence influence bioactivity (Quail *et al.*, 2005).

In (I) and (II), the packing of the molecules is governed by van der Waals interactions. Additionally, in (I), two weak C—H$\cdots\pi$ interactions are observed (Table 1). In (III), the packing of the molecules is effected by C2—H2*A*$\cdots$O1 interactions (Table 2 and Fig. 4), generating a $C_1^1(5)$ graph-set motif (Etter, 1990; Bernstein *et al.*, 1995) to form a linear chain running along the *b* axis. No C—H$\cdots\pi$ interactions are observed in (II) and (III), and no π–π interactions are observed in any of the three compounds..

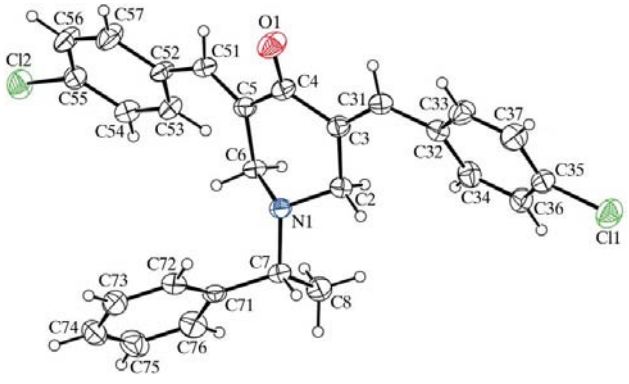


Figure 2
The molecular structure of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented as small spheres of arbitrary radii.

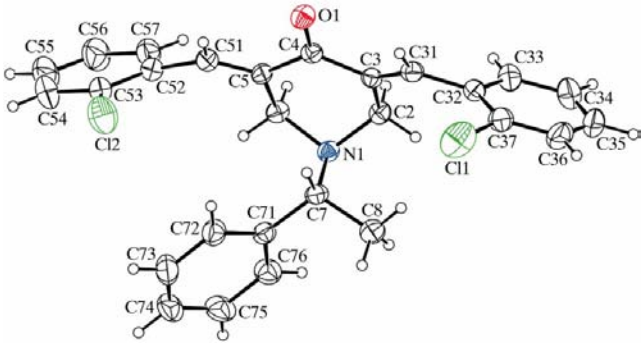


Figure 3
The molecular structure of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented as small spheres of arbitrary radii.

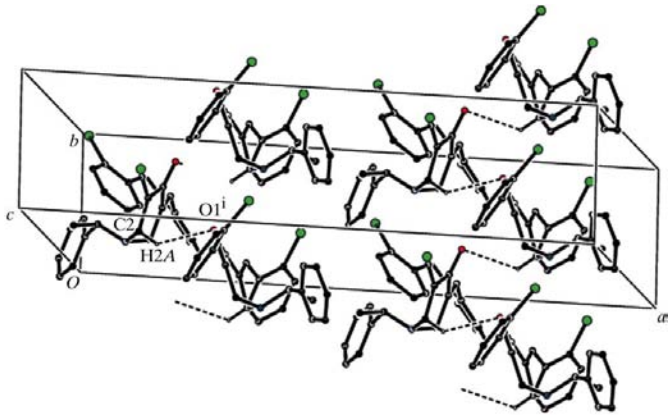


Figure 4
A partial packing view of the molecules in (III), showing the C—H$\cdots$O bonding. H atoms that do not take part in the bonding have been omitted. [Symmetry code: (i) $-x+\frac{1}{2}, y-\frac{1}{2}, -z+1$.]

Experimental

For the preparation of (I), a mixture of (*R*)-(1-phenylethyl)tetrahydropyridin-4(1*H*)-one (1 mmol 0.5 ml) and benzaldehyde (2 mmol, 0.50 ml) in ethanolic NaOH (30 ml, 10%) was stirred at room temperature for 10 min. The separated solid was filtered off and recrystallized from ethanol (yield 0.740 g, 80%; m.p. 385–386 K). For the preparation of (II), a mixture of (*R*)-(1-phenylethyl)tetrahydropyridin-4(1*H*)-one (1 mmol, 0.5 ml) and 4-chlorobenzaldehyde (2 mmol, 0.69 g) in ethanolic NaOH (30 ml, 10%) was stirred at room temperature for 10 min. The separated solid was filtered off and recrystallized from ethanol (yield 0.905 g, 83%; m.p. 412–413 K). For the preparation of (III), a mixture of (*R*)-(1-phenylethyl)tetrahydropyridin-4(1*H*)-one (1 mmol, 0.5 ml) and 2-chlorobenzaldehyde (2 mmol, 0.55 ml) in ethanolic NaOH (30 ml, 10%) was stirred at room temperature for 10 min. The separated solid was filtered off and recrystallized from ethanol (yield 0.927 g, 85%; m.p. 358–359 K).

Compound (I)

Crystal data

$C_{27}H_{25}NO$
M_r = 379.48
Orthorhombic, $P2_12_12_1$
a = 6.0890 (7) Å
b = 15.3562 (9) Å
c = 23.1522 (11) Å
V = 2164.8 (3) Å^3
Z = 4
Mo *K*α radiation
μ = 0.07 mm^{-1}
T = 293 (2) K
0.19 × 0.17 × 0.12 mm

Data collection

Nonius MACH3 four-circle diffractometer
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.987, T_{max} = 0.992
2330 measured reflections
2213 independent reflections
1421 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
3 standard reflections
frequency: 60 min
intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.032$	263 parameters
$wR(F^2) = 0.093$	H-atom parameters constrained
$S = 1.06$	$\Delta\rho_{max} = 0.11$ e Å^{-3}
2213 reflections	$\Delta\rho_{min} = -0.17$ e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

*Cg*1 and *Cg*2 are the C71–C76 and C32–C37 ring centroids.

D—H···A	D—H	H···A	D···A	D—H···A
C55—H55···*Cg*1^{i}	0.93	2.84	3.725 (4)	159
C74—H74···*Cg*2^{i}	0.93	2.97	3.645 (5)	130

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

Compound (II)

Crystal data

$C_{27}H_{23}Cl_2NO$	$V = 1125.62$ (9) Å^3
$M_r = 448.36$	$Z = 2$
Monoclinic, $P2_1$	Mo $K\alpha$ radiation
$a = 6.6409$ (3) Å	$\mu = 0.31$ mm^{-1}
$b = 12.9466$ (1) Å	$T = 293$ (2) K
$c = 13.1274$ (8) Å	0.22 × 0.13 × 0.12 mm
$\beta = 94.200$ (16)°	

Data collection

Nonius MACH3 four-circle diffractometer	2256 independent reflections
Absorption correction: ψ scan (North *et al.*, 1968)	1918 reflections with $I > 2\sigma(I)$
$T_{min} = 0.935$, $T_{max} = 0.964$	$R_{int} = 0.078$
2678 measured reflections	3 standard reflections
	frequency: 60 min
	intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.049$	$\Delta\rho_{max} = 0.34$ e Å^{-3}
$wR(F^2) = 0.139$	$\Delta\rho_{min} = -0.40$ e Å^{-3}
$S = 1.07$	Absolute structure: Flack (1983), 189 Friedel pairs
2256 reflections	Flack parameter: −0.08 (10)
281 parameters	
H-atom parameters constrained	

Compound (III)

Crystal data

$C_{27}H_{23}Cl_2NO$	$V = 2339.4$ (7) Å^3
$M_r = 448.36$	$Z = 4$
Monoclinic, $C2$	Mo $K\alpha$ radiation
$a = 25.746$ (5) Å	$\mu = 0.30$ mm^{-1}
$b = 6.1251$ (9) Å	$T = 293$ (2) K
$c = 16.1829$ (19) Å	0.22 × 0.18 × 0.11 mm
$\beta = 113.55$ (1)°	

Data collection

Nonius MACH3 four-circle diffractometer	2680 independent reflections
Absorption correction: ψ scan (North *et al.*, 1968)	1990 reflections with $I > 2\sigma(I)$
$T_{min} = 0.938$, $T_{max} = 0.968$	$R_{int} = 0.014$
2735 measured reflections	3 standard reflections
	frequency: 60 min
	intensity decay: none

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.034$	$\Delta\rho_{max} = 0.28$ e Å^{-3}
$wR(F^2) = 0.086$	$\Delta\rho_{min} = -0.23$ e Å^{-3}
$S = 1.04$	Absolute structure: Flack (1983), 407 Friedel pairs
2680 reflections	Flack parameter: −0.04 (9)
282 parameters	
H-atom parameters constrained	

Table 2
Short-contact geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2*A*···O1^{i}	0.97	2.60	3.263 (4)	126

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

Table 3
Comparison of selected geometric parameters (°) of (I), (II) and (III).

	(I)	(II)	(III)
C31—C3—C2	124.5 (3)	125.7 (4)	125.5 (3)
C51—C5—C6	125.0 (2)	125.3 (4)	124.9 (3)
C37—C32—C31	122.6 (3)	124.1 (4)	121.5 (3)
C53—C52—C51	122.8 (3)	124.5 (4)	122.2 (4)
C2—C3—C31—C32	−5.2 (5)	−0.2 (8)	8.3 (5)
C8—C7—N1—C2	−53.3 (3)	−58.6 (5)	−55.4 (4)
C6—C5—C51—C52	5.2 (5)	−1.6 (7)	−11.0 (5)
C71—C7—N1—C6	64.0 (3)	−63.4 (4)	60.0 (3)

In the absence of significant anomalous scattering for compound (I), the absolute configuration could not be reliably determined and Friedel pairs were merged. The absolute configuration was established from the configuration of the starting reagents. For compounds (II) and (III), the absolute configuration expected from the starting reagents was confirmed by the refinement of the Flack (1983) parameter. H atoms were placed at calculated positions and allowed to ride on their carrier atoms [C—H = 0.93–0.98 Å, and U_{iso}(H) = $1.2U_{eq}$(C) for CH_2 and CH groups or U_{iso}(H) = $1.5U_{eq}$(C) for CH_3 groups].

For all compounds, data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1989); cell refinement: *CAD-4 EXPRESS*; data reduction: *XCAD4* (Harms & Wocadlo, 1996); program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

The authors thank the UGC and the DST for the SAP and FIST programmes, respectively. JS thanks the UGC and the management of The Madura College, Madurai, for providing a teacher fellowship. SP thanks CSIR, New Delhi, for a major research project.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3041). Services for accessing these data are described at the back of the journal.

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