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Conformational switching caused by biphenyl substitution at the C^{α} position: ethyl 2-benzyl-2-(formylamino)-3-phenylpropionate and ethyl 3-(1,1′-biphenyl-4-yl)-2-(formylamino)-2-(4-phenylbenzyl)propionate

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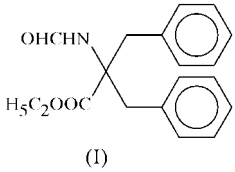
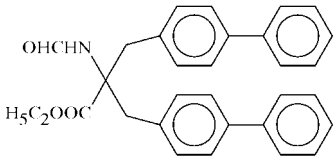
The title compounds, $C_{19}H_{21}NO_3$ and $C_{31}H_{29}NO_3$, are derivatives of α-aminoisobutyric acid, with benzyl and dibenzyl substitution. The pseudo-peptide formed by the *N*-formyl and ethyl ester substitution at the C^{α} position switches from a *trans–trans* to a *trans–cis* configuration as a result of biphenyl substitution. The packing of the compounds is stabilized by N—H···O and C—H···O hydrogen bonds.

Comment

α-Aminoisobutyric acid (Aib), which is achiral, has well established structural effects (Karle *et al.*, 1994; Ramesh & Balaram, 1999; Formaggio *et al.*, 2000). Similarly, benzyl substitution at the C^{α} position provides rigidity to the peptide backbone, and this conformational restriction is useful

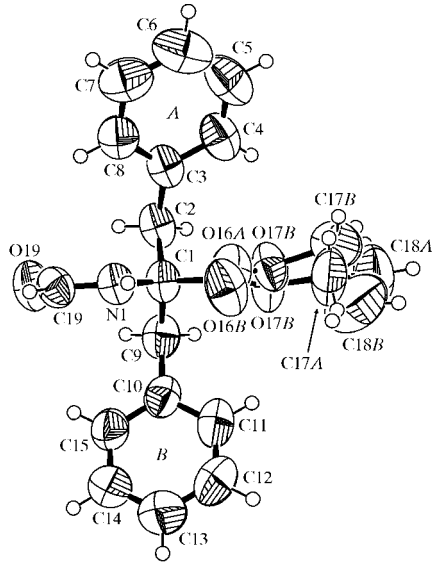


(I)

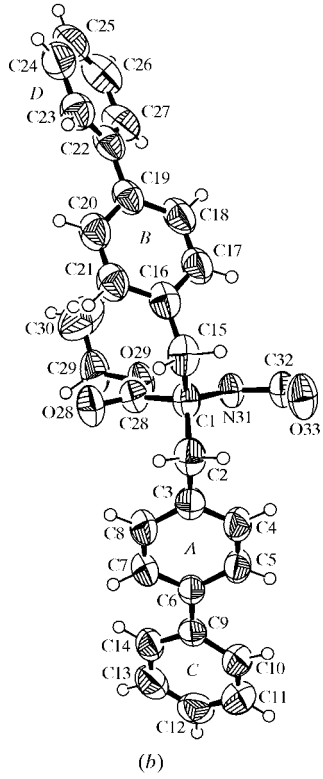


(II)

in peptide motif design (Studer & Seebach, 1995; Damodharan *et al.*, 2002; Karle & Balaram, 1990; Polese *et al.*, 1996; Kotha & Brahmachary, 2000). The effects of benzyl and phenyl substitution at the C^{α} position of Aib have been studied *via* crystal structure analyses. The two title compounds, (I), and (II), crystallize in the same ($P2_1/c$) space group from *n*-propanol–methanol (1:1) and 2-propanol solutions, respectively.



(a)



(b)

Figure 1
The molecular structures of (*a*) (I) and (*b*) (II), showing 50% probability displacement ellipsoids and the atomic numbering schemes.

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The molecular structures of the title compounds are shown in Fig. 1. Terminal atoms C18 and C17 of the ethyl ester side chains of (I) exhibit disorder. The bond angles at atoms C2 and C9 of (I), and at C2 and C15 of (II), are significantly larger than normal tetrahedral values because of the presence of the bulky substitutions [115.4 (2)° at C2 and 115.8 (3)° at C9 in (I), and 115.9 (2)° at C2 and 116.4 (2)° at C15 in (II)]. The angles between benzene rings *A* and *B* are 61.4 (2) and 61.8 (1)° in (I) and (II), respectively; the angle between rings *A* and *C* in (II) is 18.1 (1)°, and that between rings *B* and *D* in (II) is 39.8 (2)°. The additional phenyl substitution causes the molecules to be arranged along the longest axis (*viz*. the *a* axis) in (II), and a herring-bone packing arrangement is seen in both structures.

The *N*-formyl and ethyl ester chains form a pseudo-peptide, the backbone of which adopts a *trans–trans* conformation in (I) [C16—C1—N1—C19 (φ) = −178.8 (3)°, O17*A*—C16—C1—N1 (ψ) = 170.5 (5)° and O17*B*—C16—C1—N1 (ψ) = −169.8 (7)°; as a result of disorder, ψ adopt two values] and a *trans–cis* conformation in (II) [C28—C1—N31—C32 (φ) = 178.4 (2)° and N31—C1—C28—O29 (ψ) = −5.4 (3)°; Fig. 2]. This conformational switching may be due to the additional phenyl ring substitutions on either side of the C^{α} atom.

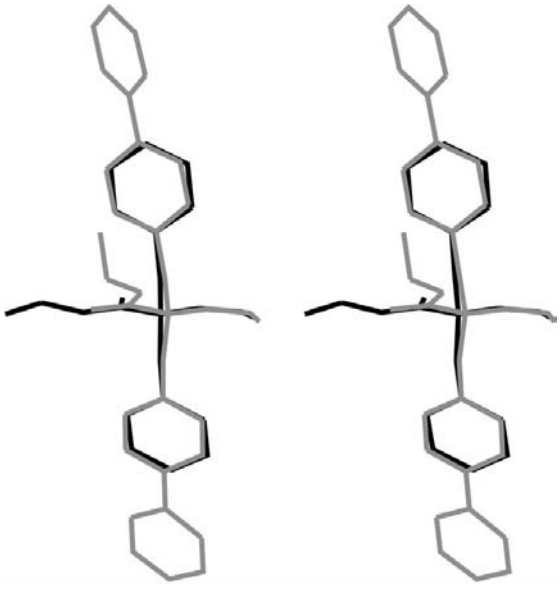


Figure 2
A stereoview of the superposition of (I) (black) and (II) (grey), showing the conformational switching of the ethyl ester chain from *trans–trans* in (I) to *cis–trans* in (II).

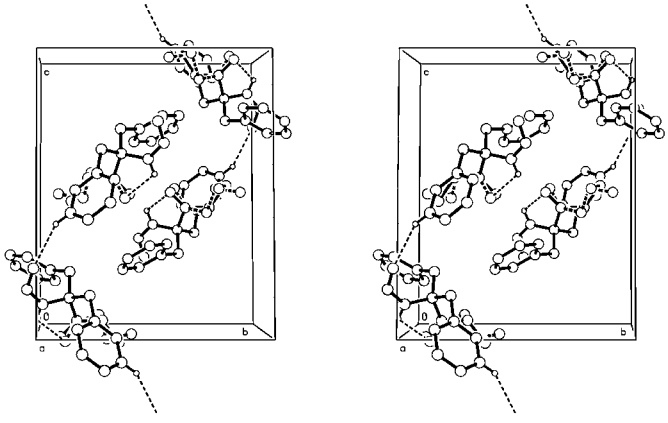


Figure 3
A stereoview of the packing of (I), showing intramolecular N—H···O interactions and intermolecular C—H···O interactions.

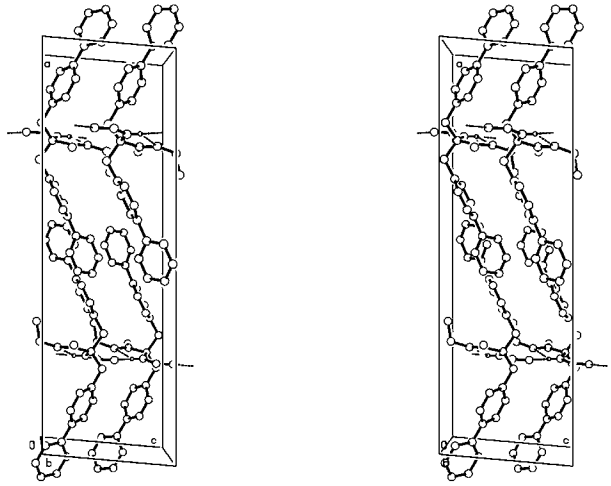


Figure 4
A stereoview of the packing of (II), showing the N—H···O interactions.

The *N*-formyl side chain is planar and in a folded conformation in both compounds [C1—N1—C19—O19 = −4.4 (5)° and C1—N31—C32—O33 = 0.7 (4)° for (I) and (II), respectively]. The ethyl ester side chains adopt different conformations in the two compounds, *viz*. −*ap* (antiperiplanar) and +*sc* (synclinal) in (I), and +*ac* (anticlinal) in (II) [C16—O17*A*—C17*A*—C18*A* = −171.9 (10)° (−*ap*) and C16—O17*B*—C17*B*—C18*B* = 82 (2)° (+*sc*) in (I) (two conformations as a result of the disorder), and C28—O29—C29—C30 = 93.8 (4)° (+*ac*) in (II)]. The switch from −*ap*/+*sc* to +*ap* can be attributed to the biphenyl substitutions (Fig. 3).

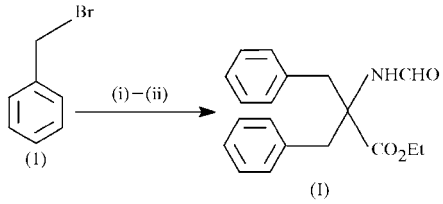
Intramolecular N—H···O and C—H···O hydrogen bonds are present in both structures. The N1—C1—C16 angle is 105.0 (2)°, possibly as a result of the presence of an intramolecular N1—H···O16 hydrogen bond, whereas the corresponding angle (N31—C1—C28) in (II) is 110.2 (2)° (Fig. 4). The bifurcated N31—H31···O29(x, y, z)/O33(x, $\frac{3}{2}-y$, $z-\frac{1}{2}$) hydrogen bond may be the reason for the widening of this bond angle.

The packing of both structures is stabilized by C—H···O and N—H···O interactions. Atom O19 of the *N*-formyl group in (I) forms an intermolecular C5—H5···O19 hydrogen bond, which is replaced by an N31—H31···O33 hydrogen bond in (II) (Tables 1 and 2, and Figs. 3 and 4).

Experimental

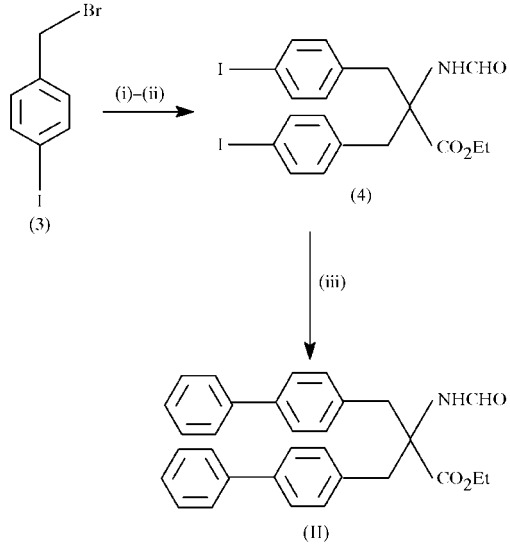
Reaction of benzyl bromide, (1), with ethyl isocyanoacetate in the presence of a phase-transfer catalyst, such as tetrabutylammonium sulfate, in acetonitrile/potassium carbonate gave a coupling product.

Hydrolysis of the coupling product with concentrated HCl in the presence of diethyl ether gave the formyl derivative (I).



(i) ethyl isocyanoacetate, K_2CO_3, CH_3CN
(ii) conc. HCl, diethyl ether

Similarly, compound (4) was prepared from *p*-iodobenzyl bromide, (3). A Suzuki–Miyaura coupling reaction (Kotha *et al.*, 2002) of (4) with benzeneboronic acid in the presence of Pd^0 as catalyst gave the cross-coupling product (II).



(i) ethyl isocyanoacetate, K_2CO_3, CH_3CN, (ii) conc. HCl, diethyl ether
(iii) Ph–$B(OH)_2$, $Pd(PPh_3)_4$

Compound (I)

Crystal data

$C_{19}H_{21}NO_3$	Mo $K\alpha$ radiation
M_r = 311.37	Cell parameters from 3802 reflections
Monoclinic, $P2_1/c$	θ = 2.1–27.9°
a = 9.980 (2) Å	μ = 0.08 mm^{-1}
b = 11.853 (3) Å	T = 293 (2) K
c = 14.575 (4) Å	Rectangular block, colorless
β = 94.147 (4)°	0.52 × 0.43 × 0.42 mm
V = 1719.6 (7) Å^3	
Z = 4	
D_x = 1.203 Mg m^{-3}	

Data collection

Bruker SMART CCD area-detector diffractometer	R_{int} = 0.023
ω scans	θ_{max} = 27.9°
13 797 measured reflections	$h = -12 \rightarrow 12$
3802 independent reflections	$k = -13 \rightarrow 15$
2295 reflections with $I > 2\sigma(I)$	$l = -18 \rightarrow 19$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0598P)^2 + 0.3098P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.062	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2)$ = 0.161	$\Delta\rho_{max}$ = 0.22 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.11 e Å^{-3}
3802 reflections	
245 parameters	
H-atom parameters constrained	

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

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1···O16*A*	0.86	2.22	2.657 (15)	111
N1—H1···O16*B*	0.86	2.11	2.55 (2)	111
C5—H5···O19^{i}	0.93	2.46	3.314 (3)	152
C2—H2*B*···O19	0.97	2.57	3.168 (3)	119
C9—H9*A*···O19	0.97	2.64	3.170 (3)	114

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

Compound (II)

Crystal data

$C_{31}H_{29}NO_3$	Mo $K\alpha$ radiation
M_r = 463.55	Cell parameters from 5898 reflections
Monoclinic, $P2_1/c$	θ = 2.0–28.0°
a = 26.761 (5) Å	μ = 0.08 mm^{-1}
b = 10.9424 (19) Å	T = 293 (2) K
c = 8.5818 (15) Å	Rectangular block, colorless
β = 95.068 (3)°	0.54 × 0.45 × 0.45 mm
V = 2503.2 (8) Å^3	
Z = 4	
D_x = 1.230 Mg m^{-3}	

Data collection

Bruker SMART CCD area-detector diffractometer	R_{int} = 0.052
ω scans	θ_{max} = 28.0°
21 471 measured reflections	$h = -34 \rightarrow 34$
5898 independent reflections	$k = -14 \rightarrow 14$
2853 reflections with $I > 2\sigma(I)$	$l = -11 \rightarrow 10$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0465P)^2 + 0.6112P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)]$ = 0.080	$(\Delta/\sigma)_{max}$ = 0.001
$wR(F^2)$ = 0.161	$\Delta\rho_{max}$ = 0.19 e Å^{-3}
S = 1.05	$\Delta\rho_{min}$ = −0.12 e Å^{-3}
5898 reflections	
316 parameters	
H-atom parameters constrained	

Table 2
Hydrogen-bonding geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N31—H31···O29	0.86	2.12	2.556 (2)	111
N31—H31···O33^{ii}	0.86	2.21	2.936 (3)	142
C15—H15*B*···O33	0.97	2.49	3.137 (3)	124
C2—H2*A*···O33	0.97	2.55	3.139 (3)	119

Symmetry code: (ii) $x, \frac{3}{2} - y, z - \frac{1}{2}$.

H atoms were positioned geometrically and treated as riding, with C—H distances of 0.93–0.97 Å and N—H distances of 0.86 Å.

For both compounds, data collection: *SMART* (Bruker, 1999); cell refinement: *SAINT* (Bruker, 1999); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 (Farrugia, 1997); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1665). Services for accessing these data are described at the back of the journal.

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