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N-(*tert*-Butoxycarbonyl)-α-aminoisobutyryl-α-aminoisobutyric acid methyl ester: two polymorphic forms in the space group $P2_1/n$

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The title compound (systematic name: methyl 2-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropanamido}-2-methylpropanoate), $C_{14}H_{26}N_2O_5$, (I), crystallizes in the monoclinic space group $P2_1/n$ in two polymorphic forms, each with one molecule in the asymmetric unit. The molecular conformation is essentially the same in both polymorphs, with the α-aminoisobutyric acid (Aib) residues adopting φ and ψ values characteristic of α-helical and mixed 3_{10}- and α-helical conformations. The helical handedness of the *C*-terminal residue (Aib2) is opposite to that of the *N*-terminal residue (Aib1). In contrast to (I), the closely related peptide Boc-Aib-Aib-OBn (Boc is *tert*-butoxycarbonyl and Bn is benzyl) adopts an α_L-P_{II} backbone conformation (or the mirror image conformation). Compound (I) forms hydrogen-bonded parallel β-sheet-like tapes, with the carbonyl groups of Aib1 and Aib2 acting as hydrogen-bond acceptors. This seems to represent an unusual packing for a protected dipeptide containing at least one α,α-disubstituted residue.

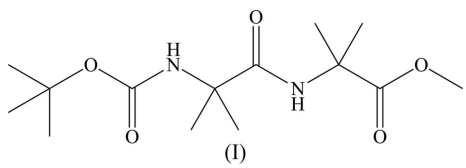
Comment

α-Aminoisobutyric acid (Aib) is an achiral nonproteinogenic amino acid found in peptaibiotics, a group of fungal peptides with antibiotic activity (Degenkolb & Brückner, 2008; Toniolo & Brückner, 2009). Peptaibiotics, exemplified by alamethicin (Pandey *et al.*, 1977), are believed to exert their biological effect by folding into amphipathic helices that oligomerize, forming voltage-gated transmembrane ion channels (Mueller & Rudin, 1968; Nagaraj & Balaram, 1981; Fox & Richards, 1982). Key to the biological activity of peptaibiotics is the (conformational) preference of Aib for helical conformations. As was first recognized by Ramachandran & Chandrasekaran (1972) and, independently, by Marshall & Bosshard (1972), the Aib residue is almost invariably restricted to φ and ψ values corresponding to the right- (φ = −60±20° and ψ = −30±20°) or left-handed (φ = 60±20° and ψ = 30±20°) 3_{10}- or α-helical regions of the Ramachandran plot (Venkatraman *et al.*, 2001). It has been known for a long time that Aib can increase the conformational stability of peptide helices (Burgess & Leach, 1973; Karle & Balaram, 1990) with both α- and 3_{10}-helical hydrogen-bonding patterns (Marshall *et al.*, 1990). The introduction of Aib residues into polypeptide chains limits the range of conformations accessible to the peptide because of the extra methyl group at the C^α atom, forcing the peptide chain into a left- or right-handed helical conformation or nucleating a β-turn (Aravinda *et al.*, 2003). Numerous X-ray diffraction studies of short Aib-based model peptides have demonstrated their preference for 3_{10}-helical structures (Karle & Balaram, 1990; Toniolo & Benedetti, 1991; Toniolo *et al.*, 2001). A review of crystal structures of synthetic tri-, tetra- and pentapeptides containing at least one Aib residue showed that almost all form incipient 3_{10}-helices (Toniolo *et al.*, 1983). However, while shorter Aib peptides preferentially adopt type III/III′ β-turn and 3_{10}-helical conformations, longer Aib peptides are able to form α-helical structures (Butters *et al.*, 1981; Schmitt *et al.*, 1982; Pavone *et al.*, 1990).

Although 3_{10}- and α-helical conformations are statistically by far the most prevalent conformations observed for Aib in crystal structures of Aib-containing peptides, a number of Aib residues have also been found to adopt polyproline II conformations, in particular in structures of protected di- and tripeptides (Aravinda *et al.*, 2008). Other nonhelical conformations are, however, very rare. Notably, because of the severe steric clash between the carbonyl group of the preceding residue and one of the methyl groups, β-strand conformations are energetically very unfavourable (Aravinda *et al.*, 2008), making Aib one of the best β-sheet-breaking amino acids (Moretto *et al.*, 1989; Toniolo *et al.*, 2001).

Aib residues at the *C*-terminus of a helix have a tendency to adopt a different conformation from the rest of the molecule. In a recent investigation of 143 crystal structures of Aib-containing helical peptides with more than three residues, 66.2% of the *C*-terminal Aib residues were found to adopt helical conformations corresponding to a different helical handedness than the body of the peptide, and 20.3% to adopt polyproline II conformations (Aravinda *et al.*, 2008).

The title compound, (I), was synthesized as part of an ongoing effort to develop a generic methodology for the conformational stabilization of synthetic analogues of 3_{10}-helical protein segments (Jacobsen *et al.*, 2009, 2011).



(I)

Many biologically important protein–protein interactions are mediated by helical protein segments and could therefore, in principle, be modulated by synthetic peptides with similar

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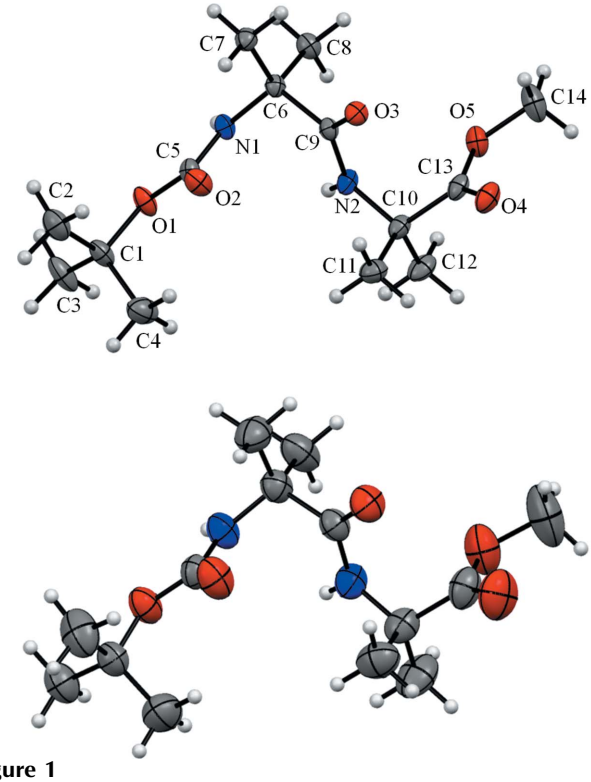

Figure 1
The molecular structure of (I) in polymorph *A* at 105 K (top) and in polymorph *B* at 293 K (bottom). The atomic numbering scheme is the same for both polymorphs. Displacement ellipsoids are drawn at the 50% probability level.

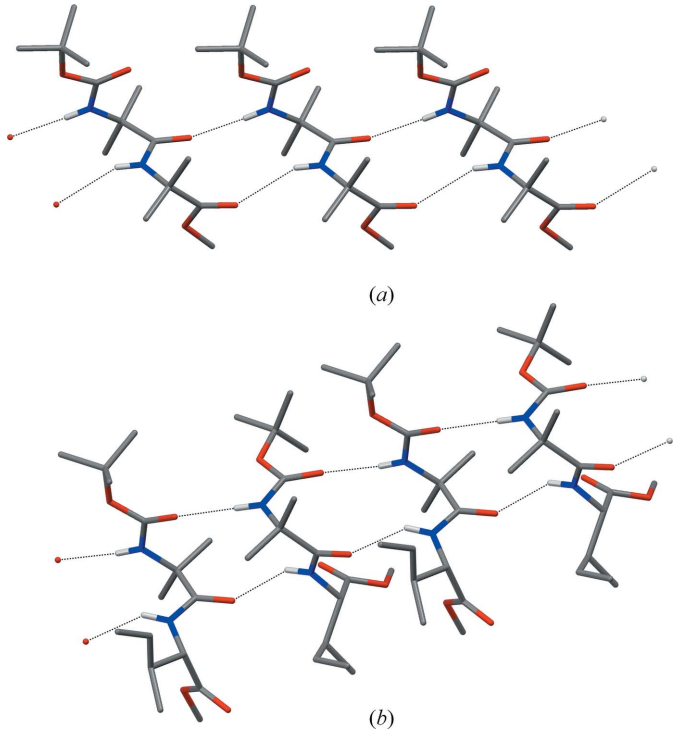

Figure 2
(*a*) The hydrogen-bonded tape parallel to the shortest crystallographic axis (about 6.1 Å) occurring in both polymorphs of (I) (the drawing is for form *A*). (*b*) The hydrogen-bonded tape in the structure of Boc-Aib-L-Ile-OMe (CSD refcode AJOLEQ; Nilofarnissa *et al.*, 2000).

primary structures and conformations. Because the entropy reduction associated with ligand–receptor binding is likely to be smaller for a prestructured or conformationally restricted peptide than for a related random coil peptide, the ability of Aib to induce or stabilize helical conformations makes Aib-containing peptides mimicking protein segments potentially valuable in drug discovery. Improved proteolytic stability is another beneficial effect of a higher degree of helicity in solution (Banerjee *et al.*, 2002), which derives from the fact that proteases recognize their substrates in a β-strand conformation (Tyndall *et al.*, 2005).

Diffraction data were collected for two needle-shaped crystals, which proved to represent two different polymorphs of (I), hereafter denoted *A* and *B*, which both belong to the monoclinic space group $P2_1/n$ (see *Experimental*). The molecular structure of (I) is depicted in Fig. 1. The conformation is virtually the same in both polymorphic forms, as reflected by the torsion angles listed in Table 1 and the r.m.s. deviation of 0.157 Å for the best fit between heavy atoms. The φ and ψ values are characteristic of α-helical and mixed 3_{10}- and α-helical conformations. An α-helix is defined by the presence of two or more consecutive $i \rightarrow i+4$ intramolecular hydrogen bonds and thus involves at least six residues. Similarly, two or more consecutive $i \rightarrow i+3$ intramolecular hydrogen bonds constitute the defining feature of a 3_{10}-helix. It is difficult to label the conformation of a single isolated residue as 3_{10}- or α-helical exclusively based on its torsion angles. For the purpose of this study, we define the backbone conformation of a single isolated residue to be α-helical if a hypothetical oligopeptide with the same torsion angles as the said residue would be α-helical, *i.e.* would form consecutive $i \rightarrow i+4$ intramolecular hydrogen bonds. Notably, the helical handedness of the *C*-terminal residue Aib2 is opposite to that of the *N*-terminal residue Aib1 in both polymorphs, which helps to avoid unfavourable intramolecular contacts (Van Roey *et al.*, 1983) [as (I) is achiral and crystallizes in a centrosymmetric space group, it is not meaningful to designate the conformations of Aib1 and Aib2 as left- or right-handed]. Interestingly, Aib2 in the closely related protected dipeptide Boc-Aib-Aib-OBn [Cambridge Structural Database (CSD; Version 5.32 of November 2010; Allen, 2002) refcode BAJROT10 (Van Roey *et al.*, 1983); Table 1] adopts a polyproline II conformation (or its mirror image conformation) instead of a 3_{10}- or α-helical conformation.

Pairs of strong hydrogen bonds (Tables 2 and 3) link the peptide molecules of (I) into tapes, as shown in Fig. 2(*a*). In form *A*, these are supported by two reasonably linear C—H···O=C contacts with H···O < 2.60 Å; these are essentially missing in form *B* as the pertinent H···O distances are >2.85 Å. A similar tape motif has previously only been found for Boc-α-methyl-L-Phe-L-Val-OBn (CSD refcode CAPZIC; Van Roey *et al.*, 1981). Other protected Aib*-Xaa dipeptides in the CSD, where Aib* is either Aib or another α,α-disubstituted amino acid and Xaa is a chiral amino acid, form a second type of tape motif that in a sense constitutes a 'frame shift' compared with (I), as the pair of carbonyl acceptors is

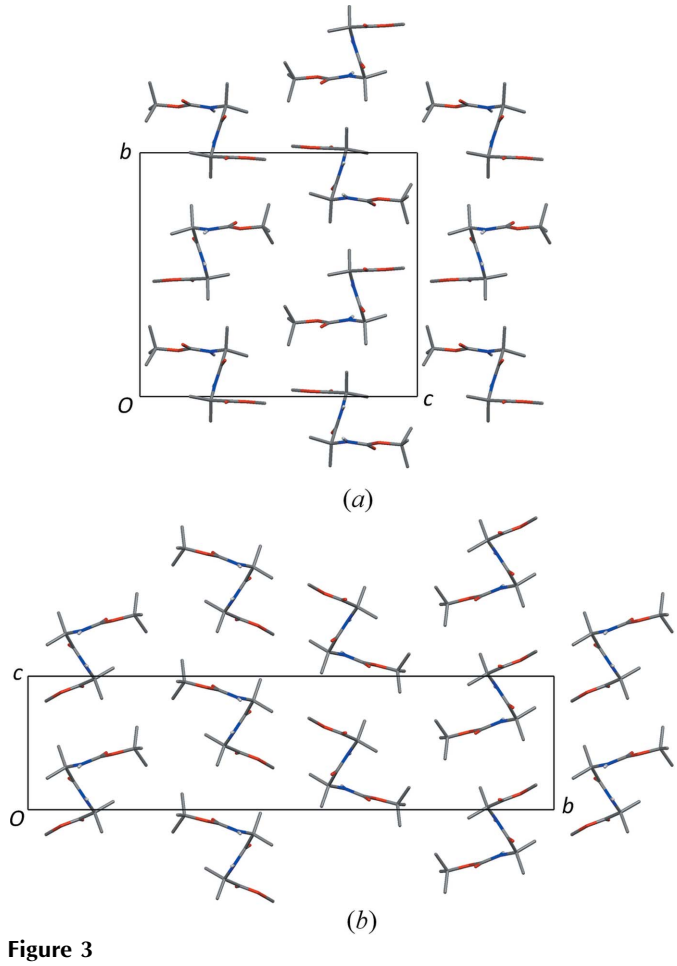

Figure 3
The crystal packing of (I) in (*a*) polymorph *A* and (*b*) polymorph *B*, both viewed along the short *a* axis.

shifted one residue towards the *N*-terminal end of the peptide, corresponding to atoms O2 and O3 in Fig. 1 rather than atoms O3 and O4 used for (I) (Tables 2 and 3). Furthermore, the Aib* residue in every second molecule in the tape adopts a conformation corresponding to the opposite helical handedness (Fig. 2*b* and Table 1). All such structures have two molecules in the asymmetric unit. The same hydrogen-bonding pattern is also observed for the benzyl ester analogue of (I) (CSD refcode BAJROT10; Van Roey *et al.*, 1983) and for one out of three Xaa-Aib* peptides. Molecules in Table 1 with two α,α-disubstituted amino acid residues, where at least one is different from Aib, are evidently too crowded to form tape motifs and instead form various simple hydrogen-bonded chains.

Recent studies have revealed the importance of $n\rightarrow\pi^*$ C$=$O$_i\rightarrow$C$_{i+1}=$O hyperconjugative interactions between consecutive amide groups in stabilizing 3_{10}-helical, α-helical and polyproline II conformations (Bretscher *et al.*, 2001; Hodges & Raines, 2006; Jakobsche *et al.*, 2010), in particular when the distance *d* from atom O$_i$ to atom C$_{i+1}$ is less than 3.2 Å (Bartlett *et al.*, 2010). In a 3_{10}-helix, one such interaction can be worth as much as 1.3 kcal mol^{-1} (5.4 kJ mol^{-1}; 1 kcal mol^{-1} = 4.184 kJ mol^{-1}) (Bartlett *et al.*, 2010). If an ester is the electron-density acceptor, it has been found that an $n\rightarrow\pi^*$ C$=$O$_i\rightarrow$C$_{i+1}=$O interaction can provide 0.7 kcal mol^{-1} of stabilization energy (Hinderaker & Raines, 2003). The observed O$_i$ to C$_{i+1}$ distances are 2.916 (2) and 2.663 (2) Å for Aib1 and Aib2, respectively, in polymorph *A*, while the corresponding values for polymorph *B* are 2.861 (3) and 2.730 (3) Å. The crystal structures of (I) thus provide good examples of $n\rightarrow\pi^*$ C$=$O$_i\rightarrow$C$_{i+1}=$O stabilizing interactions in a short peptide. A helical or polyproline II conformation allows the lone pair on the carbonyl O atom to interact with the antibonding C$_{i+1}=$O orbital along an angle of attack very close to the Bürgi–Dunitz angle (107°), the preferred angle of attack of a nucleophile at a carbonyl group (Bürgi *et al.*, 1973). Significantly, the O$_i$—C$=$O$_{i+1}$ angles for both polymorphic forms of (I) are very close to the Bürgi–Dunitz angle, with values of 108.80 (11) and 103.01 (11)° for Aib1 and Aib2, respectively, in polymorph *A*, and 107.42 (16) and 104.08 (18)°, respectively, in polymorph *B*.

The overall crystal packing arrangements of the two polymorphs, illustrated in Fig. 3, are quite different, despite the occurrence of hydrogen-bonded tapes in both forms, as shown in Fig. 2. The *B* form is more clearly divided into layers.

Experimental

α-Aminoisobutyric acid methyl ester hydrochloride was obtained by treating aminoisobutyric acid with thionyl chloride in methanol solution (Jacobsen *et al.*, 2011). Compound (I) was synthesized by standard solution-phase peptide coupling of α-aminoisobutyric acid methyl ester, which was generated *in situ* from α-aminoisobutyric acid methyl ester hydrochloride by treatment with *N*,*N*-diisopropylethylamine, with commercially available *N*-(*tert*-butoxycarbonyl)-α-aminoisobutyric acid. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) was used as coupling reagent and 1.0 equivalents of 1-hydroxybenzotriazole (HOBt) was added to catalyse the reaction (Jacobsen *et al.*, 2011). A small quantity of (I) (about 5 mg) was dissolved in ethyl acetate (30 µl). Needle-shaped crystals appeared as water vapour diffused into the solution at room temperature. Data were first collected under ambient conditions because of a temporary failure of the low-temperature device. When the cooling unit was available again, data were recorded for a second crystal taken from the same batch. Although there were no obvious differences in appearance, this crystal proved to be a different polymorph. We thus had data for two concomitant forms, *A* (data collected at low temperature) and *B* (ambient). Several other crystals were subsequently tested to find a good specimen for collection of a low-temperature data set for form *B* (the original crystal had unfortunately been lost), but only crystals of form *A* were found, suggesting that *A* was the dominant polymorph in the crystalline sample. Crystals of form *A* can also be cooled and heated without being converted to form *B*.

Polymorph *A* of (I)

Crystal data

C$_{14}$H$_{26}$N$_2$O$_5$
M_r = 302.37
Monoclinic, $P2_1/n$
a = 6.116 (3) Å
b = 15.662 (7) Å
c = 17.967 (8) Å
β = 97.878 (6)°
V = 1704.7 (13) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 105 K
0.78 × 0.22 × 0.13 mm

Table 1
Main torsion angles (°) in the crystal structures of protected dipeptides in the CSD.

Abbreviations: Boc is *tert*-butoxycarbonyl, Cbz is carboxybenzyl, B = Aib, B* is another α,α-disubstituted amino acid, I is isoleucine, V is valine, A is alanine, F is phenylalanine, Me is methyl, Bn is benzyl, ^{t}B is *tert*-butyl and L is leucine.

Compound or CSD refcode	Sequence	φ_1†	ψ_1	φ_2	ψ_2	Inverse‡
Polymorph (I*A*)	Boc-B-B-OMe	58.96 (19)	40.82 (19)	−45.6 (2)	−50.47 (18)	
Polymorph (I*B*)	Boc-B-B-OMe	56.4 (3)	42.5 (3)	−50.5 (3)	−49.1 (3)	
BAJROT10	Boc-B-B-OBn	59.6	52.0	−51.5	138.4	i
PARDUH	Boc-B-B*-OMe	61.5	32.8	177.0	−179.4	
		62.6	33.3	177.3	179.2	
PUXHOF	Boc-B*-B*-OMe	55.0	42.7	−56.0	−34.7	i
VEYQAR	Cbz-B*-B*-OMe	65.5	26.6	−35.5	−50.8	i
AJOLEQ	Boc-B-I-OMe	63.9	45.8	−68.0	−29.8	
		57.2	44.3	122.1	−148.1	i
CAPZIC	Boc-B*-V-OBn	58.9	33.3	−57.2	−44.2	
GANPEQ	Cbz-B-A-O^{t}B	57.8	41.8	−78.9	170.54	
		58.8	46.3	133.3	−174.9	i
OBAZIA	Boc-B*-A-OMe	56.1	45.8	−95.1	−177.9	i
		58.4	42.8	145.8	−24.4	
OFUXOC	Boc-B*-L-OMe	60.8	47.1	−72.3	−36.2	
		64.3	48.7	122.7	−9.6	i
PASGUL	Boc-B-F-OMe	62.1	44.1	−75.9	1.6	
		53.7	50.7	122.0	−164.0	i
XOWVAG	Boc-B-L-OMe	58.1	46.7	−80.7	−0.5	
		58.4	44.5	112.9	−165.7	i
LAGFII	Boc-V-B*-OMe	73.2	−127.3	55.2	32.2	i
TIRJOT	Cbz-A-B-O^{t}B	76.6	−156.2	−51.0	−44.7	i
ZAQVUI	Cbz-L-B*-OMe	90.6	32.2	−43.7	−53.1	i

† For (I), with reference to Fig. 1, the listed torsion angles are: φ_1 = C5—N1—C6—C9, ψ_1 = N1—C6—C9—N2, φ_2 = C9—N2—C10—C13 and ψ_2 = N2—C10—C13—O5. ‡ To facilitate comparison between structures, molecules indicated by 'i' have been inverted to obtain the same sign for the first torsion angle φ_1.

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2007)
T_{min} = 0.917, T_{max} = 0.988
11873 measured reflections
4100 independent reflections
2595 reflections with $I > 2\sigma(I)$
R_{int} = 0.048

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.126
S = 1.02
4100 reflections
196 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.28 e Å^{-3}
$\Delta\rho_{min}$ = −0.24 e Å^{-3}

Polymorph *B* of (I)

Crystal data

$C_{14}H_{26}N_2O_5$
M_r = 302.37
Monoclinic, $P2_1/n$
a = 6.0679 (15) Å
b = 33.743 (9) Å
c = 8.583 (2) Å
β = 92.266 (3)°
V = 1756.0 (8) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 293 K
0.80 × 0.11 × 0.10 mm

Data collection

Bruker APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Bruker, 2007)
T_{min} = 0.814, T_{max} = 0.991
10165 measured reflections
3105 independent reflections
1584 reflections with $I > 2\sigma(I)$
R_{int} = 0.052

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.125
S = 1.00
3105 reflections
197 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.15 e Å^{-3}
$\Delta\rho_{min}$ = −0.18 e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for polymorph *A* of (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.840 (19)	2.12 (2)	2.963 (2)	175.6 (18)
N2—H2···O4^{i}	0.86 (2)	2.44 (2)	3.227 (2)	151.6 (17)
C3—H32···O2^{i}	0.98	2.51	3.298 (2)	137
C11—H112···O1^{ii}	0.98	2.57	3.511 (2)	160

Symmetry codes: (i) $x-1, y, z$; (ii) $x+1, y, z$.

Table 3
Hydrogen-bond geometry (Å, °) for polymorph *B* of (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···O3^{i}	0.86 (2)	2.16 (2)	3.008 (3)	170 (2)
N2—H2···O4^{i}	0.85 (2)	2.44 (2)	3.197 (3)	148 (2)

Symmetry code: (i) $x+1, y, z$.

Positional parameters were refined for H atoms bonded to N atoms. Methyl H atoms were positioned with idealized geometry and fixed at C—H = 0.98 (form *A*, 105 K) or 0.96 Å (form *B*, 293 K). U_{iso}(H) values were set at 1.2U_{eq}(N) for N—H groups or at 1.5U_{eq}(C) for methyl groups.

For both polymorphs, data collection: *APEX2* (Bruker, 2007); cell refinement: *SAINT-Plus* (Bruker, 2007); data reduction: *SAINT-Plus*. Program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008) for polymorph *A*; *SHELXTL* (Sheldrick, 2008) for polymorph *B*. Program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008) for polymorph *A*; *SHELXTL* for polymorph *B*. Molecular graphics: *SHELXL97* for polymorph *A*; *SHELXTL* for polymorph *B*. Software used to prepare material for publication: *SHELXL97* for polymorph *A*; *SHELXTL* for polymorph *B*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ3206). Services for accessing these data are described at the back of the journal.

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