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From small structural modifications to adjustment of structurally dependent properties: 1-methyl-3,5-bis[(*E*)-2-thienylidene]-4-piperidone and 3,5-bis[(*E*)-5-bromo-2-thienylidene]-1-methyl-4-piperidone

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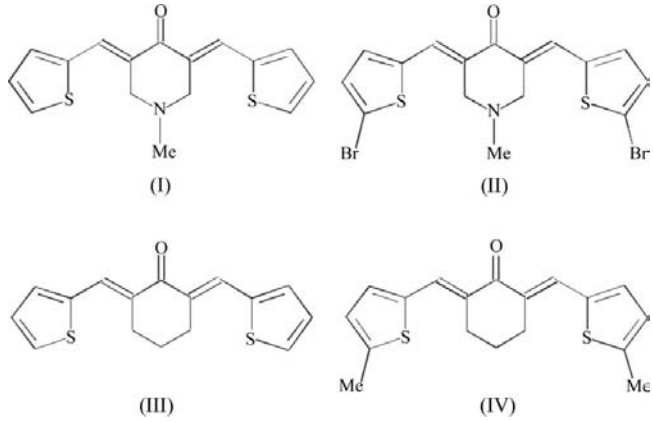
The molecules of the title compounds, $C_{16}H_{15}NOS_2$, (I), and $C_{16}H_{13}Br_2NOS_2$, (II), are *E*,*E*-isomers and consist of an extensive conjugated system, which determines their molecular geometries. Compound (I) crystallizes in the monoclinic space group $P2_1/c$. It has one thiophene ring disordered over two positions, with a minor component contribution of 0.100 (3). Compound (II) crystallizes in the noncentrosymmetric orthorhombic space group $Pca2_1$ with two independent molecules in the unit cell. These molecules are related by a noncrystallographic pseudo-inversion center and possess very similar geometries. The crystal packings of (I) and (II) have a topologically common structural motif, *viz*. stacks along the *b* axis, in which the molecules are bound by weak C—H···O hydrogen bonds. The noncentrosymmetric packing of (II) is governed by attractive intermolecular Br···Br and Br···N interactions, which are also responsible for the very high density of (II) (1.861 Mg m^{-3}).

Comment

Cross-conjugated dienones of the bis-arylidenecycloalkanone series and related piperidones have recently attracted considerable attention. These compounds are used in the construction of different polymers (Yakimansky *et al.*, 2002; Aly *et al.*, 2003), and in the design of crystals with nonlinear optical (Kishore & Kishore, 1993; Kawamata *et al.*, 1995, 1996; Sarkisov *et al.*, 2005) and fluorescent (Nesterov *et al.*, 2003, 2008) properties. Furthermore, it is well known that they possess a variety of biological activities, such as antiviral (El-Subbagh *et al.*, 2000), antibacterial (Lyrand *et al.*, 1999; Amal Raj *et al.*, 2003) and antiphlogistic activity (Rovnyak *et al.*, 1982).



Recently, instead of aryl substituents, the use of heterocyclic ligands was suggested, as these are able to bind important metal cations to form diverse coordination associates (Vatsadze *et al.*, 2006). However, to our knowledge, there are very few structurally characterized compounds of this type in the literature (Vatsadze *et al.*, 2006). In this paper, we describe two new cross-conjugated piperidones with thienylidene substituents in the side chains, namely 1-methyl-3,5-bis[(*E*)-2-thienylidene]-4-piperidone, (I), and 3,5-bis[(*E*)-5-bromo-2-thienylidene]-1-methyl-4-piperidone, (II), which represent modified analogs of the recently reported compounds 2,6-bis[(2-thienyl)methylidene]cyclohexanone, (III) (Vatsadze *et al.*, 2006), and 2,6-bis[(5-methylthiophene-2-yl)methylene]-cyclohexanone, (IV) (Liang *et al.*, 2007) (see scheme above). One purpose of our investigation was to analyze the influence of small structural modifications of the molecules on their structurally dependent properties. It should be noted that these compounds are potential antitumor (anticancer) agents (Dimmock *et al.*, 1992, 1994, 2001), and even small differences in the structures may cause significant changes in their biological activity.

Compound (I) crystallizes in the monoclinic space group $P2_1/c$. One thiophene ring is disordered over two positions related by a 180° rotation about the C6—C7 bond. The minor component contribution refined to 0.100 (3) (Fig. 1).

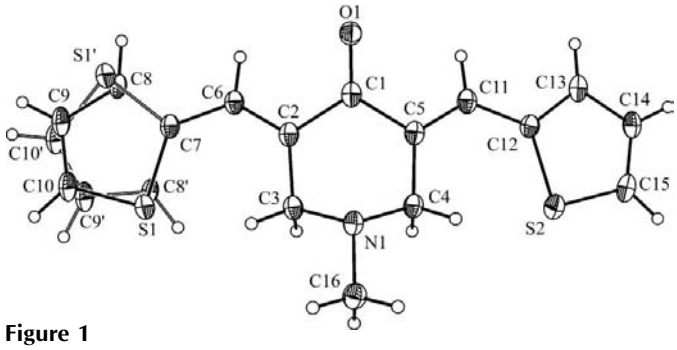


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. The alternative position of the disordered thiophene ring is drawn with open lines. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

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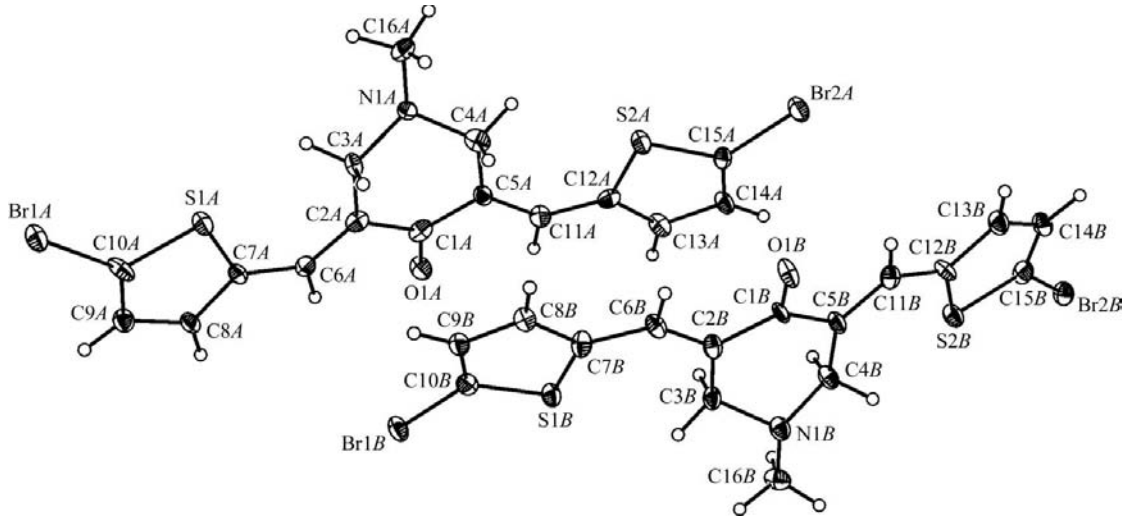


Figure 2
The molecular structure of (II), showing the atom-numbering scheme. The two independent molecules, *A* and *B*, related by a noncrystallographic pseudo-inversion center, are depicted. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

In general, the linear structure of conjugated bonds is the more favorable, and deviations from this rule are usually a result of specific reasons such as steric factors, hydrogen bonds and different attractive interactions. Quantum-chemical calculations using the density functional theory method of the *GAUSSIAN03* program, B3LYP functional, 6-31G* basis set (Frisch *et al.*, 2003), also show that the minimum of the potential energy surface corresponds to the major conformer (conformer *A*) found experimentally in the crystal structure of (I) (see Fig. 3). Although the energy differences between the three conformers, denoted *A*, *B* and *C*, are not large, there is a clear trend for compounds with larger deviations of the conjugated bonds from the linear structure to be less stable. In the crystal structure of (I), the presence of the minor conformer *B* may be explained by the weak intermolecular C6—H6*A*···S1′(1 − *x*, −*y*, −*z*) hydrogen bond [C6···S1′ = 3.487 (2) Å, H6*A*···S1′ = 2.78 Å and C6—H6*A*···S1′ = 132°].

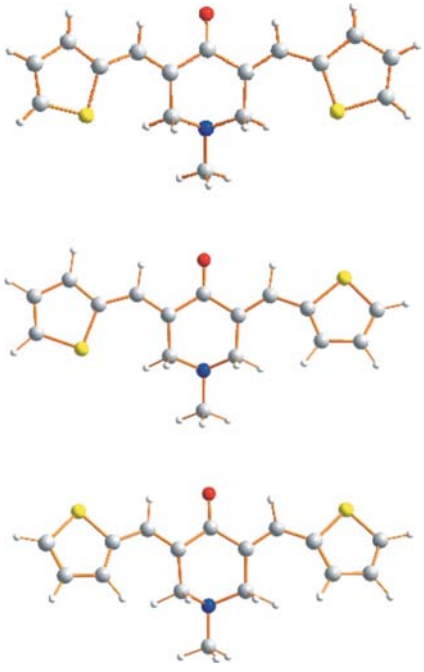


Figure 3
The minimum potential energies found experimentally for conformers *A* (top; $\Delta E = 0$ kcal mol^{-1}; 1 kcal mol^{-1} = 4.184 kJ mol^{-1}), *B* (middle; $\Delta E =$ 0.68 kcal mol^{-1}) and *C* (bottom; $\Delta E = 1.34$ kcal mol^{-1}) of (I).

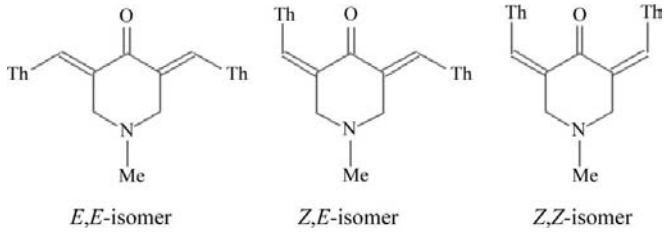
Compound (II) crystallizes in the noncentrosymmetric orthorhombic space group $Pca2_1$, with two independent molecules, *A* and *B*, in the unit cell (Fig. 2). However, in the crystal structure, molecules *A* and *B* are related by a noncrystallographic pseudo-inversion center with coordinates [0.3045 (2), 0.7536 (6), 0.5553 (2)]. Consequently, molecules *A* and *B* possess very similar geometries (Fig. 4), and only the average values of the geometric parameters of (II) are discussed below.

In the molecules of both compounds, the central piperidone ring adopts a flattened boat conformation; atoms N1 and C1 lie 0.702 (1) and 0.242 (1) Å in (I), and 0.699 (3) and 0.158 (3) Å in (II), respectively, out of the C2/C3/C4/C5 plane. Atom N1 of the heterocycle has pyramidal coordination, as revealed by the sums of the bond angles about this atom of 332.6 (2)° in (I) and 330.2 (3)° in (II). The methyl group occupies the more sterically favored equatorial position.

Both (I) and (II) contain three planar fragments. The first of these includes the plane of the piperidone ring (atoms C1–C5; P_A), while the planar fragments P_B [S1/C6–C10 in (I) and Br1/S1/C6–C10 in (II)] and P_C [S2/C11–C15 in (I) and Br2/S2/C11–C15 in (II)] include a thiophene ring and adjacent atoms. The dihedral angles P_A/P_B, P_A/P_C and P_B/P_C between these fragments are 13.2 (1), 17.0 (1) and 27.4 (1)°, respectively, in (I), and 10.9 (3), 13.9 (3) and 23.4 (3)° in (II).

The molecules of (I) and (II) can exist as *E*,*E*-, *Z*,*E*- and *Z*,*Z*-isomers (see scheme below; Th denotes thiophene). Evidently, the *E*,*E*-isomers observed for (I) and (II), both in the solid state and in solution (see ^{1}H NMR data in *Experimental*), are preferred because of steric reasons. Nevertheless,

they may undergo isomerization into the *Z*,*E*- and *Z*,*Z*-isomers in solution upon irradiation with visible light (Vatsadze *et al.*, 2006).



Interestingly, the introduction of the Br atoms in the thiophene rings of (II) does not give rise to significant changes to its molecular geometry compared with that of (I). Moreover, their structural features are similar to those of compounds (III) and (IV). It is surprising that, despite the presence of a bulkier N—CH_3 fragment on the central piperidone ring compared with a CH_2 fragment, compounds (I) and (III) are isostructural. These findings allow us to propose that the molecular structures of compounds (I)–(IV), as well as the crystal structures of compounds (I) and (III), are defined by similar effects.

The molecular geometries of compounds (I)–(IV) are determined by an extensive conjugated system that is quite stable to the influence of substituents of different types. For this reason, neither the introduction of simple substituents (methyl and halide) to peripheral parts, nor the replacement of one fragment on the saturated part of the central piperidone cycle by another of comparable dimensions, can alter its structure substantially. Thus, any small modifications of compounds containing analogous systems will mainly affect their molecular arrangement (or their crystal packing in the case of the solid state), and, consequently, their chemical properties as a whole.

In the case of dibenzylidenecycloalkanones, it has previously been established that intermolecular C—H···O hydrogen bonds between the carbonyl O atom and a H atom of the methylene groups of the central ring are an important factor in the design of crystals with nonlinear optical properties (Kawamata *et al.*, 1998). These hydrogen-bonding interactions possibly contribute to the isostructurality of (I) and (III). The topologically common structural motif (stacks along the *b* axis, in which the molecules are bound by C—H···O hydrogen bonds) is also maintained in the crystal structures of

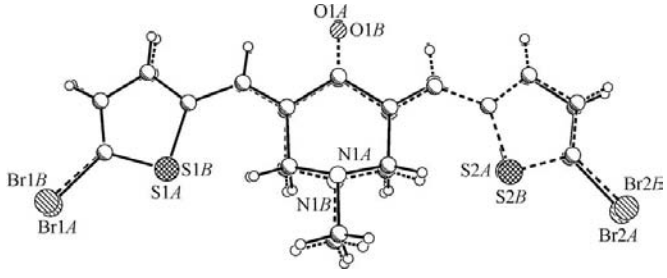


Figure 4
A comparison of the conformations of molecules *A* (solid lines) and *B* (dashed lines) in (II).

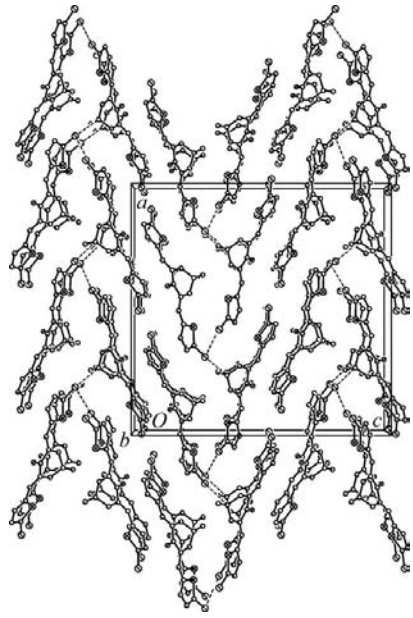


Figure 5
A packing diagram of (II), viewed along the *b* axis. Dashed lines indicate intermolecular attractive Br···Br and Br···N interactions. H atoms have been omitted for clarity.

(II) and (IV) (Table 1). However, in the crystal structure of (IV), the stacks are shifted relative to each other compared with the crystal structures of (I) and (III), due to the presence of additional peripheral methyl groups, resulting in the space group $P2_1/n$.

It is very important to note that the crystal packing of the molecules of (I), (III) and (IV) is centrosymmetric. However, in order for any compound to display nonlinear optical properties, its crystal packing should be noncentrosymmetric. To this end, we decided to use the well known attractive intermolecular halogen–halogen (Desiraju & Parthasarathy, 1989; Price *et al.*, 1994; Saha *et al.*, 2006) and halogen–nitrogen interactions (Desiraju & Harlow, 1989; Lucassen *et al.*, 2007). It was suggested that, owing to these interactions, the introduction of Br atoms at the peripheral positions of the thiophene rings of (III) does not destroy its common structural motif, but results in a shift of the stacks in such a manner that the crystal packing of the compound loses the crystallographic inversion center. Indeed, compound (II) has a noncentrosymmetric crystal structure (see above), while the common structural motif is preserved.

The intermolecular Br···Br [Br1*A*···Br2*B*($\frac{1}{2} - x$, $1 + y$, $\frac{1}{2} + z$) = 3.591 (2) Å] and Br···N [Br1*A*···N1*B*($1 - x$, $2 - y$, $\frac{1}{2} + z$) = 3.168 (4) Å] interactions result in a very high density for (II) (1.861 Mg m^{-3}), even among bromine-containing compounds. The average crystal density of bromine-containing organic compounds with short Br···Br contacts is 1.75 (2) Mg m^{-3} [184 hits; Cambridge Structural Database (Allen, 2002), 2009 release], but without such contacts the density is lower, at 1.619 (6) Mg m^{-3} (1137 hits). The crystal packing of (II) is presented in Fig. 5.

Comparison of the structures of (I) and (II) with analogous compounds has shown that their molecules are similar to

piperidones used as anticancer agents (Das *et al.*, 2007). Their combination of remarkable features suggests potential application of these compounds as agents for cancer treatment.

Experimental

For the preparation of (I), a mixture of 1-methyl-4-piperidone (1.13 g, 0.01 mol) and thiophene-2-carbaldehyde (2.24 g, 0.02 mol) was treated with alcoholic NaOH (50 ml, 10%) and stirred at room temperature for 30 min. The crude product was filtered and recrystallized from ethanol to give yellow plate-like crystals of (I) (yield 2.41 g, 80%; m.p. 385–387 K). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.89 [*s*, 2H, CH (vinyl)], 7.11–7.52 [*m*, 6H, CH (thiophene)], 3.76 (*s*, 4H, CH_2), 2.55 (*s*, 3H, CH_3).

For the preparation of (II), a mixture of 1-methyl-4-piperidone (1.13 g, 0.01 mol) and 5-bromothiophene-2-carbaldehyde (3.82 g, 0.02 mol) was treated with alcoholic NaOH (50 ml, 10%) and stirred at room temperature for 30 min. The crude product was filtered and recrystallized from methanol to give pink needle-like crystals of (II) (yield 4.32 g, 94%; m.p. 422–423 K). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 [*s*, 2H, CH (vinyl)], 7.04–7.09 [*m*, 4H, CH (thiophene)], 3.67 (*s*, 4H, CH_2), 2.56 (*s*, 3H, CH_3).

Compound (I)

Crystal data

$C_{16}H_{15}NOS_2$
M_r = 301.41
Monoclinic, $P2_1/c$
a = 15.108 (5) Å
b = 12.609 (4) Å
c = 7.523 (2) Å
β = 93.962 (4)°
V = 1429.8 (8) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.37 mm^{-1}
T = 100 K
0.55 × 0.24 × 0.12 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.824, T_{max} = 0.957
14615 measured reflections
3779 independent reflections
2841 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.121
S = 1.01
3779 reflections
188 parameters
24 restraints
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.51 e Å^{-3}
$\Delta\rho_{min}$ = −0.49 e Å^{-3}

Compound (II)

Crystal data

$C_{16}H_{13}Br_2NOS_2$
M_r = 459.21
Orthorhombic, $Pca2_1$
a = 23.222 (3) Å
b = 5.8840 (7) Å
c = 23.994 (3) Å
V = 3278.6 (7) Å^3
Z = 8
Mo $K\alpha$ radiation
μ = 5.20 mm^{-1}
T = 100 K
0.50 × 0.30 × 0.20 mm

Data collection

Bruker APEXII CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.111, T_{max} = 0.353
49136 measured reflections
10192 independent reflections
7285 reflections with $I > 2\sigma(I)$
R_{int} = 0.099

Table 1
Intermolecular C—H···O hydrogen bonds (Å, °) in compounds (I)–(IV).

D—H···A	D—H	H···A	D···A	D—H···A
(I) within stacks				
C4—H4A···O1^{iv}	0.99	2.67	3.624 (3)	161
(I) between stacks				
C15—H15A···O1^{v}	0.95	2.36	3.278 (3)	163
(II) within stacks				
C4A—H4A···O1A^{iii}	0.99	2.55	3.441 (6)	150
C4B—H4C···O1B^{vi}	0.99	2.60	3.493 (6)	150
(II) between stacks				
C13A—H13A···O1B^{vi}	0.95	2.45	3.159 (6)	131
C8B—H8B···O1A^{iii}	0.95	2.42	3.144 (6)	133
(III) within stacks				
C3—H1···O1^{i}	0.97	2.62	3.421 (7)	140
(III) between stacks				
C16—H14···O1^{ii}	0.93	2.46	3.333 (7)	157
(IV) within stacks				
C3—H1···O1^{iii}	0.97	2.57	3.441 (3)	149

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

H atoms were placed in calculated positions and refined in the riding model, with C—H = 0.95–0.99 Å and U_{iso}(H) = 1.5U_{eq}(C) for CH_3 groups or 1.2U_{eq}(C) for other groups.

20 distance restraints were used to fit the ideal conformations for both orientations of the disordered thiophene ring in compound (I). The S—C distances were fixed at 1.740 (2) (S1—C7 and S1′—C7) and 1.710 (2) Å (S1—C10 and S1′—C10′) (four restraints). Single-bond C—C distances were fixed at 1.420 (2) Å (two restraints), and double-bond C═C distances were fixed at 1.400 (2) (C7═C8 and C7═C8′) and 1.360 (2) Å (C9═C10 and C9′═C10′) (four restraints). S···C distances were fixed at 2.570 (2) (S1···C9 and S1′···C9′) and 2.550 (2) Å (S1···C8 and S1′···C8′) (four restraints). C···C distances were fixed at 2.490 (2) (C7···C10 and C7···C10′), 2.340 (2) (C7···C9 and C7···C9′) and 2.320 (2) Å (C8···C10 and C8···C10′) (six restraints). Moreover, it was taken into account that the thiophene ring is flat (two restraints), and the anisotropic displacement parameters for both the S atoms and the corresponding C atoms of the thiophene ring are equal (three restraints). 21 reflections, with experimentally observed F^2 deviating significantly from the theoretically calculated F^2 were omitted from the refinement.

For both compounds, data collection: *APEX2* (Bruker, 2005); cell refinement: *SAINT-Plus* (Bruker, 2001); data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GZ3158). Services for accessing these data are described at the back of the journal.

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