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(±)-6-Benzyl-3,3-dimethylmorpholine-2,5-dione and its 5-monothio and 2,5-dithio derivatives

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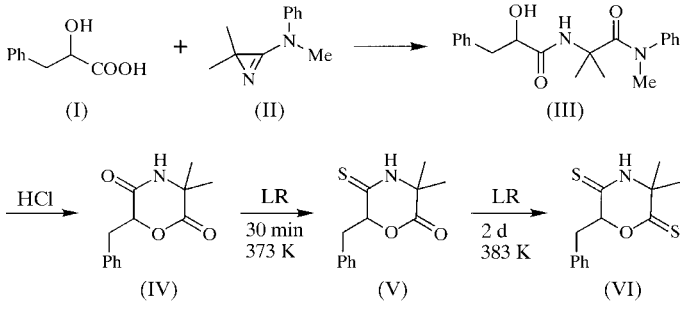
The morpholine ring of the title dione, $C_{13}H_{15}NO_3$, shows a boat conformation that is distorted towards a twist-boat, with the boat ends being the two Csp^3 atoms of the ring. The benzyl substituent is in the favoured '*exo*' position. In the monothione derivative, (±)-6-benzyl-3,3-dimethyl-5-thioxomorpholin-2-one, $C_{13}H_{15}NO_2S$, this ring has a much flatter conformation that is midway between a boat and an envelope, with the dimethyl end being almost planar. The orientation of the benzyl group is '*endo*'. The dithione derivative, (±)-6-benzyl-3,3-dimethylmorpholine-2,5-dithione, $C_{13}H_{15}NOS_2$, has two symmetry-independent molecules, which show different puckering of the morpholine ring. One molecule has a flattened envelope conformation distorted towards a screw-boat, while the conformation in the other molecule is similar to that in the monothione derivative. Intermolecular hydrogen bonds link the molecules in the three compounds, respectively, into centrosymmetric dimers, infinite chains, and dimers made up of one of each of the symmetry-independent molecules.

Comment

Some years ago, we showed that diamides akin to compound (III) (see Scheme), which are conveniently prepared by the reaction of hydroxy acids with 3-amino-2*H*-azirines, can be cyclized by treatment with HCl gas in a non-nucleophilic solvent (Obrecht & Heimgartner, 1984, 1987; Heimgartner, 1991*a*; Heimgartner *et al.*, 1999). This method, the so-called 'direct amide cyclization', has been used widely to prepare cyclic depsipeptides by lactone formation (Obrecht & Heimgartner, 1984, 1990; Magirius, 1995; Koch & Heimgartner, 2000; Koch *et al.*, 2000). In the case of larger rings, the cyclization occurs *via* 1,3-oxazol-5(4*H*)-ones as intermediates and ring enlargement by intramolecular nucleophilic attack of the hydroxy group at the oxazolone C═O group (Heimgartner *et al.*, 1999). On the other hand, a mechanism *via* an intermediate oxonium ion is more likely for the formation of the six-membered morpholine-2,5-diones.

In connection with our investigations of 1,3-dipolar cycloadditions with thiocarbonyl compounds (*cf.* Heimgartner, 1986, 1991*b*; Linden *et al.*, 1999; Mloston & Heimgartner, 2000), we also became interested in the thio analogues of morpholinediones as C═S dipolarophiles. The mono- and dithio analogues are attractive models for the study of the chemoselectivity (dipolarophilicity) of different π-systems in 1,3-dipolar cycloadditions. The racemic morpholine-2,5-dione (IV) was prepared following the described protocol of Obrecht & Heimgartner (1987). Subsequent successive thionation with Lawesson reagent (LR) led almost quantitatively to the monothione (V) and then to the morpholine-2,5-dithione (VI), although the latter reaction was sluggish with a low yield. As part of the full characterization of compounds (IV), (V), and (VI), their low-temperature crystal structures have been determined.



In each compound, the bond lengths and angles are generally within normal ranges. The amide C═O and thioamide C═S bonds in the dione, (IV), and the dithione, (VI), respectively, are longer than the corresponding ester C═O and thioester C═S bonds (Tables 1 and 3). This reflects the expected greater π-electron delocalization in (thio)amide groups compared with (thio)ester groups and is consistent with the trends for such groups derived from an examination of the Cambridge Structural Database (CSD, October 2000 release; Allen & Kennard, 1993). The angles at the O and N atoms of the morpholine rings (Tables 1, 3 and 5) are signifi-

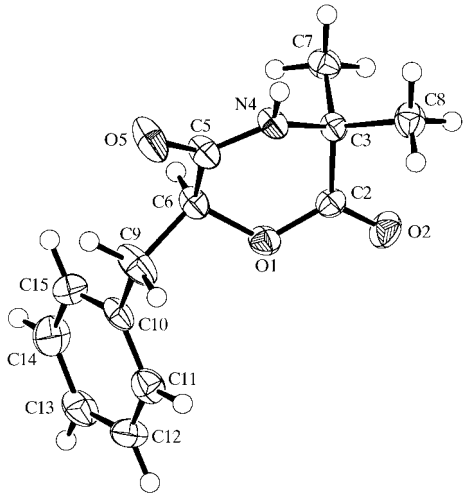


Figure 1
The molecular structure of (IV) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

cantly larger than 120°, particularly in the presence of the ring flattening observed in the monothione, (V), and dithione, (VI), derivatives, as described below.

The morpholine ring of the dione, (IV), has puckering parameters (Cremer & Pople, 1975) of Q = 0.463 (2) Å, θ = 92.4 (2)° and φ = 133.4 (2)°, which represent a conformation midway between a boat (nearest ideal values: θ = 90, φ = 120°) and a twist-boat (θ = 90, φ = 150°) (Boeyens, 1978), where the boat ends are the two Csp^3 atoms of the ring (Fig. 1) and the twist results from a slight non-planarity of the four atoms constituting the base of the boat. The r.m.s. deviation of O1, C2, N4 and C5 from their mean plane is 0.053 Å, while C3 and C6 deviate from this plane by 0.363 (3) and 0.416 (3) Å, respectively. The benzyl substituent is in the favoured '*exo*' position.

The morpholine ring of the monothione derivative, (V), has a much flatter and less twisted boat conformation (Fig. 2). The two Csp^3 atoms of the ring again form the ends of the boat, but the dimethyl end is almost coplanar with the base of the boat, so that the ring is distorted towards an envelope conformation. This is borne out by the ring-puckering parameters of Q = 0.139 (2) Å, θ = 75.2 (8)° and φ = 298.3 (10)°. The value of φ is appropriate for either an envelope or boat conformation (nearest ideal value is 300°) (Boeyens, 1978), while θ lies approximately midway between the ideal values for boat (90°) and envelope (54.7°) conformations. The r.m.s. deviation of O1, C2, N4 and C5 from their mean plane is only 0.002 Å, while C3 and C6 deviate from this plane by 0.069 (3) and 0.162 (3) Å, respectively. The orientation of the benzyl group is '*endo*', which brings the phenyl ring into a position above the body of the morpholine ring.

The asymmetric unit of the dithione derivative, (VI), has two symmetry-independent molecules (Fig. 3) and *PLATON* (Spek, 2001) confirmed that there was no additional overlooked symmetry, although the molecules are approximately related by a non-crystallographic twofold axis. The two molecules have different puckering of the morpholine ring and the orientation of the phenyl ring about the C9—C10 bond (C29—C30 in molecule *B*) also differs by a twist of about 17°. The morpholine ring of molecule *A* has puckering parameters of Q = 0.185 (2) Å, θ = 62.8 (7)° and φ = 75.2 (8)°, which represent a conformation midway between that of a slightly flattened envelope (nearest ideal values: θ = 54.7, φ = 60°) and a screw-boat (θ = 67.5, φ = 90°) (Boeyens, 1978). In contrast to compounds (IV) and (V), it is not an Csp^3 atom that is out of the plane, but the thioester C atom, C2. The r.m.s. deviation of O1, C3, N4, C5 and C6 from their mean plane is 0.022 Å, while C2 deviates from this plane by 0.250 (3) Å. The phenyl ring is positioned above the morpholine ring.

The morpholine ring in molecule *B* of (VI) has a flattened boat conformation distorted towards an envelope, similar to, but even flatter than, the conformation observed in compound (V). The ring-puckering parameters are Q = 0.097 (2) Å, θ = 101.6 (12)° and φ = 120.5 (12)°. Using the inverted molecule, which is also present in this racemic compound, θ = 78.4 (12)° and φ = 300.5 (12)°, which indicate a conformation similar to that observed for compound (V). As in (V), the two Csp^3 atoms of the ring form the ends of the boat, with the dimethyl end being almost coplanar with the base of the boat. The r.m.s. deviation of O21, C22, N24 and C25 from their mean plane is only 0.0004 Å, while C23 and C26 deviate from this plane by 0.056 (3) and 0.108 (3) Å, respectively. The orientation of the benzyl group is '*endo*', with the phenyl ring again being positioned above the morpholine ring.

There are only two structure reports cited in the CSD of compounds containing a morpholine-2,5-dione moiety, while there are no reports of any structures involving 5-thioxomorpholin-2-one or morpholine-2,5-dithione moieties. Both reported structures are simply substituted morpholine derivatives. The morpholine ring in 3-benzyl-6-isopropylmorpholine-2,5-dione was reported as having a boat conformation with the Csp^3 atoms forming the boat ends (Bolte & Egert, 1994). However, a closer examination of the puckering parameters [Q = 0.494 (2) Å, θ = 93.1 (2)° and φ = 129.3 (2)°] shows that the ring has an unflattened conformation that lies midway between a boat and a twist-boat, and which is virtually identical to that in compound (IV). Conversely, in 3-benzyl-3-hydroxy-6-methylamino-6-(2-methylpropyl)morpholine-2,5-dione (Iijima *et al.*, 1992), the

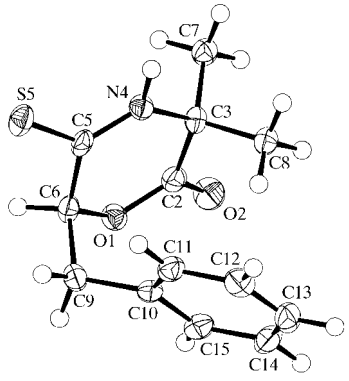


Figure 2
The molecular structure of (V) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

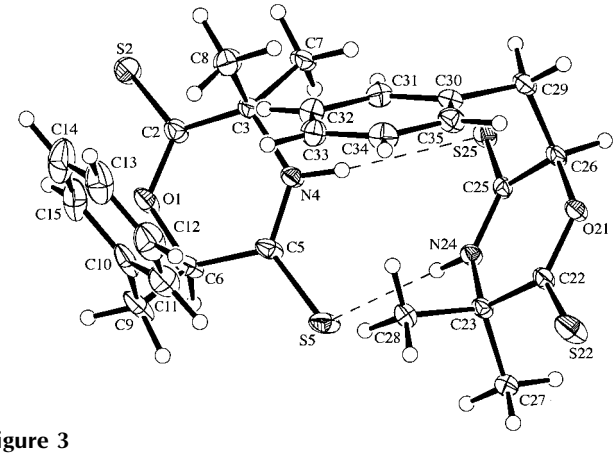


Figure 3
The molecular structure of both symmetry-independent molecules of (VI) showing the atom-labelling scheme and the hydrogen bonds (dashed lines). Molecule *A* is on the left. Displacement ellipsoids are drawn at the 30% probability level. H atoms are represented by circles of arbitrary size.

morpholine ring has an almost completely flattened boat conformation, with the two Csp^3 atoms being only 0.086 and 0.078 Å from the plane defined by the other four ring atoms, which are all 0.002 Å from their mean plane.

While a comparison of the structures of compounds (IV), (V) and (VI) might induce one to conclude that an increasing number of thione substituents in the morpholine ring leads to a greater flattening of the ring, the two previously reported structures of morpholine-2,5-dione derivatives contradict this hypothesis and suggest that the cause of the ring flattening is not necessarily related to the degree of thione substitution, but to other effects which cannot readily be deduced from the small number of determined structures of this class.

The amide N—H group of compound (IV) forms an intermolecular hydrogen bond with the amide O atom of an adjacent molecule (Table 2). This acceptor molecule then donates back to the first molecule, thereby linking pairs of molecules into centrosymmetric dimers whose interactions can be described by the graph-set motif of $R_2^2(8)$ (Bernstein *et al.*, 1995). In the monothione derivative, (V), a simple change from the ester group of (IV) to a thioester group has dramatically altered the hydrogen-bonding pattern (Table 4). The acceptor atom is now the morpholine ring O atom of a neighbouring molecule and intermolecular interactions link the molecules of (V) into infinite one-dimensional chains which run parallel to the [010] direction and have a graph-set motif of $C(5)$. In compound (VI), the hydrogen-bonding pattern is similar to that in compound (IV). The acceptor atom is the thioamide S atom of the other symmetry-independent molecule in the asymmetric unit. This acceptor molecule then donates back to the first molecule, thus forming hydrogen-bonded dimers comprised of one of each of the symmetry-independent molecules (Table 6 and Fig. 3). These interactions can again be described by the graph-set motif of $R_2^2(8)$.

Experimental

Compound (III) was obtained in 92% yield by the reaction of DL-phenyllactic acid, (I) (408 mg, 2.46 mmol), and 2,2,*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine, (II) (472 mg, 2.71 mmol), in acetonitrile (20 ml) at room temperature following a known protocol (Obrecht & Heimgartner, 1987). Treatment of a solution of (III) (2.19 g, 6.44 mmol) in toluene (300 ml) at 373 K with dry HCl gas for 15 min yielded, after chromatography (silica gel, dichloromethane/diethyl ether, 6:1) and crystallization from diethyl ether, compound (IV) in 27% yield as colourless plates (m.p. 437–438 K). Lawesson reagent (Scheibye *et al.*, 1978) (240 mg, 0.59 mmol) was added to a solution of (IV) (276 mg, 1.19 mmol) in toluene (15 ml), and the mixture was heated to 373 K for 30 min. After chromatography (silica gel, dichloromethane/hexane, 3:2) and crystallization from dichloromethane/diethyl ether, compound (V) was obtained in 96% yield as colourless needles (m.p. 448–449 K). Heating a mixture of (V) (95 mg, 0.38 mmol) and Lawesson reagent (3.84 mg, 0.95 mmol) in toluene (10 ml) for 2 d under reflux led, after chromatographic separation (silica gel, dichloromethane/hexane, 1:1), to compound (VI) in 28% yield as yellow prisms (m.p. 396–397 K). Suitable single crystals of (VI) were obtained by recrystallization from diethyl ether/dichloromethane/hexane.

Compound (IV)

Crystal data

$C_{13}H_{15}NO_3$
M_r = 233.27
Triclinic, $P\overline{1}$
a = 5.699 (2) Å
b = 10.347 (3) Å
c = 11.327 (4) Å
α = 67.51 (2)°
β = 80.38 (3)°
γ = 80.35 (3)°
V = 604.5 (4) Å^3
Z = 2
D_x = 1.281 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 19.0–20.0°
μ = 0.09 mm^{-1}
T = 173 (1) K
Plate, colourless
0.50 × 0.38 × 0.12 mm

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
2927 measured reflections
2773 independent reflections
1859 reflections with $I > 2\sigma(I)$
R_{int} = 0.025
θ_{max} = 27.5°
$h = -7 \rightarrow 7$
$k = -13 \rightarrow 0$
$l = -14 \rightarrow 13$
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.130
S = 1.02
2773 reflections
160 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0530P)^2 + 0.1854P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (IV).

O1—C2	1.340 (2)	O5—C5	1.236 (2)
O1—C6	1.457 (2)	N4—C5	1.323 (2)
O2—C2	1.199 (2)	N4—C3	1.460 (2)
C2—O1—C6	120.53 (13)	C5—N4—C3	124.06 (14)

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

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O5^{i}	0.88 (2)	1.95 (2)	2.833 (2)	176 (2)

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

Compound (V)

Crystal data

$C_{13}H_{15}NO_2S$
M_r = 249.33
Monoclinic, $P2_1/n$
a = 13.901 (4) Å
b = 5.843 (6) Å
c = 16.559 (5) Å
β = 112.70 (2)°
V = 1240.7 (13) Å^3
Z = 4
D_x = 1.335 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 24 reflections
θ = 18.0–20.0°
μ = 0.25 mm^{-1}
T = 173 (1) K
Needle, colourless
0.50 × 0.20 × 0.15 mm

Data collection

Rigaku AFC-5*R* diffractometer
ω–2θ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.696, T_{max} = 0.963
3261 measured reflections
2854 independent reflections
1926 reflections with $I > 2\sigma(I)$
R_{int} = 0.034
θ_{max} = 27.5°
$h = 0 \rightarrow 18$
$k = 0 \rightarrow 7$
$l = -21 \rightarrow 19$
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on F^2	H atoms: see below
$R[F^2 > 2\sigma(F^2)] = 0.052$	$w = 1/[\sigma^2(F_o^2) + (0.0820P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.151$	$(\Delta/\sigma)_{max} = 0.001$
$S = 1.04$	$\Delta\rho_{max} = 0.53$ e Å^{-3}
2854 reflections	$\Delta\rho_{min} = -0.36$ e Å^{-3}
160 parameters	

Table 3
Selected geometric parameters (Å, °) for (V).

S5—C5	1.669 (2)	O2—C2	1.204 (3)
O1—C2	1.347 (3)	N4—C3	1.470 (3)
O1—C6	1.455 (3)	N4—C5	1.315 (3)
C2—O1—C6	124.30 (19)	C5—N4—C3	128.6 (2)

Table 4
Hydrogen-bonding geometry (Å, °) for (V).

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···O1^{i}	0.90 (3)	2.22 (3)	3.092 (4)	164 (2)

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

Compound (VI)

Crystal data

$C_{13}H_{15}NOS_2$	$Z = 4$
$M_r = 265.39$	$D_x = 1.327$ Mg m^{-3}
Triclinic, $P\overline{1}$	Mo $K\alpha$ radiation
$a = 8.6915$ (13) Å	Cell parameters from 25 reflections
$b = 11.896$ (3) Å	$\theta = 19.0$–$20.0°$
$c = 13.661$ (4) Å	$\mu = 0.38$ mm^{-1}
$\alpha = 75.62$ (2)°	$T = 173$ (1) K
$\beta = 76.211$ (16)°	Prism, yellow
$\gamma = 84.971$ (18)°	0.48 × 0.40 × 0.30 mm
$V = 1328.2$ (6) Å^3	

Data collection

Rigaku AFC-5*R* diffractometer	$R_{int} = 0.021$
ω–2θ scans	$\theta_{max} = 27.5°$
Absorption correction: ψ scan (North *et al.*, 1968)	$h = -11 \rightarrow 11$
$T_{min} = 0.781$, $T_{max} = 0.891$	$k = -15 \rightarrow 0$
6399 measured reflections	$l = -17 \rightarrow 17$
6101 independent reflections	3 standard reflections
4424 reflections with $I > 2\sigma(I)$	every 150 reflections
	intensity decay: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0823P)^2 + 0.0825P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.049$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.142$	$\Delta\rho_{max} = 0.54$ e Å^{-3}
$S = 1.05$	$\Delta\rho_{min} = -0.41$ e Å^{-3}
6101 reflections	
319 parameters	
H atoms: see below	

For each compound, the methyl H atoms were constrained to an ideal geometry with $U_{iso}(H) = 1.5U_{eq}(C)$. The amino H atoms were refined freely. All other H atoms were constrained to ride on their parent atoms with $U_{iso}(H) = 1.2U_{eq}(C)$. For (V), the ψ scans showed a more severe absorption profile than predicted theoretically and this is attributed to the anisotropic shape of the crystal.

For all compounds, data collection and cell refinement: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991); data reduction: *TEXSAN* (Molecular Structure Corporation, 1999); structure solution: *SHELXS*97 (Sheldrick, 1997); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976).

Table 5
Selected geometric parameters (Å, °) for (VI).

S2—C2	1.624 (2)	S22—C22	1.628 (2)
S5—C5	1.670 (2)	S25—C25	1.685 (2)
O1—C2	1.331 (3)	O21—C22	1.331 (2)
O1—C6	1.455 (3)	O21—C26	1.458 (2)
N4—C5	1.319 (3)	N24—C25	1.308 (3)
N4—C3	1.473 (3)	N24—C23	1.476 (2)
C2—O1—C6	124.91 (18)	C22—O21—C26	126.03 (16)
C5—N4—C3	128.14 (19)	C25—N24—C23	128.93 (18)

Table 6
Hydrogen-bonding geometry (Å, °) for (VI).

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···S25	0.89 (3)	2.58 (3)	3.469 (2)	173 (3)
N24—H24···S5	0.91 (3)	2.42 (3)	3.293 (2)	163 (2)

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1460). Services for accessing these data are described at the back of the journal.

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