

2-Phenylmalonpiperadide and 2-phenylmalonmorpholide

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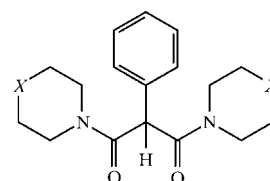
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The structures of 2-phenylmalonpiperadide [systematic name: 2-phenyl-1,3-bis(piperidin-1-yl)propane-1,3-dione, $C_{19}H_{26}N_2O_2$, (I)] and 2-phenylmalonmorpholide [systematic name: 1,3-dimorpholino-2-phenylpropane-1,3-dione, $C_{17}H_{22}N_2O_4$, (II)], have been determined and both their molecular conformations and packing arrangements compared. Although chemically similar, compounds (I) and (II) exhibit different molecular conformations. The only general conformational similarities are that their respective carbonyl groups are orientated in the same direction and the heterocyclic rings exist in the chair arrangement. General similarities in the packing arrangements arise due to both compounds having the same space group ($P2_12_12_1$) and a similar alignment of their phenyl-substituted backbone with respect to the c axis. Similar C—H \cdots O hydrogen-bonding associations are listed for the carbonyl O atoms, while only one of the morpholine O atoms is involved in any such association.

Comment

Symmetrical malonamides can be prepared by two classical methods (Burgada, 1964), with both involving the reaction of two molar equivalents of an amine with either diethyl malonate or malonyl dichloride. A third, more modern but less efficient, synthesis involves the reaction of two molar equivalents of a base or amine with 3-oxopyrazolo[1,2- a]pyrazol-8-ylum-1-olate (Zvilichovsky & David, 1982), a compound also derived from either diethyl malonate or malonyl dichloride. The nucleophilic cleavage of derivatives of 3-oxopyrazolo[1,2- a]pyrazol-8-ylum-1-olate to produce symmetrical malonamides was also investigated by Potts *et al.* (1988), who studied the decomposition of these compounds using morpholine, aniline or water. Experimental runs were performed in tetrahydrofuran at 298 K and took from a few seconds to several days for a complete reaction, depending on the substituents of the initial pyrazolo[1,2- a]pyrazole, with one of the slowest reactions being seen for 5,7-dimethyl-2-phenyl-

1-oxo-1 H -pyrazolo[1,2- a]pyrazol-4-ylum-3-olate. We decided to continue investigating the nucleophilic cleavage of this compound using a variety of nucleophiles, including both piperidine and morpholine, with all resultant products being 2-phenylmalonamide derivatives. Interestingly, a search of the April 2003 release of the Cambridge Structural Database (Allen, 2002) reveals that there are 37 reported structures of malonamides, including both symmetrical and unsymmetrical analogues, yet of these there is only one 2-phenylmalonamide derivative, that being the amide itself (Sakamoto *et al.*, 2000). Reported here are the crystal structures of both 2-phenylmalonpiperadide, (I), and 2-phenylmalonmorpholide, (II).



(I) $X = CH_2$

(II) $X = O$

Compounds (I) and (II) share crystallographic similarities by both packing in the same non-centrosymmetric space group and sharing similar cell dimensions and cell volumes. The only chemical difference between the two compounds is the substitution of the piperidyl 4-position CH_2 groups in (I) for the morpholine O atoms in (II), with the loss of *ca* 104 Å³ in cell volume. However, these two O atoms have the potential to cause a difference in the solid-state packing of (II), as opposed to (I), because exposed O atoms can act as hydrogen-bond acceptors, in addition to the two malonamide carbonyl O atoms. Comparative molecular conformations for (I) and (II) are shown in Figs. 1 and 2, respectively, while selected torsion angles are listed in Tables 1 and 3.

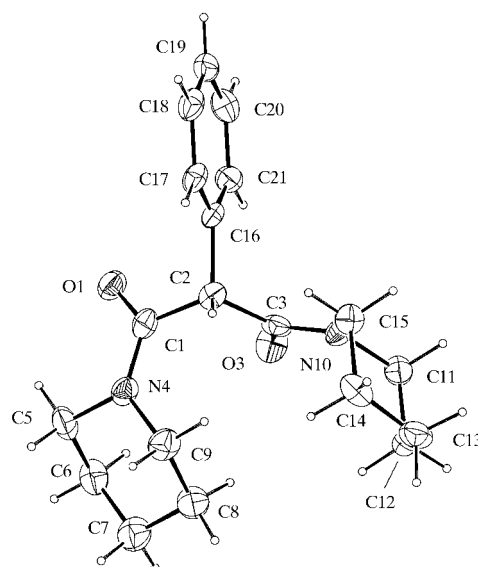


Figure 1

The molecular configuration and atom-numbering scheme for (I). Displacement ellipsoids are drawn at the 50% probability level.

With both saturated heterocyclic ring systems in the chair conformation and the carbonyl groups orientated in the same direction for both molecules, the important torsion angles become those containing the C16—C2 bond, specifically N4—C1—C2—C16 and C16—C2—C3—N10, because the backbone torsion angles for the two compounds, *viz.* N4—C1—C2—C3 and C1—C2—C3—N10, are inversely similar. The conformation of 2-phenylmalonamide itself differs from both (I) and (II) by having the carbonyl groups arranged in opposing directions and the backbone chain much flatter. Comparative torsion angles are 98.15 (N1—C1—C2—C4), 101.16 (C4—C2—C3—N2), -26.26 (N1—C1—C2—C3) and 134.11° (C1—C2—C3—N4) (note that in 2-phenylmalonamide, atom C4 = C16).

The C—H \cdots O hydrogen-bonding associations for compounds (I) and (II) are listed in Tables 2 and 4, respectively, and although both compounds are arranged very differently, the malonamide carbonyl O atoms in each are involved in the same number of intermolecular C—H \cdots O associations. In

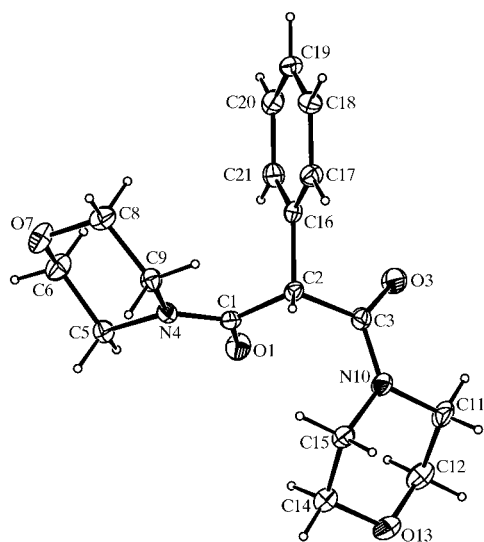


Figure 2
The molecular configuration and atom-numbering scheme for (II). Displacement ellipsoids are drawn at the 50% probability level.

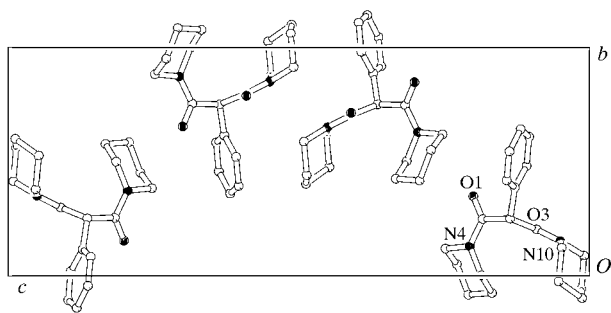


Figure 3
Packing diagram of (I), viewed down the *a* axis. Note that atom O3 is obscured by atom C3.

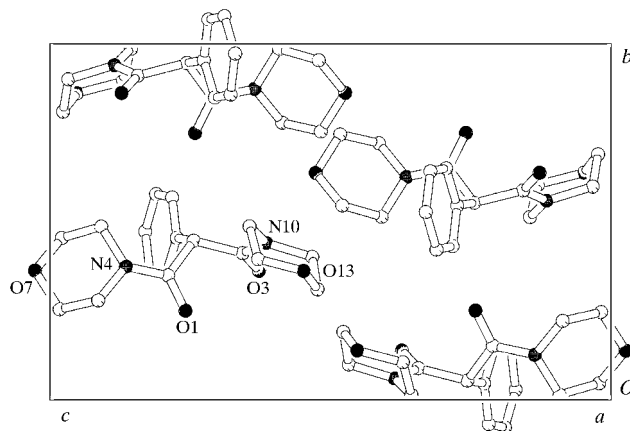


Figure 4
Packing diagram of (II), viewed down the *a* axis.

addition, there is only one listed association to a morpholine O atom (O13), indicating that the morpholine O atoms do not have much effect on the difference in the molecular packing. The unit cells for (I) and (II), both viewed down the *a* axis, are shown in Figs. 3 and 4. Interestingly, the phenyl rings in both compounds are arranged almost perpendicular to the *c* axis, orientating the main length of the backbone in the same direction as the *c* axis. However, apart from these general packing similarities, the two structures remain considerably different. The occurrence of crystallographic differences between chemically similar compounds, such as (I) and (II), is interesting and in the structures discussed in this paper have no apparent cause. Additional comparative compounds would be those containing thiomorpholine, piperazine or any minor 4-position derivative of piperidine or piperazine.

Experimental

For (I), a 2:1 molar ratio of piperidine (0.71 g, 8.33 mmol) and 5,7-dimethyl-2-phenyl-1-oxo-1*H*-pyrazolo[1,2-*a*]pyrazol-4-ylidium-3-olate (1.00 g, 4.20 mmol) was refluxed in tetrahydrofuran (THF, 100 ml) for 48 h. Upon cooling the reaction, the solvent was removed under reduced pressure. The crude product was redissolved in minimal THF and precipitated by pouring into cool deionized water (100 ml). Collection *in vacuo* yielded an off-white powder (0.94 g, 72%; m.p. 416–419 K). Spectroscopic analysis, IR (ν_{\max} , KBr, cm^{-1}): 1647 (*s*) and 1626 (*s*) (CO); ^1H NMR (400 MHz, d_6 -DMSO, Me_4Si , p.p.m.): 1.40 (*m*, 12H, CH_2), 3.40 (*m*, 8H, NCH_2), 5.40 (*s*, 1H), 7.30 (*m*, 5H, ArH); *m/z* (ES): 315 (MH^+ , 15%), 337 ($\text{M} + \text{Na}$, 39%), 651 ($2\text{M} + \text{Na}$, 100%). Compound (II) was produced using a method analogous to that used for (I), using morpholine (1.45 g, 1.67 mmol) and 5,7-dimethyl-2-phenyl-1-oxo-1*H*-pyrazolo[1,2-*a*]pyrazol-4-ylidium-3-olate (2.00 g, 8.33 mmol). The final product was collected *in vacuo* as a white powder (2.33 g, 88%, m.p. 459–461 K). Spectroscopic analysis, IR (ν_{\max} , KBr, cm^{-1}): 1658 (*s*) and 1633 (*s*) (CO); ^1H NMR (400 MHz, d_6 -DMSO, Me_4Si , p.p.m.): 3.27–3.63 (*br m*, 16H, NCH_2 and OCH_2), 5.51 (*s*, 1H), 7.21–7.39 (*m*, 5H, ArH); *m/z* (ES): 319 (MH^+ , 30%), 341 ($\text{M} + \text{Na}$, 100%), 659 ($2\text{M} + \text{Na}$, 73%). Crystals of both compounds were grown from CHCl_3 solutions.

Compound (I)*Crystal data*

C₁₉H₂₆N₂O₂
M_r = 314.42
 Orthorhombic, *P*2₁2₁2₁
a = 6.1652 (3) Å
b = 10.2718 (5) Å
c = 26.1962 (17) Å
V = 1658.95 (16) Å³
Z = 4
D_x = 1.259 Mg m⁻³

Mo *K*α radiation
 Cell parameters from 6419 reflections
 $\theta = 2.9\text{--}27.5^\circ$
 $\mu = 0.08\text{ mm}^{-1}$
T = 120 (2) K
 Plate, colourless
 0.15 × 0.10 × 0.04 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SORTAV; Blessing, 1995)
T_{min} = 0.988, *T_{max}* = 0.997
 6936 measured reflections

2177 independent reflections
 1013 reflections with *I* > 2σ(*I*)
R_{int} = 0.176
 $\theta_{\text{max}} = 27.5^\circ$
h = −7 → 7
k = −9 → 13
l = −34 → 25

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.069
wR(*F*²) = 0.177
S = 0.94
 2177 reflections
 209 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0705P)^2]$
 where $P = (F_o^2 + 2F_c^2)/3$

(Δ/σ)_{max} < 0.001
 $\Delta\rho_{\text{max}} = 0.34\text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.34\text{ e \AA}^{-3}$
 Extinction correction: SHELXL97
 Extinction coefficient: 0.012 (3)

Table 1

Selected torsion angles (°) for (I).

O1–C1–C2–C16	19.1 (7)	C16–C2–C3–O3	−96.3 (6)
N4–C1–C2–C16	−159.0 (5)	C1–C2–C3–O3	24.2 (7)
O1–C1–C2–C3	−102.6 (6)	C16–C2–C3–N10	83.4 (6)
N4–C1–C2–C3	79.3 (5)	C1–C2–C3–N10	−156.1 (5)

Table 2

Hydrogen-bonding and short-contact geometry (Å, °) for (I).

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
C5–H51···O1	0.99	2.34	2.757 (7)	104
C9–H91···O1 ⁱ	0.99	2.52	3.436 (7)	153
C11–H112···O3	0.99	2.32	2.735 (7)	104
C15–H151···O3 ⁱⁱ	0.99	2.43	3.177 (7)	132
C17–H17···O1 ⁱⁱ	0.95	2.59	3.340 (7)	136

Symmetry codes: (i) 2 − *x*, *y* − ½, ½ − *z*; (ii) 1 + *x*, *y*, *z*.**Compound (II)***Crystal data*

C₁₇H₂₂N₂O₄
M_r = 318.37
 Orthorhombic, *P*2₁2₁2₁
a = 8.3900 (1) Å
b = 10.8464 (2) Å
c = 17.0838 (4) Å
V = 1554.65 (5) Å³
Z = 4
D_x = 1.360 Mg m⁻³

Mo *K*α radiation
 Cell parameters from 6411 reflections
 $\theta = 1.0\text{--}30.5^\circ$
 $\mu = 0.10\text{ mm}^{-1}$
T = 120 (2) K
 Block, colourless
 0.60 × 0.40 × 0.26 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SORTAV; Blessing, 1995)
T_{min} = 0.944, *T_{max}* = 0.975
 9999 measured reflections

2032 independent reflections
 1909 reflections with *I* > 2σ(*I*)
R_{int} = 0.066
 $\theta_{\text{max}} = 27.5^\circ$
h = −9 → 10
k = −11 → 14
l = −18 → 22

Refinement

Refinement on *F*²
R[*F*² > 2σ(*F*²)] = 0.039
wR(*F*²) = 0.103
S = 1.12
 2032 reflections
 209 parameters
 H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.0639P)^2 + 0.2187P]$
 where $P = (F_o^2 + 2F_c^2)/3$

(Δ/σ)_{max} < 0.001
 $\Delta\rho_{\text{max}} = 0.38\text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.35\text{ e \AA}^{-3}$
 Extinction correction: SHELXL07
 Extinction coefficient: 0.067 (7)

Table 3

Selected torsion angles (°) for (II).

O1–C1–C2–C16	106.91 (18)	C16–C2–C3–O3	−20.3 (2)
N4–C1–C2–C16	−71.0 (2)	C1–C2–C3–O3	100.5 (2)
O1–C1–C2–C3	−13.8 (2)	C16–C2–C3–N10	158.25 (16)
N4–C1–C2–C3	168.29 (15)	C1–C2–C3–N10	−81.0 (2)

Table 4

Hydrogen-bonding and short_contact geometry (Å, °) for (II).

<i>D</i> –H··· <i>A</i>	<i>D</i> –H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> –H··· <i>A</i>
C2–H2···O1 ⁱ	1.00	2.41	3.344 (2)	155
C17–H17···O1 ⁱ	0.95	2.50	3.361 (2)	150
C5–H52···O1	0.99	2.32	2.747 (2)	105
C9–H92···O13 ⁱⁱ	0.99	2.51	3.275 (2)	134
C11–H112···O3	0.99	2.31	2.738 (3)	105
C12–H122···O3 ⁱⁱⁱ	0.99	2.43	3.305 (2)	148

Symmetry codes: (i) 2 − *x*, ½ + *y*, ½ − *z*; (ii) ½ − *x*, 1 − *y*, ½ + *z*; (iii) ½ + *x*, ½ − *y*, 1 − *z*.

All H atoms were included in the refinement at calculated positions in the riding-model approximation, with C–H distances set at 0.95 (aryl H), 0.99 (CH₂) and 1.00 Å (C–H), and isotropic displacement parameters set equal to 1.25*U*_{eq} of the carrier atom. The high *R_{int}* value for (I) was the result of weak high-angle data. The numbers of Friedel pairs for (I) and (II) were 1386 and 1195, respectively. In the absence of large atoms in both structures or strong anomalous dispersion effects, the Friedel opposites were merged prior to refinement.

For both compounds, data collection: DENZO (Otwinowski & Minor, 1997) and COLLECT (Nonius, 1998); cell refinement: DENZO and COLLECT; data reduction: DENZO and COLLECT; program(s) used to solve structure: SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: SHELXL97 (Sheldrick, 1997); molecular graphics: PLUTON94 (Spek, 1994) and PLATON97 (Spek, 1997); software used to prepare material for publication: SHELXL97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1184). Services for accessing these data are described at the back of the journal.

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