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1,4-Dimorpholinobenzene

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Key indicators

Single-crystal X-ray study
T = 173 K
Mean σ(C–C) = 0.003 Å
R factor = 0.052
wR factor = 0.115
Data-to-parameter ratio = 15.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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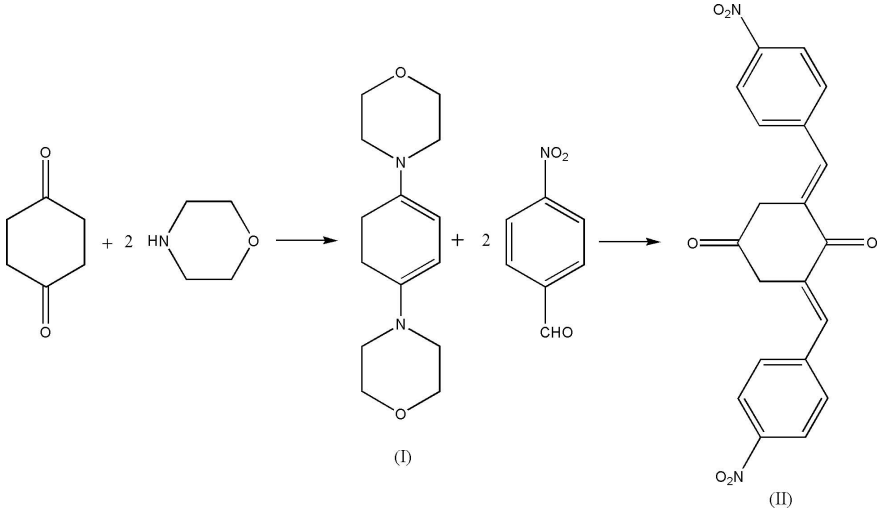
In the crystal structure of the title compound, $C_{14}H_{20}N_2O_2$, there is a center of symmetry at the centroid of the benzene ring; the asymmetric unit is, therefore, one half molecule. The morpholine ring is in a chair conformation.

Comment

A major objective of our laboratories is the preparation of various conjugated styryl ketones as candidate antineoplastic alkylating agents. These compounds have demonstrated a selective affinity for thiols and not amino or hydroxy groups (Mutus *et al.*, 1989); these latter two groups are found in nucleic acids. Thus, genotoxic properties of α,β-unsaturated ketones may be absent. Studies have revealed that the incorporation of a nitro group into the aryl ring of a styryl function increased cytotoxic potencies compared to a number of other substituents (Dimmock *et al.*, 2003). This result may be due to the strong electron-attracting effects of the nitro group and/or its reduction to toxic species. Furthermore, the theory of sequential cytotoxicity, which was proposed by one of the authors, states that some cancer cells are more susceptible to successive chemical assaults than the corresponding normal cells (Dimmock *et al.*, 2000). These considerations led to the proposal to synthesize and evaluate the antineoplastic properties of (II), which contains a 1,5-diaryl-3-oxo-1,4-pentadienyl group having a nitro substituent on both aryl rings. This molecule should permit sequential attacks on the electron-deficient olefinic C atoms.

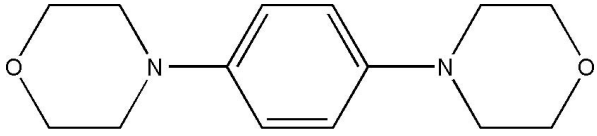


(I) (II)

The initial route attempted is indicated in the reaction scheme above, although the formation of structural isomers of (I) and (II) was possible.

It was expected that morpholine would react with cyclohexane-1,4-dione to produce the bis-enamine (I), which would

subsequently condense with 4-nitrobenzaldehyde to obtain (II). However, the product isolated was identified by X-ray crystallography as 1,4-dimorpholinobenzene, (III).



(III)

Compound (III) has been synthesized previously by the palladium-catalysed reaction between 1,4-dibromobenzene and morpholine (Witulski *et al.*, 1998; Beletskaya *et al.*, 1999), as well as by the condensation of 1,4-diaminobenzene and bis(2-chloroethyl) ether (Axe & Freeman, 1934). The synthetic route to (III) described in this report appears to be novel, although the condensation between cyclohexane-1,4-dione and either pyrrolidine or piperidine, leading to the formation of 1,4-bis(1-pyrrolidinyl)benzene or 1,4-bis(1-piperidinyl)benzene, respectively, has been reported (Leonard & Sauers, 1956). The tentative conclusions, therefore, are that morpholine reacted with cyclohexane-1,4-dione to produce (I), which was oxidized to the title product, (III), and that 4-nitrobenzaldehyde was not involved in the reaction pathway.

The two morpholino groups are in chair conformations and are twisted relative to the aromatic ring, so that the torsion angle C3—C2—N1—C7 is 5.2 (3)°, whereas the angle C1—C2—N1—C4 is −46.2 (2)°.

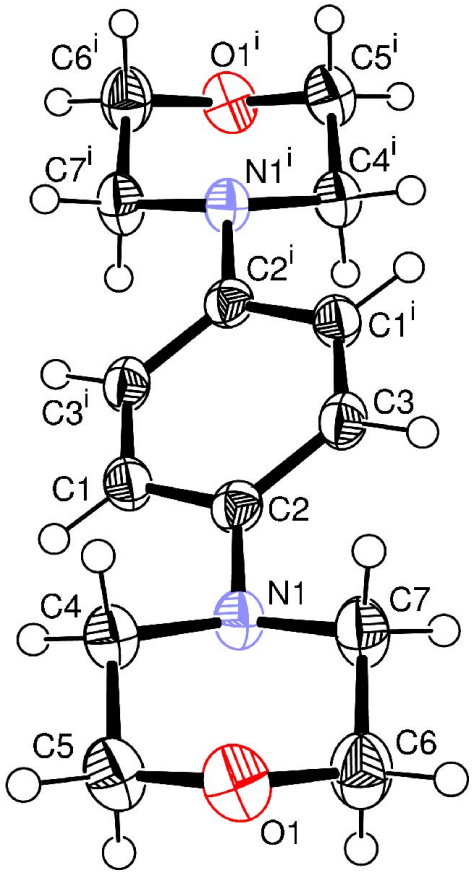


Figure 1
A general *ORTEP-3* view (Farrugia, 1997) of (III), with non-H atom displacement ellipsoids drawn at the 50% probability level. For clarity, H atoms are drawn as small spheres of arbitrary size. [Symmetry code: (i) $1-x, -y, -z$.]

Experimental

A solution of cyclohexane-1,4-dione (4.0 g, 0.035 mol), morpholine (6.75 g, 0.11 mol) and 4-toluenesulfonic acid (20 mg) in toluene (100 ml) was heated under reflux in a Dean–Stark apparatus for 8 h. After the addition of 4-nitrobenzaldehyde (11.0 g, 0.073 mol), the reaction mixture was heated under reflux for 8 h. Water (40 ml) was added and the mixture was heated at 333–343 K for 5–6 h, after which time toluene was removed *in vacuo*. The mixture was extracted once with chloroform and the organic extract was washed with aqueous sodium bicarbonate solution (5% *w*/*v*, 20 ml) and dried over anhydrous sodium sulfate. Removal of the solvent led to the isolation of a semi-solid which was chromatographed on silica gel 60 (63–200 mesh), using a mixture of *n*-hexane and ethyl acetate (9:1) as eluting solvent, to produce (III) as yellow crystals [m.p. 463 K; literature m.p. 469 K (Axe & Freeman, 1934)]. Analysis calculated for $C_{14}H_{20}N_2O_2$: C 67.71, H 8.12, N 11.28%; found: C 67.51, H 7.92, N 11.35%.

Crystal data

$C_{14}H_{20}N_2O_2$
$M_r = 248.32$
Monoclinic, $P2_1/c$
$a = 6.9410\ (7)$ Å
$b = 8.1410\ (9)$ Å
$c = 11.2120\ (6)$ Å
$\beta = 90.994\ (6)°$
$V = 633.46\ (10)$ Å^3
$Z = 2$
$D_x = 1.302$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 1414 reflections
$\theta = 1.0–27.5°$
$\mu = 0.09$ mm^{-1}
$T = 173\ (2)$ K
Plate, yellow
0.25 × 0.25 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
Thick-slice φ and ω scans
2081 measured reflections
1232 independent reflections
856 reflections with $I > 2\sigma(I)$
$R_{int} = 0.033$
$\theta_{max} = 26.0°$
$h = -8 \rightarrow 8$
$k = -9 \rightarrow 10$
$l = -13 \rightarrow 13$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.052$
$wR(F^2) = 0.115$
$S = 1.11$
1232 reflections
82 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.03P)^2 + 0.2441P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}

H atoms were placed in calculated positions (C—H = 0.99 Å for methylene C atoms and 0.95 Å for aromatic C atoms), with U_{iso} values constrained to be 1.2 times U_{eq} of the carrier atom for methylene and aromatic H atoms.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997) and *PLATON* (Spek, 2003).

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