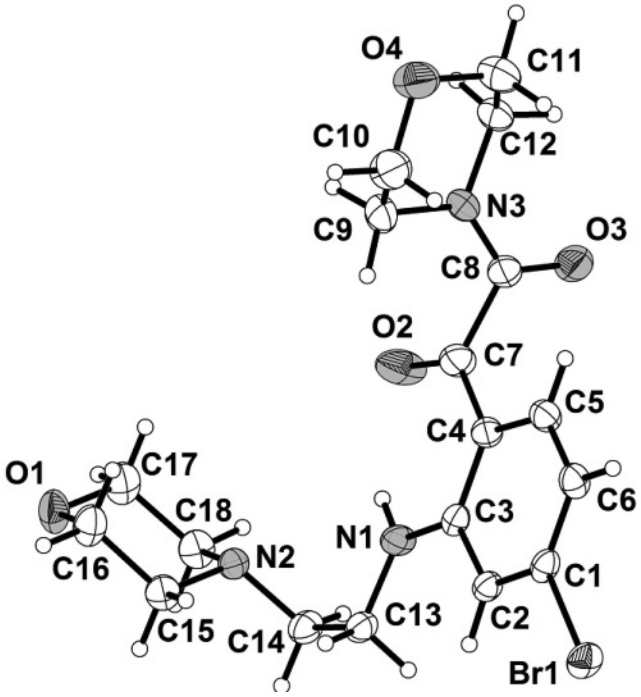
Crystal structure of 1-(4-bromo-2-(2-morpholinoethylamino)phenyl)-2-morpholinoethane-1,2-dione, $C_{18}H_{24}BrN_3O_4$

Li Ma, Ai-Min Li, Chong-Qing Wan and Sheng-Li Cao*

Department of Chemistry, Capital Normal University, Beijing 100048, P. R. China

Received November 11, 2013, accepted August 20, 2014, available online September 02, 2014, CCDC no. 1267/4134



Abstract

$C_{18}H_{24}BrN_3O_4$, monoclinic, $P2_1/c$ (no. 14), a = 15.5575(7) Å, b = 10.3792(5) Å, c = 11.9486(5) Å, β = 95.125(2)°, V = 1921.7 Å^3, Z = 4, $R_{gt}(F)$ = 0.0261, $wR_{ref}(F^2)$ = 0.0654, T = 296 K.

Table 1. Data collection and handling.

Crystal:	yellow blocks, size 0.20×0.25×0.30 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	21.67 cm^{-1}
Diffractometer, scan mode:	Bruker APEXII CCD, φ and ω
$2\theta_{max}$:	50.02°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	13685, 3389
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 2874
$N(param)_{refined}$:	236
Programs:	SHELX [7], DIAMOND [8]

Source of material

To a solution of 6-bromo-1-(2-bromoethyl)indoline-2,3-dione (0.33 g, 1 mmol) in *N*,*N*-dimethylformamide (5 ml) was added morpholine (0.35 g, 4 mmol). The mixture was stirred for 48 h at room temperature, then 30 ml water was added to the solution and extracted with ethyl acetate (20 ml × 3). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation. The residue was isolated by column chromatography on silica gel with methylene chloride/methanol = 99:1 (*v*/*v*) as an eluent. Besides the major product, 6-bromo-1-(2-morpholinoethyl)indoline-2,3-dione, the title compound 1-(4-bromo-2-(2-morpholinoethylamino)phenyl)-2-morpholinoethane-1,2-dione was obtained. Yellow crystals of the title compound were obtained by slow evaporation of the solution of methylene chloride/methanol = 99:1 (*v*/*v*) at room temperature (m.p. 196-198 °C).

Discussion

1*H*-indole-2,3-dione derivatives have driven much attention for their bioactivities on anti-HIV [1], anticonvulsant [2] and antitumor activities [3,4]. It has been reported that the introduction of substituents at the N atom of indolin-2-ones enhances their cytotoxicity against a variety of cancer cell lines [5,6]. In an attempt to obtain compounds that might also exhibit antitumor properties, we carried out the reaction of 6-bromo-1-(2-bromoethyl)indoline-2,3-dione with an excess of morpholine. Interestingly, an unexpected nucleophilic attack of morpholine at the C2 position of 6-bromo-1-(2-bromoethyl)indoline-2,3-dione led to the formation of the title compound. In the crystal structure of the title compound, there are two morpholine rings with chair conformations and the corresponding bond distances and angles in these morpholine rings are roughly the same. One of the morpholine rings links to the arene ring via two carbonyl groups, and the other is connected to the arene ring through a N2–C14–C13–N1 bridge. Herein, the bond lengths of C7=O2 is 1.224(3) Å and that of C8=O3 is 1.218(3) Å. In the crystal structure, there is a N1–H1···O2 intramolecular hydrogen bond, with the D···A distance of 2.682(3) Å and D–H···A angle of 132.8(2)°.

Table 2. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{iso}
H(2A)	4*e*	1.0172	0.0899	0.6707	0.045
H(5A)	4*e*	1.1842	–0.2498	0.8147	0.052
H(6A)	4*e*	1.0681	–0.1821	0.9055	0.052
H(9A)	4*e*	1.3657	–0.1023	0.7752	0.078
H(9B)	4*e*	1.4562	–0.1510	0.7439	0.078
H(10A)	4*e*	1.4631	–0.1192	0.9345	0.089
H(10B)	4*e*	1.3826	–0.2083	0.9438	0.089
H(11A)	4*e*	1.3951	–0.4315	0.9184	0.078
H(11B)	4*e*	1.4837	–0.4901	0.8906	0.078
H(12A)	4*e*	1.4687	–0.4023	0.7138	0.063
H(12B)	4*e*	1.3849	–0.4817	0.7311	0.063
H(13A)	4*e*	1.1040	0.2300	0.5565	0.051
H(13B)	4*e*	1.0358	0.1399	0.4908	0.051
H(14A)	4*e*	1.1210	0.1280	0.3406	0.057
H(14B)	4*e*	1.0996	0.2725	0.3642	0.057
H(15A)	4*e*	1.2196	0.3501	0.5355	0.056
H(15B)	4*e*	1.2105	0.4193	0.4181	0.056
H(16A)	4*e*	1.3464	0.4608	0.5091	0.068

* Correspondence author (e-mail: slcao@cnu.edu.cn)

Table 2. continued.

Atom	Site	x	y	z	U_{iso}
H(16B)	4*e*	1.3653	0.3126	0.5185	0.068
H(17A)	4*e*	1.3830	0.1933	0.3550	0.073
H(17B)	4*e*	1.3752	0.2629	0.2380	0.073
H(18A)	4*e*	1.2279	0.2949	0.2498	0.060
H(18B)	4*e*	1.2491	0.1472	0.2607	0.060
H(1A)	4*e*	1.1853	0.0195	0.5145	0.053

Table 3. Atomic coordinates and displacement parameters (in Å^2).

Atom	Site	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br(1)	4*e*	0.93397(1)	0.01642(2)	0.86145(2)	0.0425(1)	0.0577(2)	0.0519(2)	0.0015(1)	0.0208(1)	–0.0066(1)
C(1)	4*e*	1.0328(1)	–0.0407(2)	0.7938(2)	0.033(1)	0.042(1)	0.042(1)	–0.0056(9)	0.0119(8)	–0.0104(9)
C(2)	4*e*	1.0518(1)	0.0221(2)	0.6986(2)	0.032(1)	0.039(1)	0.042(1)	–0.0008(8)	0.0065(8)	–0.0042(8)
C(3)	4*e*	1.1239(1)	–0.0155(2)	0.6424(2)	0.032(1)	0.039(1)	0.039(1)	–0.0052(8)	0.0071(8)	–0.0040(8)
C(4)	4*e*	1.1739(1)	–0.1215(2)	0.6874(2)	0.037(1)	0.037(1)	0.046(1)	0.0029(9)	0.0113(9)	–0.0018(9)
C(5)	4*e*	1.1511(1)	–0.1810(2)	0.7854(2)	0.046(1)	0.036(1)	0.049(1)	0.0024(9)	0.0105(9)	0.0014(9)
C(6)	4*e*	1.0817(1)	–0.1419(2)	0.8399(2)	0.048(1)	0.040(1)	0.044(1)	–0.003(1)	0.0156(9)	0.0003(9)
C(7)	4*e*	1.2487(1)	–0.1663(2)	0.6343(2)	0.047(1)	0.050(1)	0.060(1)	0.009(1)	0.020(1)	0.005(1)
C(8)	4*e*	1.2908(1)	–0.2946(2)	0.6707(2)	0.042(1)	0.044(1)	0.058(1)	0.007(1)	0.020(1)	–0.001(1)
C(9)	4*e*	1.4064(2)	–0.1733(2)	0.7833(3)	0.058(2)	0.037(1)	0.101(2)	–0.004(1)	0.015(1)	–0.007(1)
C(10)	4*e*	1.4333(2)	–0.1951(3)	0.9036(3)	0.065(2)	0.058(2)	0.098(2)	0.002(1)	–0.002(2)	–0.028(2)
C(11)	4*e*	1.4455(2)	–0.4167(3)	0.8778(2)	0.073(2)	0.052(2)	0.071(2)	0.014(1)	0.002(1)	–0.003(1)
C(12)	4*e*	1.4182(2)	–0.4063(2)	0.7558(2)	0.054(1)	0.037(1)	0.068(2)	0.008(1)	0.011(1)	–0.004(1)
C(13)	4*e*	1.0969(1)	0.1593(2)	0.5035(2)	0.033(1)	0.049(1)	0.045(1)	0.0012(9)	0.0059(9)	0.0029(9)
C(14)	4*e*	1.1312(1)	0.1977(2)	0.3942(2)	0.039(1)	0.058(1)	0.043(1)	–0.001(1)	–0.0004(9)	0.008(1)
C(15)	4*e*	1.2406(1)	0.3514(2)	0.4615(2)	0.049(1)	0.047(1)	0.047(1)	0.001(1)	0.015(1)	–0.005(1)
C(16)	4*e*	1.3358(2)	0.3784(2)	0.4721(2)	0.056(1)	0.053(1)	0.062(2)	–0.012(1)	0.013(1)	–0.011(1)
C(17)	4*e*	1.3529(2)	0.2609(2)	0.3112(2)	0.062(2)	0.055(2)	0.069(2)	–0.004(1)	0.033(1)	–0.010(1)
C(18)	4*e*	1.2579(1)	0.2303(2)	0.2971(2)	0.058(1)	0.053(1)	0.042(1)	–0.002(1)	0.014(1)	–0.003(1)
N(1)	4*e*	1.1429(1)	0.0476(2)	0.5491(1)	0.0396(9)	0.050(1)	0.046(1)	0.0091(8)	0.0171(8)	0.0066(8)
N(2)	4*e*	1.2231(1)	0.2277(2)	0.4062(1)	0.0374(9)	0.0408(9)	0.0345(9)	0.0000(7)	0.0055(7)	0.0031(7)
N(3)	4*e*	1.3660(1)	–0.2903(2)	0.7344(2)	0.050(1)	0.032(1)	0.070(1)	0.0043(8)	0.0061(9)	–0.0028(8)
O(1)	4*e*	1.3696(1)	0.3810(2)	0.3656(2)	0.064(1)	0.0473(9)	0.077(1)	–0.0132(8)	0.0323(9)	–0.0048(8)
O(2)	4*e*	1.2779(1)	–0.1135(2)	0.5544(2)	0.078(1)	0.091(1)	0.092(1)	0.040(1)	0.056(1)	0.041(1)
O(3)	4*e*	1.2575(1)	–0.3930(2)	0.6319(2)	0.0502(9)	0.053(1)	0.085(1)	0.0028(8)	0.0056(8)	–0.0183(9)
O(4)	4*e*	1.4885(1)	–0.3036(2)	0.9196(2)	0.064(1)	0.066(1)	0.094(1)	0.0110(9)	–0.015(1)	–0.024(1)

Acknowledgments. The authors are grateful to National Natural Science Foundation of China (project No. 20972099) and Beijing Municipal Commission of Education (project No. KZ201210028035) for financial support. The authors thank the editor for providing the figure.

References

1. Bal, T. R.; Anand, B.; Yogeeswari, P.; Sriram, D.: Synthesis and evaluation of anti-HIV activity of isatin β-thiosemicarbazone derivatives. Bioorg. Med. Chem. Lett. **15** (2005) 4451–4455.
2. Siddiqui, N.; Alam, M. S.; Stables, J. P.: Synthesis and anticonvulsant properties of 1-(amino-*N*-arylmethanethio)-3-(1-substituted benzyl-2,3-dioxoindolin-5-yl) urea derivatives. Eur. J. Med. Chem. **46** (2011) 2236–2242.
3. Prakash, C. R.; Raja, S.: Indolinones as Promising Scaffold as Kinase Inhibitors: A Review. Mini-Rev. Med. Chem. **12** (2012) 98–119.
4. Lin, H. H.; Wu, W. Y.; Cao, S. L.; Liao, J.; Ma, L.; Gao, M.; Li, Z. F.; Xu, X.: Synthesis and antiproliferative evaluation of piperazine-1-carbothiohydrazide derivatives of indolin-2-one. Bioorg. Med. Chem. Lett. **23** (2013) 3304–3307.
5. Lidia, M.; Julie, M. L.; John, B. B.; Stephen, G. P.; Danielle, S.; Marie, R.; Kara, L. V.: *N*-Phenethyl and *N*-naphthylmethyl isatins and analogues as in vitro cytotoxic agents. Bioorg. Med. Chem. **16** (2008) 3118–3124.
6. Penthala, N. R.; Yerramreddy, T. R.; Madadi, N. R.; Crooks, P. A.: Synthesis and in vitro evaluation of *N*-alkyl-3-hydroxy-3-(2-imino-3-methyl-5-oxoimidazolidin-4-yl)indolin-2-one analogs as potential anticancer agents. Bioorg. Med. Chem. Lett. 20 (2010) 4468–4471.
7. Sheldrick, G. M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
8. Brandenburg, K.: DIAMOND. Visual Crystal Structure Information System. Version 3.2i. Crystal Impact, Bonn, Germany 2012.