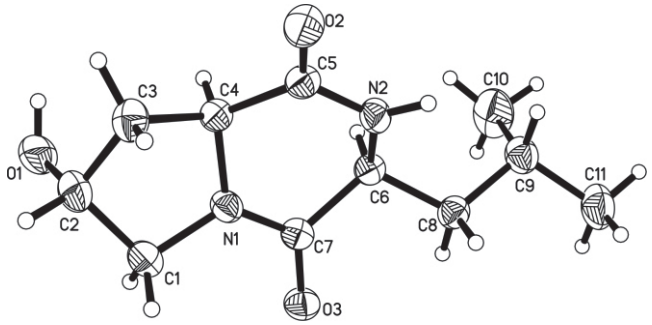
Crystal structure of hexahydro-7-hydroxy-3-(2-methylpropyl)pyrrolo [1,2-*a*]pyrazine-1,4-dione, $C_{11}H_{18}N_2O_3$

Yan Zhang and Xin-Xiang Lei*

College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, Zhejiang Province, P. R.China

Received October 03, 2014, accepted February 25, 2015, available online May 21, 2015, CCDC no. 1267/4258



Abstract

$C_{11}H_{18}N_2O_3$, orthorhombic, $P2_12_12_1$ (no. 19), a = 6.3149(5) Å, b = 9.6242(7) Å, c = 19.671(2) Å, V = 1195.5 Å^3, Z = 4, $R_{gt}(F)$ = 0.0386, $wR_{ref}(F^2)$ = 0.1061, T = 298 K.

Table 1. Data collection and handling.

Crystal:	colourless blocks, size 0.14×0.18×0.26 mm
Wavelength:	Cu K_α radiation (1.54178 Å)
μ:	7.56 cm^{-1}
Diffractometer, scan mode:	Bruker APEX II area detector, φ and ω
$2\theta_{max}$:	131.98°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	7812, 1949
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\ \sigma(I_{obs})$, 1910
$N(param)_{refined}$:	148
Programs:	SHELX, PLATON, SADABS [1–3]

Source of material

Antimicrobial cyclic dipeptides C6, a novel polyketide, was isolated from the metabolites of *Streptomyces sp* a soil sample. Strain was cultured for six day in a 5L fermenter in glycerol/corn meal medium (50 g L-1, glycerol, 25 gL-1corn meal, yeast extract 5 gL-1, pH 7.0 prior to sterilization) at 301(2) K, stirring at 200 rpm. The culture filtrate was separated by centrifugation from the mycelium and subjected to HP-20 resin. After washing with water, a crude product was obtained through elution with methanol. The eluate was concentrated in vaccuo and lyophilized. Then, the crude extract was separated by normal phase chromatography on silica gel (methanol). Next, the sample was purified by HPLC detection of high pressure reverse phase. Suitable single crystals of the title compound were obtained after one week by slow evaporation from methanol solution.

Experimental details

All H atoms attached to C atoms and O atom were introduced using the HFIX command in the SHELXL-97 program [1]. N–H distance restrained to 0.86 Å with U_{iso} = 1.2U_{eq}(parent atom) and O–H distance restrained to 0.82 Å, the U_{iso} values of the hydrogen atoms of methylene groups was set to 1.5U_{eq}(C) and the U_{iso} values of all other hydrogen atom were set to 1.2U_{eq}(C, N,O) [2, 3]. The data collection with Cu-K_α radiation yielded a completeness of 94.2 % (θ_{max}= 65.99°) only.

Discussion

Biological activity of cyclic peptides [termed as 2,5-diketopiperazines] are ubiquitous in nature, and they represent the simplest and first fully characterized small peptides [4, 5]. Because these molecules have antibacterial, anticancer, weeding, and antivirus features, they are potential drug candidates [6–9]. The cyclic peptide compounds have a wide range of biological activities such as anti-tumor, anti-HIV, anti-bacterial, anti-malaria have attracted more concern research on it [10]. However, the cyclic dipeptide C6 demonstrates activity against avian influenza [11]. The bond lengths and angles derived from the title structure, are within normal ranges. The O2–C5 and O3–C7 bond distances [1.220(2) Å and 1.235(2) Å], are typical for C=O groups. The N2–C5 distance [1.333(3) Å], and N1–C7 distance [1.327(2) Å], are shorter than a N–C single bond, due to the amide structure. The molecules are connected by hydrogen bonds [N2–H2A···O3 = 2.9924(19) Å, angle of 147.4° and O1–H1···O3 = 2.808(2) Å, angle of 147.4°], which stabilize the crystal structure.

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

Atom	Site	x	y	z	U_{iso}
H(2A)	4*a*	0.1922	1.0910	0.7905	0.056
H(1)	4*a*	0.7338	0.7721	0.5913	0.103
H(1A)	4*a*	0.1781	0.8955	0.5505	0.067
H(1B)	4*a*	0.2448	0.7422	0.5695	0.067
H(2)	4*a*	0.5145	0.9060	0.5120	0.068
H(3A)	4*a*	0.7137	0.9970	0.6142	0.065
H(3B)	4*a*	0.5053	1.0779	0.5938	0.065
H(4)	4*a*	0.5461	0.8718	0.6963	0.049
H(6)	4*a*	0.2093	0.8260	0.7871	0.049
H(8A)	4*a*	–0.1739	0.8255	0.7866	0.057
H(8B)	4*a*	–0.1630	0.9872	0.7800	0.057
H(9)	4*a*	–0.0030	1.0038	0.8870	0.068
H(10A)	4*a*	0.1703	0.7923	0.8950	0.143
H(10B)	4*a*	–0.0458	0.7121	0.8952	0.143
H(10C)	4*a*	0.0168	0.8057	0.9572	0.143
H(11A)	4*a*	–0.3881	0.8528	0.8903	0.119
H(11B)	4*a*	–0.3731	1.0147	0.8827	0.119
H(11C)	4*a*	–0.3045	0.9432	0.9509	0.119

* Correspondence author (e-mail: xinxianglei@gmail.com)

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}
N(1)	4*a*	0.2625(3)	0.8749(2)	0.64949(8)	0.0478(8)	0.0449(8)	0.0401(9)	–0.0060(7)	–0.0006(6)	–0.0047(6)
N(2)	4*a*	0.2366(3)	1.0273(2)	0.76335(8)	0.0475(8)	0.0394(7)	0.052(1)	–0.0022(7)	0.0050(7)	–0.0130(6)
O(1)	4*a*	0.6291(3)	0.7525(2)	0.56860(8)	0.072(1)	0.0684(9)	0.065(1)	0.0092(9)	–0.0046(8)	–0.0244(8)
O(2)	4*a*	0.5070(2)	1.1623(1)	0.72754(8)	0.0566(8)	0.0454(7)	0.085(1)	–0.0131(7)	0.0122(7)	–0.0183(7)
O(3)	4*a*	–0.0577(2)	0.7799(1)	0.66904(7)	0.0503(7)	0.0515(7)	0.0563(9)	–0.0111(6)	–0.0030(6)	–0.0063(6)
C(1)	4*a*	0.2756(4)	0.8397(2)	0.5770(1)	0.061(1)	0.062(1)	0.043(1)	–0.002(1)	–0.0022(9)	–0.0051(9)
C(2)	4*a*	0.5040(4)	0.8732(2)	0.5590(1)	0.068(1)	0.062(1)	0.041(1)	–0.002(1)	0.0077(9)	0.0016(8)
C(3)	4*a*	0.5615(4)	0.9892(2)	0.6087(1)	0.060(1)	0.047(1)	0.056(1)	–0.005(1)	0.0115(9)	0.0026(8)
C(4)	4*a*	0.4564(3)	0.9415(2)	0.67420(9)	0.0421(9)	0.0361(8)	0.046(1)	–0.0011(7)	0.0001(7)	–0.0022(7)
C(5)	4*a*	0.4042(3)	1.0552(2)	0.7245(1)	0.0417(9)	0.0362(8)	0.053(1)	–0.0011(8)	–0.0017(8)	–0.0032(7)
C(6)	4*a*	0.1237(3)	0.8943(2)	0.76243(9)	0.0420(9)	0.0350(8)	0.045(1)	0.0006(7)	–0.0003(7)	–0.0005(7)
C(7)	4*a*	0.0993(3)	0.8443(2)	0.68929(9)	0.047(1)	0.0317(7)	0.045(1)	–0.0022(8)	–0.0024(7)	–0.0002(6)
C(8)	4*a*	–0.0899(3)	0.9066(2)	0.7981(1)	0.0440(9)	0.0454(9)	0.052(1)	–0.0009(9)	0.0024(7)	–0.0023(7)
C(9)	4*a*	–0.0822(4)	0.9196(2)	0.8753(1)	0.061(1)	0.058(1)	0.052(1)	–0.007(1)	0.0084(9)	–0.0039(9)
C(10)	4*a*	0.0246(6)	0.7961(4)	0.9087(2)	0.114(2)	0.113(2)	0.059(2)	0.026(2)	0.011(2)	0.026(2)
C(11)	4*a*	–0.3080(5)	0.9339(3)	0.9023(2)	0.078(2)	0.087(2)	0.074(2)	–0.010(2)	0.027(1)	–0.019(1)

Acknowledgments. The work was financed by Zhejiang Provincial Natural Science Foundation of China under Grant No.LY14B020010.

References

1. Sheldrick, G.M.: A short history of SHELX. Acta Crystallogr. **A64** (2008) 112–122.
2. Spek, A. L.: Structure validation in chemical crystallography. Acta Crystallogr. **D65** (2009) 148–155.
3. Bruker AXS Inc.: Bruker AXS SADABS, Version 2.03, SAINT, Version 6.02, Bruker AXS Inc. Madison, Winsonsin, USA 2002.
4. Prasad, C.: Bioactive cyclic dipeptides. Peptides. **15** (1995) 151–164.
5. Corey, R. B.: The crystal structure of diketopiperazine. J. Am. Chem. Soc. **60** (1938) 1568–1604.
6. Hirano, S.; Ichikawa, S.; Matsuda, A.: Structure-activity relationship of truncated analogs of caprazamycins as potential anti-tuberculosis agents. Bioorg. Med. Chem. **16** (2008) 428–436.
7. Van Der Merwe, E.; Huang, D.; Petersen, D.; Kilian, G.; Milne, P. J.; Van de Venter, M.; Frost, C.: The synthesis and anticancer activity of selected diketopiperazines. Peptides. **29** (2008) 1305–1311.
8. King, R. R.; Calhoun, L. A.: The thaxtomin phytotoxins: Sources, synthesis, biosynthesis, biotransformation and biological activity. Phytochem. **70** (2009) 833–841.
9. Sinha, S.; Srivastava, R.; Clercq, E. D.; Singh, R. K.: Synthesis and Antiviral Properties of Arabino and Ribonucleosides of 1,3-Dideazaadenine, 4-Nitro-1, 3-dideazaadenine and Diketopiperazine. Nucleosides: Nucleotides Nucleic Acids. **23** (2004) 1815–1824.
10. Fang, Z. F.; Yu, S. S.; Zhou, W. Q.: A new isocoumarin from metabolites of the endophytic fungus Alternaria tenuissima (Nees & T. Nees: Fr.) Wiltshire. Chinese Chem. Lett. **23** (2012) 317–320.
11. Chen, Z.; Song, A. R.; Chao, K.; Fang, H.; Qin, D.: From Faming Zhuanli Shenqing (2014) CN 103800332 A 20140521.