Crystal structure of cyclonovobiocin, $C_{44}H_{42}N_2O_{12}$

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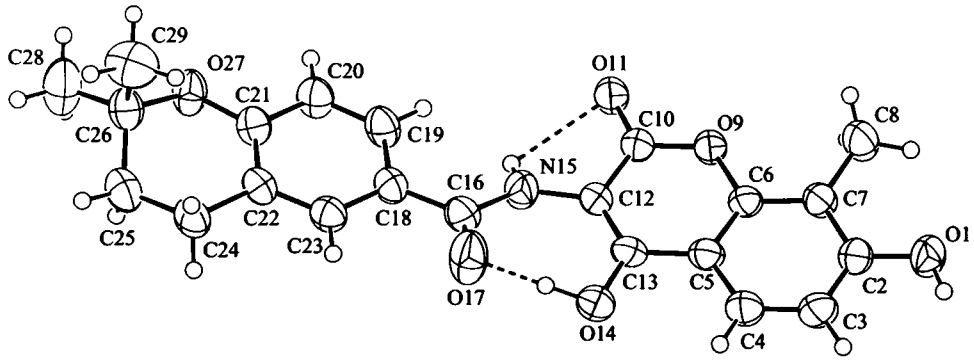

Abstract

$C_{44}H_{42}N_2O_{12}$, monoclinic, $P12_1/c1$ (no. 14), a = 5.437(5) Å, b = 32.564(5) Å, c = 10.922(5) Å, β = 99.818(5)°, V = 1905.4 Å^3, Z = 2, $R_{gt}(F)$ = 0.052, $wR_{ref}(F^2)$ = 0.174, T = 293 K.

Source of material

Novobiocin (0.613 g, 0.001 mol) and dibromozinc (1.126 g, 0.005 mol) were carefully dissolved in 20 mL of hot ethanoic acid and maintained 24 hours at 50 °C. Cyclonovobiocin crystallized as translucent needles. A suitable crystal was taken for diffraction studies.

Discussion

Novobiocin is a coumarin antibiotic first discovered in *Streptomyces spheroides* [1]. The biological activity is due to the inhibition of bacterial DNA gyrase [1]. Recent works demonstrated that novobiocin can bind to the C-terminal nucleotide-binding region of hsp90 leading to decrease in hsp90 client proteins in various cancer cell lines [2]. However, novobiocin exhibits a weak inhibitory activity against hsp90. As a part of our work concerning structure-activity relationships for novobiocin and hsp90, new noviose-free novobiocin analogs have been prepared. Cyclonovobiocinic acid, obtained after acidic hydrolysis of novobiocin [3], was studied by X-ray crystallography.

The title compound is an amide having a 3-amino-4,7-dihydroxy-8-methylcoumarin (A) and 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carboxylic acid (B). The coumarin entity (A) has a planar conformation with a largest deviation of 0.045(2) Å for C12 from the best plane P1 (C2-C7/O9/C10/C12/C13), defined by two six-member rings P2 (C2/C7) and P3 (C5/C6/O9/C10/C12/C13) which make a dihedral angle of 3.1(1)°. Electron localization was found at the short C12—C13 bond with a length of 1.367(3) Å. The wide angle of C12–C13–O14 and the narrow angle of O14–C13–C5 give the hydroxy group a tilt to the C4 direction. In B entity, the atoms C25 and C26 are displaced out of the P4 plane [C18-C24/O27] from –0.380(3) Å and 0.335(3) Å, respectively, in a half-chair conformation. P4 makes a dihedral angle of 7.44(9)° with P1. The torsion angle C12–N15–C16–C18 between A and B entities is 171.0(2) Å. In addition the very short intramolecular hydrogen bond O14–H14···O17 (2.490(2) Å, 176°) forms a double bridge between A and B with N15—C12 bond. The crystal packing is governed by one intermolecular hydrogen bond O1–H1···O11^i (2.698(3) Å, 151° (i: x–1,–y+½,z–½)).

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Table 1. Data collection and handling.

Crystal:	colorless, parallelepipedic, size 0.20 × 0.30 × 0.35 mm
Wavelength:	Mo K_α radiation (0.71073 Å)
μ:	1.01 cm^{-1}
Diffractometer, scan mode:	Nonius KappaCCD, φ/ω
$2\theta_{max}$:	53.08°
$N(hkl)_{measured}$, $N(hkl)_{unique}$:	11738, 3855
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\,\sigma(I_{obs})$, 2756
$N(param)_{refined}$:	263
Programs:	SIR92 [4], SHELXL-97 [5], CAMERON [6], WinGX [7]

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

Atom	Site	x	y	z	U_{iso}
H(1)	4*e*	0.7278	0.1864	0.7117	0.072
H(3)	4*e*	0.5081	0.2466	0.7038	0.067
H(4)	4*e*	0.4971	0.3120	0.7815	0.065
H(8A)	4*e*	1.2151	0.1875	0.9113	0.091
H(8B)	4*e*	1.2406	0.2094	1.0407	0.091
H(8C)	4*e*	1.3960	0.2250	0.9415	0.091
H(15)	4*e*	1.2440	0.4062	1.1141	0.066
H(19)	4*e*	1.3903	0.4450	1.2415	0.062
H(20)	4*e*	1.5293	0.4978	1.3738	0.062
H(23)	4*e*	0.7522	0.5060	1.1270	0.057
H(24A)	4*e*	0.6982	0.5691	1.3021	0.067

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(24B)	4e	0.7672	0.5837	1.1754	0.067
H(25A)	4e	0.8766	0.6311	1.3464	0.072
H(25B)	4e	1.0898	0.6222	1.2699	0.072
H(28A)	4e	1.4377	0.6213	1.5693	0.126
H(28B)	4e	1.2402	0.6539	1.5101	0.126

Table 2. Continued.

Atom	Site	x	y	z	U_{iso}
H(28C)	4e	1.4379	0.6370	1.4336	0.126
H(29A)	4e	1.1312	0.5709	1.6119	0.121
H(29B)	4e	0.9170	0.5562	1.5062	0.121
H(29C)	4e	0.9081	0.6004	1.5627	0.121
H(14)	4e	0.673(6)	0.398(1)	0.961(3)	0.12(1)

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}
O(1)	4e	0.8496(2)	0.19082(4)	0.7656(1)	0.0569(8)	0.0476(8)	0.0690(9)	−0.0051(6)	−0.0066(7)	−0.0115(7)
C(2)	4e	0.8370(3)	0.22963(6)	0.8096(2)	0.050(1)	0.042(1)	0.049(1)	−0.0061(8)	0.0033(8)	−0.0002(8)
C(3)	4e	0.6369(3)	0.25573(5)	0.7649(1)	0.052(1)	0.055(1)	0.054(1)	−0.0059(9)	−0.0112(9)	0.0010(9)
C(4)	4e	0.6310(3)	0.29484(5)	0.8112(1)	0.048(1)	0.052(1)	0.056(1)	0.0045(9)	−0.0083(9)	0.0014(9)
C(5)	4e	0.8227(3)	0.30918(6)	0.9018(2)	0.0429(9)	0.046(1)	0.0406(9)	0.0035(8)	0.0009(8)	0.0048(8)
C(6)	4e	1.0192(3)	0.28229(6)	0.9442(2)	0.0403(9)	0.041(1)	0.0402(9)	−0.0020(7)	−0.0029(7)	0.0019(7)
C(7)	4e	1.0304(3)	0.24220(6)	0.9018(2)	0.042(1)	0.040(1)	0.049(1)	−0.0017(8)	0.0011(8)	0.0023(8)
C(8)	4e	1.2395(4)	0.21341(6)	0.9535(2)	0.056(1)	0.046(1)	0.074(1)	0.0051(9)	−0.009(1)	−0.003(1)
O(9)	4e	1.2153(2)	0.29509(4)	1.0329(1)	0.0451(7)	0.0392(7)	0.0525(8)	0.0045(5)	−0.0100(6)	−0.0045(5)
C(10)	4e	1.2319(3)	0.33427(6)	1.0765(2)	0.048(1)	0.040(1)	0.045(1)	0.0035(8)	−0.0027(8)	−0.0006(8)
O(11)	4e	1.4179(2)	0.34311(4)	1.1521(1)	0.0528(8)	0.0450(8)	0.0674(9)	0.0072(6)	−0.0176(7)	−0.0073(7)
C(12)	4e	1.0358(3)	0.36275(5)	1.0330(2)	0.048(1)	0.040(1)	0.0421(9)	0.0077(8)	0.0005(8)	0.0001(8)
C(13)	4e	0.8311(3)	0.35040(6)	0.9501(2)	0.045(1)	0.046(1)	0.0405(9)	0.0087(8)	−0.0011(8)	0.0052(8)
O(14)	4e	0.6392(3)	0.37427(5)	0.9053(1)	0.0547(8)	0.058(1)	0.0610(9)	0.0199(7)	−0.0136(7)	−0.0045(7)
N(15)	4e	1.0890(3)	0.40214(5)	1.0847(2)	0.051(1)	0.045(1)	0.062(1)	0.0098(7)	−0.0063(8)	−0.0107(7)
C(16)	4e	0.9405(4)	0.43428(6)	1.0959(2)	0.049(1)	0.045(1)	0.051(1)	0.0080(8)	0.0074(9)	0.0013(8)
O(17)	4e	0.7160(3)	0.43405(5)	1.0488(2)	0.0499(9)	0.067(1)	0.119(1)	0.0132(7)	−0.0084(9)	−0.034(1)
C(18)	4e	1.0512(3)	0.46918(5)	1.1720(2)	0.045(1)	0.039(1)	0.049(1)	0.0055(8)	0.0101(8)	0.0008(8)
C(19)	4e	1.2886(4)	0.46770(6)	1.2459(2)	0.045(1)	0.044(1)	0.068(1)	0.0104(8)	0.0101(9)	−0.0019(9)
C(20)	4e	1.3723(3)	0.49930(6)	1.3245(2)	0.0362(9)	0.050(1)	0.067(1)	0.0062(8)	0.0047(9)	−0.0057(9)
C(21)	4e	1.2229(3)	0.53372(6)	1.3308(2)	0.0402(9)	0.042(1)	0.055(1)	0.0011(8)	0.0131(8)	−0.0017(8)
C(22)	4e	0.9909(3)	0.53710(5)	1.2544(2)	0.043(1)	0.039(1)	0.054(1)	0.0058(8)	0.0106(8)	0.0040(8)
C(23)	4e	0.9084(3)	0.50435(6)	1.1771(2)	0.043(1)	0.047(1)	0.052(1)	0.0070(8)	0.0056(8)	0.0018(8)
C(24)	4e	0.8362(4)	0.57523(6)	1.2593(2)	0.051(1)	0.046(1)	0.067(1)	0.0130(9)	0.004(1)	−0.0012(9)
C(25)	4e	0.9886(4)	0.61006(6)	1.3255(2)	0.067(1)	0.045(1)	0.071(1)	0.009(1)	0.019(1)	0.002(1)
C(26)	4e	1.1578(3)	0.59597(6)	1.4434(2)	0.045(1)	0.046(1)	0.064(1)	0.0054(8)	0.0168(9)	−0.0057(9)
O(27)	4e	1.3210(2)	0.56329(4)	1.4128(1)	0.0405(7)	0.0495(8)	0.078(1)	0.0031(6)	0.0081(6)	−0.0165(7)
C(28)	4e	1.3345(5)	0.63016(8)	1.4937(3)	0.069(2)	0.065(2)	0.117(2)	0.002(1)	0.012(2)	−0.028(2)
C(29)	4e	1.0156(5)	0.57935(9)	1.5398(2)	0.073(2)	0.100(2)	0.076(2)	0.012(1)	0.031(1)	0.012(1)

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