Yu-Mei Qin, Xue Zou, Dan Long, Chun Ji* and Chun-Shen Zhao*

The crystal structure of methyl 2-(benzylamino)-5-(benzyloxy)benzoate, $C_{22}H_{21}NO_3$

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	0.22 × 0.20 × 0.18 mm
Wavelength:	Mo K α radiation (0.71073 Å)
μ :	0.09 mm ⁻¹
Diffractometer, scan mode:	Bruker SMART, φ and ω -scans
$\theta_{\max}$, completeness:	25°, >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	5850, 3142, 0.025
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 2178
$N(\text{param})_{\text{refined}}$:	236
Programs:	Bruker programs [1], SHELX [2, 3]

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Abstract

$C_{22}H_{21}NO_3$, triclinic, $P\bar{1}$ (no. 2), $a = 5.757(3)$ Å, $b = 12.106(5)$ Å, $c = 13.139(6)$ Å, $\alpha = 93.725(12)^\circ$, $\beta = 92.508(15)^\circ$, $\gamma = 92.508(15)^\circ$, $V = 891.3(7)$ Å³, $Z = 2$, $R_{\text{gt}}(F) = 0.0474$, $wR_{\text{ref}}(F^2) = 0.1429$, $T = 296(2)$ K.

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The crystal structure is shown in the figure. Table 1 contains crystallographic data and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Source of material

All chemicals, reagents and solvents are of analytical grade and are commercially available. Preparation of methyl

2-(benzylamino)-5-(benzyloxy) benzoate: methyl 2-amino-5-hydroxybenzoate (5 g, 29.91 mmol) was dissolved in DMF (100 mL) at room temperature, followed by (bromomethyl)benzene (10.23 g, 59.82 mmol) and potassium carbonate (12.40 g, 89.73 mmol) in order. Then the mixture reacted under stirring at room temperature for 12 hours. Subsequently, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was dehydrated with anhydrous sodium sulfate and concentrated at reduced pressure to afford a yellow liquid. The crude mixture was purified by silica gel column chromatography, eluted with petroleum ether to give a white solid (7.83 g, yield 75.36%). ¹H NMR (600 MHz, CDCl₃) δ 7.85 (s, 1H), 7.55 (d, $J = 3.1$ Hz, 1H), 7.41 (d, $J = 7.4$ Hz, 2H), 7.38–7.29 (m, 7H), 7.26–7.23 (m, 1H), 7.03 (dd, $J = 9.1, 3.1$ Hz, 1H), 6.58 (d, $J = 9.1$ Hz, 1H), 4.98 (s, 2H), 4.42 (d, $J = 5.0$ Hz, 2H), 3.86 (s, 3H). Crystals were grown in hexane at room temperature.

Experimental details

All hydrogen atoms were placed in geometrically calculated positions. The U_{iso} values of the hydrogen atoms of methyl groups were set to 1.5 $U_{\text{eq}}(\text{C}_{\text{methyl}})$ and the U_{iso} values of all other hydrogen atoms were set to 1.2 U_{eq} .

Discussion

Methyl 2-(benzylamino)-5-(benzyloxy)benzoate is widely used in the fields of medicine, organic synthesis and fine chemicals. It is an important intermediate for the synthesis of bentazon and anthranilate compounds and can be used to prepare herbicides and fungicides [4]. It can participate in the synthesis of camptothecin and benzodiazepine

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	x	y	z	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
N1	−0.3232(3)	0.56148(13)	0.22361(11)	0.0512(4)
H1A	−0.2768	0.4991	0.2117	0.061*
O1	0.2515(3)	0.49495(11)	0.39942(10)	0.0557(4)
O2	0.1484(3)	0.86967(11)	0.53476(9)	0.0568(4)
O3	−0.0365(3)	0.42349(12)	0.28202(11)	0.0662(5)
C1	−0.6365(4)	0.64603(16)	−0.00613(14)	0.0515(5)
H1	−0.7911	0.6060	0.0010	0.062*
C2	−0.5857(5)	0.70763(17)	−0.09043(15)	0.0600(6)
H2	−0.7065	0.7089	−0.1395	0.072*
C3	−0.3609(5)	0.76633(19)	−0.10219(16)	0.0654(6)
H3	−0.3279	0.8085	−0.1585	0.078*
C4	−0.1841(5)	0.76298(19)	−0.03083(16)	0.0656(6)
H4	−0.0297	0.8024	−0.0391	0.079*
C5	−0.2325(4)	0.70136(17)	0.05397(14)	0.0530(5)
H5	−0.1098	0.6994	0.1018	0.064*
C6	−0.4590(3)	0.64331(15)	0.06803(13)	0.0423(5)
C7	−0.5213(4)	0.57879(17)	0.16102(14)	0.0512(5)
H7A	−0.6156	0.6191	0.2029	0.061*
H7B	−0.6206	0.5052	0.1386	0.061*
C8	−0.2030(3)	0.63532(15)	0.29992(12)	0.0424(5)
C9	−0.2605(4)	0.74157(16)	0.32312(13)	0.0480(5)
H9	−0.3829	0.7613	0.2847	0.058*
C10	−0.1423(4)	0.81595(16)	0.39994(14)	0.0482(5)
H10	−0.1869	0.8846	0.4139	0.058*
C11	0.0445(4)	0.79020(15)	0.45772(13)	0.0441(5)
C12	0.1088(4)	0.68876(15)	0.43560(13)	0.0438(5)
H12	0.2362	0.6720	0.4730	0.053*
C13	−0.0120(3)	0.61027(14)	0.35853(12)	0.0406(4)
C14	0.0593(3)	0.50104(16)	0.34136(13)	0.0440(5)
C15	0.3336(4)	0.84049(16)	0.59599(14)	0.0528(5)
H15A	0.4702	0.8388	0.5557	0.063*
H15B	0.2789	0.7658	0.6199	0.063*
C16	0.4030(4)	0.92601(15)	0.68491(13)	0.0459(5)
C17	0.6250(4)	0.99605(17)	0.69514(16)	0.0603(6)
H17	0.7307	0.9938	0.6439	0.072*
C18	0.6925(5)	1.06991(19)	0.78103(19)	0.0730(7)
H18	0.8434	1.1171	0.7874	0.088*
C19	0.5383(5)	1.07381(19)	0.85661(17)	0.0706(7)
H19	0.5849	1.1227	0.9149	0.085*
C20	0.3159(5)	1.0057(2)	0.84629(16)	0.0689(7)
H20	0.2097	1.0091	0.8972	0.083*
C21	0.2485(4)	0.93227(17)	0.76092(16)	0.0585(6)
H21	0.0963	0.8862	0.7544	0.070*
C22	0.3417(4)	0.39306(16)	0.38666(17)	0.0620(6)
H22A	0.2195	0.3290	0.3997	0.093*
H22B	0.4765	0.3982	0.4338	0.093*
H22C	0.3893	0.3841	0.3180	0.093*

alkaloids circumdatin F and circumdatin C for the preparation of anticancer drugs [5, 6]. At the same time, it is also an important starting material for the preparation of bis aromatic

compounds useful in treatment of respiratory disorders and inflammation [7, 8]. In addition, it can be used to prepare Pin1 inhibitors and therapeutic or prophylactic agents for inflammatory diseases and cancer [9].

The structure of the title compound was elucidated by spectroscopic methods (NMR) and X-ray diffraction. The crystal structure shows that the methyl benzoate moiety connects the two benzyl groups *via* an oxygen atom and a nitrogen atom, respectively. There is one molecule in the asymmetric unit. All bond lengths and angles in the crystal structure are within the normal range. The crystal structure shows that each molecule is stabilized by an intramolecular N—H···O hydrogen bond (distance = 2.035 Å), and the intermolecular packing is stabilized by the van der Waals forces.

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References

1. BRUKER. SMART APEX software (5.624) for SMART APEX detector, Bruker Axs Inc. Madison, WI, USA (2001).
2. Sheldrick, G. M.: SHELXTL, Version 6.10. Bruker AXS Inc., Madison, WI, USA (2000).
3. Sheldrick, G. M.: A short history of SHELX. *Acta Cryst.* **A64** (2008) 112–122.
4. Furuya, T.; Okada, A.; Harayama, H.; Abe, Y.; Shimizu, N.; Yasukouchi, E.; Kato, Y.: Preparation of anthranilate compounds or their salts, and agricultural and horticultural fungicides containing them. *PCT Int. Appl.* (2016) WO 2016182021.
5. Subbaraju, G. V.; Mohan, H. R.; Harikrishna, M.; Shankar, M.: A process for the preparation of camptothecin. *Indian Pat. Appl.* (2014) IN 2009CH02057.
6. Witt, A.; Bergman, J.: Total syntheses of the benzodiazepine alkaloids circumdatin F and circumdatin C. *J. Org. Chem.* **66** (2001) 2784–2788.
7. Pelcman, B.; Almeida, M.; Katkevics, M.; Nilsson, P.; Schaal, W.; Olofsson, K.: Bis aromatic compounds for use in the treatment of inflammation. *U.S. Pat.* (2011) US 20110294853.
8. Pelcman, B.; Almeida, M.; Katkevics, M.; Nilsson, P.; Schaal, W.; Olofsson, K.: Preparation of bis aromatic compounds as leukotriene C₄ synthase production inhibitors useful in treatment of respiratory disorders and inflammation. *PCT Int. Appl.* (2010) WO 2010029300.
9. Asano, T.; Nakatsu, Y.; Ito, H.; Okabe, T.: Preparation of novel anthranilic acid-based compounds, and Pin1 inhibitors and therapeutic agents for inflammatory diseases and cancer using them. *PCT Int. Appl.* (2019) WO 2019031472.