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ORIGINAL PAPER

C–H···π and C=O···π Intermolecular Interactions in Dibenzyl-3,6-dimethylpyrazine-2,5-dicarboxylate

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Abstract A new pyrazine compound, has been synthesised and characterised by single-crystal X-ray diffraction: monoclinic, $P2_1/c$ with $a = 11.0707(3)$ Å, $b = 5.23700(10)$ Å, $c = 16.6997(5)$ Å, $\beta = 103.5385(16)°$, $Mr = 376.40$, $V = 941.30(4)$ Å^3, $Z = 2$. Each molecule possesses C_i symmetry with the two halves of the molecule related by an inversion centre. C–H···π and C=O···π interactions held the molecules together.

Keywords Pyrazine · Antituberculotic activity · Intermolecular interactions

Introduction

Pyrazines are important compounds in supramolecular chemistry namely in the design of polynuclear metal complexes. Such complexes provide the opportunity for the study of magnetic exchange mechanisms [1–3]. They are also present in the volatiles responsible for the roasted aromas of cooked food such as roasted coffee beans and roasted peanuts [4–6]. Pyrazines play also important roles as intermediates for perfumes, pharmaceuticals and agricultural chemicals. Amides and sulfonamides of pyrazines have been used as anti-diabetics, nutrition supplement, insecticides and fungicites [7]. Pyrazine ring is important for antimycobacterial activity of some drugs used in the treatment of *tuberculosis*. One example is pyrazinamine, one of the frontline agents prescribed for the treatment of *Mycrobacterium tuberculosis*. New drugs and/or new derivates of old drugs, such as pyrazinamide, have been prepared and studied in the last years and the quest for new pyrazines is intense [8–11].

We have synthesised the title compound as a potential antituberculotic agent. Preliminary biological assays in HT-29 cells showed that the dibenzyl-3,6-dimethylpyrazine-2,5-dicarboxylate is not cytotoxic and in vitro antituberculosis activity tests are currently being done.

Experimental

Preparation of Dibenzyl-3,6-dimethylpyrazine-2,5-dicarboxylate

The title compound was prepared through the general conditions of the Knorr reaction for pyrroles but using a open flask to allow a large presence of air in the reaction medium to permit an easier auto-condensation of the 2-imino derivatives of the benzyl 3-oxobutanoate [12]. In a typical experiment, to a solution of 2 mL (10 mmol) of methyl 4-acetyl-5-oxohexanoate in 100 mL of acetic acid are added 2 mL (10 mmol) of benzyl 3-oxobutanoate in 50 mL of aqueous sodium nitrite 1 M. After 1 h 10 g of granular Zn are added drop wise at 50 °C. After 2 h 500 mL of water are added to precipitate the crude material that was filtrated, dried under vacuum and crystallized. The first crystallization from dichloromethane/hexane affords the benzyl 4-(3-methoxy-3-oxopropyl)-3,5-dimethyl-1

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H-pyrrole-2-carboxylate (0.47 g, 15% yield). The filtrate was then dried and the remaining material was crystallized from ethanol to give 0.94 g of pale yellow crystals of dibenzyl 3,6-dimethylpyrazine-2,5-dicarboxylate (25% yield), that were collected and dried under vacuum before X-ray analysis.

Crystal structure determination

A crystal of the title compound with prismatic shape and pale yellow colour and having approximate dimensions of 0.37 × 0.17 × 0.10 mm was glued on a glass fiber and mounted on a Bruker Apex II difractometer. Diffraction data were collected at room temperature 293(2) K using graphite monochromated Mo Kα ($\lambda = 0.71073$ Å). Data were processed using PLATON and an absorption correction (using SADABS) was applied which resulted in transmission factors ranging from 0.973 to 0.991 [13, 14]. Data were corrected for Lorentz and Polarization effects. Reflections with $2\theta \leq 74°$ were used for structure solution and refinement.

The structure was solved by direct methods using SHELXS-97 [15]. It was refined by full-matrix least-squares on F^2 using the SHELXL-97 program [15]. All the hydrogen atoms were placed at calculated positions and allowed to ride on their parent atoms using SHELXL-97 defaults. The final least-squares cycle was based on 1654 observed reflections [$I > 2\sigma(I)$] and 128 variable parameters, converged with $R = 0.0345$ and $wR = 0.1358$ for room temperature. Crystallographic details, selected interatomic distances and angles and geometric details of H-bonds are given in Tables 1, 2 and 3 respectively.

Results and Discussion

Crystal Structure of the Title Compound

The structure of the title compound together with the atom-numbering scheme, is illustrated in Fig. 1. The packing diagram and the formation of chains is shown on Fig. 2. Selected bond lengths and angles are listed in Table 2.

Dibenzyl 3,6-dimethylpyrazine-2,5-dicarboxylate crystallizes in space group $P2_1/c$ with two molecules per unit cell. Each molecule possesses C_i symmetry with the two halves of the molecule related by an inversion center (Fig. 1). The pyrazine ring is therefore planar. The carboxylate group and C3 and C5 are also in the main molecular plane. The outer phenyl rings are twisted out of this plane making a dihedral angle of 74.58(8)°, with the pyrazine ring plane.

Table 1 Summary of crystallographic results

Temperature (K)	293(2)
Empirical formula	$C_{22}H_{20}N_2O_4$
Formula weight	376.40
Wavelength (Å)	0.71073
Crystal system	monoclinic
Space group	$P2_1/c$
a (Å)	11.0707(3)
b (Å)	5.2370(10)
c (Å)	16.6997(5)
β (°)	103.5385(16)
Volume (Å^3)	941.30(4)
Z	2
Calculated density (g/cm^3)	1.328
Absorption coefficient (mm^{-1})	0.092
F(000)	396
Crystal size (mm^3)	0.37 × 0.17 × 0.10
θ range for data collection (°)	1.89–37.24
Index ranges	$-18 \leq h \leq 18$, $-8 \leq k \leq 8$, $-28 \leq l \leq 28$
Reflections collected/unique	45317/4778
Completeness to $\theta = 51°$	99.9%
Transmission factors (min/max)	0.973/0.991
Data/restraints/parameters	1654/0/128
Goodness-of-fit on F^2	1.150
Final *R* indices [$I > 2\sigma(I)$]	0.0345 /0.1069
R indices (all data)	0.0506/0.1358
Largest diff. peak and hole (e Å^{-3})	−0.230 /0.186
CCDC Number	CCDC 656082

Table 2 Selected bond lengths (Å) and angles (°)

N1–C1	1.334(2)
N1–C2	1.339(2)
C4–O1	1.198(2)
C4–O2	1.3220(18)
C4–O2–C5	114.29(13)
C7–C6–C5–O2	79.4(2)

Table 3 Geometric details of the C–H···π and C=O···π intermolecular interactions (Å, °)

	H, O···π	C···π	Angle
C10–H10···π[a]	2.94	3.659(2)	135
C4–O1···π[b]	3.4469(16)	3.8093(16)	98.32(11)

[a] π system of the phenyl ring with symmetry operator 1−x, −1/2 + y, 1/2 − z

[b] π system of the pyrazine ring with symmetry operator x, −1 + y, z

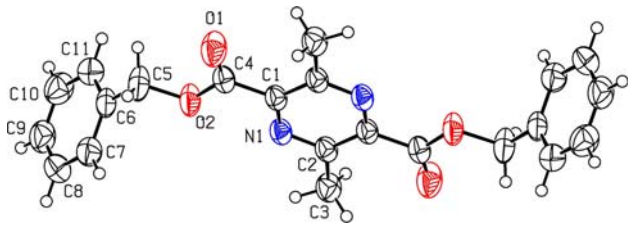

Fig. 1 ORTEPII plot of the title compound. Displacement ellipsoids are drawn at the 50% level

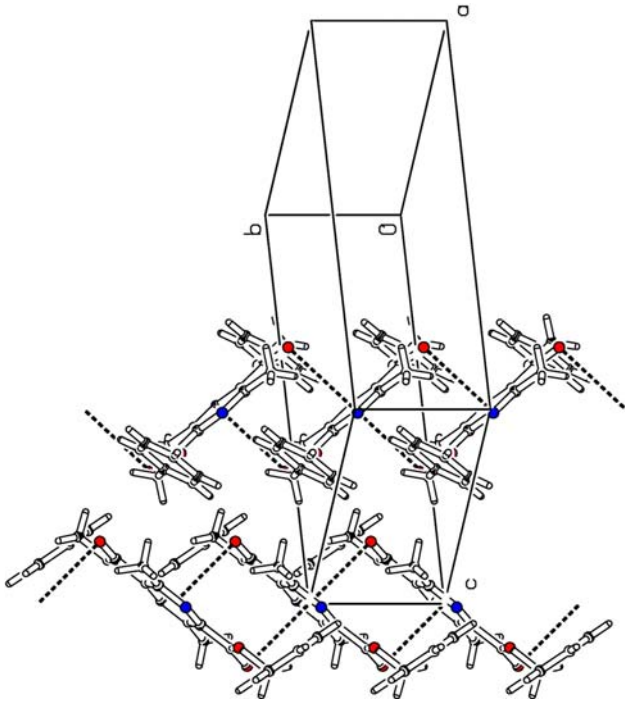

Fig. 2 Partial content of the unit cell of the title compound showing the chain formation via the carbonyl···π interactions (depicted as dashed lines)

Although there are not conventional hydrogen bonding donors in this compound, there are intermolecular interactions promoting the crystal cohesion. C10 carbon shares its attached hydrogen atom with the aromatic π system of a neighbouring phenyl ring. In this interaction the C10···Centroid $(1 - x, -1/2 + y, 1/2 - z)$ distance is 3.659(2) Å and the bond angle is 135°, configuring a type V interaction according to the classification of Malone et al. with the hydrogen atom interacting with the ring edge carbon atoms [16]. Other less usual interactions are observed in the molecular assembling: carbonyl···π interactions (Fig. 2, Table 3). The carboxylate carbonyl group is almost parallel to the pyrazine ring giving rise to the interaction of the lone pair of atom O1 to the pyrazine ring. The C4=O1···Centroid angle is 98.32(11)° and the oxygen atom and the π system are separated by 3.4469(16) Å. This interaction joins the molecules in chains along the c axis.

Supplementary Material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC 656082. Copies of this information may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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