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Comunicaciones cortas

Synthesis and X-ray crystal structure of 8- (4-bromophenoxy) caffeine

Síntesis y estructura cristalina de rayos X de 8- (4-bromofenoxi) cafeína

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Abstract:

8- (4-bromophenoxy) caffeine was synthesized, and its absolute crystal structure was determined by single crystal techniques. The title compound crystallizes in the orthorhombic space group P2.2.2. with a= 7.9056(3), b= 9.1413(3), c= 20.2023(6) Å, and Z=4. The caffeine group makes a dihedral angle of 58.18(9) ° with the bromofenoxy moiety The structure consists of discrete molecule with weak intramolecular hydrogen bond between hydrogen of the methyl group of imidazole ring and oxygen atom of the carbonyl group. The packing of the molecules is oriented in an anti-parallel fashion.

Keywords: crystal structure, caffeine analogs, synthesis, Ullmann's reaction, X-ray diffraction, 8-fenoxycaffeine derivatives.

Resumen:

Se reporta la síntesis y la estructura cristalina absoluta determinada por técnicas de monocristales del 8- (4-bromofenoxi) cafeína. El compuesto cristaliza en el grupo espacial ortorrómbico P212121 , y posee los siguientes parámetros cristalográficos: a= 7.9056(3), b= 9.1413(3), c= 20.2023(6) Å, Z=4. El grupo cafeína tiene un ángulo diedro de 58.18(9)o con el grupo bromofenoxi. La estructura está formada de moléculas discretas, las cuales presentan un puente de hidrógeno intramolecular entre un átomo de hidrógeno del grupo metilo del anillo imidazol, y el átomo de oxígeno del grupo carbonilo. El empaquetamiento de las moléculas está orientado de forma antiparalela.

Palabras clave: estructura cristalina, análogos de la cafeína, síntesis, reacción de Ullmann, difracción de rayos X, derivados de la 8-fenoxicafeína.

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INTRODUCTION

Caffeine is a central nervous system stimulant of the methylxanthine class, and it is the world's most widely consumed psychoactive drug (Daly, 2007). Despite the widespread use of caffeine, it still has the ability to surprise, mostly in relation to its biological activity (Agyemang and Oppong, 2013; Ribeiro and Sebastiao, 2010; Waldvogel, 2003); but not only, recently scientists from the University of California, Los Angeles (UCLA), and Solargiga Energy in China have reported that caffeine improves the performance and thermal stability of perovskite solar cells; their research shows that caffeine can help make apromising alternative to traditional solar cells more efficient at converting light to electricity (Wang and Jingjing, 2019).

Caffeine was the first adenosine receptor (AR) antagonists described in the literature and also has an influence on an extended set of biological process (Muller and Jacobson, 2011) There are several known mechanisms of action to explain the effects of caffeine; the most prominent is that it reversibly blocks the action of adenosine on its receptor and consequently prevents the onset of drowsiness induced by adenosine (Ribeiro *et al*., 2002, Rogozin *et al*., 2008). Caffeine and various analogs, the latter designed to enhance potency and selectivity toward specific biological targets, have played key roles in defining the nature and role of adenosine receptors, phosphodiesterases, and calcium release channels in physiological processes. Such xanthines and other caffeine-inspired heterocycles now provide important research tools and potential therapeutic agents for intervention in Alzheimer's disease, asthma, cancer, diabetes, and Parkinson's disease. Such compounds also have activity as analgesics, anti-inflammatories, behavioral stimulants, diuretics (Tavares and Sakata, 2012).

A large number of derivatives and analogues were subsequently synthesized and evaluated as AR antagonists (Mitkov *et al*., *2007 ;* Georgieva *et al*., *2014* .). Their remarkable biological activities and novel structure features have stimulated many laboratories to the synthesis and the study of the relationship between molecular structure and biological activity (Romero-Hernández, 2016). Following with our interest about the studies of new 8-fenoxi caffeine derivatives we report in this paper the synthesis and the crystal structure of 8- (4-bromophenoxy) caffeine.

MATERIALS AND METHODS

Experimental

Commercially available starting materials and reagents for synthesis were acquired from commercial sources (Fluka, Merck and BDH), and were used without additional purification. The melting point was determined in a capillary tube in Electrothermal 9150 equipment. Crystals suitable for X-Ray analysis were obtained by slow evaporation of an ethanol solution.

Synthesis of 8-(4′-bromofenoxi) caffeine (BPC)

The 8-bromocaffeine intermediate was synthesized, as previously reported, from caffeine, hydrobromic acid at 40%, and hydrogen peroxide at 30% (Romero-Hernández, 2016) (Scheme 1).

The title compound BPC was obtained from 8-bromocaffeine and bromophenol by nucleophilic aromatic substitution using copper as catalyst and the Ullmann′s reaction. (Scheme 2)

General procedure

In a 50 mL flask coupled to a condenser protected with a tube of CaCl2 anhydrous calcium the following reagents were mixed: 0.82g (3 mmol) of 8-bromocaffeine, (2mmol) of bromophenol, 0.55g (4 mmol) of sodium carbonate, 0.013g (2mmol) of powder of copper, 4 drops of pyridine and 15 mL of dimethylformamide. The reaction mixture was refluxed during 6hr. The precipitated solid was dissolved in 15 mL of ethanol and filtered to remove the sodium carbonate and copper. Further purification of BPC was accomplished by recrystallization from ethanol. Yield 51%, m. p. 233-234.C

X-ray data collection and structure analysis of BPC

The data were collected on a Bruker APEXII-CCD diffractometer using Mo Kα radiation (0.71073 Å) and graphite crystal incident beam monochromator. Numerical absorption correction from crystal shape was made. The cell determination and the final cell parameters were acquired on all reflections using the Bruker SAINT software. Data integration and scaled was also carried out using the Bruker SAINT soft included in APEX2 software suit. The space group was determined from systematic absences. Intensity data were collected at temperature of 296ºK using ω-2Θ scan. 2Θmax for data collection: = 52.72º, Index ranges: h_{min} -9, h_{max} 9; k_{min} -11, k_{max} 11; l_{min} -25, l_{max} 25. A total of 34613 reflections were collected, of which were 2960 independent, and 2591 observed reflexions. As a check on crystal and electronic stability, several standard reflections were measured; the intensities of these standards remained constant within experimental errors, through data collection.

The structure was solved by Direct Methods and Fourier synthesis using the program SHELXS97 and refined on F. with SHELXL97 (Sheldrick, 1997 and 2015), contained in WinGX program suite (Farrugia, 2012). Non-H atoms were refined anisotropically by full matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U_{eq} of their parent atoms. ORTEP-3 and Mercury softwares were used to prepare the illustration.

RESULTS AND DISCUSSION

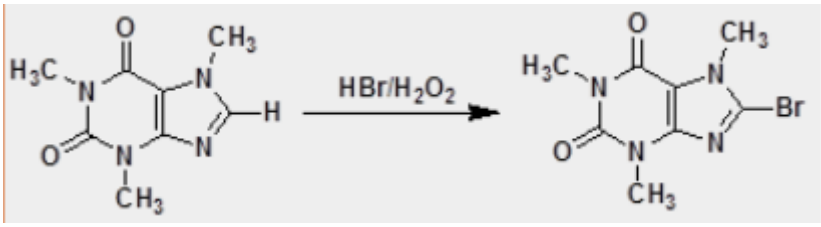
Single crystal structure determination

The absolute structure is reported (Flack parameter =0.007(8). The details of crystal data and structure refinement are summarized in Table I. A view of the molecule showing the labeling of the non-H atoms is shown in Fig. 1. Selected bond lengths and bond angles of BPC are given in Table II. Atomic coordinates and anisotropic displacement parameters are listed in supplementary information file.

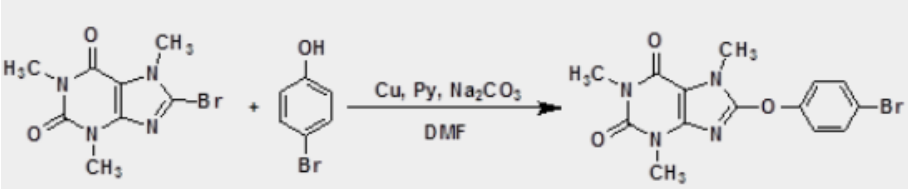
The caffeine core of the BPC molecule contains two fused rings, a pyrimidinedione and imidazole. The pyrimidinedione contains two amide functional groups that exist predominately in a zwitterionic resonance. The nitrogen atoms N3 and N4 are double bonded to their adjacent amide carbons atoms (N3-C10=1.370(3), N3-C8=1.373(3), N4-C10=1.394(3) Å). The molecule does not have a planar configuration: the caffeine group makes a dihedral angle of 58.15(9) º with the bromofenoxy moiety, and the torsion angle between N1-C7-O1-C4 is 20.6(5) º.

The crystal structure of BPC viewed along the c axis is shown in Figure 2. The structure consists of discrete molecule with weak intramolecular hydrogen bond between hydrogen of the methyl group of imidazole ring and oxygen atom of the carbonyl group (C12-H12A...O3). The packing of the molecules is oriented in an

anti-parallel fashion; this is in agreement with the previously packing reported for the crystal structure of anhydrous caffeine (Lehmann and Stowasser, 2007; Enright and Terskikh, 2007). The packing is assumed to be dictated assumed to be dictated by van der Waals interactions. Bond distances and angles are close to expected values (Heyrovska and Narayan, 2011).



SCHEME. 1
Reaction of bromation of caffeine.



SCHEME. 2
Synthetic route for 8-(4′-bromofenoxy) caffeine.

TABLE 1
Crystal data and single crystal refinement parameters of structure BPC.

Crystal data	
Chemical formula	$C_{14}H_{13}BrN_4O_3$
Formula weight	365.19
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (^oK)	296(2)
a, b, c (Å)	7.9056(3), 9.1413(3), 20.2023(6)
Cell volume ($Å^3$)	1459.97(9)
Z	4
D_{calc} (g/cm^3)	1.661
Crystal size (mm)	0.18, 0.14, 0.11 colorless
Absorption coefficient, mm^{-1}	2.834
Numerical absorption correction from crystal shape was made	T_{min}=0.6294, T_{max}=0.7457
Refinement´s result	
Refinement on F^2	
Extinction correction	none
Total number of l. s. parameters	202
ωR (F^2)	0.071
S = GooF	1.057
R_1 for 2591 Fo>4σ(Fo) R_1 for all 2958 data	0.0292 0.0369
Flack x	0.007(8) (classical fit to all intensities)
Largest diff. peak and hole, e A^{-3}	$\Delta\rho_{max}$=0.17 $\Delta\rho_{min}$ = -0.55

TABLE 2.
Selected bond lengths (Å) and angles (°) for of BPC.

N1-C7	1.314 (3)		N4-C10	1.394 (4)
N1-C8	1.354 (3)		N4-C11	1.427 (3)
N2-C7	1.341 (3)		C7-O1	1.342 (3)
N2-C9	1.399 (3)		C8-C9	1.365 (3)
N3-C10	1.370 (3)		O1-C4	1.399 (3)
N3-C8	1.373 (3)		Br-C1	1.896(2)
C10-N4-C11	126.9 (2)		N4-C2-N1	124.4 (3)
N4-C10-N3	116.9 (2)		C9-N2-C7	104.4(2)
N4-C11-C9	111.0 (2)		C8-N1-C7	101.9 (2)
C11-C9-C8	123.4 (2)		N2-C7-N1	115.9 (2)
C10-N3-C8	119.7 (2)			
H-Bonds	D-H	H...A	D...A	<(DH...A) (°)
C12-H12A...O3 #1	0.96	2.58	3.258(5)	127.9

Symmetry operators:#1 x, y, z

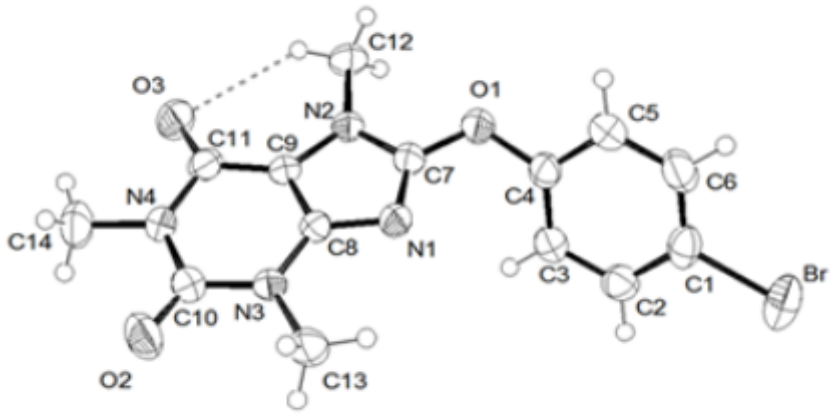


FIG. 1
A view of the molecule of 8-(4′-bromofenoxy) caffeine showing the numbering scheme. Displacement ellipsoids are drawn at 50% probability level for non-H atoms, H atoms are represented by spheres of arbitrary radius. Intramolecular hydrogen bond is represented by dotted lines.

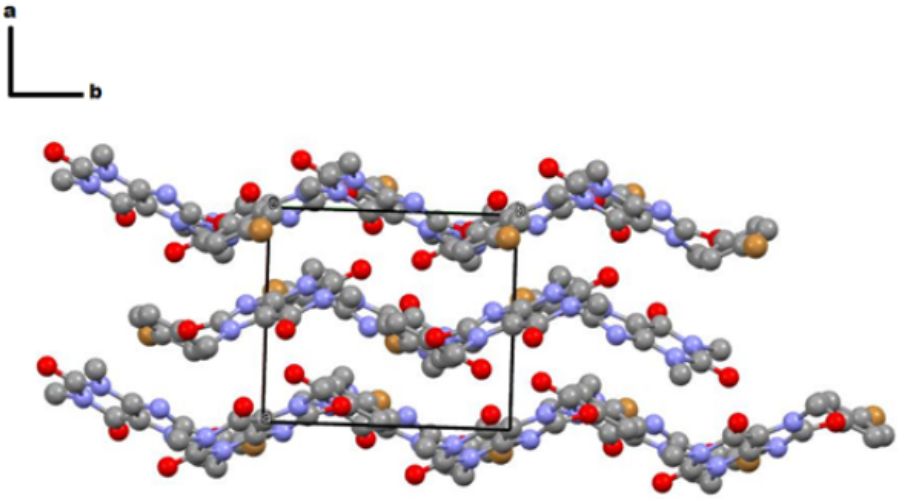


FIG. 2
View of the packing of the BPC molecules along the "c" axis.

CONCLUSION

The structure of 8- (4-bromophenoxy) caffeine consists of discrete molecule with weak intramolecular hydrogen bond between hydrogen of the methyl group of imidazole ring and oxygen atom of the carbonyl group. The packing of the molecules is oriented in an anti-parallel fashion and is assumed to be dictated by van der Waals interactions. Bond distances and angles are close to expected values.

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Additional information

SUPPORTING INFORMATION: Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1916599. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax +44 1223 336033, email: deposit@ccdc.cam.ac.uk