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Crystal structure analysis of a β– lactam compound (3R)-1'-(1-(4-methoxyphenyl)-4-oxo-3-phenylazetidin-2-yl)-1-methyl-2-oxo-1',6′,7′,7a′-tetrahydrospiro[indoline-3,3'-pyrrolizine]-2',2'(5'H)-dicarbonitrile

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Abstract: The β-lactam compound containing (3R)-1'-(1-(4-methoxyphenyl)-4-oxo-3-phenylazetidin-2-yl)-1-methyl-2-oxo-1',6',7',7a'-tetrahydrospiro[indoline-3,3'-pyrrolizine]-2',2'(5'H)-dicarbonitrile crystallizes in monoclinic C2/c space group. Crystal data were collected using BRUKER SMART APEX II CCD X-ray diffractometer. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures to the final R_1 of 0.048 using SHELXL programs.
Key Words: β-lactam, crystal structure.

Introduction

The role of β-lactam antibiotics is well known[1]. The most commonly used β-lactam antibiotics for the therapy of infectious diseases are penicillin and cephalosporin[2]. β-lactam based antibiotics have been successfully used in the treatment of infectious diseases for many years [3]. In view of its potential applications, the crystal structure determination of the titled β-lactam compound was carried out.

Experimental

X-ray Structure Determination

Single crystal of the compound suitable for x-ray diffraction was obtained by slow evaporation method. Three dimensional intensity data were collected on a Bruker[4] SMART APEX CCD Diffractometer using graphite monochromatized Mo-Kα radiation (λ= 0.71073 Å) at the CAS in Crystallography and Biophysics, University of Madras, Chennai. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares procedures using the SHELXL programs[5]. All the non-hydrogen atoms were refined using isotropic and later anisotropic thermal parameters. The hydrogen atoms were included in the structure factor calculation at idealized positions by using a riding model, but not refined. Images were created with the ORTEP-3[6]. The crystallographic data for the compound are listed in Table 1.

Table 1. Crystal data and structure refinement for the titled compound

Compound	1
Empirical formula	$C_{33}\ H_{29}\ N_5\ O_3$
Formula weight	543.61
Temperature(K)	293(2)
Wavelength(Å)	0.71073
Crystal system, Space group	Monoclinic C2/c
Unit cell dimensions a(Å) b(Å) c(Å) α(º) β(º) γ(º)	 27.2481(12) 8.1709(3) 26.3750(11) 90.00 99.067(4) 90.00
Volume($Å^3$)	5798.8(4)
Z, D_{cal} (Mgm^{-3})	8, 1.245
Absorption coefficient (mm^{-1})	0.082
F(000)	2288
Crystal size(mm)	0.30×0.25× 0.20
Theta range for data collection(º)	1.51 to 28.55
Limiting indices	-36<=h<=35, -10<=k<=10, -35<=l<=35
Reflections collected / unique	49609 / 7313
R(int)	0.039
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7317 / 2 / 376
Goodness-of-fit on F^2	1.011
Final R indices [I>2σ(I)]	R1= 0.048, wR2 = 0.138
R indices (all data)	R1= 0.093, wR2 = 0.112
Largest diff. peak and hole($e.Å^{-3}$)	0.24 and −0.28

Synthesis of the compound

To a reaction mixture of 2-[(1-(4-methoxyphenyl)-4-oxo-3-phenylazetidin-2-yl)methylene] malo nonitrile (1 mmol), N-methyl isatin (1.1 mmol) and proline (1.1 mmol) was refluxed in methanol until completion of the reaction was evidenced by TLC analysis. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude reaction mixture was dissolved in dichloromethane and washed with water followed by brine solution. The organic layer was separated and dried over sodium sulfate, filtered and evaporation of the organic solvent was carried out under reduced pressure. The product was separated by column chromatography using hexane and ethyl acetate (3:7) as an eluent to give colorless solid. The product was dissolved in ethyl acetate and heated for two minutes. The resulting solution was subjected to crystallization by slow evaporation of the solvent resulting in single crystals suitable for x-ray diffraction studies.

Results and Discussion

The pyrrolidine ring 1 (N2/C17/C18/C22/C23) adopts an *envelope* conformation. The other pyrrolidine ring 2 (N2/C18/C19/C20/C21) adopts a *twisted* conformation. The atom C20 in the pyrrolidine ring 2 is disordered over two positions (C20/C20') with a site occupancy factor of 0.543(7):0.457(7), respectively. The *β*-lactam ring (N1/C8/C9/C10) makes a dihedral angle of 37.83(2)° with the pyrrolidine ring 1, a dihedral angle of 76.79(2)° with the pyrrolidine ring 2 and it makes a dihedral angle of 42.58(2)° with the pyrrolidine ring 3 (N3/C22/C26/C31/C32). The dihedral angle between pyrrolidine ring 1 and 2 is 43.77(2)°. The pyrrolidine ring 2 makes a dihedral angle of 78.64(1)° with the pyrrolidine ring 3. The oxygen atom O2 attached with the *β*-

lactam ring deviates by 0.1330(2) Å. The oxygen atom O3 attached with the pyrrolidine ring 3 deviates by −0.0611(2) Å. The methyl carbon atom C33 attached with the pyrrolidine ring 3 deviates by −0.0514(3)Å. The packing of the crystal is stabilized by intra and intermolecular C—H…O hydrogen bonds. It also features C—H…N an intramolecular hydrogen bond (Table 2).

Table 2: Hydrogen-bond geometry [Å] for compound

D—H…A	D—H	H…A	D…A	D—H…A
C8—H8…O2^{i}	0.98	2.56	3.351(2)	137
C27—H27...N4^{ii}	0.93	2.57	3.268(3)	132
C33--H33B…O3^{iii}	0.96	2.38	3.311(3)	163
C17—H17…O3	0.98	2.38	3.052(2)	125
C33—H33C…O3	0.96	2.51	2.866(3)	102

Symmetry code: i) **−x,−y,−z,** ii) **−x,y,1/2−z,** iii) **1/2−x,1/2+y,1/2−z**

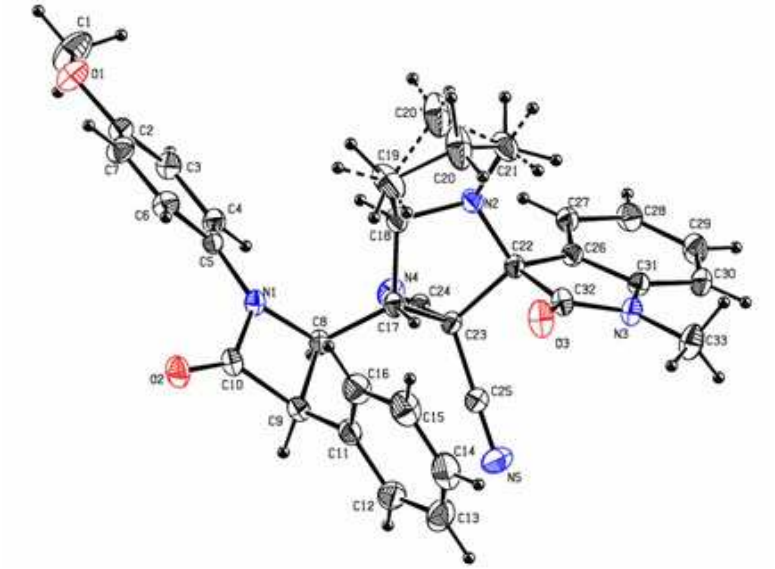

Fig 1. The molecular structure of the titled compound, with atom labeling. Displacement ellipsoids are drawn at the 30% probability level.

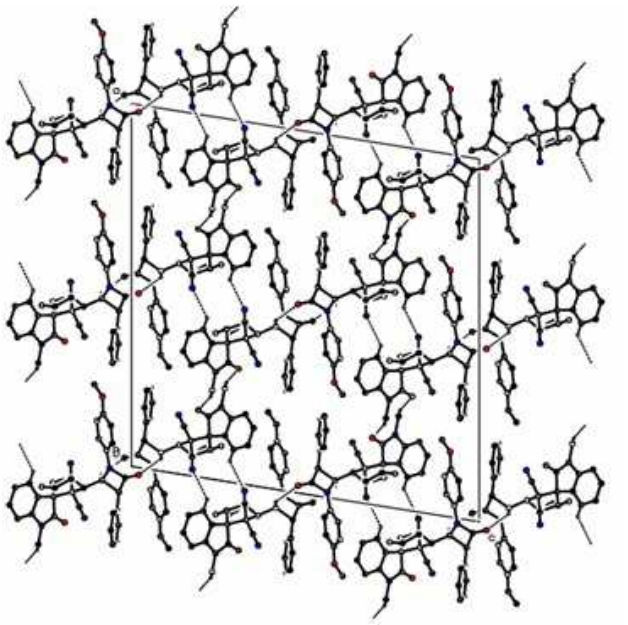

Fig. 2. The crystal packing of the titled compound viewed along the *b* axis. The hydrogen bonds are shown as dashed lines (see Table 2 for details; H-atoms not involved in H-bonds have been excluded for clarity).

Table 3: Selected Bond lengths (Å)

Selected bonds	Bond lengths (Å)	Selected bonds	Bond lengths (Å)
C1-O1	1.404(3)	N2 -C21	1.472(2)
C2- O1	1.368(2)	N2 -C18	1.483(2)
C2 -C3	1.379(3)	C18 -C19	1.519(3)
C2 -C7	1.383(3)	C19 -C20	1.461(5)
C3 -C4	1.385(2)	C19 -C20	1.500(7)
C4 -C5	1.376(2)	C20 -C21	1.526(5)
C5 -C6	1.390(2)	C20'- C21	1.525(6)
C5 -N1	1.419(2)	C22 -C26	1.508(2)
C6 -C7	1.370(3)	C22 -C32	1.569(2)
C8 -N1	1.485(2)	C22 -C23	1.570(2)
C8 -C17	1.524(2)	C23 -C25	1.468(2)
C8 -C9	1.571(2)	C23 -C24	1.476(2)
C9 -C11	1.503(3)	C24 -N4	1.134(2)
C9 -C10	1.522(3)	C25 -N5	1.138(2)
C10- O2	1.203(2)	C26 -C27	1.374(2)
C10 -N1	1.373(2)	C26 -C31	1.383(2)
C11 -C12	1.374(3)	C27 -C28	1.391(2)
C11 -C16	1.388(3)	C28 -C29	1.380(3)
C12 -C13	1.401(3)	C29 -C30	1.381(3)
C13 -C14	1.367(4)	C30 -C31	1.379(2)
C14 -C15	1.354(4)	C31 -N3	1.410(2)
C15 -C16	1.381(3)	C32 -O3	1.212(2)
C17 -C18	1.525(2)	C32 -N3	1.355(2)
C17 -C23	1.563(2)	C33 -N3	1.452(2)
N2- C22	1.445(2)		

Table 4: Selected Bond angles (deg)

Selected angles	Bond angles (deg.)	Selected angles	Bond angles (deg.)	Selected angles	Bond angles (deg.)
O1- C2- C3	124.74(2)	C14 -C15 -C1	119.4(3)	C24 -C23 C17	109.43(1)
O1- C2- C7	115.60(2)	C15 -C16- C1	121.2(2)	C25 -C23-C22	113.03(1)
C3 -C2- C7	119.66(2)	C8 -C17 -C18	118.26(1)	C24 -C23-C22	110.45(1)
C2- C3 -C4	119.69(2)	C8 -C17- C23	113.43(1)	C17 -C23-C22	101.28(1)
C5- C4- C3	120.55(2)	C18- C17 -C2	101.04(1)	N4 -C24 -C23	176.78(2)
C4- C5 -C6	119.55(2)	C22 -N2- C21	117.76(2)	N5 -C25- C23	179.4(2)
C4 -C5- N1	121.52(2)	C22 -N2 -C18	111.83(1)	C27 -C26-C31	120.21(2)
C6- C5 -N1	118.83(2)	C21 -N2- C18	109.30(1)	C27-C26- C22	130.46(2)
C7 -C6 -C5	119.76(2)	N2 -C18 -C19	105.35(2)	C31-C26 -C22	109.29(2)
C6 -C7 -C2	120.77(2)	N2 -C18- C17	105.14(1)	C26-C27- C28	118.71(2)
N1- C8- C17	115.69(1)	C19 -C18 -17	117.13(2)	C29-C28 -C27	120.09(2)
N1- C8- C9	86.92(1)	C20 -C19-C18	109.7(2)	C28-C29- C30	121.76(2)
C17 -C8- C9	118.04(1)	C20' -C19-C18	100.4(3)	C30- C31-C26	121.98(2)
C11 -C9 -C10	116.80(2)	C19 -C20-C21	105.5(3)	C30- C31- N3	127.97(2)
C11- C9- C8	119.95(1)	C19 -C20'-C21	103.7(4)	C26- C31 -N3	110.03(2)
C10- C9 -C8	85.37(1)	N2 -C21- C20'	101.2(3)	O3 -C32- N3	125.75(2)
O2 -C10- N1	131.42(2)	N2- C21 -C20	106.8(2)	O3 -C32 -C22	126.39(2)
O2 -C10 -C9	135.48(2)	N2 -C22- C26	114.66(1)	N3 -C32- C22	107.84(2)
N1 -C10- C9	93.06(1)	N2 -C22 -C32	117.39(2)	C10 -N1 -C5	128.76(1)
C12 -C11- C1	118.6(2)	C26 -C22-C32	101.24(1)	C10 -N1- C8	94.35(2)
C12 -C11- C9	120.58(2)	N2- C22 C-23	100.81(1)	C5 -N1 -C8	131.38(1)
C16- C11- C9	120.78(2)	C26- C22-C23	115.96(1)	C32- N3- C31	111.43(2)
C11 -C12- C1	119.9(2)	C32 -C22-C23	107.25(1)	C32- N3 -C33	123.10(2)
C14 -C13 -C1	119.8(3)	C25-C23- C24	107.84(1)	C31- N3- C33	125.31(1)
C15- C14- C1	121.1(3)	C25-C23- C17	114.69(1)	C2- O1- C1	117.96(2)

Conclusion

The crystal structure analysis of a novel *β*-lactam compound was studied using x-ray diffraction method. In the compound the packing of the crystal structure is stabilized by intermolecular and intramolecular C—H…O hydrogen bonds. It also features a C—H…N hydrogen bond.

Acknowledgments

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Crystallographic data for the structure reported here have been deposited with CCDC (Deposition No's. CCDC 967795). These data can be obtained free of charge via http: // www.ccdc.com. ac. uk/ conts/ retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk.

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