Crystal Structure of 4,4-Dimethyl-1-[2-phenyl-1-(phenylamino)ethyl]-piperidin-2,6-dione

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The structure of 4,4-dimethyl-1-[2-phenyl-1-(phenylamino)ethyl]piperidin-2,6-dione crystallizes in the orthorhombic space group $Pna2_1$ with unit-cell parameters $a = 22.9565(14)\text{Å}$, $b = 6.3725(4)\text{Å}$, $c = 24.6677(17)\text{Å}$, $Z = 8$ and $V = 3608.6(4)\text{Å}^3$. The structure was solved by direct methods, and the final R value is 0.0826. There exists two crystallographically independent molecules in the asymmetric unit. The piperidine ring makes dihedral angles of $65.24(2)^\circ$ and $56.48(2)^\circ$ respectively, with the phenyl and phenylamino moieties of molecule-I (the corresponding values for molecule-II are $53.17(2)^\circ$ $59.02(2)^\circ$ and respectively). Few X-H...A inter- and intramolecular hydrogen interactions have been observed.

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Piperidine compounds, during the past few years, have found prominent mention in clinical and preclinical studies.¹ The piperidine ring is a distinct structural feature of a variety of alkaloid natural products and drug candidates. Piperidine, a pharmacologically active biogenic amine, is a normal constituent in the brain and urine of mammals and humans.² It shows potent nicotine-like actions on the peripheral and central nervous systems.³ It has also been suggested that piperidine affects neural mechanisms governing the regulation of emotional behavior, sleeping and extrapyramidal function.⁴

The title compound was synthesized from dimedone (1.40 g, 10 mmol) taken in 30 ml of DMF. Dry K_2CO_3 (1.38 g, 10 mmol) was added to it with stirring. Then, phenylisothiocyanate (1.19 ml, 10 mmol) was added to the solution, and the reaction mixture was refluxed for 6 h. Bromoethylacetate (10 mmol) and dry K_2CO_3 (1.38 g, 10 mmol) were added to it, and the reaction mixture was again stirred for another 8 h. The reaction mixture was then poured into 100 ml of cold water. The crude product thus obtained was filtered and dried. Single crystal growth for X-ray studies was attempted with a variety of organic solvents.

Fig. 1 Chemical structure of 4,4-dimethyl-1-[2-phenyl-1-(phenylamino)ethyl]piperidin-2,6-dione.

However, crystallization of this compound was achieved with a chloroform-methanol combination that yielded thin yellowish shining rectangular plate-shaped crystals (Fig. 1).⁵

Three-dimensional intensity data for a poorly grown single-crystal were collected by using X'calibur single-crystal X-ray diffractometer with CCD set-up [$Mo K_\alpha$ radiation ($\lambda = 0.71073\text{Å}$)]. CrysAlisPro software was used for data collection, data reduction and space-group determination.⁶ The structure was solved by direct methods using SHELXS86 software. A full matrix least-squares refinement of the non-hydrogen atoms with isotropic temperature factors was carried out using SHELXL97. Subsequent cycles of refinement yielded a final R -factor of

Table 1 Crystal and experimental data

Chemical Formula: $C_{21}H_{24}N_2O_2$	
Formula weight = 336.43	
$T = 293(2)\text{K}$	
Crystal system: orthorhombic	Space group: $Pna2_1$
$a = 22.9565(14)\text{Å}$	
$b = 6.3725(4)\text{Å}$	
$c = 24.6677(17)\text{Å}$	
$V = 3608.6(4)\text{Å}^3$	
$Z = 8$	
$D_x = 1.239\text{ g/cm}^3$	
Radiation: $Mo K_\alpha$ ($\lambda = 0.71073\text{Å}$)	
Crystal size = $0.30 \times 0.20 \times 0.20\text{ mm}^3$	
No. of reflections collected = 22346	
θ range for data collection: 3.05 to 30.14°	
Data/restraints/parameters = 9139/1/452	
Goodness-of-fit on $F^2 = 0.930$	
R indices [$I > 2\sigma(I)$]: $R1 = 0.0826$, $wR2 = 0.1891$	
R indices (all data): $R1 = 0.1908$, $wR2 = 0.2328$	
Measurement: X'calibur single crystal X-ray diffractometer with CCD camera	
Programs system: CrysAlisPro	
Structure determination: SHELXS-97	
CCDC deposition number: 727345	

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Table 2 Selected bond distances (Å) and bond angles (°) for non-hydrogen atoms (e.s.d.'s are given in parentheses)

Molecule-I									
C(7)-C(14)	1.334(5)	C(7)-C(5)	1.412(6)	O(2)-C(19)	1.231(6)	N(1)-C(14)	1.346(5)		
N(1)-C(13)	1.445(6)	O(1)-C(15)	1.269(5)	N(2)-C(19)	1.434(6)	N(2)-C(15)	1.426(6)		
N(2)-C(14)	1.451(6)	C(19)-C(18)	1.515(6)	C(17)-C(16)	1.507(8)	C(17)-C(18)	1.496(7)		
C(17)-C(20)	1.529(8)	C(15)-C(16)	1.512(6)	C(17)-C(21)	1.563(7)				
C(14)-C(7)-C(5)	124.4(4)	C(14)-N(1)-C(13)	127.5(3)	C(15)-N(2)-C(19)	120.5(4)				
C(15)-N(2)-C(14)	119.8(4)	C(19)-N(2)-C(14)	119.6(4)	C(6)-C(5)-C(7)	120.7(4)				
C(4)-C(5)-C(7)	120.0(4)	C(12)-C(13)-N(1)	121.4(4)	C(8)-C(13)-N(1)	117.7(4)				
O(2)-C(19)-N(2)	123.8(4)	O(2)-C(19)-C(18)	117.5(4)	N(2)-C(19)-C(18)	118.7(4)				
C(7)-C(14)-N(1)	121.5(4)	C(7)-C(14)-N(2)	121.1(4)	N(1)-C(14)-N(2)	117.4(4)				
C(18)-C(17)-C(16)	108.8(4)	C(16)-C(17)-C(20)	109.2(5)	C(18)-C(17)-C(20)	111.6(5)				
C(18)-C(17)-C(21)	109.4(4)	C(16)-C(17)-C(21)	109.1(5)	C(20)-C(17)-C(21)	108.8(4)				
C(17)-C(18)-C(19)	116.9(4)	O(1)-C(15)-N(2)	124.0(4)	O(1)-C(15)-C(16)	117.0(4)				
N(2)-C(15)-C(16)	119.0(4)	C(17)-C(16)-C(15)	114.7(4)						
Molecule-II									
N(1'-C(14'))	1.321(5)	N(1'-C(13'))	1.437(5)	O(2'-C(19'))	1.246(5)	O(1'-C(15'))	1.243(6)		
N(2'-C(15'))	1.435(6)	N(2'-C(19'))	1.455(6)	N(2'-C(14'))	1.462(6)	C(7'-C(14'))	1.337(6)		
C(7'-C(5'))	1.405(6)	C(15'-C(16'))	1.482(7)	C(19'-C(18'))	1.490(6)	C(17'-C(21'))	1.507(9)		
C(17'-C(16'))	1.524(7)	C(17'-C(20'))	1.525(7)	C(17'-C(18'))	1.539(7)				
C(14'-N(1'-C(13'))	124.2(3)	C(15'-N(2'-C(19'))	119.0(4)	C(15'-N(2'-C(14'))	122.2(4)				
C(19'-N(2'-C(14'))	118.8(4)	C(14'-C(7'-C(5'))	128.4(4)	O(1'-C(15'-N(2'))	122.0(5)				
O(1'-C(15'-C(16'))	117.9(4)	N(2'-C(15'-C(16'))	119.9(5)	C(12'-C(13'-N(1'))	119.9(4)				
C(8'-C(13'-N(1'))	120.7(4)	C(6'-C(5'-C(7'))	121.4(4)	C(4'-C(5'-C(7'))	117.5(4)				
N(1'-C(14'-C(7'))	122.3(4)	N(1'-C(14'-N(2'))	120.8(4)	C(7'-C(14'-N(2'))	117.0(4)				
O(2'-C(19'-N(2'))	123.4(4)	O(2'-C(19'-C(18'))	116.7(4)	N(2'-C(19'-C(18'))	119.9(4)				
C(21'-C(17'-C(20'))	110.2(5)	C(21'-C(17'-C(16'))	110.5(5)	C(16'-C(17'-C(20'))	108.9(4)				
C(21'-C(17'-C(18'))	110.4(5)	C(20'-C(17'-C(18'))	109.8(5)	C(16'-C(17'-C(18'))	107.0(4)				
C(19'-C(18'-C(17'))	115.6(4)	C(15'-C(16'-C(17'))	115.0(4)						

0.0826. The relatively large value of the *R*-factor could be due to poor-quality crystallization of this material.

The crystal and experimental data are given in Table 1. The selected bond lengths and angles are summarized in Table 2. An ORTEP view of the molecule with atomic labeling (thermal ellipsoids are drawn at 50% probability) is shown in Fig. 2.⁷

There are two crystallographically independent molecules in the asymmetric unit that are held in a reversed orientation. The conformation of the independent molecules is significantly different. The piperidine ring is non-planar. The asymmetry parameters for this ring are $\Delta C_2 = 14.82$ and $\Delta C_s = 8.14$.^{8,9} The conformational difference between the two molecules is mainly derived from significant differences of the torsion angles of C13-N1-C14-N2 and C5-C7-C14-N2. These angles are 159.24(4)° and 148.99(4)°, respectively, for molecule-I [-148.96(4)° and -163.12(1)°, respectively, for molecule-II]. The bond angles [C13-N1-C14 = 127.5(3) and N2-C14-N1 = 117.4(4)] and [124.2(3)° and 121.4(4)] for molecule-I and II show significant deviations, which could be due to some strain caused by rings attached through the common bond C14-N1. The torsion around this bond [C13-N1-C14-N2 = 159.24(4)° in molecule-I and -148.96(4)° in molecule-II] is also quite large, and the dihedral angles between rings I and III of both the asymmetric molecules are 56.48(2)° and 59.02(2)°, respectively. All other bond lengths and angles in both molecules are within the expected ranges.¹⁰

The dihedral angle between ring-I (C8-C13) and ring-II (C1-C6) of molecule-I is 46.29(2)° [45.14(1)° for molecule-II]. The magnitude of dihedral angle between ring-II (C1-C6) and ring-III (C15-C19/N2) is 65.24(2)° and 53.17(2)°, respectively, for both crystallographically independent molecules. Both molecules packed in a unit cell are stabilized by the some weak C-H...X (X=O, N) and N-H...O type of intra and intermolecular hydrogen bonds.

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Fig. 2 General view of molecule with atomic numbering scheme (thermal ellipsoids drawn at 50% probability).

Table 3 Atomic coordinates (Å × 10⁴) and equivalent isotropic displacement parameters (Å × 10³) involving non-hydrogen atoms

Molecule-I					Molecule-II				
Atom	x	y	z	<i>U</i> _{eq}	Atom	x	y	z	<i>U</i> _{eq}
C7	3125(2)	7655(5)	3074(2)	28(1)	N1'	4330(2)	2572(5)	1274(2)	39(1)
O2	2730(2)	13004(5)	3983(2)	66(1)	O2'	5355(1)	2082(6)	1682(2)	64(1)
N1	3408(1)	10064(5)	3739(2)	42(1)	O1'	4729(2)	-2842(5)	382(2)	63(1)
O1	2097(1)	8202(7)	2649(2)	69(1)	N2'	4976(2)	-261(7)	1018(2)	64(1)
N2	2477(2)	10507(7)	3321(2)	65(1)	C7'	4052(2)	242(6)	595(2)	33(1)
C5	3684(2)	7022(7)	2903(2)	41(1)	C15'	5082(2)	-2155(8)	719(2)	51(1)
C13	3879(2)	8909(7)	3988(2)	47(1)	C8'	3612(2)	5296(7)	1465(2)	50(1)
C19	2384(2)	12360(7)	3640(2)	41(1)	C13'	3758(2)	3215(7)	1444(2)	40(1)
C14	3019(2)	9353(6)	3375(2)	40(1)	C12'	3367(2)	1754(8)	1616(2)	60(1)
C4	3834(2)	4928(7)	2910(2)	52(1)	C5'	3577(2)	1321(7)	368(2)	45(1)
C8	4385(2)	9961(9)	4091(2)	66(1)	C14'	4434(2)	927(7)	963(2)	49(1)
C2	4769(2)	5781(9)	2519(2)	63(1)	C19'	5409(2)	451(8)	1407(2)	50(1)
C17	1324(2)	12467(7)	3312(2)	55(1)	C4'	3065(2)	206(8)	290(2)	61(1)
C3	4377(2)	4365(8)	2715(3)	67(2)	C10'	2691(2)	4436(8)	1824(2)	59(1)
C1	4628(2)	7860(9)	2512(2)	58(1)	C17'	6137(2)	-2213(8)	1024(2)	59(2)
C6	4071(2)	8450(8)	2704(2)	55(1)	C18'	5946(2)	-814(8)	1500(2)	63(1)
C18	1830(2)	13608(8)	3554(2)	62(1)	C6'	3625(2)	3333(8)	202(2)	59(1)
C12	3808(2)	6900(9)	4158(2)	57(1)	C2'	2647(3)	3232(14)	-136(3)	86(2)
C15	2055(2)	9861(7)	2931(2)	49(1)	C16'	5602(2)	-3447(7)	843(2)	57(1)
C16	1532(2)	11246(9)	2826(2)	65(1)	C9'	3080(2)	5921(7)	1654(2)	59(1)
C10	4759(3)	6888(15)	4536(3)	93(2)	C11'	2850(2)	2387(8)	1796(3)	60(2)
C21	853(2)	14087(9)	3126(3)	86(2)	C3'	2605(3)	1162(11)	15(3)	77(2)
C9	4826(3)	8934(16)	4368(3)	102(3)	C21'	6366(3)	-890(10)	565(3)	93(2)
C11	4260(3)	5930(10)	4418(2)	79(2)	C20'	6603(2)	-3750(10)	1213(3)	91(2)
C20	1047(2)	10954(11)	3718(3)	91(2)	C1'	3153(3)	4270(9)	-72(2)	74(2)

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