Instrumental Achievements

Crystal Structure of 1,7,7-Trimethyl-4-(4-methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione

M. Murat CANDAN,*† Engin KENDİ,* Mine Yarim, Selma SARAÇ,** and Mevlüt ERTAN****

**Department of Engineering Physics, Hacettepe University, Beytepe 06532, Ankara, Turkey*
***Hacettepe University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Sıhhiye, 06100, Ankara, Turkey*

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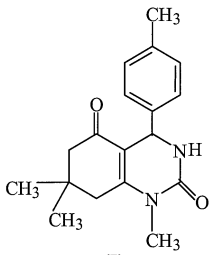
4-Aryl-1,4-dihydropyridines have gained great therapeutic significance as calcium-channel modulators in the treatment of cardiovascular diseases, such as hypertension, cardiac arrythmias or angina.[1] In recent years, interest has also been focused on aza-analogs of dihydropyridines, such as dihydropyrimidines, which show a very similar pharmacological profile to that of dihydropyridine calcium channel modulators.[2] In a continuation of these studies, ring annihilation has also been investigated; further, the synthesis and calcium antagonist activities of some condensed derivatives, such as 4-aryl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline-2-thione and 4-aryl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones, have been described.[3,4]

The objective of the present syntheses was to construct a 4-aryl-1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dion ring system. 1,7,7-Trimethyl-4-(4-methylphenyl)-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-dione was obtained from a Biginelli-type cyclocondensation[5] of 5,5-dimethylcyclohexane-1,3-dione with urea and benzaldehyde.

The title compound (I) (Fig. 1) was obtained and its structure was analyzed by standard analytical techniques (UV, IR, NMR, mass spectroscopy and elemental analysis). In order to obtain information about the stereochemistry of the molecule and to confirm the assigned structure, an x-ray analysis of (I) was undertaken.

A mixture containing 5,5-dimethyl-1,3-cyclohexanedione (97%) (1.107 g, 0.0075 mol), substituted benzaldehyde (0.005 mol), *N*-methylurea (0.38 g, 0.005 mol) and 37% HCl (4 drops)



(I)

Fig. 1 Chemical structure.

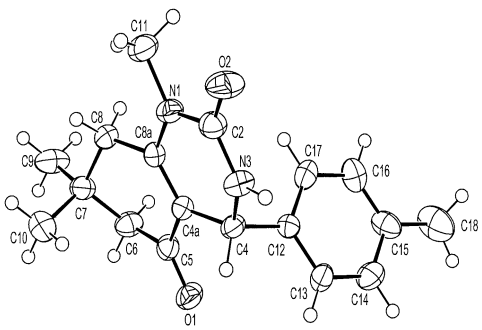


Fig. 2 Perspective view of the molecular structure of the title compound along with the atom-numbering scheme. The displacement ellipsoids are drawn at the 50% probability level.

† To whom correspondence should be addressed.

Table 1 Crystal and experimental data

Formula: $C_{18}H_{22}N_2O_2$	
Formula weight = 298.36	
Crystal system: monoclinic	
Space group: $P2_1/c$	$Z = 4$
a = 11.091(2)Å	
b = 8.067(1)Å	
c = 17.660(3)Å	β = 95.96(4)°
V = 1571.6(4)Å^3	
D_c =1.261 g/cm^3	
μ (Cu K$_\alpha$) = 0.623 mm^{-1}	
T = 295 K	
Yellow	
F(0 0 0) = 640	
Crystal size: 0.48 × 0.24 × 0.06 mm	
$2\theta_{max}$ = 133.3°	
R = 0.065	
Rw = 0.087	
No. of reflection used = 2273	($I > 2\sigma(I)$)
No. of parameters = 199	
Goodness-of-fit = 1.13	
$(\Delta/\sigma)_{max}$ = 0.0006	
$(\Delta\rho)_{max}$ = 0.60 eÅ^{-3}	
$(\Delta\rho)_{min}$ = –0.78 eÅ^{-3}	
Measurements: Enraf Nonius CAD-4 diffractometer	
Program system: CAD-4 EXPRESS Software	
Structure determination: MolEN	
Treatment of hydrogen atoms: geometric calculation	
Refinement: full matrix least-squares (MolEN)	

Table 2 Final atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms

Atom	*x*	*y*	*z*	B_{eq}/Å^2
O1	-0.0030(2)	0.5538(3)	0.1252(1)	3.52(4)
O2	0.3460(2)	0.0402(3)	0.2967(1)	4.26(5)
N1	0.3420(2)	0.2236(3)	0.1977(1)	2.89(5)
N3	0.1743(2)	0.1859(3)	0.2652(1)	2.98(5)
C2	0.2884(3)	0.1420(4)	0.2561(2)	2.96(6)
C4	0.0931(2)	0.2904(3)	0.2156(2)	2.54(5)
C4a	0.1643(2)	0.3845(3)	0.1618(2)	2.41(5)
C5	0.1008(2)	0.5123(4)	0.1149(2)	2.71(5)
C6	0.1650(3)	0.5845(4)	0.0512(2)	3.38(6)
C7	0.3007(3)	0.6074(4)	0.0728(2)	2.93(5)
C8	0.3560(2)	0.4428(4)	0.1023(2)	2.75(5)
C8a	0.2819(2)	0.3496(3)	0.1551(2)	2.37(5)
C9	0.3626(3)	0.6590(5)	0.0028(2)	4.55(7)
C10	0.3228(3)	0.7406(4)	0.1337(2)	4.26(7)
C11	0.4647(3)	0.1720(4)	0.1848(2)	3.80(7)
C12	-0.0072(2)	0.1843(3)	0.1734(2)	2.40(5)
C13	-0.1258(2)	0.2022(4)	0.1883(2)	3.04(6)
C14	-0.2162(3)	0.1017(4)	0.1522(2)	3.66(6)
C15	-0.1897(3)	-0.0187(4)	0.1010(2)	3.56(6)
C16	-0.0705(3)	-0.0353(4)	0.0863(2)	3.85(7)
C17	0.0195(3)	0.0642(4)	0.1217(2)	3.42(6)
C18	-0.2879(4)	-0.1276(5)	0.0617(2)	5.73(9)

$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* (\boldsymbol{a}_i \cdot \boldsymbol{a}_j)$.

Table 3 Selected geometric parameters (Å, °)

O1 – C5	1.230 (3)	N3 – C2	1.340 (4)
O2 – C2	1.226 (4)	N3 – C4	1.458 (3)
N1 – C2	1.405 (4)	C4a – C8a	1.351 (4)
N1 – C8a	1.392 (3)	C4 – C12	1.534 (4)
N1 – C11	1.464 (4)	C15 – C18	1.510 (5)
C2-N1-C8a	121.5 (2)	C4a-C5-C6	117.2 (2)
C2-N3-C4	127.7 (2)	C5-C6-C7	113.0 (2)
N1-C2-N3	116.2 (2)	C6-C7-C8	109.3 (2)
N3-C4-C4a	109.9 (2)	N1-C8a-C8	116.0 (2)
C2-N1-C8a-C4a	-8.3 (4)	N3-C4-C12-C17	-64.6 (3)
C2-N3-C4-C4a	-15.6 (4)	C4a-C5-C6-C7	-38.3 (4)
N3-C4-C12-C13	112.9 (3)	C6-C7-C8-C8a	-42.6 (3)

in absol. ethanol was heated at reflux for an appropriate period. After cooling to ambient temperature for 24 h, the crystalline product was filtered, washed with 50% ethanol (25 ml) and recrystallized from ethanol. (I) was prepared from 0.005 mol (0.61 g) of 4-methylbenzaldehyde (99%). Yield: 0.31 g (20.23%).

A perspective view of the title molecule (I) showing the atom-numbering scheme is presented in Fig. 2. Table 1 gives the crystal and relevant x-ray data of the structure. The fractional coordinates and mean-temperature factors along with estimated standard deviations for non-hydrogen atoms are listed in Table 2; selected geometric parameters are given in Table 3.

All of the bond lenghts and angles were normal in the structure. The phenyl rings are planar and the quinazoline ring system deviates from planarity with the C6 and C7 atoms deviating by 0.250(3) and –0.425(3)Å, respectively, on the least-squares plane through C5, C4a, C8a and C8. The phenyl ring at C4 is nearly perpendicular to the quinazoline ring system with a dihedral angle of 88.4(1)°. The observed bond lengths of both C–O in the structure are normal for a C^2_{sp}=O bond.

The crystal structure of the title compound is stabilized by inter-molecular hydrogen bonds. There is also an intra-molecular C–H···O hydrogen bond in the structure, which is between H4 and O1.

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