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Synthesis and Crystal Structures of 2-Amino-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile and 2-Amino-4-phenyl-4a,5,6,7-tetrahydro-4*H*-naphthalene-1,3,3-tricarbonitrile

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2-Amino-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile with m.f. $C_{11}H_{13}N_3$ was synthesized using simple multicomponent reaction of cyclohexanone, malononitrile and acetaldehyde. However, in an effort to synthesize another analogue of **I** using benzaldehyde in placement of acetaldehyde, 2-amino-4-phenyl-4a,5,6,7-tetrahydro-4*H*-naphthalene-1,3,3-tricarbonitrile (**II**) [$C_{19}H_{16}N_4$] was formed. The compounds **I** and **II** were crystallized in triclinic and orthorhombic crystal system with space group *P-1* and *Pbca*. The two carbon atoms in tetrahydroquinoline-3-carbonitrile were disordered over two positions which were refined using EADP constraint. The dihedral angle puckering parameters of different planes were measured. It is found that both of these molecules are involved in classical N-H…N type hydrogen bonding interaction which forms dimers through the formation of different ring motifs *i.e.* $R_2^2(8)$ and $R_2^2(12)$. In quinoline-3-carbonitrile N-H…N interactions forms sheets along *ab* plane while in naphthalene-1,3,3-tricarbonitrile infinite two dimensional network stabilize the crystal structure along (0 0 1) plane.

Keywords: Carbonitrile, Synthesis, Crystal structures, C–N···H Hydrogen bonding.

INTRODUCTION

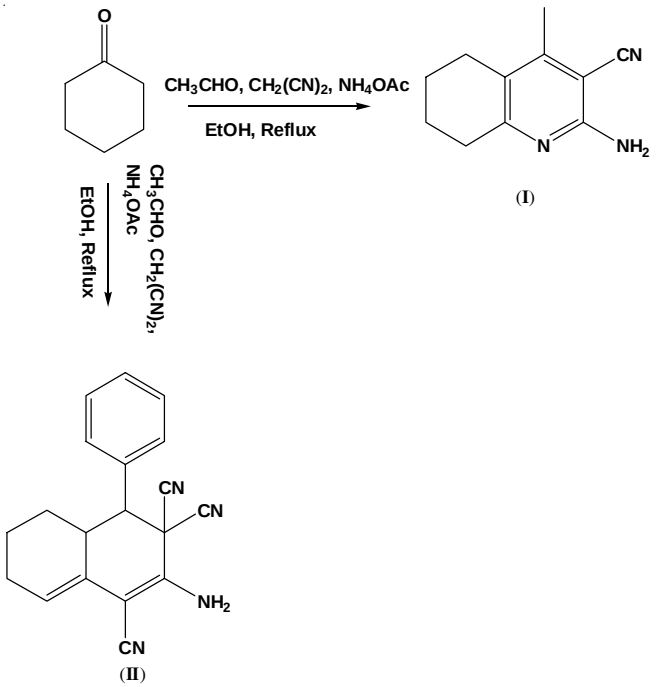
Quinoline and hydroquinoline ring systems occupy a significant position in the research ongoing in medicinal chemistry. A long range of quinoline compounds, natural and synthetic are in clinical use for the treatment of malaria. Recent literature contains several research articles dealing with the new synthetic routes and biological profiles of such compounds, for example, 4*H*-pyrano[3,2-h]quinoline and 7*H*-pyrimido-[4',5':6,5]pyrano[3,2-h]quinoline derivatives are recently discovered as potent antitumor agents[1]. Some new tetrahydroquinoline derivatives are found as plasma cholesteryl ester transfer protein (CETP) inhibitors[2], while 2-oxo-1,4-disubstituted-1,2,5,6-tetrahydro-benzo[h]quinoline-3-carbonitriles are reported as cytotoxic and antiviral agents[3]. They have been observed to bind efficiently with DNA and exhibit antitumour activity[4], antifungal[5], HIV entry inhibitors[6] and nonsteroidal selective androgen receptor modulators[7]. During our search for new biologically active heterocyclic compounds, we have reported quinoline compounds as potent HIV inhibitors[8], antileishmanial agents[9] and benzothiazine compounds as anti-HIV agents[10-12], antioxidants and antibacterial agents[13].

EXPERIMENTAL

The title compounds were synthesized by using reported methodology[14] for the tetrahydroquinoline precursor compound **I**. However, in an attempt to synthesize analogue of **I** by replacing benzaldehyde for acetaldehyde in the same method, the unexpected formation of 2-amino-4-phenyl-4a,5,6,7-tetrahydro-4*H*-naphthalene-1,3,3-tricarbonitrile (**II**) was resulted.

Compound **I:** A mixture of cyclohexanone (0.98 g, 0.01 mol) with acetaldehyde (0.44 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (1.15 g, 0.015 mol) in ethanol (20 mL) was refluxed for 1 h. The reaction mixture was then stirred overnight at room temperature and the obtained solid was recrystallized from ethanol to obtain pure product. Yield, 40 %, m.p. 279 °C (**Scheme-I**).

Compound **II:** A mixture of cyclohexanone (0.98 g, 0.01 mol) with benzaldehyde (1.08 mL, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (1.15 g, 0.015 mol) in ethanol (20 mL) was refluxed for 1 h. The reaction mixture was then stirred overnight at room temperature and the obtained solid was recrystallized from ethanol to obtain pure product. Yield, 62 %, m.p. 253 °C (**Scheme-I**).



Scheme-I: Synthesis layout for compounds **I** and **II**

The crystals were mounted on Bruker KAPPA Apex II CCD diffractometer using thin glass pin supported by copper rods. Data collection was done at 296 K. SAINT was used for cell refinement as well as data reduction[15] while the structure solution and final refinement was achieved through SHELXS-97[16]. PLATON[17], in-built with WinGX[18] was used for molecular graphics. All the non-hydrogen atoms were refined with anisotropic displacement parameters. The aromatic and aliphatic C---H hydrogen atoms were positioned geometrically and refined as riding atom over their parent carbon atoms with $U_{iso}(H) = 1.2\text{-}1.5\ U_{eq}(C)$ and distances are C-H = 0.93 Å for aromatic, C-H = 0.96 Å for methene, C-H 0.97 Å for methyl and C-H = 0.98 for chiral carbon atoms. The hydrogen atoms bended to the nitrogen atom N-H = 0.86-0.91 Å, were positioned *via* fourier map and refined freely with $U_{iso}(H) = 1.2\ U_{eq}(N)$.

The crystal data was deposited at the Cambridge Crystallographic Data Centre and it has been assigned the deposition number as CCDC 995966 and 995967. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

The two synthesized molecules 2-amino-4-methyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (**I**) and 2-amino-4-phenyl-4*a*,5,6,7-tetrahydro-4*H*-naphthalene-1,3,3-tricarbonitrile (**II**) contains amino and nitrile groups which are responsible for the classical hydrogen bonding interactions. There is no non-classical interaction in molecules. The details of data collections, crystallographic parameters and information on structure refinements are given in Table-1. Tables 2 and 3 contain the information regarding the selected bond angles and bond lengths, respectively. The ORTEP diagrams of molecules **I** and **II** are shown in Figs. 1 and 2, respectively. In the crystal structure of **I**, two carbon atoms (C3 & C4) of cyclohexene ring are disordered over two positions which were refined using the EADP constraint due to which we can say that there are two cyclohexene rings as (C1/C2/C3A/C4A/C5/C6) **A** and (C1/C2/C3B/C4B/C5/C6) **B**. The root mean square (r.m.s) deviation values for the planes of connected atoms of each ring A and B are 0.2075(3) Å and 0.1890(4) Å, respectively. The dihedral angle between the ring **A** and **B** is 9.38(2)° while these are oriented at dihedral angle of 4.65(2)° and 4.85(2)° with

TABLE-1
CRYSTAL DATA AND STRUCTURE REFINEMENT FOR I and II

Empirical formula	$C_{11}H_{13}N_3$	$C_{19}H_{16}N_4$
Formula weight	187.24	300.36
Temperature/K	296.15	296.15
Crystal System	Triclinic	Orthorhombic
Space group	P-1	Pbca
a/Å	8.3274(6)	15.804(3)
b/Å	8.7495(12)	8.6127(17)
c/Å	8.8686(7)	23.561(4)
α/°	95.977(6)	90.00
β/°	117.229(4)	90.00
γ/°	112.230(7)	90.00
Volume/Å^3	500.78(9)	3207.0(10)
Z	2	8
ρ_{calc}mg/mm^3	1.242	1.244
μ/mm^{-1}	0.077	0.077
F(000)	200.0	1264.0
Crystal size/mm^3	0.34 × 0.28 × 0.20	0.40 × 0.32 × 0.28
2θ range for data collection	5.34 to 52°	4.32 to 51.98°
Index ranges (h, k, l)	-10 ≤ h ≤ 10, -10 ≤ k ≤ 10, -10 ≤ l ≤ 10	-18 ≤ h ≤ 13, -6 ≤ k ≤ 10, -29 ≤ l ≤ 24
Reflectioned collected	7247	11358
Independent reflections	1964[R(int) = 0.0226]	2863[R(int) = 0.0756]
Data/restraints/parameters	1964/6/135	2863/0/215
Goodness-of-fit on F^2	1.080	1.009
Final R indexes [I >= 2σ(I)]	R_1 = 0.0531, wR_2 = 0.1545	R_1 = 0.0624, wR_2 = 0.1608
Final R indexes [I >= 2σ(I)]	R_1 = 0.0701, wR_2 = 0.1703	R_1 = 0.1192, wR_2 = 0.1942
Largest diff. peak/hole/e Å^{-3}	0.24/-0.17	0.27/-0.18

TABLE-2
SELECTED BOND LENGTHS OF MOLECULE **I** and **II**

I						**II**					
Atom	Atom	Length (Å)	Atom	Atom	Length (Å)	Atom	Atom	Length (Å)	Atom	Atom	Length (Å)
N1	C10	1.345(2)	C3B	C4B	1.501(9)	N1	C9	1.354(4)	C8	C9	1.525(4)
N2	C1	1.345(2)	C4A	C5	1.534(4)	N2	C17	1.121(4)	C8	C17	1.478(4)
N2	C10	1.338(2)	C4B	C5	1.516(6)	N3	C18	1.136(4)	C8	C18	1.478(4)
N3	C11	1.140(2)	C2	C3B	1.526(6)	N4	C19	1.136(3)	C9	C10	1.354(4)
C2	C3A	1.501(5)	C9	C11	1.431(2)						
C3A	C4A	1.540(7)									

TABLE-3
SELECTED BOND ANGLES OF MOLECULE **I** and **II**

I							
Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C10	N2	C1	119.06(14)	C1	C6	C5	121.05(16)
N2	C1	C2	114.50(15)	1	C6	C7	117.67(15)
N2	C1	C6	123.90(15)	C7	C6	C5	121.27(15)
C6	C1	C2	121.59(16)	C6	C7	C8	121.44(16)
C1	C2	C3B	114.0(3)	C9	C7	C6	118.54(15)
C3A	C2	C1	114.5(2)	C9	C7	C8	120.01(16)
C3A	C2	C3B	28.2(2)	C7	C9	C10	120.33(15)
C2	C3A	C4A	109.5(4)	C7	C9	C11	120.97(15)
C4B	C3B	C2	111.8(4)	C10	C9	C11	118.67(15)
C5	C4A	C3A	109.7(3)	N1	C10	C9	122.35(15)
C3B	C4B	C5	111.1(5)	N2	C10	N1	117.17(15)
C4B	C5	C4A	28.5(2)	N2	C10	C9	120.48(15)
C6	C5	C4A	113.3(2)	N3	C11	C9	177.68(19)
C6	C5	C4B	114.4(3)				
II							
C2	C1	C6	118.8(3)	N1	C9	C10	125.2(3)
C2	C1	C7	118.4(3)	C10	C9	C8	119.8(2)
C6	C1	C7	122.8(3)	C9	C10	C11	124.7(2)
C3	C2	C1	120.6(4)	C9	C10	C19	116.3(2)
C4	C3	C2	120.1(4)	C19	C10	C1	119.0(2)
C3	C4	C5	120.6(4)	C10	C11	C12	115.9(2)
C4	C5	C6	119.6(4)	C16	C11	C10	121.6(3)
C1	C6	C5	120.2(4)	C16	C11	C12	122.5(3)
C1	C7	C8	109.9(2)	C7	C12	C13	111.9(2)
C1	C7	C12	117.3(2)	C11	C12	C7	110.8(2)
C12	C7	C8	110.0(2)	C11	C12	C13	110.5(2)
C9	C8	C7	112.4(2)	C14	C13	C12	111.6(3)
C17	C8	C7	112.1(2)	C15	C14	C13	111.8(3)
C17	C8	C9	109.1(2)	C14	C15	C16	111.4(3)
C18	C8	C7	107.2(2)	C11	C16	C15	124.7(3)
C18	C8	C9	108.5(2)	N2	C17	C8	179.0(4)
C18	C8	C17	107.4(2)	N3	C18	C8	179.5(4)
N1	C9	C8	115.0(3)	N4	C19	C10	177.7(3)

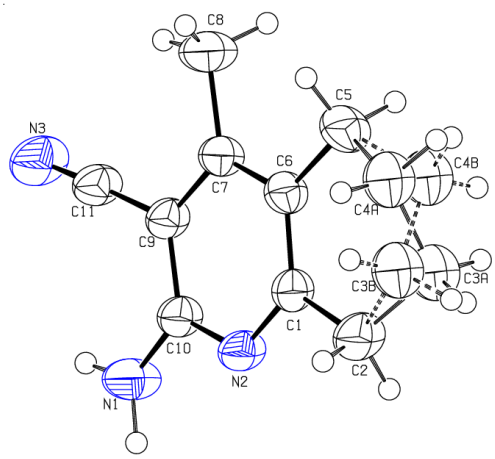


Fig. 1. ORTEP diagram of **I** drawn at 50 % probability of thermal ellipsoid

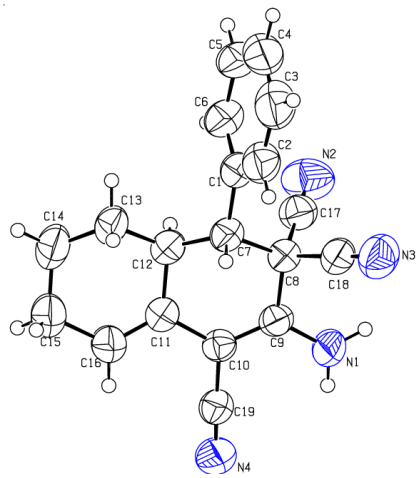


Fig. 2. ORTEP diagram of II drawn at 50 % probability of thermal ellipsoid

respect to pyridine ring. The puckering parameters[19] for the planes defined by atoms of each ring of cyclohexene are Q = 0.5085 (3) Å, θ = 50.37(7)º and φ = 150.16(3)º for A, Q = 0.4636 (7) Å, θ = 129.96(4)º and φ = 330.76 (4)° for **B**. The amino and nitrile groups involve in the formation of dimers through N-H…N interactions and generate eight and twelve membered ring motifs which can be represented mathematically[20] as $R_2^2(8)$ and $R_2^2(12)$, respectively Fig. 3. These interactions produced infinite sheets along *ab* plane Fig. 4, Table-4.

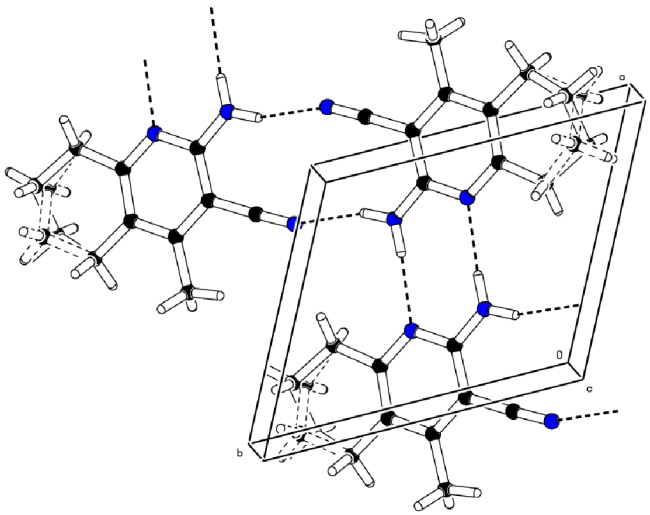


Fig. 3. A unit cell view of molecule **I** showing formation of dimers

The crystal structure of **II** contains two fused cyclohexene rings (C7-C12) **C** and (C11-C16) **D** and an aromatic ring (C1-C6) **E**. The r.m.s deviation values for ring C and D are 0.1969 (2) Å and 0.1934(2) Å, two fused rings are twisted at an angle of 10.65(2)°. The aromatic ring (C1-C6) is oriented at dihedral angle of 73.09(9)° and 74.12(9)° with respect to **C** (C7-C12) and **D** (C11-C16), respectively. The puckering parameters[19] for the planes defined by atoms of cyclohexene are Q = 0.4824 (1) Å, θ = 52.25(3)° and φ = 340.81(2)° for C, Q = 0.4739 (5) Å, θ = 130.62(3)° and φ = 325.18 (8)° for D. The classical N-H…N interaction forms dimers and generate twelve membered ring motif $R_2^2(12)$ which further connected through another N-H…N interaction and form infinite two dimensional network along (0 0 1) plane Figs. 5 and 6 (Table-4).

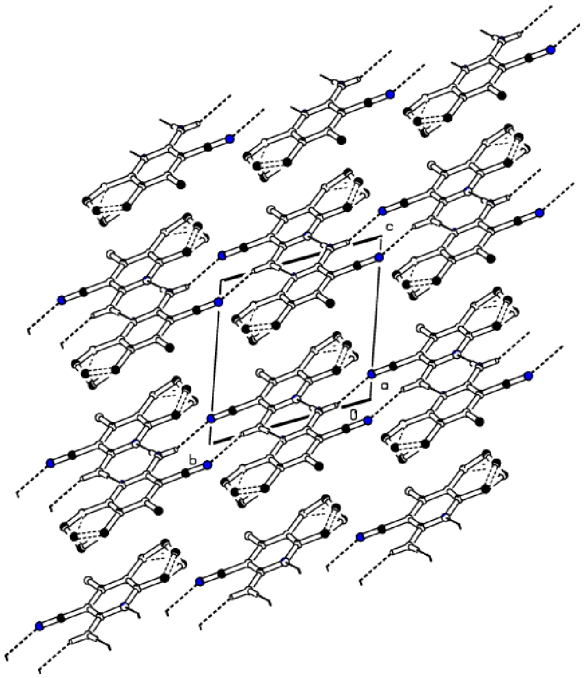


Fig. 4. Unit cell packing diagram showing hydrogen bonding interactions using dashed lines

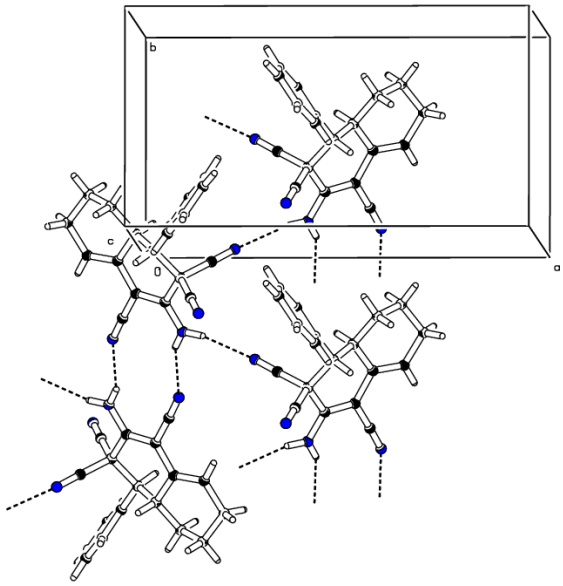


Fig. 5. Hydrogen bonding interactions showing two dimensional network

TABLE-4
HYDROGEN BOND GEOMETRY IN **I** AND **II** (Å, °)

D	H	A	d(D-H) (Å)	d(H-A) (Å)	d(D-A) (Å)	D-H-A (°)
I						
N1	H1A	N2[1]	0.91(2)	2.15(2)	3.056(2)	175.8(17)
N1	H1A	N2[1]	0.91(2)	2.15(2)	3.056(2)	175.8(17)
N1	H1B	N3[2]	0.86(2)	2.33(2)	3.143(2)	157.5(18)
N1	H1B	N3[2]	0.86(2)	2.33(2)	3.143(2)	157.5(18)
[1]1-X, 1-Y, -Z; [2]2-X, 2-Y, -Z						
II						
N1	H1A	N2[1]	0.88(4)	2.25(4)	3.066(5)	153(3)
N1	H1A	N2[1]	0.88(4)	2.25(4)	3.066(5)	153(3)
N1	H1B	N4[2]	0.88(4)	2.23(4)	3.034(4)	152(3)
N1	H1B	N4[2]	0.88(4)	2.23(4)	3.034(4)	152(3)
[1]1/2-X, -1/2 + Y, + Z; [2]-X, -1-Y, -Z						

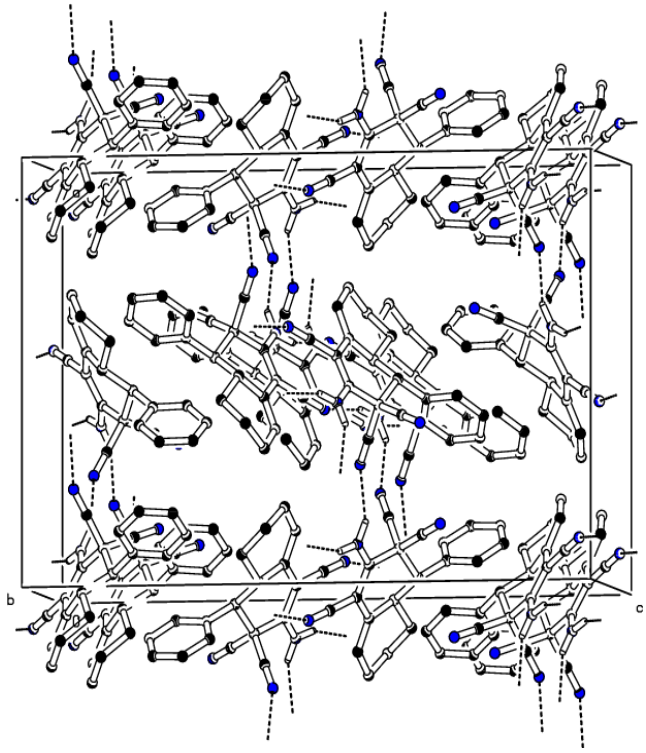


Fig. 6. Unit cell packing diagram showing hydrogen bonding interactions using dashed lines

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