Synthesis and structure analysis of N^1,N^4,3,6-tetramethyl-N^1,N^4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxamide

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N^1,N^4,3,6-Tetramethyl-N^1,N^4-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxamide was prepared from 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine, bis(trichloromethyl) carbonate and *N*-methylaniline. Its structure was confirmed by single-crystal X-ray diffraction. This reaction yields the title compound rather than N^1,N^2,3,6-tetramethyl-N^1,N^2-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2- dicarboxamide. The central tetrazine ring of the title compound exhibits a boat conformation and is therefore not homoaromatic.

Keywords: tetrazine, X-ray diffraction, calculation, boat conformation

1,2,4,5-Tetrazine derivatives have good reactivities,[1,2] and have been widely used in organic synthetic chemistry and medicinal chemistry.[3–8] Dihydro-1,2,4,5-tetrazine has four isomers, namely 1,2-, 1,4-, 1,6- and 3,6-dihydro-1,2,4,5-tetrazine. Homoaromatic structures have been demonstrated by X-ray diffraction in the 1,6-dihydro structures.[9] There still seems to be some doubt as to whether the 1,4-dihydro structures have homoaromaticity. For example, X-ray diffraction was reported to show that 3,6-bis(4-chlorobenzyl)-1,4-dihydro-1,2,4,5-tetrazine has an obvious chair conformation without a homoaromatic structure,[10] but 1,3,4,6-tetramethyl-1,4-dihydro-1,2,4,5-tetrazine has been analysed by X-ray diffraction and a possible homoaromatic structure was identified.[11] There seems to be confusion over the structures of 1,2- and 1,4-dihydro-1,2,4,5-tetrazine isomers, and the same compound is often formulated as both structures. In most cases, the dihydro structure, which would be the first reaction product, is presented. Some scientists believe that rearrangement can occur between 1,2- and 1,4-dihydro-1,2,4,5-tetrazine isomers.[3]

In a continuation of our work on the structure–activity relationship of 1,2,4,5-tetrazine derivatives,[10,12,13] we have obtained a yellow crystalline compound that was the product of the reaction of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine, bis (trichloromethyl) carbonate (BTC) and *N*-methylaniline. The route of synthesis is shown in Scheme 1. The intermediate raw material of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine was prepared according to literature methods.[14–16] However, IR, NMR, and MS studies failed to confirm whether the substituted groups of the nitrogen are located at the 1,4 or 1,2 position (compound **1** or **2**). Their structures were confirmed by single crystal X-ray diffraction.

The single-crystal structure of compound **1** was determined by X-ray crystallography. The molecular structure of compound **1** is illustrated in Fig.1. Selected bond lengths are listed in Table 1. In the molecule, the N2=C3 [1.282(3) Å] and N5=C6 [1.272(3) Å] bonds correspond to typical double bonds of C=N, and the C3–N4 [1.394(3) Å], N4–N5 [1.421(2) Å], C6–N1 [1.396(3) Å] and N1–N2 [1.434(3) Å] bond lengths correspond to typical single bonds. Therefore, the tetrazine ring is the 1,4-dihydro structure with the *N*-substituted groups at the 1,4-positions and not the 1,2-positions, the compound being N^1,N^4,3,6-tetramethyl-N^1,N^4-diphenyl-1,2,4,5-tetrazine-1,4-dicarboxamide (**1**), rather than N^1,N^2,3,6-tetramethyl-N^1,N^2-diphenyl- 1,2,4,5-tetrazine-1,2-dicarboxamide (**2**). So the product of the reaction of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine, BTC and *N*-methylaniline has the 1,4-dicarboxamide structure rather than the 1,2-dicarboxamide structure.

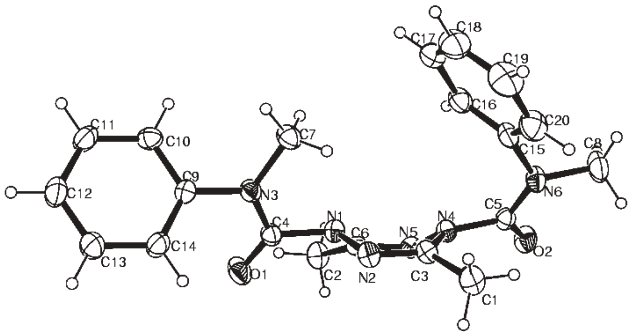
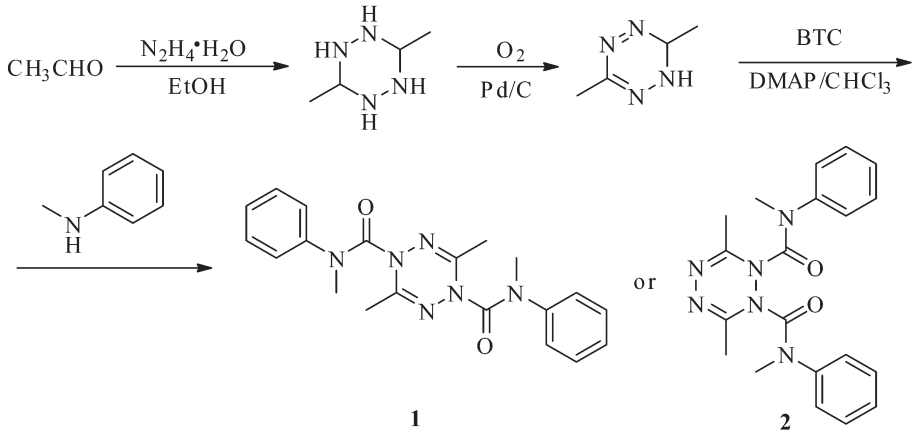


Fig. 1 The crystal structure of **1**, shown with 30% probability displacement ellipsoids.



Scheme 1 Route of synthesis.

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Table 1 Selected bond lengths (Å)

Bond lengths			
N1–N2	1.434(3)	N2-C3	1.282(3)
C3–N4	1.394(3)	N4-N5	1.421(2)
N5–C6	1.272(3)	C6-N1	1.396(3)

Table 2 Least-squares plane

Orthonormal equation of Plane1	7.8212 (43) x + 3.6127 (182) y + 7.0675 (156) z = 6.3706 (100)			
Atom	N2	C3	N5	C6
	0.0221 (10)	–0.0221 (10)	0.0223 (10)	–0.0222 (10)

In compound **1**, the atoms N2, C3, N5 and C6 are coplanar, with the largest deviation from the N2/C3/N5/C6 plane (Plane 1) being 0.0223 (10) Å for atom N5. The least-squares plane is listed in Table 2. The adjacent N1 and N4 atoms deviate from plane **1** by –0.4295 (28) and –0.4168 (28) Å, respectively. The dihedral angle between plane 1 and the N1/N2/C6 plane is 34.43 (18)°, and between plane 1 and the N4/N5/C3 plane is 33.67 (16)°. The central six-member ring of compound **1**, the tetrazine ring, has an obvious boat conformation and is therefore not homoaromatic. The dihedral angles between the N2/C3/N5/C6 plane and the two phenyl rings of the C9/C10/C11/C12/C13/C14 and C15/C16/C17/C18/C19/C20 planes are 68.84 (10) and 46.14 (11)°, respectively. And two phenyl rings form a dihedral angle of 79.78 (9)°.

As shown in the packing of compound **1** (Fig. 2), there exist intramolecular hydrogen contacts (Table 3). The C–H···N and C–H···O type of intramolecular interaction play major role in stabilising the molecules in the unit cell.

Experimental

Melting points were determined on a X-4 melting point apparatus and uncorrected. IR spectra were taken on a Thermo Nicolet Avatar 370 FT-IR spectrophotometer (KBr pellets). H spectra were recorded on a Bruker Avance (500M) spectrometer. MS spectra were obtained on a Thermo Scientific ITQ 1100TM mass spectrometer.

N^1,N^4,3,6-tetramethyl-N^1,N^4-diphenyl-1,2,4,5-tetrazine-1,4-dicarboxamide (**1**): Bis(trichloromethyl) carbonate (5.198 g, 17.5 mmol) was dissolved in $CHCl_3$ (50 mL) with magnetic stirring, the solution of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine (1.472 g, 13.1 mmol) and 4-dimethylamino pryidine (0.656 g, 5.4 mmol) in $CHCl_3$ (60 mL) was added dropwise with stirring at 0 °C. Then the mixture was allowed to reach room temperature and subsequently refluxed for 8 h. A solution of *N*-methylaniline (5.198 g, 48.5 mmol) and $CHCl_3$ (30 mL) was added dropwise with stirring at 5 °C. The mixture was refluxed for 44h and washed with water. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (15:1, v/v) as eluent to afford compound **1** (1.547 g, yield 31.1%) as a yellow solid. A solution of the compound in ethanol was concentrated gradually at

Table 3 Hydrogen bonds bond lengths (Å) and angles (°)

Donor–H···Acceptor	D–H	H···A	D···A	D–H···A
C1–H1A···N6	0.96	2.59	3.161(3)	118.6
C2–H2A···O1	0.96	2.09	2.797(3)	128.8
C7–H7C···N2	0.96	2.52	3.075(3)	117.1

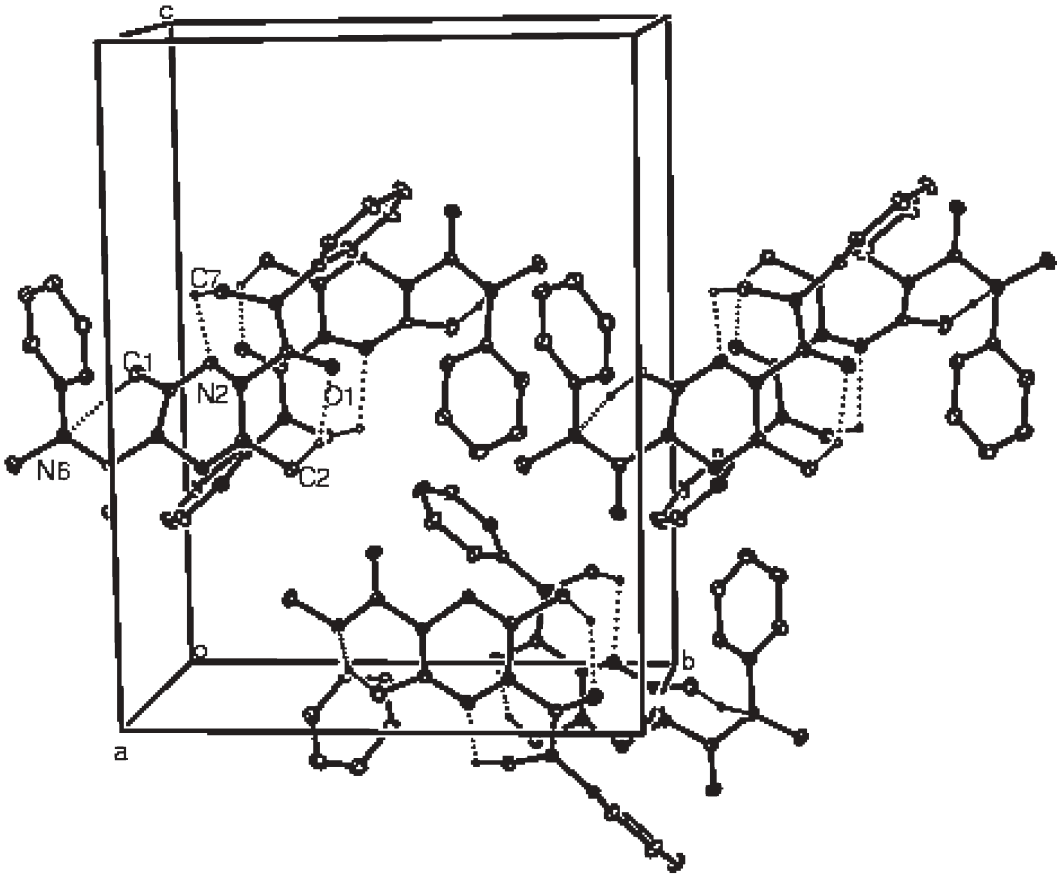

Fig. 2 A portion of the crystal packing of **1**. Hydrogen bonds are shown as dashed lines. H atoms not involved in hydrogen bonding are omitted for clarity.

room temperature to afford yellow bars which are suitable for X-ray diffraction. M.p. 121–124 °C. IR (KBr, cm^{-1}): 3445, 1706, 1687, 1621, 1436, 1391, 1112, 1064, 950. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (t, J = 8 Hz, 4H, Ph), 7.23 (d, J = 7.5 Hz, 2H, Ph), 7.089–7.107 (m, 4H, Ph), 3.296(s, 6H, -NCH_3), 1.957(s, 6H, CH_3). MS (EI): m/z: 378 $[M]^+$. MS (ESI): m/z: 379 $[M+H]^+$, 401 $[M+Na]^+$. HRMS (ESI): m/z $[M+H]^+$ Calcd for $C_{20}H_{23}N_6O_2$: 379.1882; found: 379.1891.

Crystal data of compound **1**: A yellow bar of dimensions 0.40 × 0.26 × 0.22 mm^3 was used for data collection with a Bruker SMART CCD area-detector diffractometer with graphite monochromated Mo $K\alpha$ radiation (λ = 0.71073 Å). A summary of crystal data is presented in Table 4.

The structure was solved by direct method procedures as implemented in the SHELXS97[17] program. The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using the SHELXL97[18] program. H atoms were added at calculated positions and refined using a riding model. H atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl H atoms) times the equivalent isotropic displacement parameters of their parent atoms, and C–H distances were restrained to 0.96 Å for methyl H atoms and 0.93 Å for phenyl H atoms, while N–H distances were set to 0.86 Å. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 863916. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033 or E-mail: deposit@ccdc.cam.ac.uk).

Table 4 Crystal data and structure refinement

Chemical formula	$C_{20}H_{22}N_6O_2$
Colour/shape	Yellow/bar
Formula weight	378.44
Temperature (K)	298(2)
Wavelength (Å)	0.71073
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 9.0870(15) Å
	b = 12.818(2) Å
	c = 16.669(3) Å
Volume ($Å^3$)	1941.6(6)
Z	4
Density (calculated) (g cm^{-3})	1.295
Absorption coefficient (mm^{-1})	0.088
θ range for data collection (deg)	2.00–28.35
Limiting indices	–11/12, –10/17, –19/21
Reflections collected/unique	11689/4441 (R_{int} = 0.0270)
Absorption correction	Multi-scan
Max. and min. transmission	0.981, 0.965
Data/restraints/parameters	4441/0/254
Extinction coefficient	0.028(3)
Goodness of fit on F^2	1.044
Final R indices [$I > 2\sigma(I)$]	R^1 = 0.0531, wR^2 = 0.1385
R indices (all data)	R^1 = 0.0627, wR^2 = 0.1450
Largest diff. peak and hole (e $Å^{-3}$)	0.306, –0.257

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