

# Synthesis and structure of dimethyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate

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Dimethyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate was prepared from methyl chloroformate and 3,6-diphenyl-1,2(or 1,4)-dihydro-1,2,4,5-tetrazine and its structure elucidated by X-ray analysis. This reaction yields the title compound rather than dimethyl 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxylate. The 2,3-diazabutadiene group in the central six-membered ring of tetrazine is not planar and the tetrazine ring has a twist conformation.

**Keywords:** 1,2,4,5-tetrazine, crystal structure, conformation

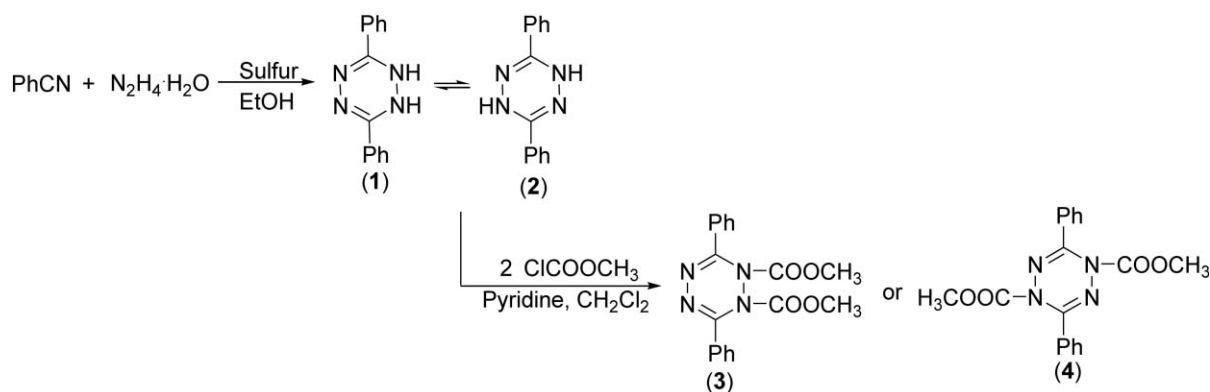
1,2,4,5-Tetrazine derivatives have been widely used in organic synthetic chemistry and medicinal chemistry.<sup>1,2</sup> Dihydro-1,2,4,5-tetrazine has four isomers, namely 1,2-, 1,4-, 1,6- and 3,6-dihydro-1,2,4,5-tetrazine. In almost all the cases that have been studied by X-ray diffraction, the dihydro derivatives were best described as 1,4-dihydro isomers, with the 1,2-dihydro isomer being very rare. There seems to be much confusion over the structures of 1,2- and 1,4-dihydro-1,2,4,5-tetrazines 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, or authors have formulated their compounds in the dihydro structure which seemed to be the most accepted at that time. Some scientists believe that rearrangement can occur between compounds (1) and (2), so that compounds can contain a mixture of the two isomers.<sup>3</sup> Every compound should have a unique CAS number in Chemical Abstracts, but some 1,2- and 1,4-dihydro-1,2,4,5-tetrazine compounds have the same CAS number. For example, the CAS number of both 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine, (1), and 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine, (2), is 14478-73-0.<sup>4,5</sup>

In a continuation of our work on the structure–activity relationship of 1,2,4,5-tetrazine derivatives,<sup>6–8</sup> we have obtained a colourless crystalline compound that was the sole product of the reaction of methyl chloroformate and 3,6-diphenyl-1,2(or 1,4)-dihydro-1,2,4,5-tetrazine. The latter was prepared according to the procedure of Abdel-Rahman *et al.*<sup>9</sup> As Scheme 1 shows, there are two possible compounds, (3) and (4), for the product. However, IR, <sup>1</sup>H NMR and MS studies failed to prove whether the N,N'-substituents were located at the 1,2- or 1,4-positions. The structural identity of the product was resolved using single-crystal X-ray diffraction.

The two essentially identical molecules forming the asymmetric unit of (3) are shown in Fig. 1. In both molecules, the N2=C7 [1.209(18) Å] and N4=C17 [1.329(19) Å] bonds correspond to typical C=N double bonds, and the C7–N1 [1.460(20) Å], N1–N3 [1.450(16) Å], C17–N3 [1.340(20) Å] and N4–N2 [1.389(17) Å] bond lengths correspond to typical single bonds. Therefore, the tetrazine ring corresponds to 1,2-dihydro-1,2,4,5-tetrazine and the N-substituents are at the 1,2-positions, thus proving that the compound is dimethyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate, (3), rather than dimethyl 3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine-1,4-dicarboxylate, (4). The other molecule of the both molecules is identical. Selected bond lengths are listed in Table 1. It shows that compound (1) reacts faster than the isomer (2) in the reaction if the raw material is a mixture of the two isomers and there is rearrangement between the two isomers.

Least-squares planes are listed in Table 2. Atoms C7, N2, N4, C17 are not coplanar and atoms C27, N6, N8, C37 are not coplanar in the C=N–N=C group. The central six-membered ring of tetrazine has a twist conformation, in which atom N1 lies 0.41 (3) Å out of the central leastsquares plane (Plane 1) and the adjacent N3 atom lies 0.31 (3) Å on the opposite side, in which atom N7 lies 0.42 (3) Å out of the central leastsquares plane (Plane 2) and the adjacent N5 atom lies 0.27 (3) Å on the opposite side.

As shown in the packing of the title compound (Fig. 2), there exists one intramolecular hydrogen contact [C1–H1...N1: C1–H1 = 0.93 Å, H1...N1 = 2.51 Å, C1...N1 = 2.85 (2) Å, C1–H1...N1 = 102°]. The C1–H1...N1 type of intramolecular interaction plays a major role in stabilising the molecules in the unit cell.



**Scheme 1** Synthesis of 3.

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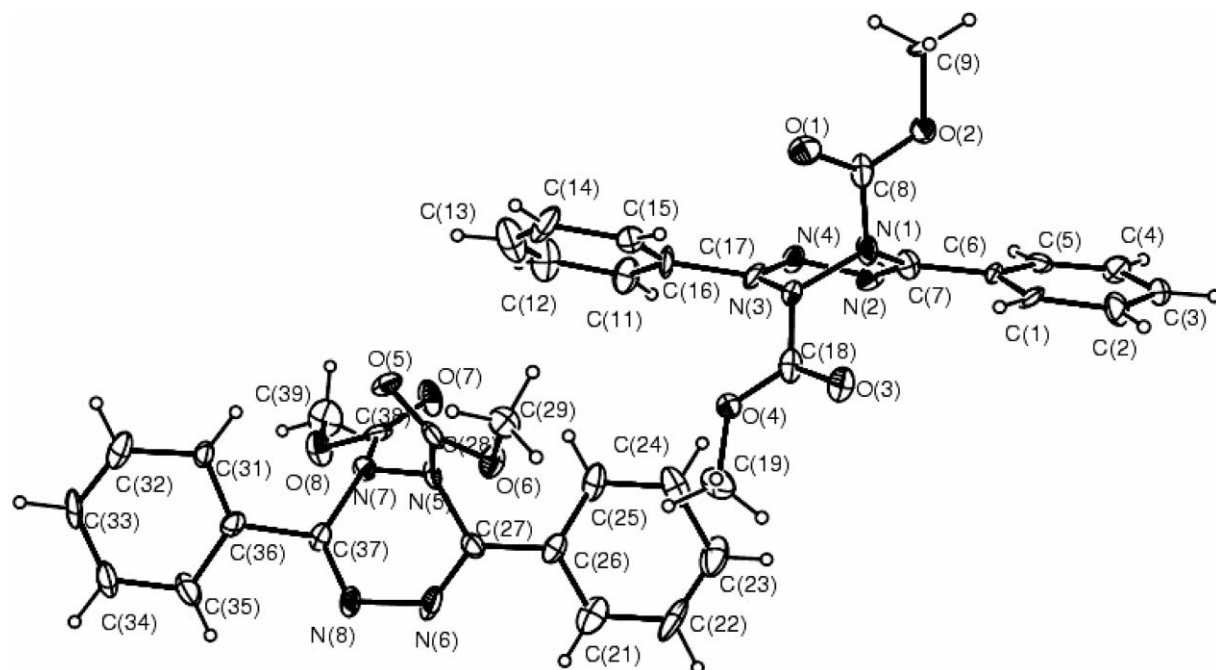


Fig. 1 The crystal structure of **3**, shown with 30% probability displacement ellipsoids.

Table 1 Selected bond lengths (Å)

Bond lengths			
N(1)–N(3)	1.450(16)	N(5)–N(7)	1.399(15)
N(1)–C(7)	1.460(20)	N(5)–C(27)	1.443(19)
N(2)–N(4)	1.389(17)	N(6)–N(8)	1.409(17)
N(3)–C(17)	1.340(20)	N(7)–C(37)	1.429(18)
N(2)–C(7)	1.209(18)	N(6)–C(27)	1.280(20)
N(4)–C(17)	1.329(19)	N(8)–C(37)	1.243(18)

Table 2 Least-squares planes

Orthonormal equation of plane1	$4.2827(901)x + 6.4351(601)y - 0.8593(2135)z = 6.1819(836)$				
	Atom	C(7)	N(2)	N(4)	C(17)
		0.0874(48)	-0.1636(90)	0.1520(86)	-0.0758(44)
Orthonormal equation of plane2	$-6.5138(536)x + 4.1570(840)y + 0.6452(2086)z = 3.5300(1219)$				
	Atom	C(27)	N(6)	N(8)	C(37)
		-0.0639(48)	0.1215(90)	-0.1192(89)	0.0616(48)

## Experimental

Melting points were determined on a XRC-1 melting point apparatus and uncorrected. IR spectra were taken on a Thermo Nicolet Avatar 370 FT-IR spectrophotometer (KBr pellets). <sup>1</sup>H spectra were recorded on a Bruker AC 400 spectrometer. MS spectra were obtained on a HP5989A mass spectrometer. C, H and N were analysed using a Carlo-Erba 1106 instrument.

*Dimethyl 3,6-diphenyl-1,2-dihydro-1,2,4,5-tetrazine-1,2-dicarboxylate (3)*: Compound (**1**) (5 mmol), prepared according to the procedure of Abdel-Rahman *et al.*<sup>9</sup> from benzonitrile and hydrazine hydrate, was dissolved in dichloromethane (20 mL) with stirring of nitrogen protection in an ice bath. Pyridine (1 mL) were added to the mixture. Methyl chloroformate (10 mmol) and dichloromethane (20 mL) were added dropwise into the mixture under 0–5 °C. The mixture was stirred at room temperature for 5 h, then washed in water and dried with anhydrous MgSO<sub>4</sub>. The solvent was removed *in vacuo* and the residue was recrystallised from ethanol to give the product (**3**) as a colourless solid (yield 67.1%). A solution of the compound in ethanol was concentrated gradually at room temperature to afford colourless prisms which are suitable for X-ray diffraction, m.p. 182–183 °C. Anal. Calcd for C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.34; H, 4.56; N, 15.94%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 3.74 (s,

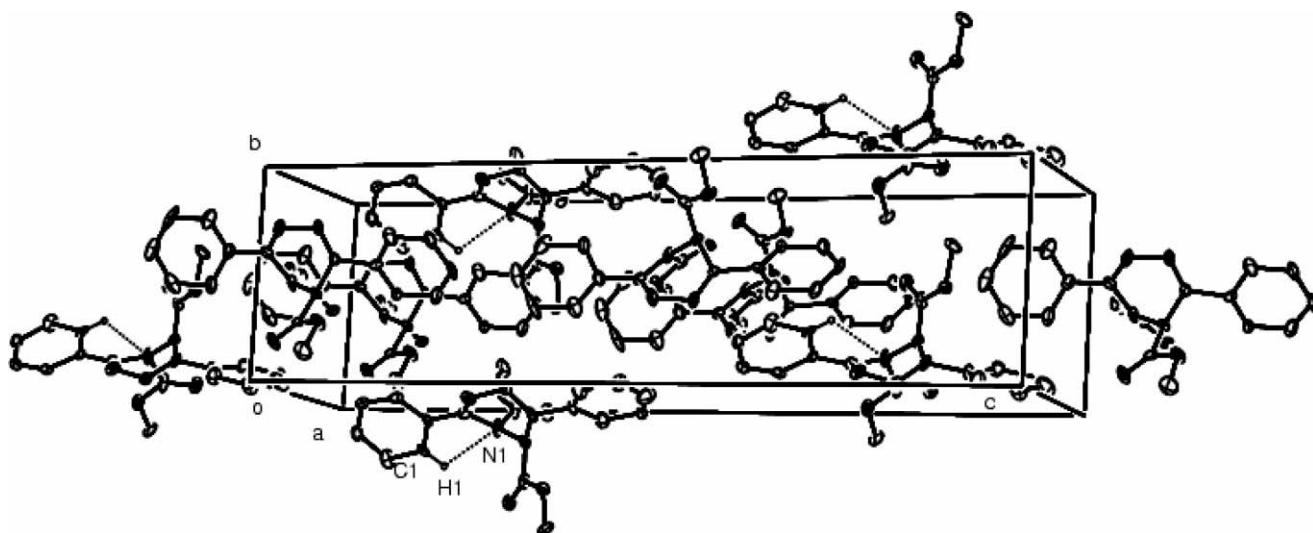


Fig. 2 A packing diagram for **3**. The dotted lines indicate hydrogen contacts.

6H, CH<sub>3</sub>), 7.48–7.55 (m, 6H, Ph), 8.06 (d,  $J = 7.1$  Hz, 4H, Ph). IR (KCl disc, cm<sup>-1</sup>): 3215, 3054, 3002, 2971, 1716, 1621, 1602, 1578, 1503, 1463, 1402, 1377, 1357, 1332, 1303, 1125, 1017. MS ( $m/z$ , relative intensity): 352 (M<sup>+</sup>, 10), 118 (100), 104 (10), 103(35), 91 (11), 77 (44), 76 (29), 59 (55), 51 (13).

*Crystal data of (3)*: C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub>,  $Mr = 352.34$ , monoclinic,  $Pc$ ,  $a = 7.725(2)$ ,  $b = 7.733(3)$ ,  $c = 28.702(8)$  Å,  $\beta = 91.83(2)^\circ$ ,  $V = 1713.7(9)$  Å<sup>3</sup>,  $D_x = 1.366$  g cm<sup>-3</sup>,  $Z = 6$ ,  $\mu = 0.099$  mm<sup>-1</sup>,  $T = 298$  K. A colourless prism of dimensions  $0.35 \times 0.20 \times 0.15$  mm<sup>3</sup> was used for data collection with an Enraf-Nonius CAD-4<sup>10</sup> diffractometer with graphite monochromated Mo-K $\alpha$  radiation ( $\lambda = 0.71073$  Å) from a rotating anode generator operating at 50 kV and 200 mA. Intensity data were collected up to a  $\theta_{\max}$  of 25.17° by the  $\omega/2\theta$  scan method. A total of 3647 reflections were collected. During data collection three standard reflections were monitored at intervals of 60 min. The ranges of  $h$ ,  $k$ ,  $l$  are  $-9$   $h$   $9$ ,  $-1$   $k$   $9$ ,  $0$   $l$   $34$ . The intensities were corrected for Lorentz and polarisation effects but not for absorption correction. The structure was solved by direct methods procedures as implemented in SHELXS97<sup>11</sup> program. The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using SHELXL97<sup>12</sup> 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 0.93 Å for phenyl H atoms and 0.96 Å for methyl H atoms. The final cycle of full-matrix least-squares refinement was based on 1230 observed reflections ( $I > 2\sigma(I)$ ) and 474 variable parameters and converged with  $R = 0.0878$  and  $wR = 0.2348$ . Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 206454.

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