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Synthesis and crystal structure of 1-isobutyryl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine

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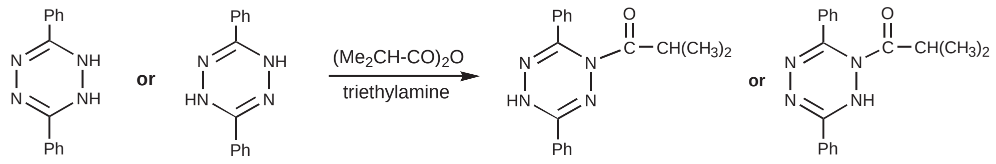
The title compound was prepared from isobutyric anhydride and 3,6-diphenyl-dihydro-1,2,4,5-tetrazine and its structure elucidated by X-ray analysis.

Keywords: crystal structures, 1,2,4,5-tetrazines, conformation



(**1**) (**2**) (**3**)

Scheme 1 Route of synthesis

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.[1] 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 1,4-dihydro-1,2,4,5-tetrazine to have a boat conformation without homoaromatic structure,[2] but 1,3,4,6-tetramethyl-1,4-dihydro-1,2,4,5-tetrazine was analysed by X-ray diffraction and a possible homoaromatic structure was identified.[3]

In continuation of our work on the structure-activity relationship of 1,2,4,5-tetrazine derivatives,[4,5] we obtained a yellow crystalline compound as the product of the reaction of isobutyric anhydride and 3,6-diphenyldihydro-1,2,4,5-tetrazine (**1**). There still seems to be much confusion over the structures of 1,2- and 1,4-dihydro-1,2,4,5-tetrazines, 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.[6] As Scheme 1 shows, there are two possible compounds, (**2**) and (**3**), for the mono-isobutyrylated product. However, IR, ^{1}H NMR and MS studies failed to prove whether the product has a homoaromatic structure and whether the hydrogen on the nitrogen is located at the 4 or 2 position (compound **2** or **3**). The structural identity of the product was resolved using single-crystal X-ray diffraction.

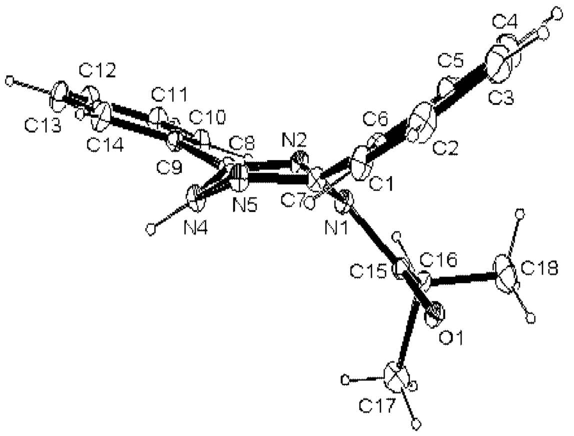


Fig. 1 Crystal structure of 2.

The molecular structure of tetrazine **2** is illustrated in Fig. 1. In **2**, the N2=C8 [1.2859(19) Å] and N5=C7 [1.270(2) Å] bonds correspond to typical C=N double bonds, and the C7-N1 [1.418(2) Å], N1–N2 [1.4335(18) Å], C8-N4 [1.368(2) Å] and N4–N5 [1.3890(19) Å] bond lengths correspond to typical single bonds. Therefore, the tetrazine ring is the 1,4-dihydro structure with the N-substituent group at the 1-position and the N-hydrogen at the 4- and not the 2-position, the compound being 1-isobutyryl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (**2**), rather than the 1,2-dihydro structure (**3**).

The atoms N2, C8, N5 and C7 are coplanar, deviations are less than ±0.024 Å, and the adjacent N1 and N4 atoms deviate from the plane by –0.4320(22) Å and –0.3319(22) Å, respectively. The dihedral angle between the N2, C8, N5, C7 plane and the N1, N2, C7 plane is 34.81(17)°, and that between the N2, C8, N5, C7 plane and the C8, N4, N5 plane is 27.90(10)°. The difference in the dihedral angles is presumably due to a steric effect of the substituent at the 1-position. The central six-membered ring of **2**, the tetrazine ring, has an obvious boat conformation and therefore is not homoaromatic.

As shown in the packing of the title compound (Fig. 2), there exists one intermolecular hydrogen contact [N4–H4···$O1^{i}$: N4–H4 = 0.860 Å, H4···O1 = 2.278 Å, N4···O1 =2.876(2) Å, N4–H4···O1 = 126.75°. *(i)* = 0.5+x, 0.5-*y*, -*z*]. The N–H···O type of intermolecular interaction plays a major role in stabilising the molecules in the unit cell.

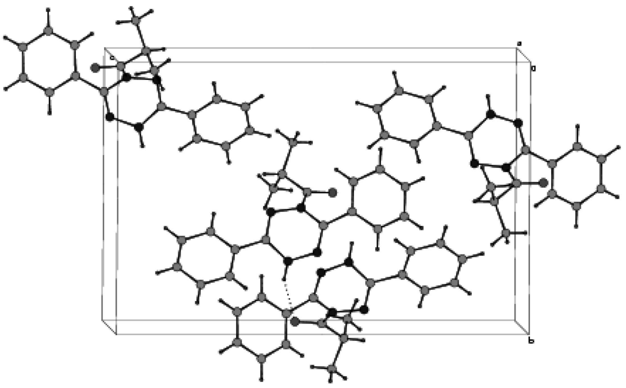


Fig. 2 A packing diagram for (2). The dotted lines indicate hydrogen contacts.

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Experimental

Melting points were determined on a XRC-1 Melting Point apparatus. IR spectra were taken on a Nicolex FI-IR-170 spectrometer (KBr pellets). ^{1}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 1160 instrument.

1-Isobutyryl-3,6-diphenyl-1,4-dihydro-1,2,4,5-tetrazine (**2**): Compound **1** (1.0g, 4.2 mmol), prepared according to the procedure of Abdel-Rahman *et al*.,[7] was dissolved in dichloromethane (40 ml) with stirring. Isobutyric anhydride (1.4 g, 8.8 mmol) and triethylamine (5 ml) were added to the mixture cooled in an ice bath. The mixture was heated to reflux while stirred for 2h, then cooled, washed in water and dried with anhydrous $MgSO_4$. Solvent was removed *in vacuo* and the residue was recrystallised from ethanol to give the product (**2**) as a yellow solid (0.6 g, 46 %). A solution of the compound in ethanol was concentrated gradually at room temperature to afford yellow prisms which are suitable for X-ray diffraction, m.p. 195–196 °C. IR: ν_{max}/cm^{-1}(KBr) 3297, 2975, 2960, 2931, 2872, 1643, 1608, 1569, 1508, 1469, 1411, 1338, 1302, 1270, 1146, 1085; ^{1}H NMR (400 MHz, $CDCl_3$):δ 1.26 (d, 6H, CH_3, J = 6.84Hz), 3.48 (m, 1H, CH), 7.34–7.74 (m, 10H, Ph), 8.17 (br, 1H, NH); *m/z* (%) 306 (M^+, 2), 237 (18), 236 (100), 104 (65), 77 (50), 76 (12), 51 (21), 43(49), 41 (18); Calc. for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.76; H, 6.00; N, 18.11 %.

Crystal data of (**2**): $C_{18}H_{18}N_4O$, Mr = 306.36, orthorhombic, $P2_12_12_1$, a = 7.1475(9), b = 12.1597(16), c = 18.389(2) Å, V =1598.2(4) Å^3, D_x = 1.273 g cm^{-3}, Z = 4, μ = 0.082 mm^{-1}, T = 298 K. A yellow prism was used for data collection with an Enraf-Nonius CAD-4[8] diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) from a rotating anode generator operating at 50 kV and 200 mA. Intensity data were collected up to a θ_{max} of 27.14° by the $\omega/2\theta$ scan method. A total of 8028 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 8, –14 k 15, –23 l 21. The intensities were corrected for Lorentz and polarization effects but not for absorption correction. The structure was solved by direct methods procedures as implemented in SHELXS97[9] program. The positions of all the non-hydrogen atoms were included in the full-matrix least-squares refinement using SHELXL97 [10] program. The final cycle of full-matrix least-squares refinement was based on 2994 observed reflections ($I > 2\sigma(I)$) and 211 variable parameters and converged with R = 0.0419 and wR = 0.1152. Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 224301.

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