

First Synthesis of a 1,2,3,4-Tetrazine

Terumitsu Kaihoh, Takashi Itoh, Kentaro Yamaguchi, and Akio Ohsawa*

School of Pharmaceutical Sciences, Showa University, Tokyo 142, Japan

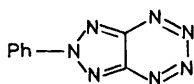
6-Phenyl[1,2,3]triazolo[4,5-*e*]-1,2,3,4-tetrazine (**2**), the first example of an aromatic 1,2,3,4-tetrazine, has been synthesized and its structure determined by X-ray crystallography.

The oxidation of 1-aminobenzotriazole is a convenient method for generation of the benzyne intermediate. The reported reaction mechanism suggested the presence of a 1,2,3,4-tetrazine ring as a precursor of benzyne.¹ 1,2,3,4-Tetrazine (**1**) is a basic aza-aromatic system, but one that has never been synthesized.² We report here the first example of a 1,2,3,4-tetrazine, compound (**2**), which was synthesized by the oxidation of the triazolotriazole (**3**).[†]

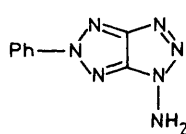
Compound (**3**) was oxidized[‡] by lead tetra-acetate in methylene chloride at 0 °C, and careful work-up gave reddish crystals [m.p. 76–77 °C (decomp.) from CH₂Cl₂, explosive on heating or impact, ¹H n.m.r. (CD₂Cl₂) δ 7.68–7.85 (3H, m), 8.63–8.80 (2H, m); ¹³C n.m.r. (CD₂Cl₂) δ 122.9 (d), 130.8 (d), 134.2 (d), 139.0 (s), 145.7 (s); ν_{max} (KBr) 3075, 1578, 1552, 1482, and 1458 cm⁻¹] in 81% yield. This compound



(1)



(2)



(3)

[†] Compound (**3**) was obtained along with the 2-amino isomer by amination of 5-phenyl[1,2,3]triazolo[4,5-*d*]-1,2,3-triazole⁶ with (*O*-mesitylenesulphonyl)hydroxylamine.⁷

[‡] A similar method was used for the synthesis of 1,2,3-triazines by oxidation of *N*-aminopyrazoles.⁸

decomposed in CH₂Cl₂ at room temperature accompanied by N₂ evolution to give the cyanotetrazole (**4**)³ and the triazole (**5**).⁴ The ¹H and ¹³C n.m.r. spectra at –20 °C showed that the foregoing reddish compound has five phenyl protons, together with a non-phenyl carbon atom.

These facts implied that this compound was the triazolotetrazine (**2**). However, it was impossible to carry out elemental analyses or mass spectroscopic measurements because of the instability of the reddish product.

The structure of (**2**) was finally established by X-ray

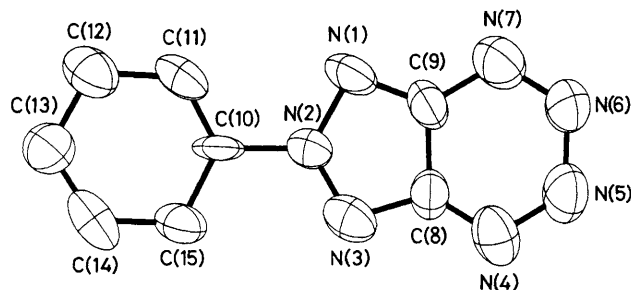
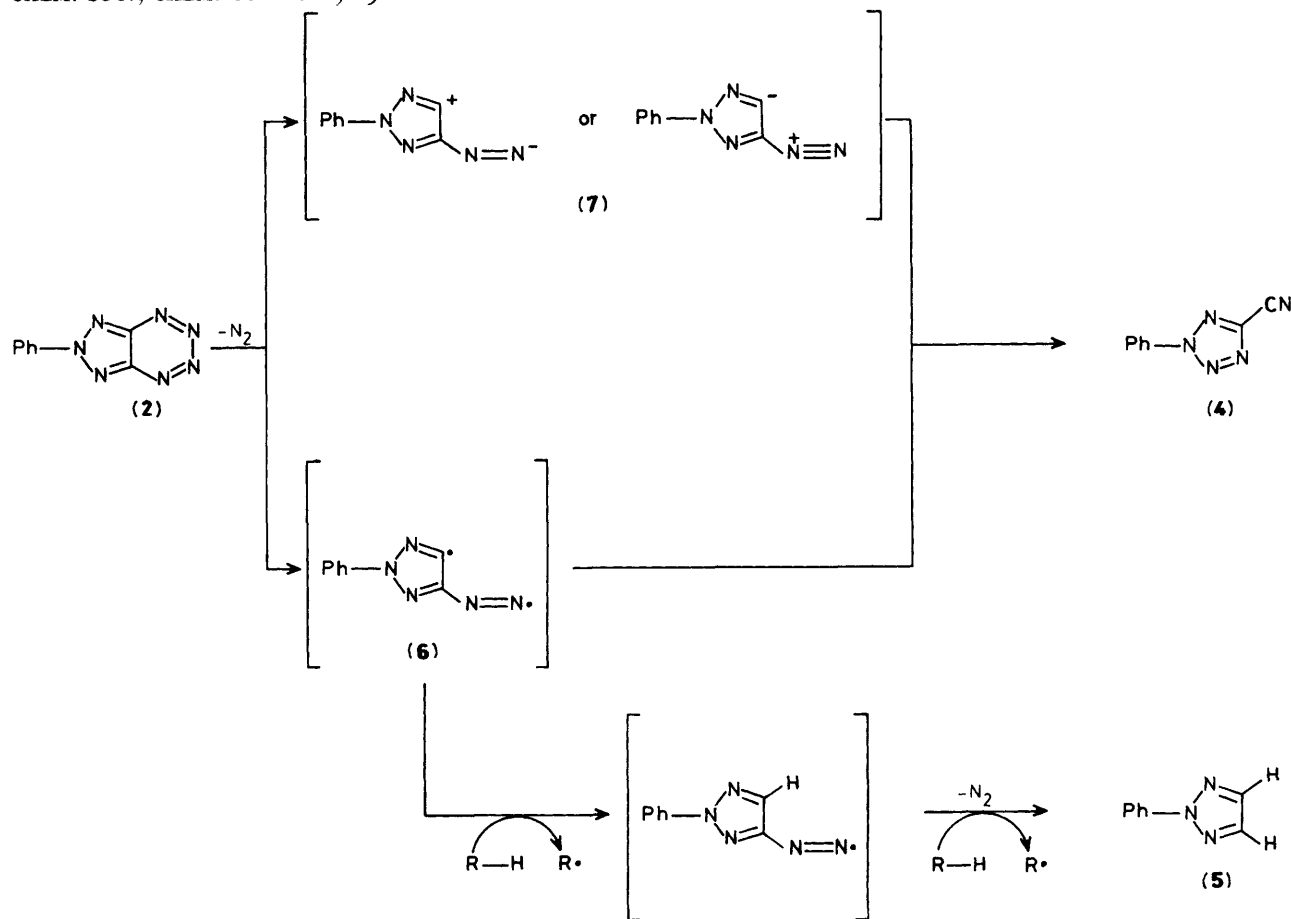


Figure 1. X-Ray crystal structure of (**2**). ORTEP view showing the atom numbering figure. Important parameters: N(1)–N(2) 1.359, N(2)–N(3) 1.299, N(2)–C(10) 1.476, N(3)–C(8) 1.351, N(1)–C(9) 1.328, C(8)–C(9) 1.444, C(9)–N(7) 1.348, N(7)–N(6) 1.308, N(6)–N(5) 1.405, C(8)–N(4) 1.268, N(5)–N(4) 1.325 Å; C(8)–C(9)–N(7) 118.57, C(9)–N(7)–N(6) 118.66, N(7)–N(6)–N(5) 119.87, N(6)–N(5)–N(4) 122.60, N(5)–N(4)–C(8) 117.51, N(4)–C(8)–C(9) 122.47 °.



Scheme 1

crystallography. § Figure 1 shows an ORTEP drawing. The tetrazine ring of (2) is essentially planar, ¶ and its bond lengths and bond angles supported its aromaticity.

The formation of (4) and (5) also suggested the presence of (2) in solution. Thus, the tetrazine (2) in solution was denitrogenated to form the biradical (6) or the zwitterion (7), which isomerized to the triazole (4). Hydrogen extraction of the biradical (6) from the solvent, followed by denitrogenation and hydrogen abstraction from the solvent gave the triazole (5) (Scheme 1).

§ *Crystal data*: $\text{C}_8\text{H}_5\text{N}_7$, reddish flake ($0.35 \times 0.45 \times 0.02 \text{ mm}^3$), $M = 199.2$, monoclinic, space group $P2_1/a$, $a = 17.651(34)$, $b = 5.362(7)$, $c = 10.860(23)$ Å, $\beta = 122.31(13)^\circ$, $V = 868.7(3.0)$ Å³, $D_c = 1.523$ g cm⁻³, $Z = 4$. 1459 Diffraction data were collected with graphite monochromated $\text{Cu-K}\alpha_1$ radiation ($\lambda = 1.54050$ Å), on Rigaku AFC-5 four-circle diffractometer. 1205 reflections [$I > \sigma(I)$] with $2\theta \leq 120^\circ$ were used in the refinement. Lorentz and polarization corrections were applied. Data were corrected for decay using standard reflections. The structure was solved by direct methods and refined by full-matrix least-squares. The final R value using anisotropic temperature factors for non-hydrogen atoms was 0.168 (R_w 0.146). The high R value was due to crystal instability; the intensities of standard reflections decayed by 15.1% during data collection. However, the standard deviations of bond lengths and angles are sufficiently low to provide a satisfactory basis for discussion ($\sigma_{\text{length}} = 0.015$ Å, $\sigma_{\text{angle}} = 0.84^\circ$). The maximum residual peak height in the final difference fourier synthesis was $0.8e/\text{Å}^3$. The atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors Issue No. 1.

¶ The distance from the least-square plane calculated from the 6-membered ring atoms (N-4, N-5, N-6, N-7, C-8, C-9) ranged from -0.018 Å to 0.016 Å.

The physical and chemical data obtained for this compound thus are consistent with structure (2). The stability of the parent 1,2,3,4-tetrazine has been discussed on the basis of M.O. calculations.⁵ In this work, we have shown that the 1,2,3,4-tetrazine ring is able to exist, at least in ring-fused form. We think that the stability of our tetrazine is due to stabilisation with respect to nitrogen elimination of an intermediate nitrene, which causes ring expansion to the triazole.

Received, 1st June 1988; Com. 8/02162G

References

- 1 C. D. Campbell and C. W. Rees, *J. Chem. Soc. (C)*, 1969, 742.
- 2 H. Neunhoeffer in 'Comprehensive Heterocyclic Chemistry' series eds. A. R. Katritzky and C. W. Rees, vol. eds. A. J. Boulton and A. McKillop, Pergamon, Oxford, 1984, vol. 3, pp. 531–572.
- 3 D. Moderhack, *Chem.-Ztg.*, 1981, **105**, 194.
- 4 H. El Khadem and Z. M. El-Shafei, *J. Chem. Soc.*, 1958, 3117.
- 5 M. J. S. Dewar and G. J. Gleicher, *J. Chem. Phys.*, 1966, **44**, 759; M. H. Palmer, A. J. Gaskell, and R. H. Findlay, *J. Chem. Soc., Perkin Trans. 2*, 1974, 778.
- 6 J. Thiele and K. Schlessner, *Liebigs Ann. Chem.*, 1897, **295**, 129.
- 7 Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.*, 1973, **38**, 1239.
- 8 A. Ohsawa, H. Arai, H. Ohnishi, and H. Igeta, *J. Chem. Soc., Chem. Commun.*, 1980, 1182; A. Ohsawa, H. Arai, H. Ohnishi, T. Itoh, T. Kaihoh, M. Okada, and H. Igeta, *J. Org. Chem.*, 1985, **50**, 5520; H. Neunhoeffer, M. Clausen, H.-D. Vötter, H. Ohl, C. Krüger, and K. Angermund, *Liebigs Ann. Chem.*, 1985, 1732; A. J. Boulton, R. Fruttero, D. K. Saka, and M. T. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1249.