Formation of Hydro-1,3-diazines by the Reaction of Benzo[*b*]cyclohepta[*e*][1,4]oxazine with α,γ-Diamines†

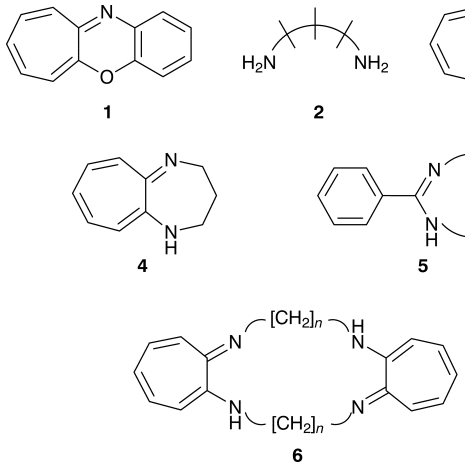
J. Chem. Research (S), 1998, 568–569†

Ohki Sato, Manabu Seshimo and Josuke Tsunetsugu*

Department of Chemistry, Faculty of Science, Saitama University, Urawa, Saitama 338-0825, Japan

Contrary to a report that the reaction of benzo[*b*]cyclohepta[*e*][1,4]oxazine **1** with α,γ-diamine **2b** produces 1,2,3,4-tetrahydrocyclohepta[*b*][1,4]diazepine **4**, the product was found to be 2-phenyl-3,4,5,6-tetrahydropyrimidine **5b** and is peculiar to the reaction of **1** with α,γ-diamines **2** as well as β-aminamide **7**.

Benzo[*b*]cyclohepta[*e*][1,4]oxazine **1**[1,2] and its derivatives[2,3] are reactive troponoids. Compound **1** reacts with various 1,2-difunctional nucleophiles to give various heterocycles by intermolecular heterocycle-exchange reactions.[2,4] It was reported that long chain α,ω-alkanediamines ($n > 4$) as nucleophiles afforded tetraazabis(tropocoronands) **6** which have metal coordination ability[5,6] and short chain alkanediamines ($n = 2$ and 3) did not afford **6** but 2,3-dihydro-1*H*-cyclohepta[*b*]pyrazine **3** and 1,2,3,4-tetrahydrocyclohepta[*b*][1,4]diazepine **4** respectively.[5] We have found that the reported structure **3** is correct but that of **4** is incorrect and actually 2-phenyl-3,4,5,6-tetrahydropyrimidine **5b**.



In absolute EtOH compounds **1** and 1,8-diaminonaphthalene **2a** were refluxed for 20 h and the orange product **5a** was isolated by column chromatography on silica gel. It showed ^{1}H NMR signals at δ 7.53 (2 H, t-like, $J = 7.2$), 7.58 (1 H, t-like, $J = 7.2$) and 7,89 (2 H, d-like, $J = 7.2$ Hz) and a mass spectral peak at m/z 244 ($M^{\cdot+}$, 100%). These data indicate that **5a** is 2-phenylperimidine and does not have a seven-membered troponoid ring. From the results of a single-crystal X-ray analysis and direct comparison with an authentic sample of 2-phenylperimidine,[7] the structure was determined unambiguously.

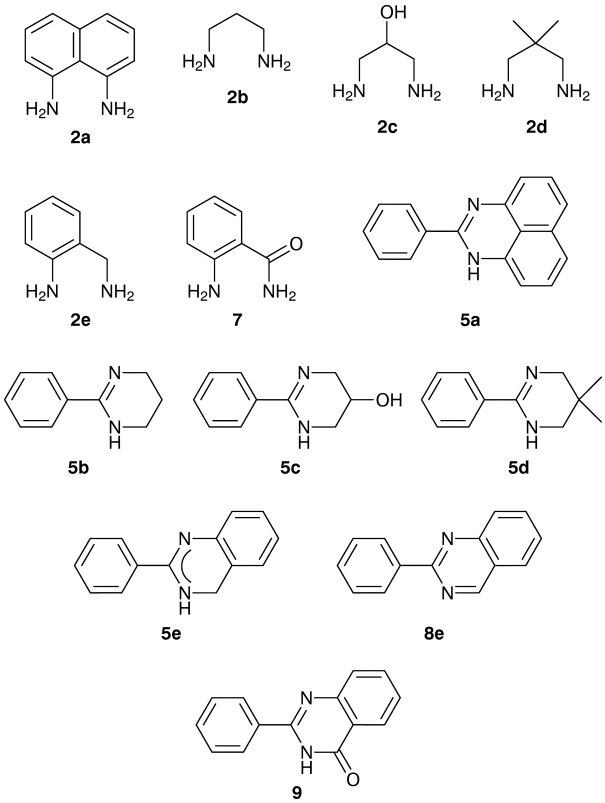
To confirm that this formation of a 2-phenyl-1,3-diazine is peculiar to α,γ-diamines, the reactions of compound **1** with some other α,γ-diamines **2b**–**2e** were carried out. Similarly the rearranged products **5b**, **5c**, **5d**, and **5e** were obtained (Table 1). The methylene protons of **5b** adjacent to the N=C and NH groups show the same chemical shift values in $CDCl_3$ and CD_3OD, suggesting that a rapid tautomerization between these moieties occurs. A similar tautomerization was observed in **5c** and **5d**. The NMR studies could not determine which isomer, 2-phenyl-1,4- or -3,4-dihydroquinazoline, is formed for **5e** or predominant in a possible equilibrium in solution. However, the results of a PM3 calculation[8] of their heats of formation (64.53 *vs.* 67.9 kcal mol^{-1}) suggest that the former is a principal isomer. In this reaction **8e** was also obtained as an autoxidized by-product of **5e**. Upon refluxing **1** and β-aminamide **7** in a mixture of THF and NaH a similarly rearranged product **9** was obtained. The IR spectrum of **9** has an absorption maximum at 1685 cm^{-1}, which shows a close resemblance to that of 4(3*H*)-pyrimidinone at 1689 cm^{-1}, suggesting that **9** has a 4(3*H*)-quinazolinone structure.

The reaction mechanism would be as shown in Scheme 1. The first-formed **A** gives the six-membered spiro compound

Table 1 The rearrangement reaction of compound **1** with **2** or **7**

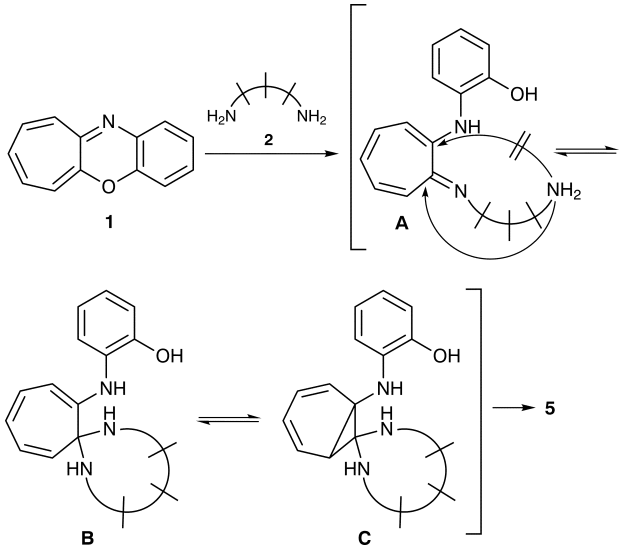
Entry	Substrate	Conditions	Product (Yield, %)
1	**2a**	EtOH/reflux	**5a** (76)
2[a]	**2b**	EtOH/reflux	**5b** (72)
3	**2c**	EtOH/reflux	**5c** (78)
4	**2d**	EtOH/reflux	**5d** (84)
5	**2e**	EtOH/reflux	**5e** (64) **8e**[b] (12)
6	**7**	THF/NaH/reflux	**9** (31)

[a]Together with a small amount of **6** ($n = 3$, 3% yield). [b]Produced by autoxidation of **5e**.



*To receive any correspondence.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.



Scheme 1

B instead of a hydrodiazepine ring. Then **B** transforms to the final product **5** *via* the norcaradiene **C** with elimination of *o*-aminophenol.

Comparison of the heats of formation of **5b** (35.20 kcal mol^{-1}) and **4** (62.82 kcal mol^{-1}) calculated by the PM3 method[8] suggests that the formation of the product is thermodynamically controlled.

Although the rearrangements of troponoid to benzenoid compounds are well known, a transformation of the former to hydro-1,3-diazines is, so far as we are aware, new.

Experimental

Mps were determined with a Mitamura air-bath apparatus and are uncorrected. Proton and ^{13}C NMR spectra ($SiMe_4$ as the internal standard) were determined with Bruker AC-200, AM-400 and/or ARX-400 spectrometers, IR spectra with a Perkin-Elmer System 2000 FT instrument and mass spectra with Shimazu QP-1000 and JEOL JMS-DX 303 spectrometers. Unless otherwise stated the spectra were taken in the following solvents/media: IR, KBr; ^{1}H (200 and 400 MHz) and ^{13}C (100 MHz) NMR, $CDCl_3$; mass spectra at 70 eV by the electron impact method. X-ray data were collected on an Enraf-Nonius CAD4F diffractometer with monochromatized Mo-Kα radiation and θ–2θ scans. The progress of most reactions was followed by TLC using Merck Kieselgel 60F_{254}. All synthetic samples were purified by column chromatography (SiO_2 or neutral Al_2O_3) and recrystallization.

2-*Phenylperimidine* **5a**.—A solution of benzo[*b*]cyclohepta[*e*][1,4]-oxazine **1** (484 mg, 2.48 mmol) and 1,8-diaminonaphthalene **2a** (1.45 g, 9.22 mmol) in ethanol (5 ml) was heated at 80 °C for 20 h. The solvents were evaporated *in vacuo* and the residue separated by column chromatography (silica gel, benzene, CH_2Cl_2, AcOEt) to give **5a**, 76% yield, orange plates, mp 186–188 °C (from hexane–CH_2Cl_2, lit.[7] mp 183–184 °C); δ_H (CD_3OD, δ 3.34) 6.62 (2 H, br d, *J* 7.2), 7.09 (2 H, dd, *J* 8.1, 0.8), 7.16 (2 H, dd, *J* 8.1, 7.2), 7.53 (2 H, t-like, *J* 7.2), 7.58 (1 H, t-like, *J* 7.2), 7.89 (2 H, d-like, *J* 7.2 Hz); δ_C (CD_3OD, δ 49.0) 120.6, 122.5, 123.2, 127.2, 128.1, 129.4, 129.8, 132.3, 135.5, 137.0, 156.9; $\tilde{\nu}_{max}$/cm^{-1} 3188, 1636, 1595, 761, 699; *m*/*z* 244 ($M^{\bullet+}$, 100), 166 ($M^{\bullet+}$–C_6H_5, 100%) (Found: C, 83.6; H, 4.9; N, 11.4. $C_{17}H_{12}N_2$ requires C, 83.58; H, 4.95; N, 11.47%). Crystal data: $C_{17}H_{12}N_2$, monoclinic, space group $P2_1/a$, $a = 9.377(6)$, $b = 14.749(5)$, $c = 9.249(6)$ Å, $\beta = 101.85(4)^\circ$, $V = 1252(2)$ Å^3, $Z = 4$, $\rho = 1.29$ g cm^{-3}, μ(Mo-Kα) = 0.721 cm^{-1}, $F(000) = 551$.

2-*Phenyl*-3,4,5,6-*tetrahydropyrimidine* **5b**.—Colorless crystals, mp 86–87 °C (from hexane–CH_2Cl_2, lit.[9] mp 86–87.5 °C); δ_H 1.86 (2 H, quint., *J* 5.8), 3.49 (4 H, t, *J* 5.8), 7.32 (2 H, t-like, *J* 6.7), 7.37 (1 H, t-like, *J* 6.7), 7.63 (2 H, d-like, *J* 6.7 Hz); δ_H (CD_3OD, δ 3.34) 2.14 (2 H, quint., *J* 5.8), 3.62 (4 H, t, *J* 5.8), 7.62 (2 H, t, *J* 7.2 Hz), 7.71–7.75 (3 H, m); δ_C 20.4, 41.8, 126.1, 128.2, 129.7, 137.0, 155.0; $\tilde{\nu}_{max}$/cm^{-1} 3298, 1623, 781, 699; *m*/*z* 160 ($M^{\bullet+}$, 50), 159 ($M^{\bullet+}$–1, 100%) (Found: C, 75.1; H, 7.5; N, 17.4. $C_{10}H_{12}N_2$ requires C, 74.97; H, 7.55; N, 17.48%).

2-*Phenyl*-3,4,5,6-*tetrahydro*-5-*pyrimidinol* **5c**.—Colorless crystals, mp 125 °C (decomp.) (from hexane–CH_2Cl_2); δ_H 3.56 (2 H, dd, *J* 12.7, 2.7), 3.73 (2 H, dd, *J* 12.7, 2.7 Hz), 4.45 (1 H, m), 7.48–7.98 (5 H, m); δ_H (CD_3OD, δ 3.34) 3.55 (2 H, dd, *J* 13.0, 3.2), 3.70 (2 H, dd, *J* 13.0, 2.7), 4.43 (1 H, tt, *J* 3.2, 2.7), 7.64 (2 H, t-like, *J* 8.0), 7.75 (1 H, t-like, *J* 8.0), 7.76 (2 H, d-like, *J* 8.0); *m*/*z* 176 ($M^{\bullet+}$, 30), 175 ($M^{\bullet+}$–1, 82), 104 (100%) (Found: C, 68.3; H, 6.9; N, 15.8. $C_{10}H_{12}N_2O$ requires C, 68.16; H, 6.86; N, 15.90%).

5,5-*Dimethyl*-2-*phenyl*-3,4,6-*trihydropyrimidine* **5d**.—Colorless plates, mp 172–174 °C (from hexane–CH_2Cl_2); δ_H 1.00 (6 H, s) 2.80 (1 H, br, NH), 3.12 (4 H, s), 7.37–7.39 (3 H, m), 7.64–7.67 (2 H, d-like, *J* 6.8 Hz); δ_H (CD_3OD, δ 3.34), 1.18 (6 H, s), 3.33 (4 H, s), 7.65 (2 H, t, *J* 7.6), 7.75–7.78 (3 H, m); δ_C 24.4, 25.4 50.6, 127.5, 128.3, 128.7, 132.6, 157.8; *m*/*z* 188 ($M^{\bullet+}$, 28), 187 ($M^{\bullet+}$–1, 80%) (Found: C, 76.4; H, 8.5; N, 14.6. $C_{12}H_{16}N_2$ requires C, 76.55; H, 8.57; N, 14.88%).

2-*Phenyl*-1,4- *and/or* -3,4-*dihydroquinazoline* **5e**.—Colorless needles, mp 142–143 °C (from hexane–CH_2Cl_2, lit.[10] mp 142 °C); δ_H 4.70 (2 H, br s), 6.89 (1 H, br d, *J* 7.3), 7.00 (1 H, ddd, *J* 7.6, 7.3, 0.8), 7.07 (1 H, br d, *J* 7.6), 7.15 (1 H, br t, *J* 7.3), 7.34 (2 H, t-like, *J* 7.0), 7.40 (1 H, t-like, *J* 7.0), 7.73 (2 H, br d, *J* 7.0 Hz); δ_H (CD_3OD, δ 3.34) 4.74 (2 H, s), 7.00–7.06 (3 H, m), 7.18 (1 H, td, *J* 7.2, 1.5), 7.49 (2 H, t-like, *J* 7.6), 7.54 (1 H, t-like, *J* 7.6), 7.81 (2 H, d-like, *J* 7.6 Hz); δ_C 44.7, 120.3, 121.5, 124.4, 125.5, 126.5, 128.0, 128.5, 129.3, 130.5, 135.4, 155.0; $\tilde{\nu}_{max}$/cm^{-1} 3217, 1586, 758, 695; *m*/*z* 208 ($M^{\bullet+}$, 58%), 207 ($M^{\bullet+}$–1, 100) (Found: C, 80.8; H, 5.8; N, 13.4. $C_{14}H_{12}N_2$ requires C, 80.74; H, 5.81; N, 13.45%).

2-*Phenylquinazoline* **8e**.—Colorless crystals, mp 98–99 °C (from hexane–CH_2Cl_2, lit.[11] mp 98–100 °C); δ_H 7.52 (4 H, m), 7.85 (2 H, t, *J* 7.6), 8.07 (1 H, d, *J* 7.6), 8.63 (2 H, d, *J* 7.6 Hz), 9.42 (1 H, s); δ_C 123.4, 126.9, 127.1, 128.4, 128.48, 128.50, 130.5, 133.9, 137.9, 150.6, 160.3, 160.9; *m*/*z* 206 ($M^{\bullet+}$, 100), 179 (43%) (Found: C, 81.5; H, 4.9; N, 13.5. $C_{14}H_{10}N_2$ requires C, 81.53; H, 4.89; N, 13.58%).

2-*Phenyl*-4-(3H)-*quinazolone* **9**.—Colorless needles, mp 240–242 °C (from hexane–CH_2Cl_2, lit.[12] mp 242.5–243.5 °C); δ_H 7.51 (1 H, dd, *J* 7.8, 6.8), 7.59 (3 H, m), 7.80 (1 H, dd, *J* 8.1, 6.8), 7.85 (1 H, d, *J* 8.1), 8.27 (2 H, m), 8.34 (1 H, d, *J* 7.8 Hz), 11.74 (1 H, br s); δ_H (CD_3OD, δ 3.34) 7.59–7.70 (4 H, m), 7.83 (1 H, dd, *J* 7.8, 0.8), 7.91 (1 H, ddd, *J* 8.0, 7.8, 1.2), 8.09 (2 H, d-like, *J* 7.6), 8.29 (1 H, dd, *J* 8.0, 1.2 Hz); δ_C 120.9, 126.3, 126.7, 127.4, 128.0, 129.0, 131.6, 132.8, 134.9, 149.5, 151.7, 163.9; $\tilde{\nu}_{max}$/cm^{-1} 1685; *m*/*z* 222 ($M^{\bullet+}$, 100%) (Found: C, 75.6; H, 4.5; N, 12.6. $C_{14}H_{10}N_2O$ requires C, 75.66; H, 4.54; N, 12.60%).

We thank Dr. Hideki Saito (Saitama University) for his helpful advice as to the measurement and analysis of the single-crystal X-ray diffraction analysis.

Received, 30th October 1997; Accepted, 22nd May 1998
Paper E/7/07825K

References

1 T. Nozoe, H. Okai and T. Someya, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2185.
2 T. Nozoe, *Heterocycles*, 1990, **30**, 1263.
3 T. Nozoe, T. Asao and K. Takahashi, *Bull. Chem. Soc. Jpn.*, 1961, **34**, 146; 1966, **39**, 1980.
4 T. Nozoe, S. Ishikawa and K. Shindo, *Heterocycles*, 1989, **28**, 733.
5 K. Shindo, H. Wakabayashi, S. Ishikawa and T. Nozoe, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2941.
6 K. Shindo, H. Wakabayashi, H. Miyamae, S. Ishikawa and T. Nozoe, *Heterocycles*, 1994, **37**, 943.
7 V. Paragamian, M. B. Baker, B. M. Puma and J. Reale Jr, *Heterocycl. Chem.*, 1968, **5**, 591; A. L. Llamas-Saiz, C. Foces-Foces, D. Sanz, R. M. Claramunt, J. Dotor, J. Elguero, J. Catalán and J. C. del Valle, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1389.
8 MOPAC, Version 6, J. J. Stewart, *QCPE Bull.*, 1989, **9**, 10.
9 G. S. Skinner and P. R. Wunz, *J. Am. Chem. Soc.*, 1951, **73**, 3814.
10 W. Reid and P. Stahlhofen, *Ber. Bunsenges. Phys. Chem.*, 1954, **87**, 1801.
11 H. E. Baumgarten, P. L. Creger and P. R. Wunz, *J. Am. Chem. Soc.*, 1958, **80**, 6609.
12 W. E. Noland and D. A. Jones, *J. Org. Chem.*, 1962, **27**, 341.