Thermal Rearrangement of a Phthalazine to a Quinazoline

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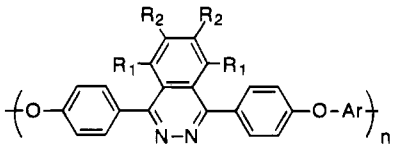
This is the first reported thermal rearrangement reaction of a phthalazine to its structural isomer, a quinazoline. We have found that heating polyphenylated phthalazines **2b–d** at 360 °C for 30 min gave the corresponding quinazolines in high yield. The less sterically crowded 1,4-bis(4-fluorophenyl)phthalazine (**2a**) gave only a low yield of quinazoline **3a**. X-ray crystallographic analysis on **3b** further confirmed our finding.

Introduction

We recently described the synthesis of poly(ether phthalazine)s **1a–c**, where Ar is derived from a bisphenol.[1] The polymers have very high glass transition



Ar = Arylene group

1a; R_1, R_2 = H

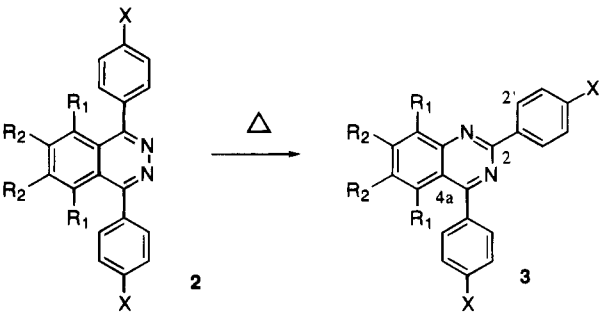
1b; R_1 = Ph, R_2 = H

1c; R_1, R_2 = Ph

temperatures and show no appreciable weight loss, by thermogravimetric analysis, up to 500 °C. Examination of the polymers by differential scanning calorimetry showed that an exothermic reaction occurred when the polymers reached about 350 °C. We speculated that the origin of the exothermic reaction may be due to a thermal rearrangement of the phthalazine moiety of the polymer. In order to further understand the molecular basis of the exothermic reaction, a series of polyphenylated phthalazine compounds **2a–d** were synthesized and used as model compounds which were heated at elevated temperatures.

Results

When tetraphenylphthalazine (**2b**) was heated in a sealed tube at 360 °C for 30 min, a new product was isolated in high yield (70% by weight) and no starting material was recovered. To our surprise, high-resolution MS indicated that this new product has exactly the same mass and molecular formula as the starting material **2b**. Extensive ^{1}H, ^{13}C, and 2D NMR experiments and other analyses were carried out on the product, and on the basis of the spectroscopic data, we assigned the product as tetraphenylquinazoline (**3b**). In particular, two pieces of evidence are noteworthy: (1) a down field proton signal at 8.6 ppm is very characteristic of a proton-2′ of a phenyl attached to the 2-position of a quinazoline; and (2) a very up-field quaternary carbon signal at 121 ppm is very characteristic of carbon-4a of quinazoline. Since no previous examples of a rearrangement of phthalazine to quinazoline have been reported, X-ray analysis was performed on the product and it confirmed the product is indeed **3b** (Figure 1).



a $R_1 = R_2$ = H, X = F
b R_1 = Ph, R_2 = H, X = H
c $R_1 = R_2$ = Ph, X = H
d $R_1 = R_2$ = Ph, X = F

Experiments have also been performed on other model compounds (Table 1). Hexaphenylphthalazines (**2c** and **2d**) were found to give the cleanest reactions and highest yields of the quinazolines **3c** and **3d**, respectively. However, in the case of the unsubstituted phthalazine **2a**, only a low yield of the quinazoline **3a** was obtained and decomposition occurred to give principally black, insoluble material.

Examination of compound **2c** by differential thermal analysis (DTA) (Figure 2) and differential scanning calorimetry (DSC) showed that the rearrangement was an exothermic reaction. The enthalpy change of the reaction was found to be 20 kcal/mole and the activation energy was found to be 39 kcal/mol.[2,3]

Cross-over reaction has been carried out using a 1:1 mixture of **2c** with **2d**. It was found that beside **3c** and **3d**, no cross-over products were detected. This suggests that the reaction is unimolecular in nature.

Discussions

One of the probable mechanisms for this rearrangement is a unimolecular pathway through a "benzvalene"-type intermediate **4** as shown in Scheme 1, similar to that suggested by Scott for the thermal rearrangement of naphthalene.[4] Skeletal rearrangement of aromatic compounds are not commonly observed except at very high temperatures. For example, the thermal automerization of naphthalene was shown to occur only above 1000 °C.[4]

[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1995.

(1) Singh, R.; Hay, A. S. *Macromolecules* **1992,** *25,* 1025.

(2) Activation energy was obtained by plotting ln B vs $1/T_{max}$ according to methods discussed in ref 3: B = heating rate, and T_{max} = temperature at peak maximum of the DTA thermogram.

(3) Kissinger, H. E. *J. Res. Natl. Bur. Stand.* **1956,** *57,* 217.

(4) Scott, L. T. *Acc. Chem. Res.* **1982,** *15,* 52.

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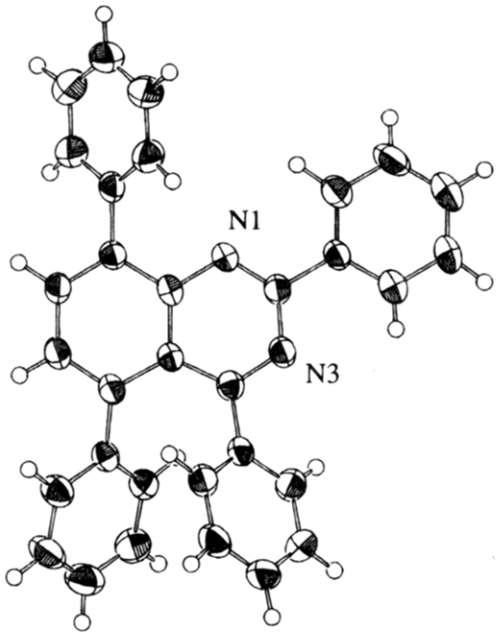


Figure 1. ORTEP diagram of **3b**.

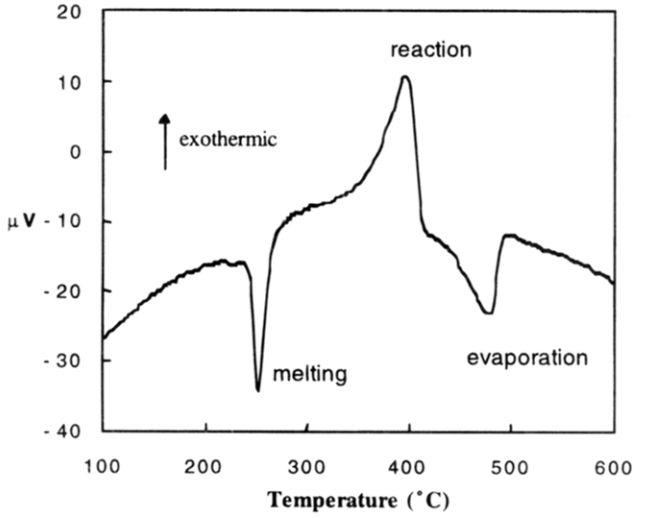


Figure 2. DTA thermograph of **2c**.

Table 1. Pyrolysis of Phthalazines

substrate	product	T, °C	t, h	yield, %	conversion, %
2a	**3a**	360	14.0	23	30
2a	**3a**	400	3.5	24	100
2b	**3b**	360	0.5	70	100
2c	**3c**	360	0.5	75	100
2d	**3d**	360	0.5	75	100

In comparison the rearrangement of the phthalazines **2b–d** is extremely facile. This may be attributable to the presence of the heteroatoms which lowers the degree of aromaticity in the phthalazine ring compared to naphthalene.

Analysis of molecular models of phthalazine **2b** (Figure 3)[5] revealed that there is significant repulsion between the phenyl rings in the peri-positions which not only forces the two rings apart but also results in an out-of-plane splaying of the pendent phenyl rings in opposite directions as occurs in 1,4,5,8-tetraphenylnaphthalene,[6]

(5) Molecular models and MM2 calculations were obtained using CAChe Scientific Inc. software.

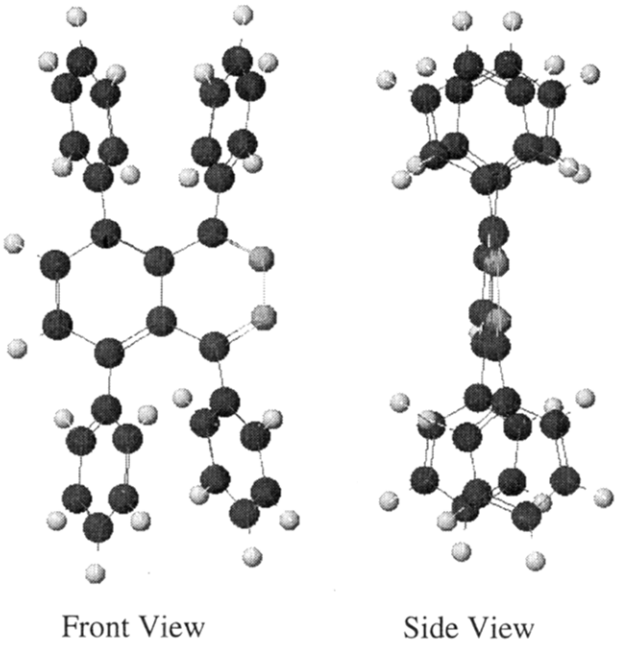
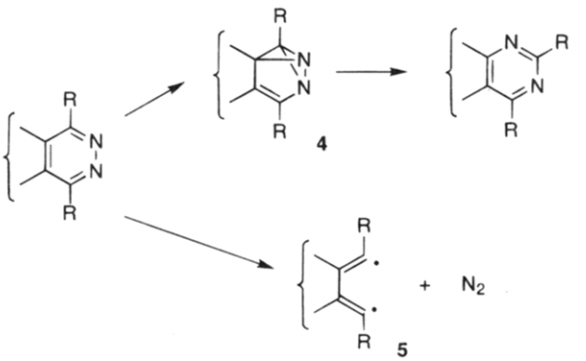


Figure 3. Molecular models of **2b**.

Scheme 1



along with some in-plane distortion of the central ring. It appears, therefore, that the presence of this steric repulsion between phenyl rings in the case of **2b–d** is a driving force for the rearrangement, since the relief of steric strain in the juxtaposed phenyl rings could compensate for the loss of aromaticity during the rearrangement process. On the other hand, in the case of **2a**, where there is much less steric strain, nitrogen elimination may have occurred preferentially which would lead to decomposition (Scheme 1); hence, only a low yield of rearrangement product **3a** is obtained.

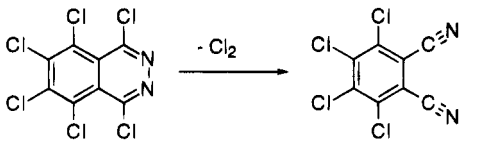
A MM2 calculation[5] also supports our argument. We have computed the strain energy difference between the phthalazines **2a–c** and their corresponding thermal rearrangement products, quinazolines **3a–c**.[7] It indeed showed that **2b** and **2c** have higher strain energy (9 kcal/mol) compared to **2a** (6 kcal/mol).

Nitrogen elimination is reported to be the dominant reaction for phthalazine compounds at elevated temperatures.[8] It has also been reported that pyrolysis of hexachlorophthalazine (**6**) gave the dicyano compound **7**.[9]

(6) Clough, R. L.; Kung, W. J.; Marsh, R. E.; Roberts, J. D. *J. Org. Chem.* **1976**, *41*, 3603.

(7) Strain energy difference is defined as strain energy of phthalazine minus strain energy of quinazoline.

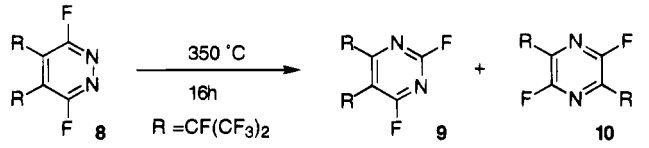
(8) Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford, 1985; pp 147–149.



6 7

Our results are the first examples of thermal rearrangement of phthalazines to a quinazolines. It also demonstrates once again the role of steric strain in controlling the course of a chemical reaction.[10]

The thermal rearrangement of phthalazine to quinazoline exhibits some similarity with the case of perfluoropyridazine **8** reported by Chambers et al., which undergoes thermal rearrangement to give a mixture of pyrimidine **9** and pyrazine **10**.[11] However, rearrangement of the perfluoropyridazine **8** is governed by electronic factors rather than steric factors and it is much slower compared to our examples.[12]



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Two possible reaction pathways for the thermal reaction of pyridazines and phthalazines may involve nitrogen elimination through a diradical intermediate **5** or rearrangement, probably through a "benzvalene"-type intermediate **4** (Scheme 1). The competition between rearrangement and elimination of nitrogen depends on a number of factors. The pyridazine **8** undergoes rearrangement because the fluorine adjacent to the nitrogen destabilizes the radical intermediate so that the rearrangement reaction is favored over nitrogen elimination.[12] Our case illustrates the importance of steric strain since the steric crowding effect could decrease the activation energy required for the rearrangement reaction, hence favoring rearrangement over nitrogen elimination.

X-ray Structure of 3b

There is still one pair of phenyl substituents at the peri-positions C4 and 5 of quinazoline **3b**. As a result of this steric overcrowding, as shown by X-ray crystallography there is a considerable degree of structural distortion in **3b**. The quinazoline parent ring is nonplanar with end-to-end twisting up to 15° (the dihedral angle between C2–N3 and C6–C7 bond), and rms deviation from the plane equal to 0.19 Å. In addition, the two phenyl groups on C-4 and 5 are displaced to opposite sides of the quinazoline ring at an angle of 27.5° to each other.

Experimental Section

^{1}H and ^{13}C NMR experiments were recorded at room temperature on Varian Unity 500 NMR spectrometers. Tetramethylsilane was used as the internal standard for the ^{1}H NMR spectra. EI mass spectra were recorded on a DuPont 21-492B spectrometer.

Synthesis of Phthalazines 2a–d. We have prevously reported the synthesis of phthalazines **2a** and **2d**.[1] **2b** and **2c** were prepared according to the reported procedure[1] with benzene used, instead of fluorobenzene, as starting material. **2b** was prepared in 65% yield: mp 342–4 °C (lit.[13] mp 344 °C). **2c** was prepared in 80% yield: mp 251–2 °C (lit.[14] 249–51 °C).

General Procedure for Static Thermolysis of Phthalazine. Thermolysis was carried out in a sealed tube containing 500 mg of phthalazine using a heated aluminum block according to the temperatures and times reported in Table 1. The product was dissolved in chloroform and filtered. Solvent was removed on a rotary evaporator, and the product was purified by column chromatography (silica gel, 10% EtOAc/low boiling petroleum ether).

2,4-Bis(4-fluorophenyl)quinazoline (3a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (dd, J = 5.9, 8.8 Hz, 2H), 8.12 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.88 (m, 3H), 7.55 (t, J = 7.3 Hz, 1H), 7.29 (dd, J = 8.3, 8.3 Hz, 2H), 7.19 (dd, J = 8.3, 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.42 (d, J_{CF} = 21.9 Hz), 115.67 (d, J_{CF} = 21.1 Hz), 121.38, 126.67, 127.13, 129.13, 130.68 (d, J_{CF} = 8.2 Hz), 132.13 (d, J_{CF} = 9.2 Hz), 133.62 (d, J_{CF} = 3.6 Hz), 133.70, 134.20 (d, J_{CF} = 2.7 Hz), 151.96, 159.18, 163.94 (d, J_{CF} = 250 Hz), 164.63 (d, J_{CF} = 250.9 Hz), 167.15; MS (EI) m/e calcd for $C_{20}H_{12}F_2N_2$ 318.09685, found 318.09690.

2,4,5,8-Tetraphenylquinazoline (3b): mp 201–3 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (dd, J = 2.0, 8.3 Hz, 2H), 8.04 (d, J = 7.3 Hz, 1H), 7.96 (dd, J = 1.5, 8.3 Hz, 2H), 7.65 (d, J = 7.32 Hz, 1H), 7.62 (dd, J = 7.3, 7.3 Hz, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.50 (m, 3H), 7.45 (dd, J = 1.5, 8.3 Hz, 2H), 7.05–7.15 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.21, 126.75, 127.36, 127.39, 127.5, 127.72, 127.85, 128.42, 128.68, 129.66, 130.05, 130.21, 130.43, 131.13, 133.11, 137.87, 138.62, 139.43, 140.23, 140.33, 140.98, 150.89, 158.1, 168.38; MS (EI) m/e calcd for $C_{32}H_{22}N_2$ 434.17829, found 434.17810.

2,4,5,6,7,8-Hexaphenylquinazoline (3c): mp 264–5 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (m, 2H), 7.41 (m, 3H), 7.23–7.37 (m, 7H), 7.05 (m, 3H), 6.85–6.95 (m, 8H), 6.72–6.77 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.15, 125.55, 125.86, 126.05, 126.24, 126.57, 126.74, 126.77, 126.84, 127.18, 128.04, 128.31, 128.57, 129.90, 130.26, 130.86, 131.41, 132.03, 132.22, 137.83, 137.98, 138.35, 139.25, 139.27, 139.47, 139.78, 141.04, 141.21, 146.02, 151.01, 157.92, 169.06; MS (EI) m/e calcd for $C_{44}H_{30}N_2$ 586.24090, found 586.24140.

2,4-Bis(4-fluorophenyl)-5,6,7,8-tetraphenylquinazoline (3d): mp 255–6 °C (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, J = 6.0, 9.5 Hz, 2H), 7.22–7.36 (m, 7H), 7.09 (dd, J = 9.5, 9.5 Hz, 2H), 6.96 (m, 3H), 6.88 (m, 5H), 6.7–6.84 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.18 (d, J_{CF} = 22.0 Hz), 115.29 (d, J_{CF} = 22.0 Hz), 120.96, 125.66, 125.94, 126.24, 126.33, 126.64, 126.81, 126.89, 126.92, 130.59 (d, J_{CF} = 8.2 Hz), 130.79, 131.37, 131.74 (d, J_{CF} = 8.2 Hz), 131.93, 132.17, 133.92 (d, J_{CF} = 2.7 Hz), 137.02 (d, J_{CF} = 3.7 Hz), 137.88, 138.16, 139.13, 139.29, 139.62, 141.41, 146.32, 151.07, 157.03, 162.43 (d, J_{CF} = 248.2 Hz), 164.48 (d, J_{CF} = 250.0 Hz), 168.00; MS (EI) m/e calcd for $C_{44}H_{28}F_2N_2$ 622.2204, found 622.2217. Anal. Calcd for $C_{44}H_{28}F_2N_2$: C, 84.87; H, 4.53; N, 4.50. Found: C, 84.99; H, 4.64; N, 4.46.

X-ray Structure Determination of 3b. Crystal dimensions 0.35 × 0.20 × 0.47 mm, measured at 21 °C on a Rigaku AFC6S diffractometer with graphite monochromated Cu K_α radiation: monoclinic; a = 19.878(2) Å, b = 16.671(4) Å, c = 14.984(1) Å; β = 69.786(6)°; V = 4660(2) Å^3; space group $P2_1/c$ (no. 14); Z = 4; D_c = 0.619 g cm^{-3}; μ(Cu Kα) = 2.61 cm^{-1}; $2\theta_{max}$ = 140°; a total of 4783 reflections were collected, 4737 were unique and 2394 observed ($|F_o| > 3\sigma|F_o|$); and 396 parameters were used for the refinement with R = 0.056 and R_w = 0.062. Calculations were performed using the Texan crystallographic software package of Molecular Structure Corporation. The

(9) Chambers, R. D.; Clark, M.; MacBride, J. A. H.; Musgrave, W. K. R.; Srivastava, K. C. *J. Chem. Soc., Perkin Trans. 1* **1974**, 125.
(10) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.
(11) Chambers, R. D.; Musgrave, W. K. R.; Sargent C. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1071.
(12) Chambers, R. D.; Clark, M.; Maslakiewicz, J. R.; Musgrave, W. K. R.; Urben, P. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1513.
(13) Fletcher, H. Br. Patent 1 028 920, 1966; *Chem. Abstr.* **1966**, *65*, 3799b.
(14) Gilchrist, T. L.; Gymer, G. E.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1747.

structure was solved by direct methods and refined by full-matrix least-squares. The non-hydrogen atoms were refined anisotropically. The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

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