Pyrolysis of *N*-(1-Phthalazinyl)-*N'*-cycloalkylidenehydrazines. Structural Elucidation of the Reaction Products

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Introduction

During our work on the elucidation of the structures of human metabolites of hydralazine,[1-4] a major drug against hypertension, and investigations of its chemistry,[5-7] we became interested in the still unknown structure of the pyrolysis product of *N*-(1-phthalazinyl)-*N'*-cyclopentylidenehydrazine (**2a**).

In 1951 Druey and Ringier[8] reported that the pyrolysis of **2a** under nitrogen atmosphere at 250 °C for 1 h led to an unidentified colorless compound with a melting point of 111–112 °C. The molecular formula of $C_{13}H_{14}N_4$ was assigned to this product based on its elemental analysis. They rejected expressedly 3-butyl-*s*-triazolo[3,4-*a*]phthalazine (**3a**) as the structure for this compound because the pyrolysis product gave a depressed mixture melting point with an authentic sample of **3a**. Furthermore, a difference in the base solubility between the pyrolysis product and authentic **3a** was noted by the authors.

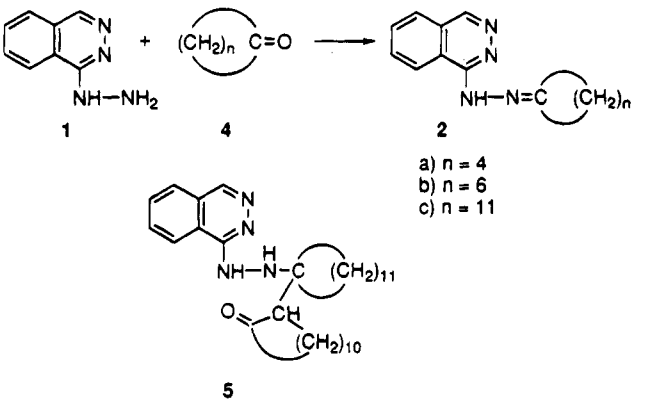
Results

The present report describes our findings of the reinvestigation of the pyrolysis of **2a**. In addition, two more hydralazones, **2b** and **2c**, prepared from cycloheptanone and cyclododecanone were included in this study. All investigated hydralazones were obtained by reacting the cycloalkanones **4a–c** with hydralazine **1** in acetic acid. They were purified by flash column chromatography. *N*-(1-Phthalazinyl)-*N'*-[1-(1-oxocyclododecan-2-yl)-cyclododecyl]hydrazine (**5**) was isolated as a byproduct from the reaction of **1** with **4c** (Scheme 1). The structural assignment of **5** is based on elemental analysis and ^1H and ^{13}C NMR spectroscopic data. Its formation can be explained by an acid-catalyzed aldol condensation.

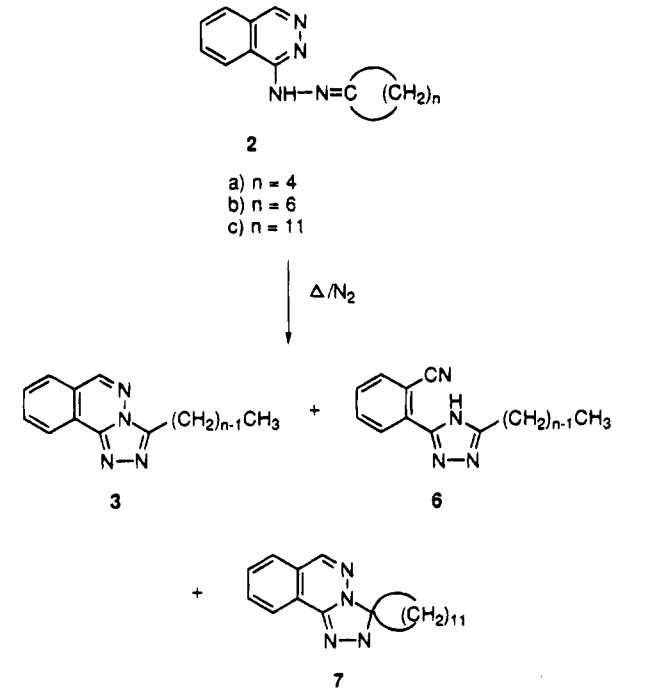
Repeating the pyrolysis of **2a** as described earlier[8] afforded in our hands a mixture of products which were separated by flash chromatography. In addition to some recovered starting material **2a**, the products were **6a**, a compound which is soluble in alkali and reprecipitable by acid, and **3a**, a compound which Druey and Ringier thought that they had never obtained (Scheme 2). The melting points obtained for **6a** and **3a** were 113–114 °C and 106 °C, respectively. The structure of **6a** was unequivocally assigned on the basis of its spectral data. The infrared spectrum showed bands at 3293 and 2216 cm^{-1} assigned to the NH or C≡N group, respectively. The mass spectrum showed ions at positions expected for the molecular ion (*m/z* 226, RI = 5) and $M^+ - CH_3CH{=}CH_2$ (*m/z* 184, 100). The formation of the latter ion can be visualized by a McLafferty rearrangement involving the side chain alkyl group. The ^1H NMR spectrum indicated the presence of nine nonaromatic and four aromatic protons. There also was one deuterium oxide exchangeable proton. This pattern is in agreement with structure **6a**. A similar ring opening of the *s*-triazolo[3,4-*a*]phthalazine system, though by a reaction with strong alcoholic potassium hydroxide solution, was already earlier observed.[9]

The structural assignment of the less polar product (mp 106 °C) **3a** was confirmed by 1D and 2D ^1H and ^{13}C

Scheme 1



Scheme 2



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(1) Zimmer, H.; McManus, J.; Novinson, T.; Hess, E. V.; Litwin, A., *Arzneim. Forsch. (Drug Res.)* **1970**, *20*, 1586.
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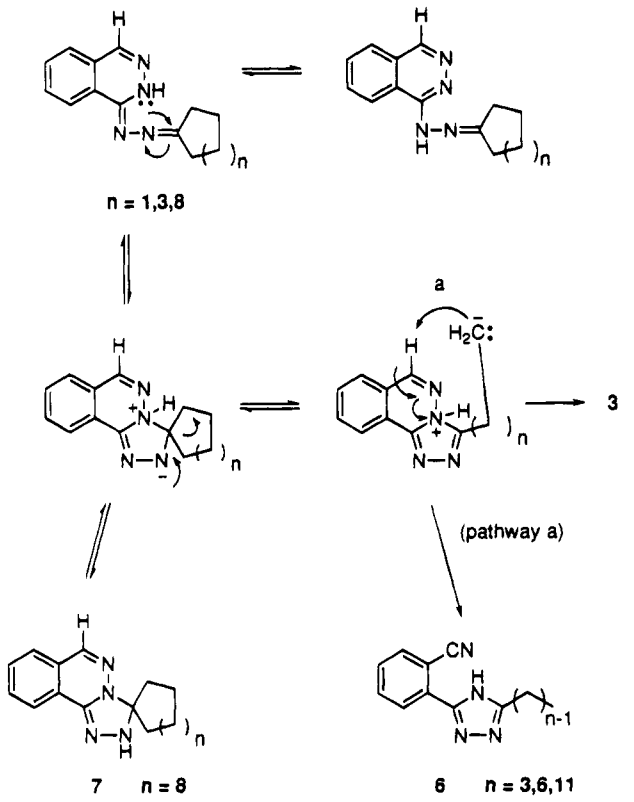
0022-3263/95/1960-1908$09.00/0

Scheme 3



NMR spectroscopy as well as mass spectrometry. To be absolutely sure on this assignment a single crystal X-ray crystallographic analysis was carried out,[10] which confirmed our structure proposal based on the NMR data.

Similarly, the pyrolysis of **2b** yielded **6b** and **3b**. Pyrolysis of **2c**, however, led to the formation of **3c** and a minor product to which the isomeric spiro structure **7** was assigned on the basis of high resolution mass spectroscopic as well as 1D and 2D ^{1}H NMR spectroscopic data. The 1D NMR showed only one deutero exchangeable signal and the 2D NMR exhibited no correlation between the aliphatic protons and protons positioned on the sp^2 hybridized carbons; thus an enamine structure isomeric with a hydralazone was excluded.

A plausible explanation for the above findings is that the pyrolysis reaction might take place via an ionic mechanism (Scheme 3). Thus the alkyl anion generated during the process could act as a base and abstract the proton of the ammonium group to give type **3** compounds. By abstracting the acidic proton from position 6 of the triazolophthalazine ring, and subsequent ring opening of the phthalazine moiety, formation of the cyano compounds **6** can be explained. A proton transfer from the ammonium ion to the nitranion yielded the spiro compound **7**.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 250 or 300 MHz. ^{13}C NMR were recorded at 62.9 MHz. GC-MS data were obtained at 70 eV. X-ray data were recorded on a Nicolet R3m diffractometer and analyzed on a MicroVAX II using the SHTLXTL PLUS series of crystallographic programs.

(10) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

***N*-(1-Phthalazinyl)-*N'*-cycloalkylidenehydrazines (2). General Procedure.** A solution of hydralazine **1** (2.5 g, 16 mmol) in acetic acid (20 mL) was treated with the appropriate cycloalkanone **4** (16 mmol) at ambient temperature and left standing for 2 days. The dark brown solution was evaporated under vacuum, and the residue was treated with aqueous solution of sodium bicarbonate and then extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness at reduced pressure. The residual orange-colored solid was subjected to flash column chromatography using ethyl acetate as an eluent.

***N*-(1-Phthalazinyl)-*N'*-cyclopentylidenehydrazine (2a)** was obtained from **1** and **4a** in a yield of 3.43 g (95%) as an orange crystalline solid; mp 111 °C (lit.[8] mp 111–112 °C); ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 4H), 2.60 (m, 4H), 7.65, 8.36 (2m, 5H), and 10.25 (s, 1H); MS *m/z* (%) 226 (M^+, 3), 197 (17), 115 (2), 103 (4), 89 (13), 71 (25), 56 (24), 40 (100).

***N*-(1-Phthalazinyl)-*N'*-cycloheptylidenehydrazine (2b)** was obtained from **1** and **4a** in a yield of 3.37 g (83%) as an orange crystalline solid: mp 88 °C; ^{1}H NMR ($CDCl_3$) δ 1.81, 2.50, 2.67 (m, t, t, 12H), 7.44, 7.59, 7.74, 8.32 (m, m, s, t, 5H), 10.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.19, 27.51, 30.42, 31.35, 37.47, 123.96, 125.69, 127.08, 131.09, 131.29, 137.08, 146.65, 170.96; MS *m/z* (%) 254 (M^+, 13), 239 (8), 225 (10), 211 (17), 197 (60), 184 (100), 115 (10). Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.83; H, 7.13. Found: C, 70.75; H, 7.04.

***N*-(1-Phthalazinyl)-*N'*-cyclododecylidenehydrazine (2c)** was obtained from **1** and **4c** in a yield of 1.64 g (51%) as an orange crystalline solid: mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 1.37, 1.64, 1.82, 2.43, 2.76 (5m, 22H), 7.42, 7.56, 7.71, 8.31 (m, m, s, m, 5H), 10.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.53, 22.92, 23.33, 23.41, 24.00, 24.18, 24.68, 25.57, 25.78, 29.23, 32.32, 123.96, 125.77, 127.13, 127.72, 131.26, 131.34, 137.17, 147.12, 167.88; MS: *m/z* (%) 324 (M^+, 3), 197 (11), 185 (21), 145 (18), 131 (17), 129 (6), 103 (17), 89 (27), 41 (100). Anal. Calcd for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70. Found: C, 73.86; H, 8.53.

***N*-(1-Phthalazinyl)-*N'*-[1-(1-oxocyclododecan-2-yl)cyclododecyl]hydrazine (5)** was obtained as byproduct from the reaction of **1** with **4c**: yield 0.59 g (15%) of an orange crystalline solid; mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 1.29, 1.70, 1.82, 2.43, 2.76 (s, t, t, q, t, 43H), 7.43, 7.57, 7.71, 8.31 (m, m, s, t, 5H), 10.26, 10.96 (2s, 2H); ^{13}C NMR ($CDCl_3$) δ 22.32, 22.56, 22.91, 23.34, 23.41, 24.01, 24.22, 24.60, 24.70, 25.58, 25.81, 29.24, 32.79, 40.34, 123.97, 125.82, 127.17, 127.72, 131.26, 131.34, 137.17, 146.11, 167.84, 212.82; γ_{max} (KBr) 3290, 1707 cm^{-1}. Anal. Calcd for $C_{32}H_{50}N_{40}$: C, 75.84; H, 9.95. Found: C, 75.67; H, 9.88.

Pyrolysis of the Hydralazones 2. General Procedure. In a three-neck round-bottom flask the appropriate **2** (8 mmol) was heated at 270 °C under nitrogen atmosphere for 1 h. The obtained residue was subjected to column chromatography (silica gel) with use of ethyl acetate as an eluent. The eluted fractions were identified by their IR and ^{1}H and ^{13}C NMR spectra. In addition, they were characterized by their C, H, N analyses and/or high-resolution mass spectra as **6**, **3**, and **7** according to their elution sequence.

3-(n-Butyl-5-(2-cyanophenyl)4*H*-*s*-triazole (6a) was obtained from **2a** in a yield of 0.17 g (39%) as a pale yellow crystalline solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 0.96 (t, 3H), 1.40, 1.79, 2.84 (m, quintet, t, 6H), 7.48, 7.67 (2t, 2H), 7.83, 8.19 (2d, 2H), 12.62 (s, 1H); MS *m/z* (%) 226 (M^+, 5), 225 (2), 211 (7), 197 (23), 184 (100), 167 (8), 149 (18), 129 (15), 88 (11).

3-n-Butyl-*s*-triazolo[3,4-*a*]phthalazine (3a) was obtained from **2a** in a yield of 0.23 g (13%) as a pale yellow crystalline solid: mp 106 °C (lit.[8] 101–102 °C); ^{1}H NMR ($CDCl_3$) δ of 0.98 (t, 3H), 1.48, 1.91, 3.22 (sextet, quintet, t, 6H), 7.75 (dd 1H), 7.91 (collapsed 2 dd, 2H), 8.60 (s, 1H), 8.62 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 13.76, 22.45, 24.05, 29.11, 122.95, 123.03, 123.66, 127.93, 130.54, 133.79, 142.57, 147.16, 151.52; MS: *m/z* (%) 226 (M^+, 3), 211 ($M^+ - CH_3$, 1), 197 (17), 184 (33), 129 (4), 40 (100).

3-(2-Cyanophenyl)-5-hexyl-4*H*-*s*-triazole (6b) was obtained from **2b** in a yield of 0.57 g (28%) of colorless crystalline solid: mp 114–116 °C, ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.36, 1.82, 2.94 (m, q, t, 10H), 7.49, 7.70 (2t, 2H), 7.80, 8.33 (2d, 2H), 12.20 (s, ^{1}H, NH); MS *m/z* (%) 254 (M^+, 8), 239 (15), 225 (7), 212 (5), 197 (46), 184 (100), 129 (22), 88 (11); HRMS (*m/z*) calcd for $C_{15}H_{18}N_4$ (M^+) 254.1533, found 254.1522.

3-n-Hexyl-s-triazolo[3,4-a]phthalazine (3b) was obtained from **2b** in a yield of 0.22 g (11%) as a pale yellow crystalline solid: mp 81 °C; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.34, 1.47, 1.93, 3.21 (m, m, quintet, t, 10H), 7.75 (dd, 1H), 7.91 (collapsed 2dd, 2H), 8.60 (s, 1H), 8.62 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 14.05, 22.53, 24.35, 27.00, 28.98, 31.43, 122.94, 123.07, 123.71, 127.97, 130.54, 133.79, 142.57, 147.12, 151.55; MS: *m/z* (%) 254 (M^+, 49), 239 (6), 238 (21), 211 (34), 197 (100), 185 (67), 146 (50), 131 (23), 129 (13), 103 (33). Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.83; H, 7.13. Found: C, 70.65, H 7.11.

3-n-Undecyl-s-triazolo[3,4-a]phthalazine (3c) was obtained from **2c** in a yield of 0.7 g (26%) as a pale yellow crystalline solid: mp 74 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H), 1.37, 1.93, 3.21 (m, quintet, t, 20H), 7.75 (dd, 1H), 7.91 (collapsed 2dd, 2H), 8.60 (s, 1H), 8.62 (d, 1H); ^{13}C NMR ($CDCl_3$) δ 14.09, 22.66, 24.35, 27.05, 29.32, 29.49, 29.58, 31.90, 122.95, 123.06, 123.71, 127.97, 130.50, 133.78, 142.52, 147.12, 151.55, MS *m/z* (%) 324 (M^+, 2), 239 (5), 197 (29), 184 (59), 129 (7), 41 (100). Anal. Calcd for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70. Found: C, 73.49; H, 8.53.

2,3-Dihydrospiro[cyclododecane-1,3′-s-triazolo[3,4-a]-phthalazine] (7c) was obtained as a byproduct from the pyrolysis of **2c** in a yield of 0.18 g (7%) as a pale yellow crystalline solid: mp 128 °C; ^{1}H NMR ($CDCl_3$) δ 1.64, 2.42, 2.79, 3.01 (m, t, q, t, 22H), 7.59, 7.79, 8.54, 8.56 (m, m, d, s, 5H), 10.23 (s, 1H); HRMS (*m/z*) calcd for $C_{20}H_{28}N_4$ (M^+) 324.2316, found 324.2290.

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Supplementary Material Available: Copies of 2D NMR spectra (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Additions and Corrections

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Toshito Sakai, Takuya Kodama, Tetsuya Fujimoto,* Kazuchika Ohta, Iwao Yamamoto,* and Akikazu Kakehi. Synthesis and Aza-Wittig Reactions of Cyclic Amino Phosphonium Salts.

Page 7145, Scheme 1. $BrCH_2CH_2(CH_2)_nCN$ and $Ph_2PCH_2CH_2(CH_2)_nCN$ should be replaced by $BrCH_2(CH_2)_nCN$ and $Ph_2PCH_2(CH_2)_nCN$.

Page 7145, Experimental Section, column 2, line 21. 3-Bromopropiononitrile (14.8 g, 100 mmol) should be replaced by 4-bromobutyronitrile (14.8 g, 100 mmol).

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