1833 with $I > 3\sigma(I)$ were retained for solution and refinement of the structure. The large number of unmeasured reflections stems from the small crystal size of 0.020 × 0.175 × 0.325 mm. The structure was solved by direct methods and refined to a final R value of 0.069. In the final refinement Fe and Cl atoms were assigned anisotropic thermal parameters and hydrogen atoms were included at calculated positions using a riding model and $U(H) = 1.2U$(bonded C). The largest feature in a final difference map was 0.5, the size of a hydrogen and of no possible chemical significance. H(45) is the largest peak on a difference map computed with it omitted. Tables of anisotropic thermal parameters, hydrogen atom coordinates, and complete tables of bond distances and angles are available as supplementary material.

Acknowledgment. We thank the National Institutes of Health (GM 26226) for support, Professor C. Castro for a preprint of ref 11, and Professor R. Weiss for informing us of his results.

Registry No. 5, 83219-58-3.

Supplementary Material Available: Tables of anisotropic thermal parameters, H atom positional parameters and isotropic thermal parameters, bond lengths and bond angles (5 pages). Ordering information is given on any current masthead page.

Selective Thermolysis Reactions of Bromo-1-nitro-1*H*-pyrazoles. Formation of 3-Nitro-1*H*- vs. 4-Nitro-1*H*-pyrazoles[1]

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Refluxing 3,4,5,-tribromo-1-nitro-1*H*-pyrazole (**1a**) in benzene results in the evolution of bromine and NO_2 and gives the 4-nitro-1*H*-pyrazole **2** and the 1-phenyl-1*H*-pyrazoles **4** and **5**, while heating **1a** in toluene gives **2** and benzyl bromide. Thermolysis of **1a** in refluxing acetonitrile affords both **2** and the isomeric 5-nitro-1*H*-pyrazole **6a**. Refluxing **1a** mixed with the electron-rich 3,5-dimethyl-1*H*-pyrazole (**7**) in all three solvents gives **6a** and 4-bromo-3,5-dimethyl-1*H*-pyrazole (**8**), whereas refluxing **1a** mixed with anisole in benzene solution gives **2** and bromoanisoles. 3,5-Dibromo-1-nitro-1*H*-pyrazole (**1b**) in refluxing acetonitrile gives mainly 3,4-dibromo-5-nitro-1*H*-pyrazole (**6a**) and 3,5-dibromo-1*H*-pyrazole (**3b**), but refluxing **1b** mixed with **7** affords 3-bromo-5-nitro-1*H*-pyrazole (**6b**). Possible mechanisms are discussed involving intramolecular rearrangements to intermediates 3-bromo-3-nitro-3*H*-pyrazoles **9a,b** and 4-bromo-4-nitro-4*H*-pyrazole **10** responsible both for the loss of bromine and NO_2 as well as for the electrophilic bromination of **7** and anisole.

Thermal intramolecular rearrangements involving a migration of a nitro group from a nitrogen to a carbon atom in the five-membered ring is a characteristic property of 1-nitro-1*H*-azoles.[2-6]

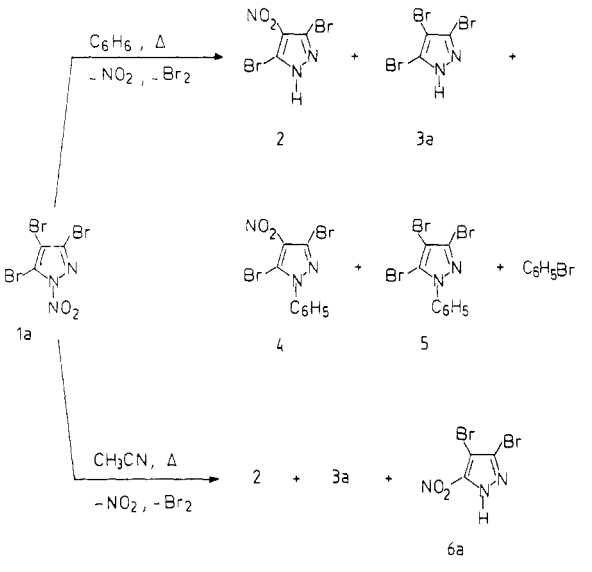
Recently[4] we reported on the thermolysis of 3-bromo-1-nitro-1*H*-indazoles. Thermolysis in refluxing benzene results in the evolution of bromine and NO_2 affording 3-bromo-1-phenyl-1*H*- and 3-nitro-1-phenyl-1*H*-indazoles in addition to 3-bromo- and 3-nitro-1*H*-indazoles. Only the latter two compounds are formed besides benzyl bromide on refluxing in toluene solution. These products, we argued, strongly suggest a radical process. Because simple N–N bond cleavage does not explain the formation of the 3-nitro-1*H*-indazoles we supposed an initial intramolecular rearrangement to a 3-bromo-3-nitro-3*H*-indazole followed by a homolytic cleavage to give either NO_2 or a bromine atom and the corresponding indazolyl radicals. In benzene subsequent homolytic substitution of a benzene molecule then affords the 1-phenyl-1*H*-indazoles.

Here we report the results of our studies of the thermolysis of 3,4,5-tribromo-1-nitro-1*H*-pyrazole (**1a**) and 3,5-dibromo-1-nitro-1*H*-pyrazole (**1b**).

Results and Discussion

Thermolysis of **1a** in refluxing benzene solution is accompanied by evolution of NO_2 and bromine, and after 3 h no **1a** is found to be present. The products obtained from the thermolysis mixture are 3,5-dibromo-4-nitro-1*H*-pyrazole (**2**), 3,4,5-tribromo-1*H*-pyrazole (**3a**), the 1-phenyl-1*H*-pyrazoles **4** and **5**, and a substantial amount of bromobenzene (see Scheme I). Refluxing **1a** in toluene for 1 h gives benzyl bromide in addition to **2** and **3a** and

Scheme I



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(1) Pyrazoles Studies. Part 19. Part 18: Berbee, R. P. M.; Habraken, C. L. *J. Heterocycl. Chem.* **1981**, *18*, 559-560.

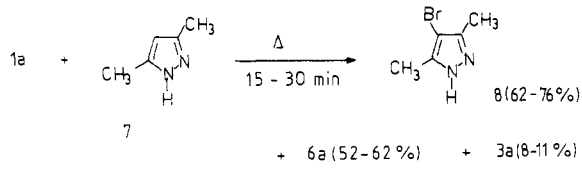
(2) Janssen, J. W. A. M.; Habraken, C. L.; Louw, R. *J. Org. Chem.* **1976**, *41*, 1758-1762 and earlier publications cited therein.

(3) (a) Habraken, C. L.; Cohen-Fernandes, P. *J. Chem. Soc., Chem. Commun.* **1972**, 38. (b) Pevzner, M. S.; Kulibabina, T. N.; Loffe, S. L.; Maslina, I. A.; Gidaspov, B. V.; Tartakovskii, V. A. *Khim. Geterotsikl. Soedin.* **1979**, *15*, 550-554.

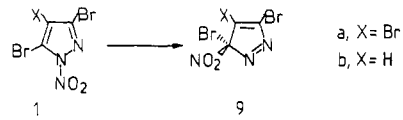
(4) Zibuck, R.; Stahl, M. A.; Barchiesi, B.; Waalwijk, P. S.; Cohen-Fernandes, P.; Habraken C. L. *J. Org. Chem.* **1984**, *49*, 3310-3314.

0022-3263/86/1951-4656$01.50/0

Scheme II



Scheme III



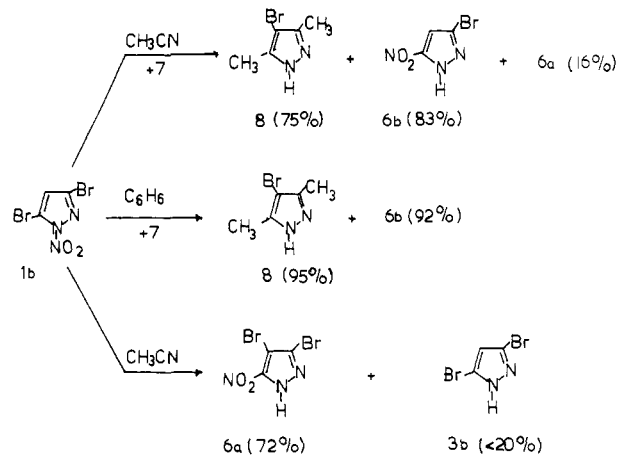
some 1-benzyl-3,4,5-tribromo-1*H*-pyrazole. On the other hand, when a solution of **1a** in toluene was allowed to stay at room temperature for 5 weeks the major product formed is the isomeric 3,4-dibromo-5-nitro-1*H*-pyrazole **6a** and benzyl bromide in addition to some **3a**, whereas refluxing **1a** for 2 h in acetonitrile gives a high yield of a mixture of **2** and **6a** (see Table I). Pertinent to all these reactions is the evolution of brown fumes, i.e., of NO_2 and bromine.

Although these findings resemble quite closely those found for the thermolysis reactions of 3-bromo-1-nitro-1*H*-indazoles,[4] two differences must also be noted. First, the variation in the dibromonitro compound formed **2**, a 4-nitro-1*H*-pyrazole on refluxing in benzene or toluene solution and **6a**, a 5-nitro-1*H*-pyrazole on either refluxing in acetonitrile or staying at room temperature in toluene solution. Second, the formation of a substantial amount of bromobenzene on thermolysis in benzene solution.

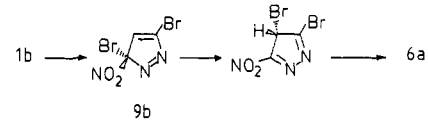
A decidedly different outcome however, is found on heating **1a** in solution mixed with an equimolar amount of 3,5-dimethyl-1*H*-pyrazole (**7**). Now, already after 15–30 min refluxing in benzene, toluene, or acetonitrile no **1a** was found to be present. No NO_2 or bromine are generated and the only products formed are almost equimolar amounts of **6a** and 4-bromo-3,5-dimethyl-1*H*-pyrazole (**8**) in addition to some **3a** (see Scheme II). Apparently, **7**, which is an electron-rich aromatic molecule and which is known to be very susceptible to electrophilic substitution in position 4,[7] is brominated by a bromonium ion releasing intermediate initially formed on thermolysis of **1a**. In the absence of **7**, i.e., in the absence of a bromonium ion trapping reagent, this intermediate then progresses along other reaction paths.

Because intramolecular migrations of a nitro group from a nitrogen to a carbon atom in 1-nitro-1*H*-pyrazoles are known to proceed by an initially formed 3-nitro-3*H*-pyrazole[2] we thereupon surmised the intermediate to be 3,4,5-tribromo-3-nitro-3*H*-pyrazole (**9a**; see Scheme III). The structure of **9a**, a geminal bromo nitro compound, is consistent with the intermediate assumed to be initially formed on thermolysis of 3-bromo-1-nitro-1*H*-indazoles.[4] Moreover, **9a** might be considered to be a bromonium-releasing molecule because in fact it is the nitro diaza analogue of hexabromocyclopentadiene which is reported to brominate efficiently electron-rich aromatic molecules.[8,9]

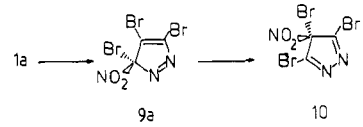
Scheme IV



Scheme V



Scheme VI



Therefore in the presence of **7** this bromonium ion releasing intermediate **9a** is trapped by **7** in a reaction affording **6a** and **8** (see Table I) in about equimolar amounts.

Assuming that a similar intermediate **9b** can be formed by initial migration of the nitro group of 3,5-dibromo-1-nitro-1*H*-pyrazole (**1b**) from the nitrogen to the adjacent carbon, we refluxed **1b** with an equimolar amount of **7** in acetonitrile solution. Again no evolution of brown fumes was observed, and the products are **8**, i.e., once more brominated **7**, and 3-bromo-5-nitro-1*H*-pyrazole **6b** besides a small amount of **6a** (see Scheme IV). **8** and **6b** are also produced on thermolysis of equimolar amounts of **1b** and **7** in refluxing benzene solution. On the other hand only **6a** and no **6b** is formed in addition to a small amount of 3,5-dibromo-1*H*-pyrazole **3b** when **1b** in the absence of **7** is refluxed in an acetonitrile solution. Presumably, in the absence of a bromonium trapping agent **9b** undergoes a subsequent bromine shift followed by hydrogen shift to give **6a** as depicted in Scheme V.

Further support for the occurrence of a bromonium ion releasing intermediate **9a** is obtained by refluxing a benzene solution of equimolar amounts of **1a** and anisole. In contrast to the reaction in the absence of anisole, now

(5) Cohen-Fernandes, P.; Habraken, C. L. *J. Org. Chem.* **1971**, *36*, 3084–3086.

(6) (a) Wrzeciono, U.; Linkowska, E.; Jankowiak, D. *Pharmazie* **1981**, *36*, 673–677. (b) Wrzeciono, U.; Linkowska, E. *Ibid.* **1980**, 35, 593–596.

(7) Kost, A. N.; Grandberg, I. I. *Advances in Heterocyclic Chemistry*; Academic: New York 1966; Vol. 6, pp 347–429. Schofield, K.; Grimmett, M. R.; Keene, B. R. T. *Heteroaromatic Nitrogen Compounds: The Azoles*; Cambridge University: London, 1976; pp 31–73.

(8) Magen, S.; Oren, J.; Fuchs, B. *Tetrahedron Lett.* **1984**, *25* 3369–3372. Fuchs, B.; Belsky, Y.; Tartakovsky, E.; Zizuashvili, J.; Weinman, S. *J. Chem. Soc., Chem. Commun.* **1982**, 778–779.

(9) Refluxing benzene solutions of 1-nitro-3-bromo-1*H*-indazoles in the presence of an equimolar amount of **7** do not afford **8**, and the same products are formed as on refluxing benzene solutions in the absecence of **7**:[4] Stahl, M. A., unpublished experiments.

(10) The presence of Br_2 in the brown fumes was tested with a freshly prepared wet fuchsine–SO_3 paper: Shriner, L. R.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1953; pp 101–102. A control experiment indicated that detection of bromine is impaired by the presence of $NO_2(N_2O_4)$.

(11) The presence of NO_2 in the fumes was determined by a red coloration of a piece of cotton wool impregnated with a freshly prepared mixture of sulfanilic acid, β-naphthylamine, and tartaric acid: Lunge, G. *Angew. Chem.* **1889**, 666–667. Romijn, G. *Pharm. Weekbl.* **1911**, *48*, 753–757.

Table I. Products of Thermolysis of 3,4,5-Tribromo-1-nitro-1*H*-pyrazole (1a) in Solution and of 1a in the Presence of 3,5-Dimethyl-1*H*-pyrazole (7) or of Anisole in Solution[a]

substrate	reacn conditions[a]	product yield, %						C_6H_5Br[c]	$C_6H_5CH_2Br$[c]	NO_2[d]	Br_2[d]
		2	6a	3a	4	5	8				
1a[b]	C_6H_6, A, 3 h	27		15		30		30		+	*d*
	$C_6H_5CH_3$, A, 1 h	50		15					50	+	*d*
	CH_3CN, A, 2 h		80	6							+
1a + **7**[b]	C_6H_6, A, 15 min		62	8			70				
	$C_6H_5CH_3$, A, 15 min		60	11			62				
	CH_3CN, A, 15 min		52	9			76				
1a	$C_6H_5CH_3$, B, 5 weeks		66[e]	8					50		
1a + anisole	C_6H_6, A, 1.5 h	40		21			*f*			+	

[a] A = refluxing solution, B = room temperature; for experimental details and workup procedures see Experimental Section. [b] Percentages give the maximum yield obtained in one of several thermolysis experiments. [c] Estimated by GLC in the crude reaction mixture. [d] Identified in the brown fumes in the condensor.[10,11] [e] Contaminated with some **2** (IR, see Experimental Section). [f] Thermolysis in the presence of an equimolar amount of anisole gave 50% of a 1:5 mixture of *o*- and *p*-bromoanisole.

in only 1.5 h **1a** is consumed, and the products are 4- and 2-bromoanisole; only a trace of bromobenzene could be detected. Interestingly, also some 4-nitroanisole was detected and the test for NO_2 was positive. The pyrazoles formed are **2** and **3a**, while no 1-phenyl-1*H*-pyrazoles are produced. Also noteworthy is that in contrast to thermolysis in benzene of **1a** in the absence of **7**, no bromobenzene is produced on heating benzene solutions of **1a** in the presence of either 3,5-dimethyl-1*H*-pyrazole (**7**) or anisole (see Table I).

The most noteworthy result in the latter experiment, however, is that the product is **2**, i.e., the 4-nitro-1*H*-pyrazole and not **6a**, the 5-nitro isomer which is formed on thermolysis of **1a** mixed with **7** in refluxing benzene. This finding, in addition to our results described above and depicted in Scheme I, leads to the assumption that under certain conditions intermediate **9a** rearranges to intermediate **10** by a second migration of the nitro group from position 3 to position 4 in the ring (see Scheme VI). Like **9a** intermediate **10** can be considered to be also a nitro diaza analogue of hexabromocyclopentadiene[8] and thus also can be a bromonium ion releasing intermediate. Perhaps the difference in outcome is due to a difference in the susceptibility for aromatic substitution, i.e., a difference in bromonium ion trapping capacity between anisole and pyrazole **7**. If so, the formation of the 5-nitro isomer **6a** on addition of **7**, the more efficient bromonium trapping agent of the two, then could indicate that **9a** is indeed the intermediate first formed.

Another characteristic feature of geminal bromo nitro compounds[4] is the capacity of homolytic cleavage of either a carbon–bromine bond or a carbon–nitrogen bond affording a bromine atom or NO_2 and accordingly generating bromine and NO_2. The neutral pyrazolyl radicals thus formed from **10** on thermolysis of **1a** in benzene solution may be then responsible for the formation of the 1-phenyl-1*H*-pyrazoles **4** and **5** by undergoing phenylation on nitrogen.[4] Generation of bromine atoms and pyrazolyl radicals can also explain the formation of benzyl bromide on thermolysis of **1a** in toluene (see Table I).

Undoubtedly, more detailed experimental studies are needed before the mechanisms of the reactions described in this report will be fully understood. Even so, the results presented here are complementary to our results on the thermolysis reactions of 3-bromo-1-nitro-1*H*-indazoles reported earlier[4] and extend our understanding of the reactivities characteristic for the chemistry of 1-nitro-1*H*-azoles.

Experimental Section

NMR spectra (expressed in part per million) were recorded on a JEOL PS-100. IR spectra (KBr) were recorded on a Beckman IR-10 instrument, and mass spectra were taken on a AEI Type MS-902 instrument. GLPC analyses were performed on a HP 5750 equipped with a 10-m SP 2100 capillary column using N_2 as carrier gas. Spraying with rhodamine B solution (0.05% in ethanol) was used for detection of nitropyrazoles on TLC. The purple colored spots characteristic for all nitroazoles turned into yellow colored spots on standing in the case of *N*-nitropyrazoles. Spraying with *o*-toluidine/KJ (0.05 N) (1:1) was used after chlorination for detection of 1- and 2-unsubstituted pyrazoles according to Reindel and Hoppe.[13] All melting points were uncorrected. For the separation of reaction products the short-column chromatography technique of Hunt and Rigby[12] was used on silica gel G (Merck) according to Stahl. The isolated products were identified by comparison with authentic samples. The detection of mixtures of **2** and **6a** and of **4** and **5** respectively was

(12) Hunt, B. J.; Rigby, W. *Chem. Ind.* (London) **1967**, 1868–1869.
(13) Zahn, H.; Rexroth, E. *Z. Anal. Chem.* **1955**, *148*, 181–186.

based on comparison of IR spectra with the IR spectra of authentic samples as well as of those of mixtures of authentic **2** and **6a** and of **4** and **5**.

Anisole and 3,5-dimethyl-1*H*-pyrazole (**7**) were high grade commercial products. Reference compounds 4-bromo-3,5-dimethyl-1*H*-pyrazole (**8**),[14] 3,5-dimethyl-4-nitro-1*H*-pyrazole, 3,4,5,-tribromo-1-phenyl-1*H*-pyrazole (**5**),[15] 3,5-dibromo-1*H*-pyrazole (**3b**),[16] 1-acetyl-3,4,5-tribromo-1*H*-pyrazole,[17] 4-bromo-3-nitro-1*H*-pyrazole,[18] and 1-benzyl-3,4,5-tribromo-1*H*-pyrazole[15] were prepared according to literature procedures.

3,5-Dibromo-4-nitro-1*H*-pyrazole (2): prepared according to the synthesis of **3a** from 4-nitropyrazole; pale yellow solid; mp 169 °C. Anal. Calcd for $C_3HBr_2N_3O_2$: Br, 59.00. Found: Br, 59.12. IR 3200 (s, N–H), 1540 (s, NO_2), 1480 (s), 1440 (s), 1400 (s), 1340 (s, NO_2), 1095 (w), 960 (s), 825 (s), 765 (m), 640 (m) cm^{-1}.

3,4-Dibromo-5-nitro-1*H*-pyrazole (6a): prepared according to the synthesis of **3a** from 3-nitro-1*H*-pyrazole;[19] pale yellow solid; mp 172 °C. Anal. Calcd for $C_3HBr_2N_3O_2$: Br, 59.00. Found: Br, 59.07. IR 3300 (s, N–H), 1550 (s, NO_2), 1500 (s), 1450 (m), 1400 (s), 1375 (s), 1335 (s, NO_2), 1195 (m), 1060 (s), 970 (s), 830 (s), 710 (s), 515 (m) cm^{-1}; High-resolution mass spectrum, calcd for $C_3NO^{79}Br_2$ *m/e* ($M^+ - O - N_2 - H$) 223.8348, found *m/e* 223.8346.

3-Bromo-5-nitro-1*H*-pyrazole (6b): mp 150–151 °C (40:60 ethanol–water) high-resolution mass spectrum, calcd for $C_3H_2{}^{79}BrN_3O_2$ *m/e* 190.9331, found *m/e* 190.9333; ^1H NMR (MeSO-d_6) δ 7.35 (s, 1, H-4). The structure assignment of **6b**, i.e., the assignment of the positions to the bromine and the nitro group in the ring, was based on mixed melting points and comparison of spectral data which showed that **6b** is not identical with 4-bromo-3-nitro-1*H*-pyrazole[18] and on the fact that further bromination of **6b** afforded **6a** in high yield.

3,5-Dibromo-4-nitro-1-phenyl-1*H*-pyrazole (4). Acetyl nitrate, prepared by mixing carefully 4.5 mL of nitric acid (*d* 1.53; 0.11 mol) and 19.4 mL of acetic anhydride (0.34 mol) while the temperature was kept between 20 and 30 °C, was chilled to 7 °C and dropped into a flask containing 0.5 g of 3,5-dibromo-1-phenyl-1*H*-pyrazole.[15] The resulting reaction mixture was allowed to stay overnight at room temperature. After the reaction mixture was poured onto ice the white precipitate formed was collected, dried, and put through a column (eluent, 160:120:20:1 heptane/toluene/chloroform/ethyl acetate), affording 0.48 g of crude **4**. Crystallization from toluene/petroleum ether (4:1) gave white crystals: mp 160–161 °C; ^1H NMR ($CDCl_3$) δ 7.59 (s); IR 1525, 1335 (NO_2) cm^{-1}; mass spectrum, *m/e* 347 (M^+), 317 ($M^+ - NO$), 301 ($M^+ - NO_2$), 77 ($C_6H_5^+$); high-resolution mass spectrum, calcd for $C_9H_5{}^{79}Br_2N_3O_2$ *m/e* 344.8750, found *m/e* 344.8756.

3,4,5-Tribromo-1*H*-pyrazole (3a).[20] Bromine (92 mmol) was added dropwise to a solution of 2.04 g (30 mmol) of pyrazole and 4.92 (123 mmol) of NaOH in 300 mL of water over a period of 1 h at room temperature. After being stirred for 3 h the solution was neutralized with hydrochloric acid (10%), and the precipitated white compound was collected by filtration after being washed with water. The total yield after crystallization from water/ethanol (2:1) was 6.6 g (72%): mp 188 °C (lit.[21] mp 184 °C); IR 3100 (m), 3020 (m), 2950–2700 (br, m), 1525 (w), 1350 (s), 1015 (w), 970 (s), 510 (w) cm^{-1}; mass spectrum, *m/e* 308/306/304/302 (M^+), 227/225/223 ($M^+ - Br$), 146/144 ($M^+ - 2Br$).

1-Nitro-3,4,5-tribromo-1*H*-pyrazole (1a) and **3,5-Dibromo-1-nitro-1*H*-pyrazole (1b).** Because of decomposition these compounds were freshly prepared each time and used without further purification for the thermolysis experiments. Nitric acid (0.7 mL; *d* 1.5) was added to a cooled solution (0–5 °C) of 2.0 g (6.56 mmol) of 3,4,5-tribromo-1*H*-pyrazole (**3a**) in 30 mL of glacial acetic acid. Acetic anhydride (10 mL) was added dropwise to the cooled solution during 10 min. The reaction mixture was stirred for 3 h at room temperature and poured on ice. The yellow-white precipitate was carefully washed with cold water and collected by filtration. After drying under vacuo at room temperature the yield of **1a** was 90% contaminated with a few percent of 1-acetyl-3,4,5-tribromo-1*H*-pyrazole:[17,22] mp 74 °C; IR 1740 (m, *N*-acetyl), 1635 (s, NO_2), 1480 (s), 1390 (m), 1340 (s), 1310 (m), 1260 (s, NO_2), 1130 (s), 1150 (s), 975 (s), 880 (s), 720 (w); high-resolution mass spectrum, calcd for $C_3N_3O_2{}^{79}Br_3$ *m/e* 346.7541, found *m/e* 346.7548, calcd for $C_3N_3O_2{}^{81}Br^{79}Br_2$, *m/e* 348.7523, found *m/e* 348.7529. Similarly 3,5-dibromo-1*H*-pyrazole (**3b**)[16] afforded 3,5-dibromo-1-nitro-1*H*-pyrazole (**1b**): yield, 71–83%; IR 3140 (H-4), 1610 (s, NO_2), 1255 (s, NO_2) cm^{-1}; ^1H NMr ($CDCl_3$) δ 6.64 (s, 1, H-4), δ 2.68 (s, *N*-acetyl, 2–3%).

Thermolysis of 1a in Benzene (3 h), Toluene (1 h), and Acetonitrile (2 h). A solution of 3 mmol (1.05 g) of **1a** in 20 mL of solvent was refluxed under a nitrogen atmosphere. In due time aliquots were taken to be tested on the presence of NO_2 and Br_2 and to be analyzed by TLC and GPLC. After completion of the reaction measured by TLC, the solvent was carefully removed by distillation. The products were separated by column chromatography on silica gel (G, according to Stahl)[4,12] eluting initially with chloroform/heptane/ethyl acetate (45:45:10) and after removal of the N-substituted reaction products with chloroform/ethyl acetate (3:1). Collected fractions were compared with reference materials on TLC, concentrated, and investigated further with the aid of IR, NMR, and mass spectroscopy when appropriate to the occasion. In addition GPLC on a SP2100 capillary column was used to detect the presence of brominated aromatics. Residual compounds on the column containing also C-nitro compounds were extracted with methanol. The average yield of the residue was about 10% by weight.

Thermolysis of 1a in Benzene, Toluene, and Acetonitrile in the Presence of Equimolar Amounts of 3,5-Dimethyl-1*H*-pyrazole (7; 15–30 min). A solution of 3 mmol (1.05 g) of **1a** and 3 mmol (0.29 g) of 3,5-dimethyl-1*H*-pyrazole (**7**) in 20 mL of solvent was refluxed under a nitrogen atmosphere. In due time a sample was taken to be tested on the presence of NO_2 and to be analyzed by TLC and GPLC. After completion of the reaction measured by TLC, the solvent was carefully removed by distillation. The products were separated by column chromatography on silica gel (G, according to Stahl)[4,12] eluting with chloroform/ethyl acetate (3:1). Collected fractions were compared with reference materials on TLC, concentrated, and investigated further with the aid of IR and NMR when appropriate to the occasion. No brominated products other than 4-bromo-3,5-dimethylpyrazole (**8**) were detected by GPLC or otherwise. Residual compounds on the column containing also C-nitro compounds were extracted with methanol. The average yield of the residue was about 10% by weight.

Thermolysis of 1a in Benzene in the Presence of an Equimolar Amount of Anisole. A solution of 2.5 mmol (270 mg) of anisole and 2.5 mmol (880 mg) of **1a** in 20 mL of benzene was refluxed under a nitrogen atmosphere. After 1.5 h TLC analysis showed the completion of the reaction by the absence of **1a** in the reaction mixture. The benzene was removed by distillation on a rotavap, and the products were separated by column chromatography[4,12] (45:45:10 chloroform/heptane/ethyl acetate), affording **2** (40%), **3a** (21%), and, as determined by GPLC, a 1:5 mixture of *o*- and *p*-bromoanisole (50%).

Thermolysis (1b) in Acetonitrile in the Presence of an Equimolar Amount of 3,5-Dimethyl-1*H*-pyrazole (7; 4–5 h). A solution of 2.4 mmol (0.65 g) of **1b** and 2.4 mmol (0.23 g) of **7** was refulxed for 4–5 h. The acetonitrile was removed by careful distillation and the products were separated by column chromatography[4,12] (1% acetic acid solution of 3:1 chloroform/ethyl acetate), affording **8** (75%), **6b** (83%), and **6a** (16%).

Thermolysis of 1b in Benzene in the Presence of an Equimolar Amount of 7. Under a slow stream of nitrogen a solution of 3.58 mmol (0.96 g) of **1b** and 3.58 mmol (0.35 g) of **7** in 20 mL of benzene was refluxed for 1.5 h. Careful distillation

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of benzene followed by column chromatography gave **6b** (92%) and **8** (95%).

Thermolysis of 1b in Acetonitrile (4–5 h). **1b** (0.92 mmol, 0.25 g) was refluxed in 15 mL of acetonitrile. TLC analysis revealed that the product was **6a** contaminated with **1b**. Recrystallization (3:7 methanol/water) gave **6a** (72%).

Reaction of 1a in Toluene at Room Temperature. After 5 weeks **1a** was totally converted as was measured by TLC. GPLC and mass spectroscopy showed the presence of benzyl bromide (50%). No benzyltoluene isomers were detected, but traces of benzoyl bromide were found. Collected fractions after column chromatography contained according to IR spectroscopy 3,4,5-tribromo-1*H*-pyrazole (**3a**, 8%) and 3,4-dibromo-5-nitro-1*H*-pyrazole (**6a**, 66%) contaminated with some 3,5-dibromo-4-nitro-1*H*-pyrazole (**2**). The test on the presence of NO_2 was negative, and the test on Br_2 was inconclusive. The yield of the residue was not determined.

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Appendix

Thermolysis of 4-Bromo-1-nitro-1*H*-pyrazole.[23] No decomposition was observed on refluxing in acetonitrile for 1 day. After refluxing for 5 days in acetonitrile 95% of 4-bromo-1-nitro-1*H*-pyrazole was recovered. Heating a solution of 4-bromo-1-nitro-1*H*-pyrazole mixed with an equimolar amount of **7** for 3 days followed by column chromatography also gave recovered **7** (100%) and 4-bromo-1-nitro-1*H*-pyrazole (75%) and 4-bromopyrazole (18%).

Registry No. **1a**, 104599-40-8; **1b**, 104599-41-9; **2**, 104599-36-2; **3a**, 17635-44-8; **3b**, 67460-86-0; **4**, 104599-39-5; **5**, 51039-46-4; **6a**, 104599-37-3; **6b**, 104599-38-4; **7**, 67-51-6; **8**, 3398-16-1; 3,5-dibromo-1-phenyl-1*H*-pyrazole, 51039-44-2; 4-bromo-1-nitro-1*H*-pyrazole, 7185-93-5; anisole, 100-66-3; pyrazole, 288-13-1.

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Syntheses of Derivatives of Protoporphyrin IX Bearing Deuteriated Methyls on the Propionate (C and D) Rings

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New syntheses of hemins that are regioselectively deuteriated in the 5- and 8-methyls (**14**) and the 8-methyl (**31**) are described. The 5,8-dilabeled porphyrin **3** was obtained via an acrylate porphyrin by conversion of deuteroporphyrin IX dimethyl ester (**2**) into the corresponding bis(acrylate) **5** using LDA, benzeneselenenyl bromide, and oxidative elimination. After base-catalyzed deuterium exchange, reduction of the acrylate to propionate, and vinylation, the required 5,8-dilabeled porphyrin was obtained. The 8-methyl-deuteriated compound **15** was obtained by total synthesis through a porphyrin **16** bearing an unsubstituted 7-position. By a mercuration/palladium–olefin reaction, the vacant position was substituted with an acrylate, and following base-catalyzed exchange, hydrogenation, and construction of the 2- and 4-vinyls, the required product was obtained. These compounds, as the corresponding iron complexes (hemins), are of interest in connection with heme/apoprotein reconstitution studies and for characterization of structure/function relationships in heme proteins.

Regioselectively deuteriated hemes have been critically important to recent advances in the characterization of heme protein structure/function relationships using proton NMR[1] and resonance Raman spectroscopy.[2] In our laboratory, methods have been developed for regioselective deuterium labeling of vinyls[3,4] and the 1-, 3-, 5-, and 8-methyls[5–7] in protoporphyrin IX dimethyl ester (**1**). Initial methyl deuteriation studies centered on total synthesis from deuteriated acetylacetone[5] and more recently via simple exchange processes using intact porphyrins.[7] Thus,

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