(25 mL) and washed with water (2 × 20 mL). The dried solvent was removed, and the residue was chromatographed over silica (3:1 hexane–ethyl acetate) to give, after crystallization from ethanol, **4** (0.23 g, 0.76 mmol, 70%) as yellow crystals: mp 242–245 °C dec; NMR δ 4.73–4.77 (m, 1 H), 5.45–5.48 (t, 1 H, J = 2.5 Hz), 6.50–6.52 (t, 1 H, J = 2.3 Hz), 6.84 (d, 1 H, J = 7.2 Hz), 7.74–7.84 (m, 3 H), 8.25–8.31 (m, 2 H), 12.93 (s, 1 H); MS 307 (M^+ + 1, 10.7), 306 (M^+, 47.3), 297 (46.9), 278 (67), 277 (100), 249 (13.6), 221 (9.2), 193 (7.9), 165 (28.1), 163 (13.7), 139 (16.4), 105 (8.3), 77 (10.2). Anal. Calcd for $C_{18}H_{10}O_5$: C, 70.59; H, 3.21. Found: C, 70.31; H, 3.53.

Registry No. **4**, 119998-28-6; **6**, 42185-95-5; **7**, 64517-18-6; **8**, 120022-33-5; **9**, 120022-34-6; **10**, 120022-35-7; **12** (isomer 1), 119998-26-4; **12** (isomer 2), 120056-18-0; **13** (isomer 1), 119998-27-5; **13** (isomer 2), 120056-19-1; 5-hexen-2-yn-1-ol, 2749-86-2; 13-dihydroxyanthraquinone, 518-83-2; benzeneselenol, 645-96-5.

Regiospecific Aryl Nitration of Meso-Substituted Tetraarylporphyrins: A Simple Route to Bifunctional Porphyrins

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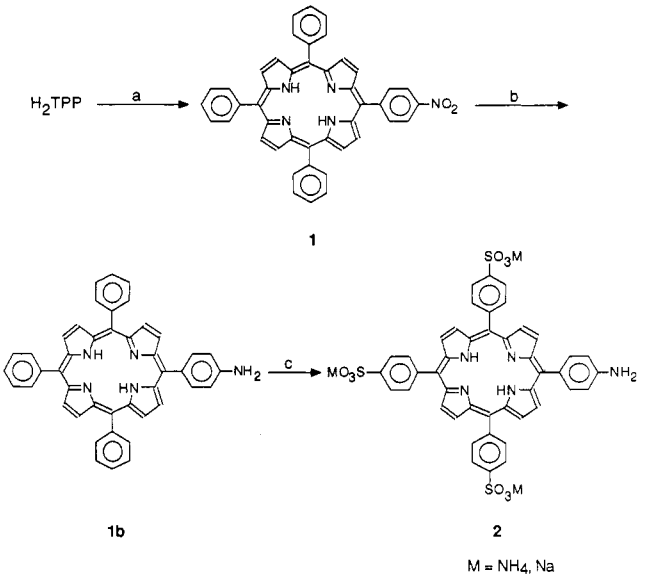
The selective localization of naturally occurring[1] and synthetic porphyrins[2] in malignant tumor tissue has been recognized for decades. Radiometalated porphyrinate derivatives have also been observed to localize in the kidney, liver, and spleen.[2c] In order to mitigate unwanted organ localization and increase tumor uptake of these derivatives, efforts have been directed at covalently attaching unsymmetrically aryl, functionalized porphyrins to tumor-selective, monoclonal antibodies.[3] The objective of this approach is to convey a stable radionuclide (metal) of diagnostic or therapeutic potential to the tumor tissue or antigen site. Unsymmetrically functionalized prophyrins have also been covalently incorporated into polymer backbones[4] as well as attached to cyclodextrins[5] and are known to serve as useful synthetic precursors to monooxygenase and allosteric enzyme model systems.[6]

All synthetic routes to unsymmetrically functionalized porphyrins such as **1a** have derived from low yield (<5%), crossed-Rothemund condensations.[3-7] Despite recent and dramatic advances in these procedures, statistical mixtures of porphyrins are obtained that are difficult and tedious to separate by preparative techniques.[8] The evolution of

Scheme I[a]

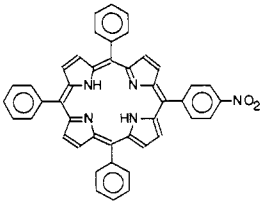


[a] (a) Fuming HNO_3 (17 equiv), $CHCl_3$, 0–5 °C (55%); (b) $SnCl_2$, concentrated HCl, 65 °C (75%); (c) concentrated H_2SO_4, 70 °C (92%).

synthetic, porphyrin enzyme mimics and radiotherapeutic agents is dependent upon access to this relatively new class of compounds.

The direct, peripheral functionalization of porphyrins using electrophiles or free radicals has been mainly restricted to modification of the macrocycle ring at either the meso or the β pyrrole carbon.[9] Electrophillic addition of sulfuric acid to the phenyl group of tetraphenylporphyrin is the only example of aryl-group modification without concomitant attack on the macrocycle ring.[10] In contrast to sulfonation, the direct nitration of metallo tetraarylporphyrinates using radical conditions has been noted to mononitrate the macrocyle at the β-position in good to excellent yields by using a variety of oxidants.[11] Both radical[12] and sulfuric acid catalyzed[13] nitrations of free-base tetraphenylporphyrin are reported to afford β and various meso substitution products. No observation of phenyl-group nitration was made in any of these studies.

In view of these limitations and our interest in developing new bifunctional chelants for our radioimmunotherapy program, we developed an attractive, alternative synthesis of mono(nitrophenyl)triphenylporphyrin (**1a**)



1a

through regiospecific aryl nitration of commercially available tetraphenylporphyrin.[14] Reduction of **1a** to the

(1) Garbo, G. M.; Kramer, J. B.; Keck, R. W.; Selman, S. H.; Kreimer-Birnbaum, M. *Anal. Biochem.* **1985**, *151*, 70.
(2) (a) Winkelman, J.; Slater, G.; Grossman, J. *Cancer Res.* **1967**, *27*, 2060. (b) Winkelman, J.; *Cancer Res.* **1961**, *22*, 589. (c) Robinson, G. D.; Alavi, A.; Vaum, R.; Staum, M. *J. Nucl. Med.* **1986**, *279*, 239.
(3) Schmidt, D.; Steffen, H. European Patent Application 127,797, 1984.
(4) (a) Hasegawa, E.; Nemoto, J.; Kangyama, T.; Tsuchida, E. *Eur. Poly. J.* **1978**, *14*, 123. (b) Tsuchida, E. *J. Macromol. Sci.* **1979**, *A13(4)*, 545.
(5) Gonzales, M. C.; Weedon, A. C. *Can. J. Chem.* **1985**, *63*, 602.
(6) (a) Takeda, J.; Ohta, S.; Hirobe, M. *Tetrahedron Lett.* **1985**, *26*, 4059. (b) Tabushi, I.; Kugimiya, S. *J. Am. Chem. Soc.* **1986**, *108*, 6926. (c) Collman, J. P.; Brauman, J. I.; Doxsee, K. M.; Halbert, T. R.; Bunnenberg, E.; Linder, R. E.; LaMar, G. N.; Del Gaudio, J.; Lang, G.; Spartalian, R. *J. Am. Chem. Soc.* **1980**, *102*, 4182.
(7) (a) Little, R. G.; Anton, J. A.; Loach, P. A.; Ibers, J. A. *J. Heterocycl. Chem.* **1975**, *12*, 343. (b) Hashimoto, Y.; Lee, C. S.; Shudo, K.; Okamoto, T. *Tetrahedron Lett.* **1983**, *24*, 1523.
(8) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C. *J. Org. Chem.* **1987**, *52*, 827.
(9) Fuhrhop, J. H. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 2, pp 131–133.
(10) (a) Busby, C. A.; Dinello, R. K.; Dolphin, D. *Can. J. Chem.* **1975**, *53*, 1554. (b) Srivastava, T. S.; Tsutui, T. *J. Org. Chem.* **1973**, *38*, 2103.
(11) (a) Baldwin, J. E.; Crossley, M. J.; Bernardis, J. *Tetrahedron* **1982**, *38*, 685. (b) Catallano, M. M.; Crossley, M. J.; Harding, M. M.; King, L. G. *J. Chem. Soc., Chem. Commun.* **1984**, 1535.
(12) Evans, B.; Smith, K. M.; Calvaleiro, J. A. S. *J. Chem. Soc. Perkin Trans. 1* **1978**, 768.
(13) Johnson, A. W.; Winter, M. *Chem. Ind.* (London) **1975**, 351.

0022-3263/89/1954-2753$01.50/0

Table I. Stepwise Aryl Nitration of Tetraarylporphyrins

porphyrin[a]	solvent	equiv of fuming HNO_3[b]	% yield[c] mono	bis	tris
H_2TPP	$CHCl_3$	17r	**1a**, 55	**3**, 5	**4a**, 0
H_2TPP	$CHCl_3$	20r	**1a**, 56	**3**, 7	
H_2TPP	CH_2Cl_2	20r	**1a**, 46		
H_2TPP	$CHCl_3$	19y	**1a**, 54		
H_2TPP	$CHCl_3$	29r	**1a**, 0	**3**, 28	**4a**, 7
H_2TPP	$CHCl_3$	35r	**1a**, 0	**3**, 2	**4a**, 2
H_2TPP	HOAc	291r			**4b**, 10[d]
p-$H_2T(CH_3)PP$	$CHCl_3$	17r	0		
m-$H_2T(CH_3)PP$	$CHCl_3$	31y	**5a**, 83	**5b**, 9	
m-$H_2T(CH_3)PP$	$CHCl_3$	40y	**5a**, 0	**5b**, 75	
m-$H_2T(OCH_3)PP$	$CHCl_3$	25y	**6a:b**,[e] 55		

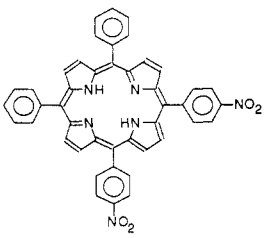
[a] Abbreviations: H_2TPP, 5,10,15,20-tetraphenylporphyrin; p-H_2TPP, 5,10,15,20-tetrakis(4-methylphenyl)porphyrin; m-$H_2T(CH_3)PP$, 5,10,15,20-tetrakis(3-methylphenyl)porphyrin; m-$H_2T(OCH_3)PP$, 5,10,15,20-tetrakis(3-methoxyphenyl)porphyrin. [b] r = red fuming nitric acid (d = 1.6); y = yellow fuming nitric acid (d = 1.5); T = 0–3 °C. [c] Percent isolated yield after silica gel chromatography. [d] Isolated yield after tin chloride reduction of **4a** to **4b**. [e] **6a:6b** = 2:1 by ^1H NMR integration.

known amino derivative **1b**[4] followed by exhaustive sulfonation to afford water-soluble porphyrin **2** allows access to polymer or antibody conjugatable porphyrins (Scheme I).

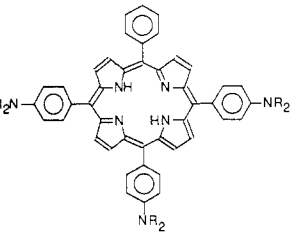
When chloroform or methylene chloride solutions of tetraphenylporphyrin (H_2TPP) were treated with excess fuming nitric acid, selective and stepwise nitration of the aryl groups at the para position was found to occur. Thus, mononitroporphyrin **1a** was obtained in good yield (Table I) as analytically pure and *chlorin-free* material after silica gel chromatography. This compound was identical with that produced via the cross-condensation route of Hasegawa and co-workers.[4] The procedure has been successfully applied with comparable results over a wide range of reaction scales (0.2–10.0 mmol) and appears to be applicable to other tetraaryl-substituted porphyrins that are not substituted at the para position.[15] Substituents at the meta position (R = OMe, CH_3) of the aromatic ring did not alter the regioselectivity or stepwise nature of the nitration.

Fuming nitric acid of two different densities (1.5 and 1.6 g mL^{-1}) was examined in the nitration of tetraphenylporphyrin, and no differences were noted in required stoichiometry to achieve mononitration. There were noticeable differences in nitration rate and nitric acid required as a function of substituent on the aromatic ring. In practice, porphyrins bearing different aromatic substituents were nitrated selectively by closely monitoring the reaction progress by TLC or HPLC during the addition. By way of note, the addition of sulfuric acid as a catalyst for the nitration of tetraphenylporphyrin led to the formation of other unidentified products as reported.[13]

Chloroform was found to be preferable to methylene chloride as a solvent for nitration and provided higher selectivity for monoaddition at complete conversion of tetraphenylporphyrin. In chloroform, the amount of dinitroporphyrins **3**, which were isolated as the only other tractible product, accompanying **1a** rarely exceeded 5% at total conversion of tetraphenylporphyrin. This "stepwise" nitration was less pronounced in further attempting to convert mononitro **1a** to dinitro **3**. In this respect, an appreciable amount of sparingly soluble trinitroporphyrin **4** was produced at total conversion of **1a**. At larger excesses of nitrating agent, none of the anticipated tetrakis(p-nitrophenyl)porphyrin[16] was produced, and macrocycle degradation was evident.



3

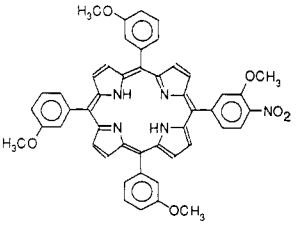


4a R = O

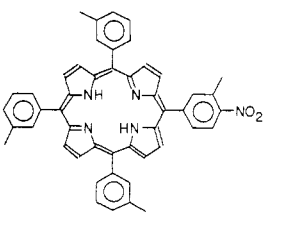
4b R = H

The use of acetic acid as a solvent proved to be of advantage in producing tractible amounts of **4b** (isolated in 10% overall yield upon reduction of **4a** with tin chloride). Although this medium has proven successful for the mono, meso nitration of octaethylporphyrin,[17] there was no indication of stepwise control in the attempted mononitration of tetraphenylporphyrin. Nitration of this compound was not observed to occur without the addition of a considerable excess (greater than 100 equiv) of fuming nitric acid with acetic acid as solvent, and then, only trinitroporphyrin **4a** was observed.

The effect of phenyl substituents on the course of nitration was examined in the case of **5a** and **6a**. Although the mononitro derivative **6a** was formed in high yield, a substantial amount of **6b** (3-methoxy-6-nitro) isomer was formed in the process. This positional variation in the mononitration was not observed in any of the other substrates examined and may be due to the strong ortho–para directive effects of the methoxy group.



5a



6a

Examination of the pyrrolic and aromatic resonances in the 300-Mz ^1H NMR spectra for dinitro derivatives **3** and **5b** revealed a 2–3:1 ratio of cis:trans products, which could not be separated preparatively. This statistical distribution was expected and was not studied in any detail.

Tin chloride reduction of **1a** in concentrated hydrochloric acid provided the known amino derivative **1b** in 74% yield after chromatography. Treatment of **1b** with concentrated sulfuric acid afforded the sparingly water-soluble sulfate salt of the dication of **2** in quantitative yield as a green glass. This material was converted to the trisammonium salt with aqueous ammonium hydroxide and rendered free of ammonium sulfate by chromatography on Sephadex G-10.

In summary, the direct aryl nitration of tetraarylporphyrins was found to be controllable (stepwise) and highly regiospecific. This approach has provided convenient synthetic access to either lipophillic or hydrophillic porphyrins, which can be covalently incorporated into bioactive macromolecules or attached to synthetic, enzymic

(14) Kruper, W. J.; Chamberlin, T. A. U.S. Patent 4,746,735, 1987.
(15) Attempted nitration of *meso*-tetra-p-tolylporphyrin resulted in formation of intractible tars.
(16) Thomas, D. W.; Martell, A. E. *J. Am. Chem. Soc.* **1956**, *78*, 1335.
(17) Buchler, J. W. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 131–133.

cofactors in a variety of ways through the aryl amine.[3,4,6,18] Efforts are currently under way to explore alternatives to the arylamine functionality available through diazonium chemistry.

Experimental Section

Mass spectra were obtained by D. Zakett (Michigan Division Analytical Labs of The Dow Chemical Co.) on either a Finnigan TSQ mass spectrometer (Q1 MS mode) or a VG ZAB-HS high-resolution mass spectrometer (FAB with xenon). ^1H and ^{13}C NMR spectra were obtained using a Varian VXR-300 spectrometer. Visible spectra were taken on a Perkin-Elmer/Hitachi 330 spectrophotometer, and infrared spectra were recorded with a Nicolet S5X FT/IR instrument.

Analytical HPLC analyses were conducted at 410 mm monitor (Spectra-Physics SP 8400 XR detector) using a Spectra-Physics SP 8700 LC pump and an SP 4200 computing integrator. Nitroporphyrins were assayed by HPLC with a DuPont, Zorbax-CN (4.6 × 250 mm) column with a flow rate of 2.0 mL/min with a mobile phase of methanol–acetonitrile–2% aqueous phosphoric acid with a gradient program: 50:50 A:B to 40:40:20 A:B:C in 10 min, 10 min at 40:40:20.

Free-base porphyrins used in this study were obtained from Mid-Century Coordination Chemicals, Inc., and contained 1–3% chlorin. All solvents employed were Fisher HPLC grade materials, which were used without further purification unless otherwise noted. All reactions were conducted under a dry nitrogen or argon atmosphere unless otherwise noted. All analytical samples were recrystallized after column chromatography and dried at 100–120 °C (1×10^{-5} mm) unless otherwise stated. Combustion analyses were performed by S. Knopnicki (Michigan Division Analytical Labs of the Dow Chemical Co.).

5-(4-Nitrophenyl)-10,15,20-triphenylporphyrin (1a) from Direct Nitration of Tetraphenylporphyrin. Tetraphenylporphyrin (2.0 g, 3.25 mmol Midcentury Coordination Chemicals, Posen, IL) was dissolved in 300 mL of pentene-stabilized chloroform under nitrogen. Red fuming nitric acid (3.4 g, 54 mmol, Baker reagent grade/sp gr = 1.6) was added to the stirred solution of porphyrin at 0–5 °C through a pressure-equalizing dropping funnel over a 2-h period. The reaction was monitored at intervals by TLC to insure total conversion of starting material (R_f = 0.88) to product (R_f = 0.78) by using chloroform/silica plates (Analtech). The dark green solution was extracted with 5 × 300-mL portions of water and dried over magnesium sulfate, sodium carbonate. The solution was concentrated to 70 mL and was applied to a silica column (18 in. × 2 in. Aldrich 62 grade 60–200 mesh) and eluted with chloroform. Fractions containing only the mononitro derivative **1a** were combined, giving mono(nitrophenyl)triphenylporphyrin in 55% yield (1.20 g, 18.1 mmol): IR ($CHCl_3$, cm^{-1}) 1597, 1521 (ν asym NO_2), 1474, 1348 (ν sym NO_2), 966; ^1H NMR ($CDCl_3$) δ 8.86 (d, 2 H, J = 5.0 Hz, β-pyrrole), 8.85 (s, 4 H, β-pyrrole), 8.69 (d, 2 H, J = 5.0 Hz, β-pyrrole), 8.54 (d, 2 H, J = 8.9 Hz, nitrophenyl), 8.31 (d, 2 H, J = 8.9 Hz, nitrophenyl), 8.19 (m, 6 H, ortho phenyl), 7.71 (m, 9 H, meta/para phenyls), −2.74 (s, 2 H, pyrrole NH); ^{13}C NMR ($CDCl_3$) δ 149.2, 147.8, 141.9, 135.1, 134.5, 131.7, 131.4, 131.3, 131.2, 130.1, 127.9, 126.8, 121.7, 121.1, 120.7, 116.6; MS (70 eV, EI) m/e (relative intensity) 659 (100% parent), 613 (14), 535 (2.5), 330 (26), 306 (21); vis (λ_{max} CH_2Cl_2 (log ϵ) 418 (5.88), 515 (4.31), 550 (3.97), 592 (3.77), 646 (3.63). Anal. Calcd for $C_{44}H_{29}N_5O_2$: C, 80.90; H, 4.32; N, 10.61. Found: C, 79.8; H, 4.46; N, 10.56.

5-(4-Aminophenyl)-10,15,20-triphenylporphyrin (1b) from Reduction of 1a. The reduction of (nitrophenyl)triphenylporphyrin was conducted according to a modification of Hasegawa's procedure.[4] (Nitrophenyl)triphenylporphyrin (2.50 g, 3.79 mmol) was dissolved in 80 mL of concentrated hydrochloric acid under nitrogen. Tin(II) chloride dihydrate (2.6 g, 11.5 mmol) was added to the solution, and the reaction was heated to 65 °C for 1 h. The porphyrin solution was cooled and added to 300 mL of cold water and was adjusted to pH 8 with concentrated ammonium hydroxide. The aqueous phase was extracted with 6 × 300-mL portions of chloroform, which were combined and dried over magnesium sulfate. The organic phase was concentrated on a rotary evaporator to 100 mL, and this solution was chromatographed through a 14 in. × 1 in. silica column (Adrich 62 grade) with methylene chloride as an eluent. The first and only band eluting from the column was the desired (aminophenyl)triphenylporphyrin (1.75 g, 2.79 mmol), which was obtained in 74% yield as analytically pure material (vacuum dried 10^{-5} mm/100 °C), R_f = 0.46 in methylene chloride/R_f = 0.23 in chloroform/$R_{f\,lit.}$ = 0.47 in chloroform:[4] ^1H NMR ($CDCl_3$) δ 8.95 (d, 2 H, J = 5.0 Hz, β-pyrrole), 8.84 (d, 2 H, J = 5.0 Hz, β-pyrrole), 8.83 (s, 2 H, β-pyrrole), 8.22 (m, 6 H, ortho triphenyl), 8.00 (d, 2 H, J = 8.2 Hz, 4-aminophenyl), 7.76 (m, 9 H, meta/para triphenyl), 7.06 (d, 2 H, J = 8.3 Hz, 4-aminophenyl), 4.02 (s, 2 H, amino), −2.73 (s, 2 H pyrrole NH); MS (70 eV, m/e 629, (5% parent), 212 (0.5), 207 (45), 149 (100). Anal. Calcd for $C_{44}H_{31}N_5$: C, 83.9; H, 4.93; N, 11.12. Found: C, 84.13; H, 4.86; N, 11.20.

5-(4-Aminophenyl)-10,15-20-tris(4-sulfonatophenyl)-porphyrin, Trisodium Salt (2a) and Trisammonium Salt (2b). (Aminophenyl)triphenylporphyrin **1b** (900 mg, 1.43 mmol) was dissolved in 40 mL of sulfuric acid (Baker 98% reagent grade) and heated with stirring to 70 °C for 2 days. The dark green solution was stirred under nitrogen for 3 more days at 25 °C and then poured into 200 mL of cold water with stirring. The dark green suspension was filtered through a medium-porosity frit and washed with 4 × 200-mL portions of deionized water. The clear eluent was tested with barium chloride to determine the absence of sulfate (turbidity), and the pH was 3.4. The green-brown porphyrinate was vacuum dried in the frit to give a 92% yield (1.16 g, 1.33 mmol) of free-base zwitterion. This material was only slightly soluble in water or DMSO, and satisfactory NMR spectra could not be obtained: ^1H NMR (DMSO-d_6 as the trisodium salt) δ 9.04 (d, 24, J = 5.1, 3 H, β-pyrrole), 8.89 (s, 4 H, β-pyrrole), 8.88 (d, 2 H, J = 5.1 Hz, β-pyrrole), 8.26 (d, 6 H, J = 8.2 Hz, 4-sulfonatophenyl), 8.14 (d, 6 H, J = 8.1 Hz, 4-sulfonatophenyl), 7.934 (d, 2 H, J = 8.4 Hz, 4-aminophenyl), 7.09 (d, 2 H, J = 8.4 Hz, 4-aminophenyl) 5.62 (s, 2 H, amino NH_2), −2.83 (s, 2 H, pyrrole NH).

The green-brown solid porphyrinate was converted to the ammonium salt **2b** by dissolution in excess concentrated ammonium hydroxide. Evaporation of solvent and high-vacuum drying of the resultant solid (50 °C, 10^{-5} mm) quantitatively provided the trisammonium salt **2b** as a lustrous purple glass. An analytical sample was provided upon passage of an aqueous solution of this material through Sephadex G-10 (75 mg of **2b** on a 0.5 in. × 20 in. column) size exclusion gel: ^1H NMR (DMSO-d_6) δ 8.93 (d, 2 H, J = 5.4 Hz, β-pyrrole), 8.84 (s, 4 H, β-pyrrole), 8.82 (d, 2 H, J = 5.4 Hz, β-pyrrole), 8.18 (d, 6 H, J = 7.8 Hz, 4-sulfonatophenyl), 8.06 (d, 6 H, J = 7.8 Hz, 4-sulfonatophenyl), 7.99 (d, 2 H, J = 8.2 Hz, 4-aminophenyl), 7.33 (s, 4 H, ammonium), 7.21 (d, 2 H, J = 8.2 Hz, 4-aminophenyl), 7.15 (s, 4 H, ammonium), 6.98 (s, 4 H, ammonium), 3.61 (broad s, 2 H, aniline NH_2), −2.84 (broad s, 2 H, pyrrole NH), signals at δ 7.33, 7.15, and 6.98 disappeared (exchanged) upon addition of one drop of D_2O; ^{13}C NMR (DMSO-d_6) δ 147.3, 141.44, 141.36, 135.4, 133.6, 131.2 (broad), 130.2 (broad), 124.1, 121.5, 119.3, 118.9, 113.9; MS (FAB, glycerol/KOH matrix, m/e (relative intensity)) 944 (100, (M − 34 + 2K); vis (λ_{max} in 0.1 M aqueous ammonium carbonate (log ϵ)) 415 (5.47), 529 (4.09), 562 (4.00), 643 (3.61). Anal. Calcd for $C_{44}H_{40}N_8O_9S_3{\cdot}3H_2O$: C, 54.2; H, 4.76; N, 11.50. Found: C, 53.76; H, 4.44; N, 10.80.

5,10-Bis(4-nitrophenyl)-15,20-diphenylporphyrin 3 from Tetraphenylporphyrin. Tetraphenylporphyrin (500 mg, 0.813 mmol) was dissolved in 75 mL of chloroform, and red fuming nitric acid (1.5 g, 23.8 mmol) was added dropwise with stirring (0–5 °C) until TLC analysis showed total conversion of mono derivative (approximately 2 h). Chromatography of the crude porphyrinic fraction on a 1 in. × 14 in. silica column provided **3** (160 mg, 0.227 mmol) as a dark purple powder (R_f = 0.41 *trans*-dinitro **3** in chloroform (R_f = 0.44 *cis*-dinitro **3** as the major product) in 28% isolated yield: ^1H NMR ($CDCl_3$) δ 8.89 (d, 2 H, J = 5.1 Hz, β-pyrrole), 8.86 (s, 2 H, β-pyrrole), 8.75 (s, 2 H, β-pyrrole), 8.72 (d, 2 H, J = 5.1 Hz, β-pyrrole), 8.59 (d, 4 H, J = 7.4 Hz, nitrophenyl), 8.34 (d, 4 H, J = 7.4 Hz, nitrophenyl), 8.19 (m, 4 H, ortho phenyls), 7.75 (m, 6 H, meta/para phenyls), −2.77 (s, 2 H, pyrrole

(18) (a) Meares, C. F.; McCall, M. J.; Reardon, D. T.; Goodwin, D. A.; Diamanti, C. I.; McTigue, M. *Anal. Biochem.* **1984**, *142*, 68. (b) Brechbeil, M. W.; Gansow, O. A.; Atcher, R. W.; Schlom, J.; Esteban, J.; Simpson, D. E.; Colcher, D. *Inorg. Chem.* **1986**, *25*, 2772.

NH); MS (EI, m/e (relative intensity)) 705 (40, M + 1), 704 (100, M^+), 659 (8, M - NO_2^+), 612 (3, M - $2NO_2^+$), 352 (10, M^{2+} doubly charged); vis (λ_{max} in methylene chloride (log ϵ)) 420 (5.50), 516 (4.30), 551 (3.97), 5.92 (3.82), 646 (3.61). Anal. Calcd for $C_{44}H_{28}N_6O_4$: C, 74.99; H, 4.00; N, 11.92. Found: C, 74.66; H, 4.08; N, 11.30.

5-(4-Nitrophenyl)-10,15,20-tris(3-methylphenyl)porphyrin (5a). A stirred solution of 5,10,15,20-tetrakis(3-methylphenyl)-porphyrin (500 mg, 0.745 mmol) in 75 mL of chloroform was treated dropwise with yellow fuming nitric acid (1.60 g, 22.8 mmol, d = 1.50) over a 1.75-h period at 0-3 °C. The reaction medium was monitored by TLC, and when conversion of starting material (R_f = 0.83 in chloroform) to mononitro **5a** (R_f = 0.75) was noted, the medium was quenched with water and extracted as usual. Chromatography was conducted on a 2 in. × 18 in. silica column with chloroform as an eluent and afforded **5** (440 mg, 0.615 mmol) in 83% yield. An analytical sample was recrystallized by diffusion of hexane into a benzene solution of **5a**: IR ($CHCl_3$, cm^{-1}) 1603, 1518 (ν asymm NO_2), 1346 (ν symm NO_2), 805; ^1H NMR ($CDCl_3$) δ 8.90 (d, 2 H, J = 4.8 Hz, β-pyrrole), 8.87 (s, 4 H, β-pyrrole), 8.36 (d, 1 H), 8.21 (m, 2 H), 8.02 (m, 6 H), 7.61 (m, 6 H), 2.89 (s, 3 H), 2.64 (s, 9 H), -2.8 (s, 2 H, pyrrole NH); ^{13}C NMR ($CDCl_3$) δ 147.6, 141.9, 138.9, 136.2, 136.1, 135.5, 132.8, 131.9, 131.4, 129.6, 126.5, 123.1, 121.1, 120.7, 116.6, 21.7, 20.4; MS (EI, m/e (relative intensity)) 715 (100, M^+), 669 (8, M - NO_2^+), 358 (95, M^{2+} doubly charged). Anal. Calcd for $C_{48}H_{37}N_5O_2$: C, 80.54; H, 5.21; N, 9.78. Found: C, 80.21; H, 4.95; N, 10.20.

5,10-Bis(3-methyl-4-nitrophenyl)-15,20-bis(3-methylphenyl)porphyrin (5b). A second fraction (R_f = 0.63 *cis*-bis-**5b**:R_f = 0.68 *trans*-bis-**5b** in 3:1 ratio) was isolated from the chromatographic separation of **5a** in 9% yield (50 mg, 0.066 mmol): IR ($CDCl_3$, cm^{-1}) 3308, 1603, 1571, 1520 (ν sym NO_2), 1347 (ν asym NO_2), 853 (ν C-NO_2); ^1H NMR ($CDCl_3$) δ 8.91 (d, 2 H, J = 4.8 Hz), 8.88 (s, 2 H), 8.80 (s, 2 H), 8.76 (d, 2 H, J = 4.8 Hz), 8.34 (d, 2 H), 8.17 (m, 4 H), 8.01 (m, 4 H), 7.60 (m, 4 H), 2.88 (s, 6 H), 2.63 (s, 6 H), -2.79 (s, 2 H, NH pyrrole); ^{13}C NMR ($CDCl_3$) δ 151.9, 150.2, 144.6, 141.6, 139.2, 138.4, 135.7, 135.0, 134.9, 131.6, 129.6 126.0, 124.6, 120.1, 23.6, 23.6; MS (70 eV, EI) m/e (relative intensity) 760 (100, M^+), 715 (8, M - NO_2^+), 380 (79, M^{2+} doubly charged). An analytical sample was recrystallized by slow diffusion of hexane into a benzene solution of **5b**. Anal. Calcd for $C_{48}H_{36}N_6O_4$: C, 75.76; H, 4.77; N, 11.05. Found: C, 75.43; H, 4.30; N, 11.27.

5-(3-Methoxy-4-nitrophenyl)-10,15,20-tris(3-methoxyphenyl)porphyrin (6a). Yellow fuming nitric acid (1.21 g, 17.2 mmol) was added to a solution of *meso*-tetrakis(3-methoxyphenyl)porphyrin (500 mg, 0.745 mmol) in 75 mL of chloroform (0-3 °C). After the usual quench and workup procedure, the crude free base was applied to a 2 in. × 17 in. silica column and eluted with chloroform and then a 1:1 solution of chloroform in methylene chloride. An inseparable mixture of **6a** and its positional isomer (3-methoxy-6-nitrophenyl) **6b** was afforded in 55% yield (290 mg, 0.372 mmol, R_f = 0.32 for **6a**, **6b**; R_f = 0.45 for starting material in chloroform): IR ($CDCl_3$, cm^{-1}) 3320, 1600, 1520 (ν asym NO_2), 1352 (ν sym NO_2), 850 (ν C-NO_2); ^1H NMR ($CDCl_3$) δ 8.94 (d, 2 H, J = 4.8 Hz), 8.91 (s, 4 H), 8.80 (d, 2 H, J = 4.8 Hz) (d, 1 H, J = 14.3 Hz), 7.95 (d, 1 H, J = 1.5 Hz), 7.86 (dd, 1 H, J = 14.3, 1.5 Hz), 7.78 (m, 6 H), 7.60 (m, 3 H), 7.30 (m, 3 H), 4.02 (s, 3 H), 3.95 (s, H), -2.79 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 158.0, 151.2, 148.8, 143.2, 131.5, 127.6, 127.5, 126.6, 124.0, 120.7, 120.6, 120.5, 120.4, 120.1, 113.6, 113.5; MS (70 eV, EI) m/e (relative intensity) 779 (80, M^+), 734 (12, M - NO_2^+), 390 (100, M^{2+} doubly charged), 367 (32, M - NO_2^{2+} doubly charged). A closer inspection of the high field ^1H NMR spectrum revealed a 2:1 ratio of **6a**:**6b**. The following specific resonances were associated with **6b**: δ 8.65 (d, J = 4.8 Hz), 8.36 (d, J = 12.0 Hz), 7.66 (d, J = 1.8 Hz), 7.22 (d, J = 12.0 Hz), 3.87 (s), -2.70 (s). Anal. Calcd for $C_{48}H_{37}N_5O_6$: C, 73.91; H, 4.79; N, 8.98. Found: C, 73.5; H, 5.03; N, 9.10.

Registry No. **1a**, 67605-65-6; **1b**, 67605-64-5; **2a** (M = Na^+), 39050-26-5; **2b** (M = NH_4^+), 68438-24-4; *trans*-**3**, 79109-32-3; *cis*-**3**, 79109-31-2; **4a**, 116430-09-2; **4b**, 116206-77-0; **5a**, 119695-92-0; *cis*-**5b**, 119720-85-3; *trans*-**5b**, 119720-86-4; **6a**, 119695-93-1; **6b**, 119695-94-2; *meso*-tetraphenylporphyrin, 917-23-7; *meso*-tetrakis(3-methoxyphenyl)porphyrin, 29114-93-0; 5,10,15,20-tetrakis(3-methylphenyl)porphyrin, 50849-45-1.

A New Reaction of 1-Bromo-2-(chloromethyl)cyclopropane in Basic Medium: A Simple Preparation of 1-(Alkoxymethylene)cyclopropanes[1]

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A study of the recent literature reveals a still growing interest in chemical transformations of 1-halo- or 1,1-dihalo-2-(halomethyl)cyclopropanes. Thus the compounds **1a** or **1** (X = Y = Br; Z = Cl) treated with magnesium, sodium, or lithium alkyls afforded bicyclobutanes **2** (Y = H)[2-4] or **2** (Y = Br),[5-7] respectively. A derivative of **1** (X = Y = Br; Z = Cl; R^1 = CH_2Cl) served as a convenient source of the strained [1.1.1]propellane (**3**), which was formed via **2**.[8] The compounds **2** and **3** were usually accompanied by variable amounts of other products. Compounds **1** (X = Y = Br; Z = Cl, OMs) underwent $Ni(CO)_4$-induced ring-opening carbonylation reactions with alcohols and amines leading to derivatives of γ,δ-unsaturated carboxylic acids **4**.[9]

On the other hand, the chain bromine atom in the *gem*-dichloro derivative of **1** (X = Y = Cl; Z = Br) was easily substituted by nucleophiles affording **5**.[10] We have found[11] the reactivity pattern of the above mentioned compound **1** to be strongly influenced by the nature of nucleophilic reagent and reaction conditions, leading to the formation of **5** and/or its mixture with methylenecyclopropane derivatives **6a,b** (Scheme I). It has been proved that **6** is produced via a series of elimination-addition reactions.

On the basis of our own results[11] and literature data[12] we expected that the reaction of **1a** with nucleophiles would afford either 1-substituted methylenecyclopropanes and/or chain substituted products.

Indeed we have found that simple stirring of **1a** with an excess of alcohols **7a-f**, in the presence of powdered sodium hydroxide and triethylbenzylammonium chloride (TEBACl) as a catalyst, in DMSO, at ambient temperature during the time indicated in Table I, gives rise to the expected 1-(alkoxymethylene)cyclopropanes **8a-f**, usually in high yields. Alcohols of different structure including aliphatic, alicyclic, as well as substituted by an aryl or heterocyclic group entered this reaction (table). On the other hand, phenols **7g-i**, thiophenol (**7j**), and nitriles **7k,l** gave the chain-substituted products **9g-l**. In these cases the formation of methylenecyclopropane derivatives **8** was not observed (by ^1H NMR spectra of the crude reaction

(1) Paper 159 in the series Reactions of Organic Anions. For Part 158, see: Wojciechowski, K.; Makosza, M. *Synthesis*, submitted.
(2) Abramova, N. M.; Zotova, S. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 697.
(3) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.
(4) D'yachenko, A. I.; Abramova, N. M.; Zotova, S. V.; Nesmeyanova, O. A.; Bragin, O. W. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1985**, 2043.
(5) Nilsen, N. O.; Skattebøl, L.; Baird, M. S.; Buxton, S. R.; Slowey, P. D. *Tetrahedron Lett.* **1984**, *25*, 2887.
(6) Düker, A.; Szeimies, G. *Tetrahedron Lett.* **1985**, *26*, 3555.
(7) Wiberg, K. B.; McClusky, J. V. *Tetrahedron Lett.* **1987**, *28*, 5411.
(8) Semmler, K.; Szeimies, G.; Belzner, J. *J. Am. Chem. Soc.* **1985**, *107*, 6410.
(9) Hirao, T.; Nagata, S.; Agawa, T. *Tetrahedron Lett.* **1985**, *26*, 5795.
(10) Steinbeck, K. *Liebigs Ann. Chem.* **1979**, 920.
(11) Jończyk, A.; Dabrowski, M.; Woźniak, W. *Tetrahedron Lett.* **1983**, *24*, 1065.
(12) Billups, W. E.; Blakeney, A. J.; Rao, N. A.; Buynak, J. D. *Tetrahedron* **1981**, *37*, 3215.
(13) Jończyk, A.; Serafin, B.; Makosza, M. *Roczniki Chem.* **1971**, *45*, 1027.

0022-3263/89/1954-2756$01.50/0