white solid. Recrystallization from ethanol gave the pyrazoles **9** as white solids (see Table IV).

1-Phenyl-6-hydroxy-1,3-hexanedione *p*-Toluenesulfonate (6). *p*-Toluenesulfonyl chloride (2.10 g, 5.50 mmol) was added to hydroxydione **1c** (1.03 g, 5.00 mmol) in 10 mL of cold pyridine. The resulting solution was allowed to stand for 16 h at 0 °C. The reaction mixture was poured into 100 mL of ice water. The product was extracted with methylene chloride (2 × 30 mL). The combined methylene chloride extracts were washed with cold 10% hydrochloric acid (50 mL) and saturated sodium bicarbonate, dried over sodium sulfate, and concentrated. The crude crystalline product was recrystallized twice from 4:1 (v/v) hexane/ether to give 1.13 g (63%) of tosylate **6**: mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 4 H), 7.37 (m, 5 H), 6.10 (s, 1 H), 4.10 (t, 2 H, J = 6 Hz), 2.52 (t, 2 H, J = 6 Hz), 2.38 (s, 3 H), 2.03 (quin, 2 H, J = 6 Hz); IR (KBr) 3350, 1600, 1570, 1350, 925 cm^{-1}; MS m/e 360.

Anal. Calcd for $C_{19}H_{20}O_5S$: C, 63.3; H, 5.6; S, 8.9. Found: C, 63.2; H, 5.8; S, 9.1.

Registry No.—**1a,** 57245-94-0; **1b,** 69706-62-3; **1c,** 23894-54-4; **1d,** 69745-21-7; **4a,** 69706-63-4; **4b,** 69706-64-5; **4c,** 69706-65-6; **4d,** 69706-66-7; **6,** 69706-67-8; **7a,** 69766-11-6; **7b,** 69706-68-9; **7c,** 69706-69-0; **7d,** 69706-70-3; **8a,** 69706-71-4; **8b,** 69706-72-5; **8c,** 69706-73-6; **9a,** 69706-74-7; **9b,** 69745-22-8; CH_3COCH_3, 67-64-1; $CH_3COCH_2CH_3$, 78-93-3; $CH_3COC_6H_5$, 98-86-2; *p*-$CH_3C_6H_4COCH_3$, 122-00-9; 4-butyrolactone, 96-48-0; ethylenediamine, 107-15-3; benzylamine, 100-46-9; hydrazine, 302-01-2.

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General Synthesis of Hydrocarbon-Soluble Porphyrins

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1,3,5,7-Tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (**2**) and 2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (**3**) were synthesized in good yield by a general route from benzyl 3-formyl-2,4-dimethylpyrrole-5-carboxylate (**4**); the final porphyrin cyclization was brought about by self-condensation of the appropriate pyrromethene salt in hot formic acid. Porphyrins **2** and **3** were shown to be approximately 14 times more soluble in toluene than is etioporphyrin I [2,4,6,8-tetraethyl-1,3,5,7-tetramethylporphyrin (**20**)] and to have considerably lower melting points [**2,** 199 °C; **3,** 124 °C; **20,** >300 °C]. Activation of the porphyrins **2** and **3** for future attachment of thiolate and imidazole-bearing substituents at the meso (methine) positions was carried out by Vilsmeier formylation [of the copper(II) complex], reduction with sodium borohydride, and then treatment of the resulting hydroxymethylporphyrins with acetic anhydride in pyridine to give the electrophilic acetoxymethylporphyrin derivatives.

In connection with synthetic approaches to cytochrome P450[1] and T-form hemoglobin[2] models bearing covalently appended apical ligands, we required porphyrin substrates which, as the hemes, would be soluble in solvents such as benzene or toluene. Moreover, for the cytochrome model, we desired that the complex should have a low oxidation potential and therefore that the target molecule should not only have eight electron-releasing peripheral substituents but also that the attached long-chain apical ligand should be joined to the porphyrin via an electron-releasing meso (methine) functionality. Our requirements seemed satisfied by the generic porphyrin **1** in which R^1 would be a long alkyl side chain and R^2 the thiolate or imidazole-bearing substituent, joined directly to the porphyrin by way of a sp^3-hybridized carbon atom. One other point of strategy was apparent; since, for simplicity, we planned to attach the meso substituent after porphyrin formation, we had to choose the "type I"[3] substituent orientation so that only one meso-substituted product would arise at that time. In this paper, we describe successful and efficient general syntheses of two such porphyrins (**2** and **3**) and report on their comparative solubility characteristics in toluene and on developmental work on elaboration of the meso (R^2 in **1**) substituent.

Results and Discussion

In order to afford maximum variability with respect to the alkyl side chains (R^1 in **1**), we chose to synthesize our lipophilic porphyrin substrates using the 3-formylpyrrole **4** as the key building block. We reasoned that Wittig-type reactions of the formyl group with long-chain alkyl phosphonium salts would provide a versatile entry into the required building blocks after catalytic hydrogenation of the corresponding unsaturated pyrroles **5**. The anticipated products **6** could then be directly inserted into the type I porphyrin synthesis developed earlier.[4]

Reaction between *tert*-butyl acetoacetate and oximinobenzyl acetoacetate under standard Knorr conditions gave the pyrrole mixed ester **7** in 40% yield. In trifluoroacetic acid, the *tert*-butyl ester was deprotected to give a quantitative yield of the pyrrole-3-carboxylic acid **8**, which was decarboxylated in 75% yield using the copper–quinoline procedure,[5] to afford the 3-unsubstituted pyrrole **9**. Gatterman formylation of **9** was unsatisfactory, but a 95% yield of the 3-formylpyrrole **4** was obtained when the Vilsmeier procedure ($POCl_3$/DMF) was used.

At this point, the synthesis diverged such that our final porphyrins might bear five or seven carbons in their alkyl side chains. These particular lengths were chosen arbitrarily but so as to give us a feel for the chain length which would typically give us a hydrocarbon-soluble and also crystalline porphyrin. Clearly, a tetramethyltetraalkylporphyrin with very long alkyl groups (C_{10-20}) would be lipophilic, but we also wished to handle crystalline porphyrins and intermediates for characterization purposes. Our prediction[6] was that C_7 side chains

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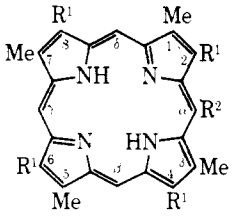
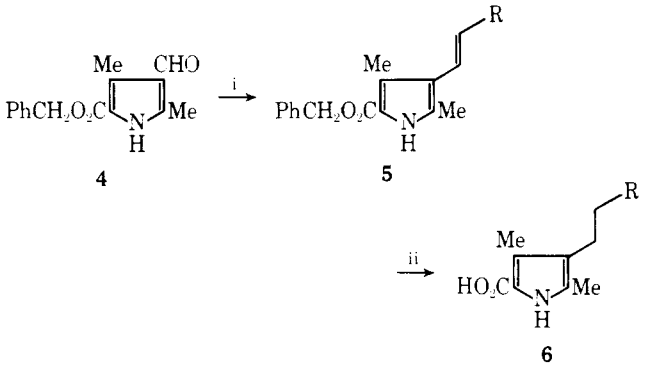


1

2, $R^1 = n\text{-}C_5H_{11}$; $R^2 = H$
3, $R^1 = n\text{-}C_7H_{15}$; $R^2 = H$
20, $R^1 = C_2H_5$; $R^2 = H$



4 5 6

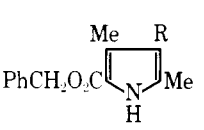
reagents: (i) $RCH_2\overset{+}{P}Ph_3\ \bar{B}r$ and LiBu; (ii) H_2/Pd–C

would be about the optimum length, but, by synthesis of a tetramethyltetrapentylporphyrin (**2**) as well, we might be able to extrapolate in the event that neither **2** nor **3** were suitable for our purposes.

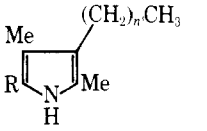
Thus, treatment of pyrrole **4** with the ylids generated (using lithium butyl) from *n*-butyl- or *n*-hexylphosphonium bromide gave 79–87% yields of the pentenyl and heptenyl pyrroles **10** and **11**, respectively. Catalytic hydrogenation gave quantitative yields of the labile carboxylic acids **12** and **13**, which were thermally decarboxylated (to give **14** and **15** respectively) and then treated with bromine in acetic acid[7] to give the kryptopyrromethene-I and -II analogues **16**, **17** and **18**, **19** in good yields from **10** and **11**, respectively. Cyclization of these pyrromethenes in hot formic acid[8] gave 46 and 40% yields of the corresponding porphyrins **2** and **3**. Overall yields of **2** and **3** from the pentenyl and heptenyl pyrroles **10** and **11**, respectively, were 22 and 15%, and these represent extremely efficient conversions from monopyrrole to isomerically pure porphyrin.

An important property of the synthetic porphyrins was that they should be more soluble in toluene than etioporphyrin I (**20**), their easily synthesized parent porphyrin. At 25 °C, porphyrin **2** was shown to be 14.0 times more soluble in toluene than was etioporphyrin I (1.58×10^{-3} M saturated solution); likewise, the tetra(*n*-heptyl)porphyrin was 14.2 times more soluble than **20**. The expected gradation in melting point behavior was also observed in the series **3**, **2**, and **20**. Highest melting was etioporphyrin I (>300 °C), with the long chain pentylphorphyrin somewhat lower (199 °C), and the tetraheptylporphyrin (**2**) (124 °C) the lowest of the three.

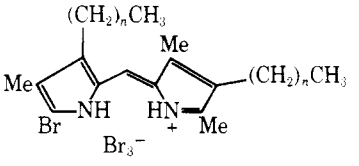
Concern that the bulky side chains might sterically inhibit Vilsmeier formylation was dispelled when treatment of the copper(II) complexes **21** and **22** (from **2** and **3**) with $POCl_3$/DMF gave 90 and 93% yields, respectively, of the formyl copper(II) complexes **23** and **24**. Reduction of the copper(II) complex **23** with sodium borohydride gave a quantitative yield of the hydroxymethylcopper(II) complex **25**, but demetalation of this with sulfuric and trifluoroacetic acids was unsuccessful, possibly owing to dimer formation.[9,10] However, demetalation of the formyl complexes **23** and **24** was readily accomplished with 1:1 sulfuric acid and trifluoroacetic acid, giving **26** and **27**, which were reduced with sodium borohydride to give the



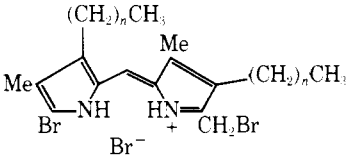
7, R = CO_2-*t*-Bu
8, R = CO_2H
9, R = H
10, R = $-CH{=}CH(CH_2)_2CH_3$
11, R = $-CH{=}CH(CH_2)_4CH_3$



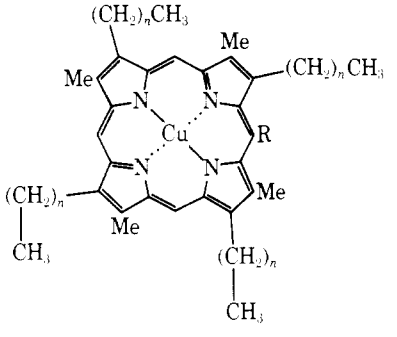
12, *n* = 4; R = HO_2C
13, *n* = 6; R = HO_2C
14, *n* = 4; R = H
15, *n* = 6; R = H



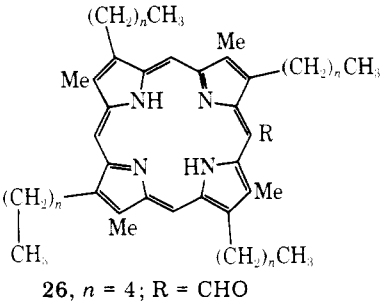
16, *n* = 4
18, *n* = 6



17, *n* = 4
19, *n* = 6



21, *n* = 4; R = H
22, *n* = 6; R = H
23, *n* = 4; R = CHO
24, *n* = 6; R = CHO
25, *n* = 4; R = CH_2OH



26, *n* = 4; R = CHO
27, *n* = 6; R = CHO
28, *n* = 4; R = CH_2OH
29, *n* = 6; R = CH_2OH
30, *n* = 4; R = CH_2OAc
31, *n* = 6; R = CH_2OAc
32, *n* = 4; R = $CH_2OCH_2CH_3$

metal-free hydroxymethylporphyrins **28** and **29** in 50 and 67% yields, respectively, from the formyl copper(II) complexes **23** and **24**.

The hydroxymethylporphyrins were activated for attachment of nucleophilic substituents by treatment with acetic anhydride in pyridine to afford the acetoxymethylporphyrins **30** and **31** in 89–91% yields. We have already shown[11] that these acetoxymethylporphrins are potent electrophiles (being the equivalent of a porphyrinyl "benzyl" carbonium ion) and

that the acetoxyl group can be displaced with even mild nucleophiles. Reactivity in the present series was confirmed by heating **30** in hot ethanol to produce a quantitative yield of the ethoxymethylporphyrin **32**. Further elaborations of these porphyrins for use as cytochrome and hemoglobin models will be described elsewhere.

Experimental Section

Melting points were measured on a microscopic hot-stage apparatus. TLC monitoring of all reactions was performed using Merck silica gel 60 F-254 precoated sheets (0.2 mm), and preparative TLC was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1.5 mm). Column chromatography was carried out on Merck neutral alumina 90 (70–230 mesh). Electronic absorption spectra were measured using a Cary 15 spectrophotometer (solutions in CH_2Cl_2), and ^1H NMR spectra were determined, either at 60 or 100 MHz, usually in $CDCl_3$ with tetramethylsilane as internal standard. Mass spectra (direct inlet, 70 eV, 50 μA, source temperature ca. 200 °C) were measured using an AEI MS 9 instrument.

Benzyl 3-(*tert*-Butoxycarbonyl)-2,4-dimethylpyrrole-5-carboxylate (7). Benzyl acetoacetate (192 g) was diluted with 250 mL of glacial acetic acid, and 76 g of sodium nitrite was slowly added with stirring at 10 °C. After 12 h, the resulting red viscous mixture was slowly added to a well-stirred solution of 158 g of *tert*-butyl acetoacetate, 154 g of ammonium acetate, and 192 g of zinc powder in 500 mL of acetic acid at between 65 and 70 °C. Upon complete addition, the mixture was stirred vigorously at 95 °C for 4 h and then carefully poured over 3 L of iced water. The product was collected by filtration, and recrystallization from the minimum volume of methanol afforded **7** (133 g; 40%): mp 123 °C (lit.[12] mp 122 °C); NMR ($CDCl_3$) τ 8.40 (s, 9 H, $C(CH_3)_3$), 7.50, 7.40 (each s, 3 H, CH_3), 4.65 (s, 2 H, CH_2Ph), 2.61 (s, 5 H, $PhCH_2$), and 0.70 (bd s, 1 H, NH).

5-(Benzyloxycarbonyl)-2,4-dimethylpyrrole-3-carboxylic Acid (8). To 133 g of **7** was added 260 mL of trifluoroacetic acid, and the reaction was stirred for 15 min at room temperature. After the solution was poured into 500 mL of water, the white precipitate was collected by filtration, washed with 50 mL of water, and then dried over phosphorus pentoxide in a vacuum desiccator to give **8** (109 g; 100%): mp 265 °C dec; NMR (Me_2SO-d_6) τ 7.60, 7.50 (each s, 3 H, CH_3), 4.67 (s, 2 H, CH_2Ph), 2.57 (s, 5 H, $PhCH_2$); MS, *m/e* (rel intensity) 273 (M^+, 100), 182 (37), 166 (60), 139 (30), 136.5 (2%). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.16; H, 5.80; N, 5.38.

Benzyl 2,4-Dimethylpyrrole-5-carboxylate (9). A mixture of 100 g of **8**, 200 mL of quinoline, and 1 g of copper(II) acetate was refluxed for 3 h, cooled, and diluted with 500 mL of ether. The quinoline was extracted with 2 N hydrochloric acid (3 × 500 mL), and the organic phase was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo. Column chromatography (Grade II alumina, toluene eluent) and subsequent trituration in ether afforded **9** (63 g; 75%): mp 99 °C (lit.[5,13] mp 102–103 °C); NMR ($CDCl_3$) τ 7.73, 7.62 (each s, 3 H, CH_3), 4.65 (s, 2 H, CH_2Ph), 4.13 (bd s, 1 H, 3-H), 2.60 (s, 5 H, $PhCH_2$), 0.75 (bd s, 1 H, NH).

Benzyl 3-Formyl-2,4-dimethylpyrrole-5-carboxylate (4). To 11 mL of dimethylformamide was added 10 mL of phosphorus oxychloride with stirring at 0 °C. A solution of 2 g of pyrrole **9** in 30 mL of dichloroethane was then added dropwise to the crystalline Vilsmeier complex, and the reaction mixture was refluxed for 1 h, neutralized with saturated potassium carbonate solution (50 mL), and then stirred for 3 h at 85 °C. Extraction with chloroform (3 × 200 mL) and subsequent evaporation in vacuo afforded a solid which was recrystallized from methanol/water and dried over phosphorus pentoxide to give white needles of **4** (2.09 g; 93%): mp 151 °C; NMR ($CDCl_3$) τ 7.47, 7.40 (each s, 3 H, CH_3), 4.65 (s, 2 H, CH_2Ph), 2.60 (s, 5 H, $PhCH_2$), 0.50 (bd s, 1 H, NH), 0.01 (s, 1 H, CHO); MS, *m/e* (rel intensity) 257 (M^+, 100), 166 (18), 150 (22), 128.5 (5). Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 69.72; H, 5.70; N, 5.58.

Benzyl 3-(1-Pentenyl)-2,4-dimethylpyrrole-5-carboxylate (10). To 100 g of triphenyl-*n*-butylphosphonium bromide[14] (mp 241–242 °C, prepared by refluxing 1-bromobutane and triphenylphosphine in *n*-butyl alcohol for 24 h) suspended in 500 mL of dry tetrahydrofuran was slowly added with stirring at room temperature and under nitrogen 150 mL of *n*-butyllithium (~2 M in hexene). A deep red color and disappearance of the salt showed that ylid formation was complete. To this solution was added 25.8 g of the aldehyde **4** in 300 mL of tetrahydrofuran, and after the solution was stirred overnight, 500 mL of water was added to quench the reaction. Extraction with ether (3 × 200 mL), drying over anhydrous sodium sulfate, and evaporation in vacuo yielded an oil, which was purified by column chromatography (silica gel, toluene eluent) and subsequently recrystallized from methanol/water to give **10** (25.9 g; 87%): mp 90 °C; NMR ($CDCl_3$) τ 9.09 (t, 3 H, $CH{=}CHCH_2CH_2CH_3$), 8.4–8.8 (m, 2 H, $CH{=}CHCH_3CH_2CH_3$), 7.6–8.0 (m, 2 H, $CH{=}CHCH_2CH_2CH_3$), 7.80, 7.69 (each s, 3 H, CH_3), 4.78 (s, 2 H, CH_2Ph), 4.34 (d of t, 1 H, J_{vinyl} = 15 Hz, J_{CH-CH_2} = 6 Hz, $CH{=}CHCH_2CH_2CH_3$), 3.84 (d, 1 H, J_{vinyl} = 15 Hz, $CH{=}CHCH_2CH_2CH_3$), 2.69 (s, 5 H, $PhCH_2$), 1.28 (bd s, 1 H, NH); MS, *m/e* (rel intensity) 297 (M^+, 100), 268 (59), 189 (25), 160 (69). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 77.03; H, 7.72; N, 4.81.

Benzyl 3-(1-Heptenyl)-2,4-dimethylpyrrole-5-carboxylate (11). This compound was prepared by the method described for **10** above, but using triphenyl *n*-hexylphosphonium bromide[15] (mp 198 °C) instead of the *n*-butyl analogue. **11** was obtained in 79% yield as white needles (mp 85 °C) after recrystallization from methanol/water: NMR ($CDCl_3$) τ 9.02–9.24 (m, 3 H, 7′-CH_3), 8.46–8.85 (m, 6 H, 4′,5′,6′-CH_2), 7.80, 7.68 (each s, 3 H, CH_3), 7.64–7.79 (m, 2 H, 3′-CH_2), 4.77 (s, 2 H, CH_2Ph), 4.35 (d of t, 1 H, J_{vinyl} = 15 Hz, J_{CH-CH_2} = 6 Hz, 2′-CH), 3.85 (d, 1 H, J_{vinyl} = 15 Hz, 1′-CH), 2.70 (s, 5 H, $PhCH_2$), 1.22 (bd s, 1 H, NH); MS *m/e* (rel intensity) 325 (M^+, 100), 268 (98), 242 (36), 190 (27%). Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.38; H, 8.24; N, 4.51.

1,3,5,7-Tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (2). The olefin **10** (6 g) was dissolved in 120 mL of tetrahydrofuran, and 0.1 mL of triethylamine was added. The mixture was hydrogenated over 10% palladium on charcoal (600 mg) until the theoretical amount of hydrogen had been taken up; it was then filtered through Celite, and the filtrate was evaporated in vacuo using a hot water bath. The resulting red oil (**14**, 6.2 g) [NMR ($CDCl_3$) τ 8.95–9.25 (m, 3 H, 5′-CH_3), 8.45–8.80 (m, 6 H, 4′,3′,2′-CH_2), 7.50–7.85 (m, 2 H, 1′-CH_2), 7.80, 7.70 (each s, 3 H, CH_3), 2.70 (s, 1 H, α-H), 1.20 (bd s, 1 H, NH)] was diluted with 15 mL of glacial acetic acid, and 3.8 mL of bromine was then added dropwise. The reaction was stirred for 15 h at room temperature, and then 100 mL of ether was slowly added with stirring. Crystals consisting[7] largely of 5-bromo-3,4′-di(*n*-pentyl)-3′,4,5′-trimethylpyrromethene perbromide (**16**) (1.97 g) were collected by filtration, and the remaining pyrromethene, largely 5-bromo-5′-bromomethyl-3′,4-dimethyl-3,4′-di(*n*-pentyl)pyrromethene hydrobromide (**17**) (1.19 g), was isolated by dilution of the mother liquor with toluene, evaporation to dryness in vacuo, trituration with ether, and then filtration.

The pyrromethenes **16** and **17** were combined and refluxed for 3 h in 20 mL of formic acid. The excess acid was distilled off, and the residue was diluted with 150 mL of chloroform, washed with 50 mL of water and then 50 mL of saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Evaporation in vacuo gave a residue which was column chromatographed (Grade II neutral alumina, dichloromethane elution). Recrystallization from dichloromethane/methanol afforded the porphyrin **2** as purple crystals (0.74 g, 22% overall yield from **10**): mp 199 °C; NMR ($CDCl_3$) τ 8.98 (t, 12 H, 5′-CH_3), 8.60–8.10 (m, 16 H, 3′,4′-CH_2), 7.80–7.45 (m, 8 H, 2′-CH_2), 6.39 (s, 1,3,5,7-CH_3), 5.99 (t, 8 H, 1′-CH_2), −0.45 (s, 4 H, *meso*-H); MS, *m/e* (rel intensity) 646 (M^+, 100), 589 (12), 532 (3), 475 (2), 417 (1), 323 (11); vis λ_{max} (CH_2Cl_2) 398 (ε 168 000), 498 (13 400), 532 (10 000), 567 (6900), 593 (1300), and 620 nm (4900). Anal. Calcd for $C_{44}H_{62}N_4$: C, 81.68; H, 9.66; N, 8.66. Found: C, 81.49; H, 9.62; N, 8.64. This porphyrin was isomerically pure using the criteria of LC and TLC in several solvent systems.

2,4,6,8-Tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (3). This compound was prepared using the method described above for **2**, but the heptenylpyrrole **11** was used as the precursor (overall yield of **3** from **11** was 15%): mp 124 °C; NMR ($CDCl_3$) τ 9.1 (t, 12 H, 7′-CH_3), 8.70–8.55 (m, 16 H, 6′,5′-CH_2), 8.53–8.35 (m, 8 H, 4′-CH_2), 8.34–8.15 (m, 8 H, 3′-CH_2), 7.78–7.60 (m, 8 H, 2′-CH_2), 6.38 (s, 12 H, 1,3,5,7-CH_3), 5.94 (t, 8 H, 1′-CH_2), −0.04 (s, 4 H, *meso*-H); MS, *m/e* (rel intensity) 758 (M^+, 100), 673 (19), 588 (5), 503 (3), 418 (2), 379 (5); vis λ_{max} (CH_2Cl_2) 398 (ε 169 000), 497 (14 100), 531 (10 300), 566 (6800), 593 (1300), and 620 nm (5200). Anal. Calcd for $C_{52}H_{78}N_4$: C, 82.26; H, 10.36; N, 7.38. Found: C, 82.33; H, 10.26; N, 7.68. This porphyrin was isomerically pure using the criteria of LC and TLC in several solvent systems.

(1,3,5,7-Tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrinato)-copper(II) (21). A saturated solution of copper(II) acetate in methanol was added dropwise to a gently refluxing solution of 100 mg of the pentylporphyrin **2** in 30 mL of dichloromethane until the visible absorption band at 621 nm had disappeared. Methanol (50 mL) was then added, and the solution was reduced in volume to 20 mL by

evaporation in vacuo. The bright red precipitate was collected by filtration, purified by column chromatography (Grade III alumina, dichloromethane elution), and then crystallized from dichloromethane/methanol to give the copper(II) complex **21** (102 mg; 93%): mp 246 °C; MS, *m/e* (rel intensity) (^{63}Cu) 707 (M^+, 100), 650 (30), 593 (12), 479 (6), 353.5 (15); vis λ_{max} (CH_2Cl_2) 399 (ϵ 379 000), 526 (13 300), and 562 nm (26 900). Anal. Calcd for $C_{44}H_{60}CuN_4$: C, 74.59; H, 8.54; N, 7.91; Cu, 8.97. Found: C, 74.32; H, 8.54; N, 8.02; Cu, 9.17.

(2,4,6,8-Tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrinato)copper(II) (22). This compound was prepared from **3** in 81% yield using the method described above for **21**: mp 130 °C; MS, *m/e* (rel intensity) (^{63}Cu) 819 (M^+, 100), 734 (26), 649 (15), 564 (12), 479 (15), 409.5 (11); vis λ_{max} (CH_2Cl_2) 398 (ϵ 388 000), 525 (13 600), and 561 (27 000). Anal. Calcd for $C_{52}H_{76}CuN_4$: C, 76.10; H, 9.33; N, 6.83; Cu, Cu, 7.74. Found: C, 75.86; H, 9.26; N, 6.77; Cu, 7.49.

(α-Formyl-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrinato)copper(II) (23). To 0.84 mL of dimethylformamide was added 1 mL of phosphorus oxychloride with stirring at 0 °C. A solution of the copper(II) porphyrin **21** (102 mg) in 50 mL of dry dichloroethane was then added dropwise to the crystalline Vilsmeier complex, and the reaction mixture was refluxed for 1 h, neutralized with 50 mL of a saturated solution of sodium acetate, and then stirred for 3 h at 85 °C. Extraction with dichloromethane (3 × 50 mL), washing with saturated sodium bicarbonate solution (100 mL) and water (100 mL), drying over anhydrous sodium sulfate, and evaporating in vacuo afforded a dark red solid which was purified by column chromatography (Grade III alumina, dichloromethane elution). Recrystallization from dichloromethane/methanol gave **23** as red crystals (95 mg; 90%): mp 210 °C; MS, *m/e* (rel intensity) (^{63}Cu) 735 (M^+, 100), 707 (91), 650 (21), 593 (8), 536 (8), 479 (8), 367.5 (4); vis λ_{max} (CH_2Cl_2) 402 (ϵ 227 000), 530 (9300), 567 (14 500), and 636 nm (2900). Anal. Calcd for $C_{45}H_{60}CuN_4O$: C, 73.38; H, 8.21; N, 7.61; Cu, 8.63. Found: C, 73.60; H, 8.28; N, 7.80; Cu, 8.37.

(α-Formyl-2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrinato)copper(II) (24). This compound was prepared from **22** in 93% yield using the method described above for **23**: mp 150 °C; MS, *m/e* (rel intensity) (^{63}Cu) 849 (M^+, 59), 821 (100), 735 (16), 650 (8), 564 (10), 479 (10), 424.5 (5); vis λ_{max} (CH_2Cl_2) 404 (ϵ 238 000), 530 (9900), 567 (15 200), and 634 nm (3100). Anal. Calcd for $C_{53}H_{76}CuN_4O$: C, 75.00; H, 9.03; N, 6.60; Cu, 7.49. Found: C, 74.98; H, 9.07; N, 6.71; Cu, 7.60.

(α-(Hydroxymethyl)-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrinato)copper(II) (25). A solution of 160 mg of sodium borohydride in 20 mL of methanol was added to 80 mg of the formylporphyrin **23** in 100 mL of dichloromethane, and the reaction mixture was stirred at room temperature for 15 h. Methanol (50 mL) was then added, and the solution volume was reduced to 20 mL by evaporation in vacuo. The red precipitate was collected by filtration and purified by column chromatography (Grade III alumina, dichloromethane elution), and the product was recrystallized from dichloromethane/methanol to give **25** (80 mg; 100%): mp 213 °C; MS, *m/e* (rel intensity) (^{63}Cu) 737 (M^+, 14), 721 (100), 707 (29), 650 (11), 593 (4), 536 (4), 479 (3), 368.5 (3); vis λ_{max} (CH_2Cl_2) 405 (ϵ 311 000), 533 (11 800), and 572 nm (17 200). Anal. Calcd for $C_{45}H_{62}CuN_4O$: C, 73.18; H, 8.19; N, 7.59. Found, C, 72.88; H, 8.26; N, 7.72.

α-Formyl-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (26). The formyl copper(II) complex **23** (76 mg) was dissolved in a solution of 10 mL of concentrated sulfuric acid and 10 mL of trifluoroacetic acid, stirred at room temperature for 2 h, and then poured over 100 mL of iced water. The aqueous solution was extracted with dichloromethane (3 × 50 mL), and the combined extracts were washed with a saturated solution of sodium bicarbonate and water, dried over anhydrous sodium sulfate, and evaporated to dryness in vacuo. Purification was achieved by column chromatography (Grade III alumina, dichloromethane elution) and repeated recrystallization from dichloromethane/methanol to yield **26** as brown crystals (36 mg; 52%): mp 198 °C; NMR ($CDCl_3$) τ 9.03 (t, 12 H, 5′-CH_3), 8.60–8.37 (m, 8 H, 4′-CH_2), 8.36–8.22 (m, 8 H, 3′-CH_2), 8.05–7.90 [m, 2 H, 2-(2′-CH_2)], 7.90–7.65 [m, 6H, 4,6,8-(2′-CH_2)], 6.74 (s, 3 H, 3-CH_3), 6.55 (s, 3 H, 1-CH_3), 6.52, 6.51 (each s, 3 H, 5,7-CH_3), 6.44–6.32 [m, 2 H, 2-(1′-CH_2)], 6.22–5.95 [m, 6 H, 4,6,8-(1′-CH_2)], 0.18 (s, 1 H, γ-*meso*-**H**), 0.10 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 674 (M^+, 7), 646 (100), 589 (20), 532 (7), 475 (3), 418 (3), 337 (1); vis λ_{max} (CH_2Cl_2) 402 (ϵ 118 000), 503 (8300), 537 (5800), 574 (5100), 625 (3200), and 657 nm (1600). Anal. Calcd for $C_{45}H_{62}N_4O$: C, 80.07; H, 9.26; N, 8.30. Found: C, 80.02; H, 9.32; N, 8.29.

α-Formyl-2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (27). The copper(II) formylporphyrin **24** was demetalated in 69% yield using the method described above for compound **26** and afforded brown crystals: mp 116 °C; NMR ($CDCl_3$) τ 9.22–9.03 (m, 12 H, 7′-CH_3), 8.84–8.71 (m, 8 H, 6′-CH_2), 8.70–8.58 (m, 8 H, 5′-CH_2), 8.53–8.39 (m, 8 H, 4′-CH_2), 8.38–8.20 (m, 8 H, 3′-CH_2), 7.98–7.88 (m, 8 H, 2′-CH_2), 7.86–7.73 [m, 6 H, 4,6,8-(2′-CH_2)], 6.65 (s, 3 H, 3-CH_3), 6.47, 6.46, 6.45 (each s, 3 H, 1,5,7-CH_3), 6.32–6.15 [m, 2 H, 2-(1′-CH_2)], 6.11–5.93 [m, 6 H, 4,6,8-(1′-CH_2)], 0.12 (s, 1 H, γ-*meso*-**H**), 0.02 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 786 (M^+, 50), 758 (100), 674 (50), 589 (25), 503 (5), 421 (5), 393 (20); vis λ_{max} (CH_2Cl_2) 403 (ϵ 135 000), 504 (9400), 538 (6700), 573 (5900), 626 (3800), and 659 nm (2000). Anal. Calcd for $C_{53}H_{78}N_4O$: C, 80.86; H, 9.99; N, 7.12. Found: C, 80.98; H, 10.16; N, 7.24.

α-(Hydroxymethyl)-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (28). A solution of 80 mg of sodium borohydride in 10 mL of methanol was added to 36 mg of the formylporphyrin **26** in 50 mL of dichloromethane, and the reaction mixture was stirred at room temperature for 15 h. The solution was diluted with 50 mL of dichloromethane, washed with water (2 × 50 mL), dried over anhydrous sodium sulfate, and then evaporated to dryness in vacuo. Purification by column chromatography (Grade III alumina, dichloromethane elution) and recrystallization from dichloromethane/hexane afforded brown crystals (35 mg; 100%): mp 283 °C; NMR ($CDCl_3$) τ 9.11–8.92 (m, 12 H, 5′-CH_3), 8.62–8.39 (m, 8 H, 4′-CH_2), 8.38–8.29 (m, 8 H, 3′-CH_2), 8.12–7.88 (m, 2 H, 2′-CH_2), 7.87–7.62 (m, 6 H, 2′-CH_2), 6.49, 6.48, 6.46, 6.45 (each s, 3 H, 1,3,5,7-CH_3), 6.22–5.98 (m, 8 H, 1′-CH_2), 3.37 (s, 2 H, α-CH_2OH), 0.16 (s, 1 H, α-*meso*-**H**), 0.01 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 676 (M^+, 100), 646 (70), 589 (16), 532 (5), 475 (4), 418 (3), 338 (7); vis λ_{max} (CH_2Cl_2) 403 (ϵ 162 000), 505 (13 200), 541 (8700), 575 (6000), and 628 nm (4300). Anal. Calcd for $C_{45}H_{64}N_4O$: C, 79.83; H, 9.53; N, 8.28. Found: C, 79.71; H, 9.44; N, 8.49.

α-(Hydroxymethyl)-2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (29). This compound was prepared in quantitative yield by the method described above for compound **28** and afforded, after recrystallization from dichloromethane/methanol, brown crystals: mp 104 °C; NMR ($CDCl_3$) τ 9.16–8.94 (m, 12 H, 7′-CH_3), 8.70–8.55 (m, 16 H, 6′,5′-CH_2), 8.54–8.38 (m, 8 H, 4′-CH_2), 8.37–8.18 (m, 8 H, 3′-CH_2), 8.04–7.88 (m, 2 H, 2′-CH_2), 7.87–7.64 (m, 6 H, 2′-CH_2), 6.51, 6.50, 6.49, 6.45 (each s, 3 H, 1,3,5.7-CH_3), 6.21–5.96 (m, 8 H, 1′-CH_2), 3.38 (s, 2 H, α-CH_2OH), 0.17 (s, 1 H, γ-*meso*-**H**), 0.04 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 788 (M^+, 44), 758 (100), 673 (43), 588 (18), 503 (18), 418 (16), 394 (11); vis γ_{max} (CH_2Cl_2) 404 (ϵ 166 000), 506 (13 400), 542 (8500), 576 (6100), and 628 nm (4400). Anal. Calcd for $C_{53}H_{80}N_4O$: C, 80.66; H, 10.22; N, 7.10. Found: C, 80.65; H, 10.27; N, 7.35.

α-(Acetoxymethyl)-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (30). The porphyrin alcohol **28** (99 mg) was dissolved in 5 mL of pyridine and 5 mL of acetic anhydride was added. The solution was stirred for 1 h at 80 °C, diluted with 50 mL of toluene, and evaporated to dryness in vacuo. Purification by column chromatography (Grade III alumina, dichloromethane elution) and subsequent recrystallization from dichloromethane afforded **30** as brick red crystals (93 mg; 89%): mp 140 °C; NMR ($CDCl_3$) τ 9.12–8.94 (m, 12 H, 5′-CH_3), 8.62–8.38 (m, 8 H, 4′-CH_2), 8.37–8.17 (m, 8 H, 3′-CH_2), 7.98–7.62 (m, 8 H, 2′-CH_2), 7.64 (s, 3 H, $OCOCH_3$), 6.50, 6.48, 6.43, 6.40 (each s, 3 H, 1,3,5,7-CH_3), 6.17–5.90 (m, 8 H, 1′-CH_2), 2.76 (s, 2 H, CH_2O), 0.11 (s, 1 H, γ-*meso*-**H**), −0.07 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 718 (M^+, 17), 660 (100), 647 (16), 589 (10), 532 (3), 475 (3), 417 (3), 359 (1); vis λ_{max} (CH_2Cl_2) 404 (ϵ 167 000), 506 (13 300), 541 (9400), 576 (6000), and 629 nm (5200). Anal. Calcd for $C_{47}H_{66}N_4O_2$: C, 78.50; H, 9.25; N, 7.79. Found: C, 78.56; H, 9.38; N, 7.99.

α-(Acetoxymethyl)-2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (31). Acetylation of the porphyrin alcohol **29** was achieved in 91% yield using the method described above for compound **30**, affording **31** as brown crystals: mp 95–96 °C; NMR ($CDCl_3$) τ 9.19–8.92 (m, 12 H, 7′-CH_3), 8.80–8.51 (m, 16 H, 6′,5′-CH_2), 8.50–8.35 (m, 8 H, 4′-CH_2), 8.34–8.12 (m, 8 H, 3′-CH_2), 7.91–7.62 (m, 8 H, 2′-CH_2), 7.58 (s, 3 H, $OCOCH_3$), 6.47, 6.46, 6.44, 6.38 (each s, 3 H, 1,3,5,7-CH_3), 6.18–5.92 (m, 8 H, 1′-CH_2), 2.73 (s, 2 H, CH_2O), 0.14 (s, 1 H, γ-*meso*-**H**), −0.03, −0.05 (each s, 1 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 830 (M^+, 81), 772 (100), 758 (41), 673 (32), 588 (24), 503 (25), 415 (19); vis λ_{max} (CH_2Cl_2) 404 (ϵ 169 000), 506 (13 400), 542 (9500), 576 (6200), 629 nm (5300). Anal. Calcd for $C_{55}H_{82}N_4O_2$: C, 79.47; H, 9.94; N, 6.74. Found: C, 79.36; H, 9.77; N, 6.84.

α-(Ethoxymethyl)-1,3,5,7-tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (32). The acetoxymethylporphyrin **30** (36 mg) was dissolved in 20 mL of dichloroethane, and 5 mL of absolute ethanol was added. The solution was refluxed for 1 h, evaporated to dryness in vacuo, column chromatographed (Grade II alumina, dichloromethane elution), and recrystallized from dichloromethane/methanol to yield **32** as purple crystals (40 mg; 100%): mp 82 °C; NMR ($CDCl_3$)

τ 9.07–8.88 (m, 12 H, 5′-C**H**$_3$), 8.58–8.35 (m, 8 H, 4′-C**H**$_2$), 8.40 (t, 3 H, OCH$_2$C**H**$_3$), 8.33–8.10 (m, 8 H, 3′-C**H**$_2$), 8.00–7.60 (m, 8 H, 2′-C**H**$_2$), 6.45, 6.43, 6.41, 6.40 (each s, 3 H, 1,3,5,7-C**H**$_3$), 6.12–5.87 (m, 8 H, 1′-C**H**$_2$), 5.86 (q, 2 H, OC**H**$_2$CH$_3$), 3.78 (s, 2 H, C**H**$_2$O), 0.11 (s, 1 H, γ-*meso*-**H**), −0.06 (s, 2 H, β,δ-*meso*-**H**); MS, *m/e* (rel intensity) 704 (M^+, 69), 660 (100), 646 (31), 589 (14), 532 (7), 475 (3), 417 (1), 352 (1); vis λ_{max} (CH_2Cl_2) 404 (ϵ 155 000), 505 (11 700), 540 (8000), 575 (5900), 628 (4000), and 659 nm (700). Anal. Calcd for $C_{47}H_{68}N_4O$: C, 80.06; H, 9.72; N, 7.95. Found: C, 79.86; H, 9.88; N, 7.72.

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Direct Metalation of Pyrimidine. Synthesis of Some 4-Substituted Pyrimidines

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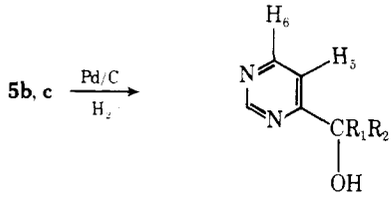
Direct metalation of 5-bromopyrimidine with lithium diisopropylamide afforded 4-lithio-5-bromopyrimidine. The intermediate lithiopyrimidine could be trapped by a variety of carbonyl compounds, giving 5-bromo-4-pyrimidine carbinols which were easily dehalogenated. The structure of each product was determined by ^{1}H NMR, mass spectra, and elemental analyses. The stability of the lithiopyrimidine was also examined. This simple two-step method represents a new method of entry into the 4-position of pyrimidine.

Considerable interest has been centered on the reaction of halogen-substituted heterocycles with strong base. Several comprehensive reviews have appeared on the subject, and evidence has been presented that these reactions do not always occur by a single pathway but instead proceed via competing mechanisms.[1,2] One of these pathways is the elimination–addition (EA) mechanism, where the position ortho to the halogen atom is first deprotonated or metalated prior to elimination of halide or metal halide. The resulting aryne can then add a nucleophile, affording the product. In the case of pyrimidine, the existence of the proposed aryne intermediate has recently been demonstrated by Promel and co-workers by the trapping of 2-*tert*-butyl-4,5-pyrimidyne with furan.[3] We now wish to report conclusive evidence for the existence of 4-lithio-5-bromopyrimidine (**2**), another intermediate in this scheme, and present some data on its stability.

Results and Discussion

The lithiopyrimidine **2**, generated by reaction of 5-bromopyrimidine (**1**) with lithium diisopropylamide (LDA), could be intercepted by a variety of carbonyl compounds to give the 4,5-disubstituted pyrimidines **5a–c** listed in Table I.

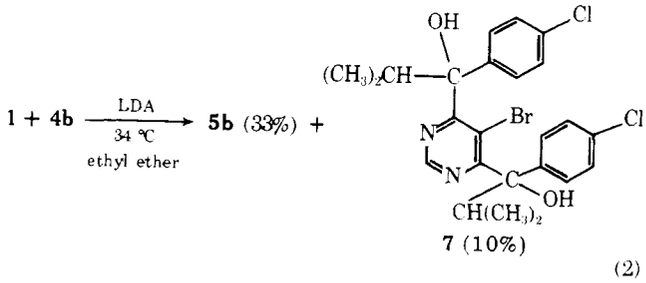
The structure of each carbinol **5a–c** was readily determined by physical data (elemental analysis, ^{1}H NMR, mass spectrum) and finally by removal of bromine from **5b** and **5c** by catalytic reduction giving the 4-substituted pyrimidines **6a** and **6b** (eq 1). The appearance of a new AB system in the ^{1}H NMR spectra of **6a** and **6b** (due to H_5–H_6 coupling) confirmed the position of substitution in **5a–c** and **6a,b.**



(1)

6a, R_1 = *p*-ClPh; R_2 = $CH(CH_3)_2$
b, R_1 = Ph; R_2 = H

The stability of **2** was of interest with respect to temperature and mode of reagent addition. When the metalation reaction (eq 2) was performed in refluxing ethyl ether with the ketone **4b**, in addition to the major product **5b** a disubstituted carbinol was also formed. The symmetrical ^{1}H NMR pattern for the isopropyl and phenyl moieties established **7** as the structure of this product. At lower temperature (−65 vs. −10 °C), reaction of **2** with benzaldehyde (**4c**) afforded only a 5% yield improvement.



(2)

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