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# GENERAL SYNTHESIS OF OCTAALYKYLPORPHYRINS

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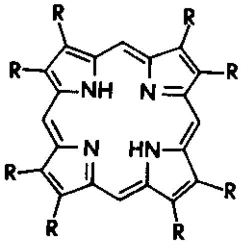
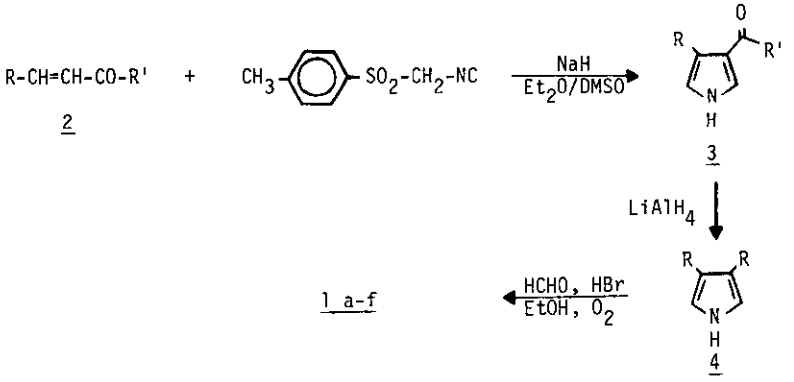
Abstract: Reaction of the α,β-unsaturated ketone, 2 a-f, with toluenesulfonyl methyl isocyanide give the 3-alkanoyl-4-alkyl pyrroles, 3 a-f. Hydride reduction of 3 a-f affords the 3,4-dialkylpyrroles 4 a-f which condense with formaldehyde to give the 2,3,7,8,12,13,17,18-octaalkylporphyrins, 1 a-f.

As a new approach leading to symmetrically substituted octaalkylporphyrins we report here a simple and general synthesis of the porphyrins 1 a-f.



| | R= |
|---|---|
| 1a | n-$C_3H_7$ |
| 1b | n-$C_4H_9$ |
| 1c | n-$C_5H_{11}$ |
| 1d | n-$C_6H_{13}$ |
| 1e | n-$C_7H_{15}$ |
| 1f | n-$C_8H_{17}$ |

In our earlier work[1,2] we described the direct synthesis of octa-substituted porphyrins starting with the reaction of α,β-unsaturated ketones and ester with toluenesulfonyl methyl isonitrile to give 3-alkanoyl-4-alkylpyyroles. These pyrroles were condensed with formaldehyde under aerobic conditions giving rise to mixtures of isomeric porphyrins.



Attempts to effect an alkanoyl to alkane reduction in these porphyrins give erratic results.[3] To circumvent this difficulty we carried out a hydride reduction of the substitute pyrroles 3 a-f which gives the 3,4-dialkylpyrroles, 4a, in high yields. Like all alkylpyrroles 4 a-f are air sensitive and should be used immediatley.[1b]

| Pyrrole 3 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| R= | n-$C_3H_7$ | n-$C_4H_9$ | n-$C_5H_{11}$ | n-$C_6H_{13}$ | n-$C_7H_{15}$ | n-$C_8H_{17}$ |
| R'= | $-COCH_2CH_3$ | $-CO(CH_2)_2CH_3$ | $-CO(CH_2)_3CH_3$ | $-CO(CH_2)_4CH_3$ | $-CO(CH_2)_5CH_3$ | $-CO(CH_2)_6CH_3$ |
| % Yield | 74 | 69 | 34 | 28 | 31 | 42 |
| m.p. | 96-98° | 70-72° | 63-65° | 66-67° | 65-67° | 42-44° |

| Pyrrole 4 | | | | | | |
|---|---|---|---|---|---|---|
| R= | n-$C_3H_7$ | n-$C_4H_9$ | n-$C_5H_{11}$ | n-$C_6H_{13}$ | n-$C_7H_{15}$ | n-$C_8H_{17}$ |
| % Yield | 70 | 76 | 86 | 87 | 89 | 85 |
| 'HMR ($\delta$) | | | | | | |
| pyrrole-H | 6.23d | 6.41d | 6.35d | 6.27d | 6.45d | 6.33d |
| $CH_2$-pyrrole | 2.37t | 2.43t | 2.38t | 2.36t | 2.46t | 2.38t |
| $^{13}$CMR ($\delta$) | | | | | | |
| $\alpha$-pyrrolic | 114.73 | 114.73 | 114.70 | 114.62 | 114.65 | 114.61 |
| $\beta$-pyrrolic | 122.53 | 122.95 | 122.94 | 122.72 | 122.81 | 122.66 |

| Porphyrin 1 | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| R= | $C_3H_7$ | $C_4H_9$ | $C_5H_{11}$ | $C_6H_{13}$ | $C_7H_{15}$ | $C_8H_{17}$ |
| % Yield (from 2) | 32 | 33 | 40 | 11 | 11 | 22 |
| m.p. | 280° * (phase change) 275-278°) | 270° (phase change) 266-267° | 229° (phase change) 222-227° | 173-175° | 151-152° | 145.5-147° |
| $HCCl_3$ λmax, nm | 399 (Soret)<br>499<br>535<br>569<br>622 | 400 (Soret)<br>500<br>535<br>569<br>622 | 400 (Soret)<br>500<br>536<br>569<br>621 | 400 (Soret)<br>500<br>535<br>569<br>621 | 400 (Soret)<br>501<br>535<br>569<br>622 | 400 (Soret)<br>501<br>535<br>569<br>621 |
| 'HMR ($\delta$)** | | | | | | |
| Meso-H | 9.97s | 9.85s | 10.00s | 10.08s | 10.05s | 10.03s |
| $-CH_2$-porph. | 4.03t | 3.95t | 4.03t | 4.15t | 4.15t | 4.10t |
| $^{13}$CMR ($\delta$)** | | | | | | |
| Meso | 96.90 | 96.70 | 96.79 | 96.78 | 96.78 | 96.79 |
| $\alpha$-pyrrolic | 144.35 | 144.07 | 144.19 | 144.08 | 144.08 | 144.19 |
| $\beta$-pyrrolic | 140.17 | 140.17 | 140.17 | 140.22 | 140.31 | 140.22 |
| $-CH_2$-porph. | 28.62 | 26.32 | 26.61 | 26.67 | 26.63 | 26.63 |

*lit.[6] sintered 276°
**nmr taken in $CDCl_3$

Using our general porphyrin procedure of refluxing an acidic, ethanolic solution of 4 with formaldehyde, first under nitrogen then exposed to air to bring the slow oxidation of the condensation product (presumably porphyrinogen) we obtained good to excellent yields of porphyrins 1 a-f.

The solubility of these porphyrins in various solvents is greatly enhanced by the presence of the alkyl substituents. Thus, octapentylporphyrin is twice as soluble in hexane as octaethylporphyrin while octaoctylporphyrin is 3.7 times as soluble. All the porphyrins, 1 a-f, are also extremely soluble in the chlorinated solvents.

## EXPERIMENTAL

3-Pentyl-4-pentanoylpyrrole, 3c: A solution of p-toluenesulfonyl methyl isocyanide[4] (20 mmol) and 6-dodecen-5-one, 2c (20 mmol) in 100 ml of diethyl ether/dimethyl sulfoxide (2:1) was added dropwise to a stirred suspension of sodium hydride (40 mmol) in 40 ml of ether. The mixture was stirred for an additional 30 min. then water (100 ml) was added. The product was extracted with ether. Evaporation of the ether under reduced pressure left a semi-solid which was crystallized from methylene chloride/pentane: yield 34%, mp. 63-65°; IR (Nujol): 3210 $cm^{-1}$ (N-H), 1640 $cm^{-1}$ (C=O); PMR ($CDCl_3$): $\delta$ 0.88 (overlapping t, 6H, $C\underline{H}_3$), 1.1-1.9 (m, 10H, $CH_3(C\underline{H}_2)_3CH_2$ and $COCH_2(CH_2)_2CH_3$), 2.70 (overlapping t, 4H, $CH_2$-pyrrole and $COCH_2$), 6.45 (m, 1H, $C_2$-pyrrole-H), 7.25 (m, 1H, $C_5$-pyrrole-$\underline{H}$), 9.00 (broad s, 1H, N-$\underline{H}$); $^{13}$CMR ($CDCl_3$): $\delta$ 13.81 and 13.93 ($CH_3$'s), 22.46 ($CH_3$-$\underline{C}H_2$'s), 26.43 ($CH_3(CH_2)_3\underline{C}H_2$), 27.24 ($CH_3CH_2\underline{C}H_2CH_2CO$), 29.66 ($CH_3(\underline{C}H_2)_2CH_2$), 31.75 ($CH_3CH_2\underline{C}H_2CH_2CH_2$), 39.63 ($\underline{C}H_2CO$), 117.33 ($C_5$-pyrrole carbon), 123.04 ($C_3$-pyrrole carbon), 124.87 ($C_2$-pyrrole carbon), 126.23 ($C_4$-pyrrole carbon), 194.44 (C=O); MS (70 eV): m/e = 220 (parent).

3,4-Dipentylpyrrole, 4c: Lithium aluminum hydride (50 ml of a 0.67 M ether solution, 33.4 mmol) was added to a sitrred solution of 3c (2.0g, 8.3 mmol) in tetrahydrofuran under nitrogen. The mixture was refluxed for three hours. To the cooled solution was added cautiously and in order, water (1.3 ml), sodium hydroxide (1.3 ml of 15% w/w aqueous solution), and water (3.9 ml). The precipitate was filtered by suction and washed with tetrahydrofuran. The tetrahydrofuran was removed under reduced pressure to yield 1.63 g (86% yield) of 4c: IR (Nujol): 3375 $cm^{-1}$ (N-N); PMR ($CDCl_3$): 50.88 (5, 6H, $CH_3$), 1.40 (m, 12H, $CH_3C\underline{H}_2C\underline{H}_2,C\underline{H}_2$) 2.38 (t, 4H, $C\underline{H}_2$-pyrrole), 6.35 (d, 2H, H-pyrrole), 7.56 (broad s, 1H, N-H; $^{13}$CMR ($CDCl_3$): $\delta$ 13.9 ($CH_3$), 22.5 ($CH_3\underline{C}H_2$) 25.2, 30.1 ($CH_3CH_2CH_2(CH_2)_2$), 31.8 ($CH_3CH_2\underline{C}H_2CH_2CH_2$), 114.7 ($C_2$-and $C_5$-pyrrole carbons), 122.9 ($C_3$-and $C_4$-pyrrole carbons).

Octapentylporphyrin 3c: A solution of 2c (578 mg, 2.54 mmol), fresh, 37% aqueous formaldehyde[5] (12 ml), and aqueous 48% hydrobromic acid (0.5 ml) in absolute ethanol (100 ml) was refluxed for 24 hours under nitrogen then exposed to air while refluxing for an additional 24 hours. The resulting solution was allowed to stand at room temperature for seven days. The ethanol was removed under reduced pressure. After neutralizing the residue with aqeuous sodium carbonate it was extracted with methylene chloride. The methylene chloride was removed and the residue chromatographed on silica gel (1:1 hexane/toluene eluent). There was obtained 233 mg (40% yield) of porphyrin **4c**. The porphyrin was recrystallized from hexane. mp (sintered 222-227°) melted 229°, $\lambda_{max}$ ($CHCl_3$): 400 nm ($\varepsilon$ 190,000), 500 (13,000), 536 (9,600), 569 (6,700), 621 (4,100); IR ($CHCl_3$): 3310 $cm^{-1}$ (N-H); PMR ($CDCl_3$): $\delta$-3.58 (broad s, 2H, N-$\underline{H}$), 1.08 (5, 24H, $C\underline{H}_3$), 1.75 (m, 32H, $CH_3CH_2\underline{CH}_2$), 2.36 (m, 16H, $\underline{C}H_2CH_2$-porphyrin) 4.03 (t, 16H, $\underline{C}H_2$-porphyrin), 10.00 (s, 4H, meso-$\underline{H}$); $^{13}$CMR ($CDCl_3$): $\delta$ 14.1 ($\underline{C}H_3$), 22.7 ($CH_3\underline{C}H_2$), 26.6 ($CH_2$-porphyrin, 32.6 ($CH_3CH_2\underline{C}H_2$), 33.6 ($CH_3CH_2CH_2$-$\underline{C}H_2$), 96.8 (meso carbons), 140.2 ("β" carbons), 144.2 ("α" carbons); MS (70 eV): m/3 = 870 (parent). Anal. Calcd for $C_{60}H_{94}N_4$: C, 82.70; H, 10.88; N, 6.43. Found: C, 82.88; H, 10.74; N, 6.40. Solubility (hexane, 20°): 2.1 g/l (2.4 x $10^{-3}$M).

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## Notes and References:

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b. K.S. Chamberlin, Ph.D. Thesis, Michigan State University, 1979.

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3. The major product from the $B_2H_6$ reduction of tetraacetyl tetraethyl porphyrin (ref. 2) prove to be the tetraalcohol accompanied by varying amounts of chlorins (ref. 1b).

4. B.E. Hoogenboom, O.H. Oldenziel, and A.M. Van Lensen, *Org. Syn.*, 1977, **57**, 50.

5. We have found that old samples of formaldehyde give little or no porphyrin.

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