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Alkylation of 5,10,15-tris(3,5-di-*t*-butyl-4-hydroxyphenyl)-20-(4-pyridyl)porphyrin.[1]

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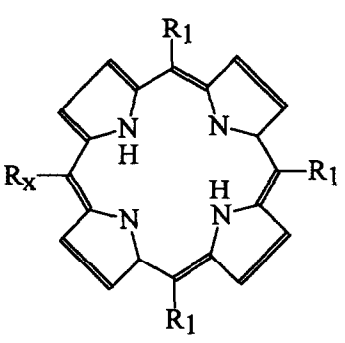
Abstract: the title porphyrin was prepared and alkylated with heptyl bromide, benzyl bromide and 4-nitrobenzyl bromide in DMF. Only with benzyl bromide did aerial oxidation occur, leading to further alkylation on the macrocyclic nitrogens and N-oxide formation on the 4-benzylpyridyl meso-substituent.

The facile aerial oxidation of 5,10,15,20-tetrakis(3,5-di-*t*-butyl-4-hydroxy-phenyl)porphyrin **1**[2] (see Scheme 1) is of interest because of its ability to produce reduced oxygen species, H_2O_2 and $OH^{\cdot}$.[3] Reduction of the oxidised porphyrin back to **1**, suggests the possibility of producing catalytic redox cycles that may find application, e.g., in fuel cells.[4] This would entail synthesis of unsymmetrically *meso*-substituted derivatives of **1**, functionalised for immobilisation on solid supports. We have made some progress in this direction,[5] synthesising and characterising porphyrins with 3,5-di-*t*-butyl-4-hydroxyphenyl (DtBHP) groups and 4-hydroxyphenyl,[5a] 3-hydroxyphenyl,[5b] and 4-nitrophenyl[5c] moieties.

Pyridyl *meso*-substituents would also provide suitable sites (via quaternisation of the nitrogen) for functionalisation and immobilisation. We report here the synthesis of the unsymmetrically *meso*-substituted porphyrin 5,10,15-tris(3,5-di-*t*-butyl-4-hydroxyphenyl)-20-(pyridyl)porphyrin **2**, and its alkylation with heptyl, benzyl, and 4-nitrobenzyl bromide. With benzyl bromide in DMF, as well as pyridine benzylation, aerial oxidation and macrocyclic di- and tetra-N-benzylation occur, ultimately with N-oxide formation on the pyridyl moiety.

EXPERIMENTAL

Uv/visible spectra were recorded on a Cecil CF 5500 double beam UV spectrophotometer, using spectroscopic grade $CHCl_3$ as solvent. ^{1}H-NMR spectra were recorded on a JEOL JNM FX 200 instrument in $CDCl_3$ using TMS (tetramethylsilane) as an internal reference. FABS mass spectra were recorded on a Vacuum Generators ZAB 2e double sector spectrometer, using 3-nitrobenzyl alcohol (3-NOBA) and



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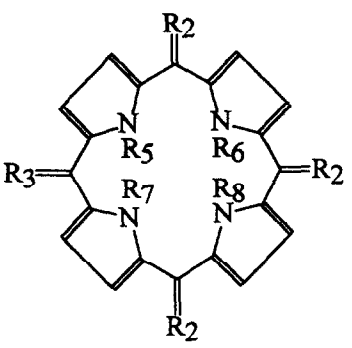

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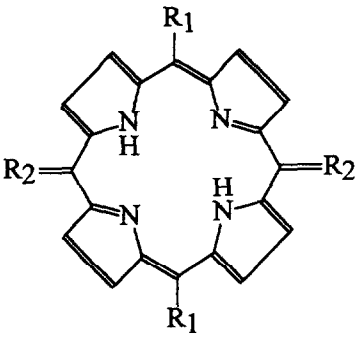

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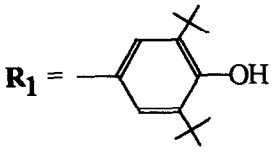
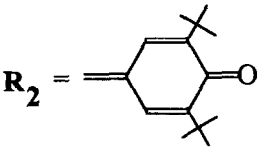
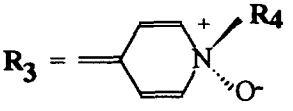
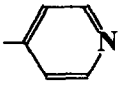
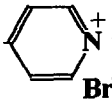






1. $R_X = R_1$

2. $R_X =$ 

3. $R_X =$  a; R_4 = -C_7H_{15}
   b; R_4 = -Bz
   c; R_4 = -4NBz

4. R_4 = -Bz: $R_5 = R_8 = R_6 = R_7$ = -Bz

5. $R_4 = R_5 = R_8$ = -Bz; $R_6 = R_7$ = H

Bz = -CH_2-C_6H_5: 4NBz = -CH_2-C_6H_4-NO_2

Scheme 1

chloroform as co-solvents. Infra-red spectra were recorded as KBr discs on a Perkin-Elmer 1420 Ratio Recording Infra Red Spectrophotometer.

Tlc was performed on Aldrich aluminium-backed silica-gel 60 F_{254} plates, and aluminium-backed neutral alumina 60 F_{254} type E. Porphyrins were separated via column chromatography on neutral alumina (Brockmann grade 3), supplied ready-made by ICN Biomedicals or as Brockmann grade 1 (150 mesh) supplied by Aldrich and converted to grade 3 by addition of, and vigorous shaking with 7% (w/v) water. Solvents and reagents were purchased from Aldrich and used as supplied.

Synthesis of Porphyrin **2** - Pyrrole (6.7 gm, 0.1 mole) and pyridine-4-carboxaldehyde (5.35 gm, 0.05 mole) were added to refluxing propionic acid (500 ml) containing 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (11.6 gm, 0.05 mole), and reflux continued during 3 hr. The reaction mixture was then concentrated to one fifth of its original volume by distillation, and the remaining propionic acid taken off under reduced pressure. After overnight cooling, the solid residue was triturated with acetone (500 ml) several times and filtered to give a mixture of porphyrins (4.5 gm) as a purple amorphous powder. The mixture was purified by flash chromatography on alumina, eluting with dichloromethane (DCM). The deep red eluant was concentrated and then rechromatographed on alumina, eluting with 60:40 DCM/n-hexane. Only the first and second fractions were collected.

The **first fraction** to be eluted from the column was concentrated and precipitated with n-hexane to yield the known *5,10,15,20-tetrakis(3,5-di-t-butyl-4-hydroxyphenyl)porphyrin* **1**[6] (650 mg, 2.3%) as a purple amorphous powder. The **second fraction** to be eluted from the column was concentrated and crystallised with n-hexane to yield the unsymmetrical *5,10,15-tris(3,5-di-t-butyl-4-hydroxyphenyl)-20-(4-pyridyl)porphyrin* **2** (1.010 gm, 2.5%) as purple microcrystals (Found: C, 80.4; H, 8.1; N, 6.6. $C_{67}H_{77}N_5O_3.{}^1/_2C_6H_{14}$ requires C, 80.61; H, 8.06; N, 6.72%). λ_{max}nm(ε mmol l^{-1}) 424(420.6), 520(14.5), 559(11.2), 594(3.95), 651(5.5). FAB-MS(3-NOBA, $CHCl_3$): found $^m/_z$ = 1000; $[M+H]^+$ requires $^m/_z$ = 1000. δ_H(ppm): 9.04, 9.01, 8.2, 8.17 (quartet, 4H, AB spin-system from pyridyl-H, J_{AB} = 5.86 Hz); 8.94 (s, 4H, pyrrole-ß-H remote from pyridyl group); 8.97, 8.95, 8.79, 8.76 (quartet, 4H, pyrrole-ß-H, adjacent to pyridyl group appear as an AB spin system, J_{AB} = 5.17Hz); 8.03 (s, 6H, DtBHP ortho-H); 5.55 (s, 3H, phenolic -OH); 1.63 (s, 54H, *t*-butyl-H); -2.69 (broad singlet, 2H, porphyrin-NH).

Alkylation of Porphyrin **2** *with 1-bromoheptane* - Porphyrin **2** (200 mg, $2*10^{-4}$ mol) was refluxed with excess 1-bromoheptane (10 ml, $6.4*10^{-2}$ mol) in DMF (50 ml) for 3 hr. DMF and excess 1-bromoheptane were removed by evaporation under vacuum, and the resulting black solid dissolved in acetone, filtered to remove some white insoluble material, evaporated to dryness, and the residue taken into a small amount of chloroform. This was applied to an alumina column, and the red band eluted with 95:5 chloroform/methanol. The red eluant was evaporated to dryness to yield *meso-5,10,15-tris(3,5-di-t-butyl-4-hydroxyphenyl)-20-(4-heptylpyridiniumyl)porphyrin bromide* **3a** as a purple amorphous powder (185 mg, 84%)(Found: C, 73.1; H, 8.2; N, 5.6. $C_{74}H_{92}BrN_5O_3.2H_2O$ requires C, 73.21; H, 7.91; N, 5.77%) λ_{max}nm(ε mmol l^{-1}) 426(95.0), 511(4.05), 593(7.8), 667(3.4). FAB-MS(3-NOBA, $CHCl_3$); Found: $^m/_z$ = 1099; $[(M-Br^-)+H]^+$ requires $^m/_z$ = 1099. δ_H(ppm): 9.86, 9.83, 8.82, 8.79 (quartet, 4H, AB spin-system from 4-pyridinium-H, J_{AB} = 5.86 Hz); 8.94 (s, 4H, pyrrole-ß-H remote from 4-pyridinium group); 9.04, 9.01, 8.77, 8.75 (quartet, 4H, pyrrole-ß-H adjacent to 4-pyridinium group appear as an AB spin-system, J_{AB} = 5.13 Hz); 8.02 (s, 6H, DtBHP ortho-H); 5.58 (s, 3H, phenolic -OH); 5.37 (t, 2H, alpha-CH_2 of heptyl group); 2.35 (broad quintet, 2H, ß-CH_2 of heptyl group); 1.63 (s, 54H, *t*-butyl-H); 1.4-1.3 (complex, 8H, -$(CH_2)_4$- of heptyl group); 0.92 (t, 3H, terminal -CH_3 of heptyl group); -2.55 (broad singlet, 2H, porphyrin-NH).

Alkylation of Porphyrin **2** *with benzyl bromide* - Porphyrin **2** (190 mg, $1.9*10^{-4}$ mol) was refluxed with excess benzyl bromide (3.5 ml, $2.9*10^{-3}$ mol) in excess DMF (50 ml) for 7 hr, and then the reaction mixture was allowed to stir at room temperature for a further 48 hr. DMF and benzyl bromide were removed by evaporation under reduced pressure, and the residue chromatographed on silica gel, eluting with acetone. The first band to elute from the column was unreacted porphyrin **2**. This was followed by two mauve coloured bands that on standing, changed colour to crimson. The **first** such product was collected and precipitated with n-hexane as a dark amorphous powder (13 mg, 5%): λ_{max}nm(ε mmol l^{-1}) 559(110.2) as first isolated; spectrum changes on standing in air, 521(105). (Found: C, 83.2; H, 7.4; N, 4.7. $C_{102}H_{108}N_5O_4$ requires C, 83.44; H, 7.36; N, 4.77%).Accurate mass MS: found, 1466.84±0.012; $C_{102}H_{108}N_5O_4$ requires 1466.8515 (reference standard polyethylene glycol, 1436.07963). This corresponds to a pentabenzylated oxidised porphyrin, monobenzylated and N-oxidised on the pyridyl *meso*-substituent and tetrabenzylated on the four macrocyclic nitrogen atoms, i.e., *5,10,15-tris(3,5-di-t-butyl-4-oxacyclohexa-2,5-dienylene)-20-(4-benzylpyridiniumyl-N-oxide)-N_{21},N_{22},N_{23},N_{24}-tetrabenzylporphyrinogen* **4**.

The **second** mauve product to be eluted from the column was collected and precipitated with n-hexane as a dark amorphous powder (45 mg, 20%). λ_{max}nm(ε mmol l^{-1}) 557(109) as first isolated; spectrum changes on standing in air, 522(101). (Found: C, 82.2; H, 7.4; N, 5.3. $C_{88}H_{96}N_5O_4$ requires C, 82.05; H, 7.46; N, 5.44%). Accurate mass MS: found, 1286.746±0.012; $C_{88}H_{96}N_5O_4$ requires 1286.7435 (reference standard polyethylene glycol, 1202.4169). This corresponds to an tribenzylated oxidised porphyrin, monobenzylated and N-oxidised on the pyridyl *meso*-substituent and dibenzylated on two of the four macrocyclic nitrogen atoms, i.e., *5,10,15-tris(3,5-di-t-butyl-4-oxacyclohexa-2,5-dienylene)-20-(4-benzylpyridiniumyl-N-oxide)-N_{21},N_{23}-dibenzylporphyrinogen* **5**.

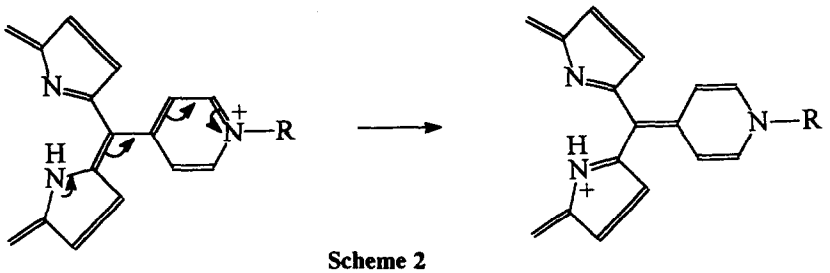
Alkylation of Porphyrin **2** *with 4-nitrobenzyl bromide* - Porphyrin **2** (100 mg, $1*10^{-4}$ mol) was refluxed with excess 4-nitrobenzyl bromide (1.1 gm, $5*10^{-3}$ mol) in DMF (50 ml) for 3 hr. DMF was removed by evaporation under vacuum, and the resulting dark solid dissolved in acetone, filtered, evaporated to dryness, and the residue taken into a small amount of chloroform. This was applied to a an alumina column, and the red band eluted with 95:5 chloroform/methanol. The red eluant was evaporated to dryness to yield *meso-5,10,15-tris(3,5-di-t-butyl-4-hydroxyphenyl)-20-(4-{4-nitrobenzyl}pyridiniumyl)porphyrin bromide* **3c** as a purple amorphous powder (120 mg, 90%)(Found: C, 72.1; H, 6.8; N, 6.7. $C_{74}H_{83}N_6O_5Br.H_2O$ requires C, 72.02; H, 6.89; N, 6.81%) λ_{max}nm(ε mmol l^{-1}) 425(130.5), 512(5.65), 595(9.9), 665(4.5). FAB-MS(3-NOBA, $CHCl_3$) Found: $^m/_z$ = 1136, 1135, 1000, 568; $[(M\text{-}Br^-)+H]^+$ requires $^m/_z$ = 1136; $[(M\text{-}Br)]^+$ requires 1135; $[(M\text{-}Br)\text{-}4\text{-nitrobenzyl}]^+$ requires 1000; $[(M\text{-}Br)+H]^{2+}$ requires 568. δ_H(ppm): 9.86, 9.83, 8.82, 8.79 (quartet, 4H, AB spin-system from 4-pyridinium-H, J_{AB} = 5.86 Hz); 8.94 (s, 4H, pyrrole-ß-H remote from 4-pyridinium group); 9.04, 9.01, 8.77, 8.75 (quartet, 4H, pyrrole-ß-H adjacent to 4-pyridinium group appear as an AB spin-system, J_{AB} = 5.13 Hz); 8.08, 7.97, 6.83, 6.72 (quartet, 4H, 4-nitrobenzyl-H, AB spin system, J_{AB} = 8.4 Hz); 8.02 (s, 6H, DtBHP ortho-H); 5.58 (s, 3H, phenolic -OH); 4.64 (broad singlet, 4H, 4-nitrobenzylic-CH_2); 1.3 (complex singlet, 54H, *t*-butyl-H); -2.53 (broad singlet, 2H, porphyrin-NH).

RESULTS AND DISCUSSION

The NMR spectra of the monopyridyl- **2** and monopyridinium-porphyrins **3a** and **3c** reported here have in common an AB spin quartet for the pyrrole-ß-protons adjacent to these *meso*-substituents. This has previously been observed in unsymmetrically *meso*-substituted porphyrins with electron-donating and withdrawing groups.[5c,7]

The uv/visible spectra exhibited by **3a** and **3c** were unusual in that three Q bands and a B band of reduced intensity are observed. This suggests the presence of a porphyrin *mono*-cation[8] (porphyrin free-

bases possess D_{2h} symmetry and exhibit a strong B band and four Q bands, while porphyrin dications, with higher symmetry (D_{4h}) show only slightly weaker B bands and two Q bands[8]). We suggest that delocalisation of pyridinium positive charge onto the macrocycle produces a resonance-stabilised monocation (see scheme 2), and that the mixture of tautomers (imparting some monocationic character) may be the reason for the three-Q-band visible spectra of **3a** and **3c**. Addition of triethylamine to solutions of these porphyrins generates the porphyrin free-base (figure).



Scheme 2

Alkylation of **2** with 1-bromoheptane or 4-nitrobenzyl bromide in DMF occurs as expected, with an n-heptyl or 4-nitrobenzyl moiety quaternising the *meso*-4-pyridyl group. Repeating this experiment using benzyl bromide, however, led to completely different products. Uv/visible spectroscopy of the two main compounds to be separated by column chromatography, indicated loss of the porphyrinic B band, to be replaced by a broad absorption at around 560 nm. On standing (either in solution, on the column, or as solid), this absorption in both compounds disappeared and was replaced by one at around 520 nm, to yield compounds **4** and **5**.

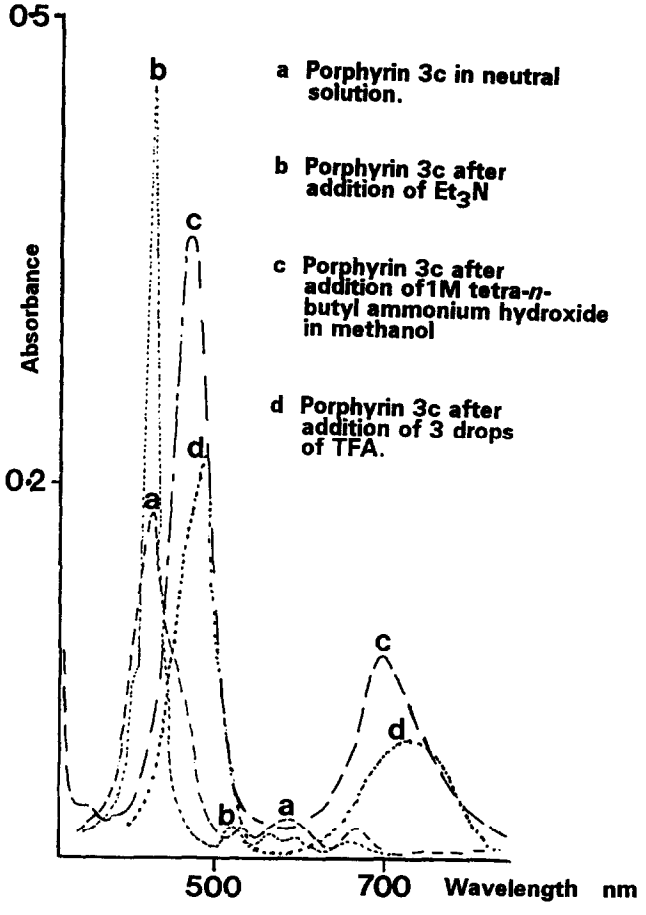
Loss of the B band in porphyrins *meso*-substituted with DtBHP groups, and the appearance of broad absorptions at longer wavelengths, are usually indicative of non-destructive oxidation of the porphyrin macrocycle, accompanied by loss of porphyrin aromaticity.[2] NMR spectra of **4** and **5** were complex (and will be reported elsewhere), but support this assertion, showing the disappearance of the high-field (above TMS) porphyrin-NH resonances, and the appearance of low field 2,5-disubstituted pyrrole-NH resonances at about 9.8-9.9 ppm.[9]

High resolution mass spectroscopy of **4** and **5** gave masses of 1466.840 and 1286.7460, corresponding to molecular formulae of $C_{102}H_{108}N_5O_4$ and $C_{88}H_{96}N_5O_4$, respectively. This, combined with low resolution mass spectroscopy indicated that both **4** and **5** were N-oxides (i.e., loss of 16 amu) and also polybenzylated (i.e., loss of $[C_7H_7]$). Support for the N-oxide formulation for **4** and **5** comes from infra-red spectroscopy which shows bands at 1310 cm^{-1} and 1280 cm^{-1}, usually assigned to N-O stretch in aromatic N-oxides.[10] Accordingly, we assign a pentabenzylated N-oxide structure to **4**, and a tribenzylated N-oxide structure to **5**, in which benzylation has occurred both at the pyridine *meso*-substituent and at the macrocyclic nitrogens. We have previously shown that the latter occurs when *meso*-tetrakis(3,5-di-*t*-butyl-4-oxacyclohexa-2,5-dienylene)porphyrinogen **6** is alkylated with a variety of alkyl and arylalkyl halides.[1]

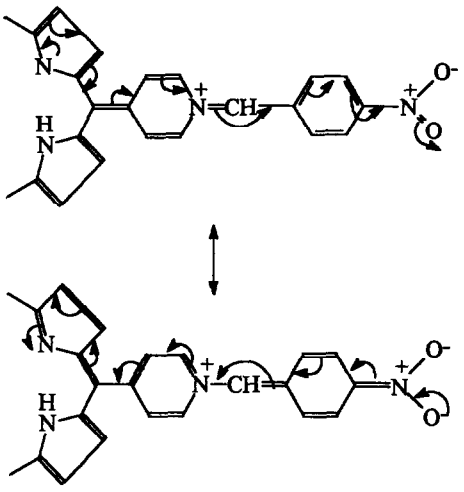
The anomalous behaviour of **2** with benzyl bromide, compared to 1-bromoheptane and 4-nitrobenzyl bromide, is explained in the following way. Benzyl bromide is known to form a relatively stable carbonium ion (compared to an alkyl bromide) in non-aqueous ionising solvents,[11] so that it is just as susceptible to S_N1 as well as S_N2 reactions, in DMF. As excess benzyl bromide is used, there will be a small equilibrium concentration of benzyl cation that will alkylate the central nitrogens of the porphyrin. This will introduce steric bulk into the area occupied by the central nitrogens, which is relieved by buckling of the macrocycle. We have previously shown[12] with porphyrin **1** that such buckling leads to a flow of electron density from the DtBHP groups onto the macrocycle, that lowers the redox potential of the porphyrin to aerial oxidation.[5a]

Support for this view comes from two quarters. First, simply refluxing porphyrin **2** in *neat* benzyl bromide for 4 hours, produces a compound with a uv/visible spectrum very similar to that of **3a** and **3c**, i.e. an unsymmetrical porphyrin *meso*-substituted with three DtBHP and one pyridinium group. This suggests that because benzyl bromide is itself not an ionising solvent, then the formation of benzyl cation is largely suppressed. Consequently, only the pyridine moiety can now react via the usual S_N2 mechanism to give **3b**. Secondly, replacing benzyl bromide with 4-nitrobenzyl bromide also suppresses the S_N1 route, even in DMF, because the electron-withdrawing 4-nitro- group destabilises the 4-nitrobenzyl cation. Thus, 4-nitrobenzyl bromide with porphyrin **2** in neutral DMF forms only the nitrobenzylpyridinium compound **3c**, with no oxidised porphyrin formed.

Both **3a** and **3c** undergo oxidation in basified solutions. Whereas **3a** on oxidation gives a uv/visible spectrum similar to the oxidised porphyrin **6** (i.e., no B band and broad, but less intense, absorbances at 530 and 590 nm[6]), **3c** gives a band (as intense as the B band of neutral **3c**) at 470 nm and a weaker band at 693 nm (see figure). On neutralisation, the **3c** spectrum does not return. These changes may be due not only to oxidation of **3c**, but removal of a 4-nitrobenzylic -CH_2 proton. This would generate negative charge that can delocalise over the macrocycle and the 4-nitrobenzyl group (see scheme 3).



Figure



Scheme 3

CONCLUSIONS

Porphyrin **2** can be alkylated in DMF at the *meso*-pyridine substituent with 1-bromoheptane and 4-nitrobenzyl bromide to give **3a** and **3c**. Alkylation with benzyl bromide under the same conditions leads ultimately to oxidised porphyrins, benzylated on the macrocycle as well as the pyridine *meso*-substituent, which are also separated as the pyridine N-oxides **4** and **5**. This was shown to be a probable consequence of the formation of benzyl cations that alkylate the central nitrogens of porphyrin **2**. This leads to distortion of the macrocycle that ultimately promotes aerial oxidation.

In basified solutions, uv/visible spectroscopy suggests that porphyrin **3c** forms a novel chromophoric system. We are currently investigating the use of this, and other alkylated oxidised porphyrins based on porphyrins **2** and **6**, as novel dyes and pigments.

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