Tetrahedron Vol. 43, No. 20, pp. 4569 to 4577, 1987
Printed in Great Britain.

0040–4020/87 \$3.00+.00

A NEW AND HIGHLY EFFICIENT SYNTHESIS OF HYDROXYPORPHYRINS

Maxwell J. Crossley,* Lionel G. King, and Simon M. Pyke

The Department of Organic Chemistry,
The University of Sydney, N.S.W. 2006, Australia.

(*Received in UK* 30 *July* 1987)

Abstract: A new synthesis of hydroxyporphyrins is reported. The method involves nucleophilic displacement of a nitro group using the sodium salt of *E*-benzaldoxime and is a general process allowing the synthesis of both β-hydroxyporphyrins and *meso*-hydroxyporphyrins. Activation of the porphyrin system towards nucleophilic attack is achieved by complexation of the macrocycle with the relatively electronegative nickel(II) or copper(II) ions. Thus, treatment of either the copper(II) or the nickel(II) chelates of 2-nitro-5,10,15,20-tetraphenylporphyrin with the sodium salt of *E*-benzaldoxime gave the corresponding 2-hydroxyporphyrin in high yield. Similar treatment of the copper(II) or the nickel(II) chelates of 5-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin gave the corresponding 5-hydroxyporphyrin, again in high yield. These reactions show that metallo-nitroporphyrins display similar electrophilic properties to much simpler nitro-arene systems. The nickel(II) 5-hydroxyporphyrin **10** was cleanly demetallated on treatment with concentrated sulfuric acid to give the corresponding free-base oxophlorin thereby greatly increasing the general utility of the hydroxylation methodology. Conversion of (5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **16** into (5-acetoxy-15-methoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **18** established that the reaction mechanism involves regiospecific replacement (*i.e.*, *ipso*-substitution) of the nitro group by the oxygen nucleophile.

The introduction of an hydroxyl group to the porphyrin periphery provides a means of modulating the properties of the porphyrin ring,[1-4] and could also provide a convenient point of attachment, by way of ether or ester linkages, for covalently linking axial ligands or potential substrate molecules to the porphyrin ring of a haemoprotein model. *meso*-Hydroxyporphyrins and their keto tautomers, the oxophlorins, are of additional interest as certain of these compounds are intermediates in haem catabolism and are precursors of the bile pigments.[4,5]

While a number of total synthesis approaches to hydroxyporphyrins have been reported,[1,4] there are very few methods which allow the functionality to be introduced at the porphyrin stage. Furthermore, no synthetic method has been reported previously for the direct, regiospecific hydroxylation of the porphyrin nucleus.

The previous, non-specific methods for the oxidation of the porphyrin periphery have involved the use of radicals. Oxygenation at a *meso*-position has been achieved with thallium trifluoroacetate,[6] with benzoyl peroxide,[7] and with hydrogen peroxide in the presence of pyridine;[8] only the later conditions afford hydroxyporphyrins directly. In the case of the haem derivative, protoporphyrin IX dimethyl ester, benzoyloxylation produced a mixture of isomers which were extremely difficult to separate.[9] Benzoyl peroxide has also been used to oxygenate the zinc(II) chelate of tetraphenylporphyrin, although only in low yield.[10]

We have previously reported the synthetic utility of both β- and *meso*-nitroporphyrins in providing a convenient access to the substitution of the porphyrin nucleus.[11-13] Recently, we have shown that alkoxide ions react with the copper(II) 2-nitroporphyrin **1** at the β-pyrrolic position adjacent to the carbon bearing the nitro group, resulting in the formation of the corresponding copper(II) 2-nitro-3,3-dialkyloxy-2,3-dihydroporphyrins, which could be converted in several steps to the 2-hydroxyporphyrin **2**;[11] the process involved an overall *cine*-substitution. Similarly, treatment of the copper(II) 2-nitroporphyrin **1** with hydroxide ion gave the corresponding 2-nitro-3-hydroxyporphyrin. Gong and

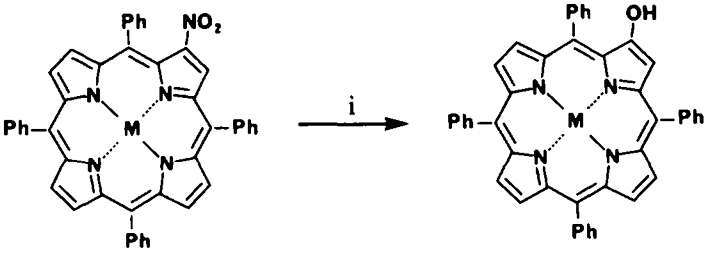
Dolphin[14] have reported that treatment of zinc(II) 5-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin **8** with methoxide resulted in the formation of zinc(II) 5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin **14**, with no product resulting from nitro group displacement being obtained.[14]

The failure of the 'hard' alkoxide nucleophiles to displace the nitro group led us to investigate the reaction of nitroporphyins with other oxygen nucleophiles. The sodium salt of *E*-benzaldoxime is an extremely nucleophilic 'soft' nucleophile which effectively displaces nitro groups in aromatic systems to give rise to the corresponding phenols.[15] As with other aromatic nucleophilic substitutions, the reaction generally requires activation by an electron withdrawing group *ortho* or *para* to the nitro group. The reaction of the sodium salt of benzaldoxime with the relatively unactivated 4-nitrobiphenyl, however, gives the corresponding phenol in low yield.[15]

In this study, the reaction of the benzaldoxime anion with nitroporphyrins was investigated. The starting nitroporphyrins are readily available using methods that we have reported earlier.[12,16] Activation of the porphyrin system towards nucleophilic substitution is achieved by complexation of the macrocycle with the relatively electronegative nickel(II) or copper(II) ions. We now report that this reaction provides a general, highly-efficient method for introduction of an hydroxyl group onto the porphyrin by the regiospecific nucleophilic substitution of a nitro group.

Results and Discussion

β-Hydroxyporphyrins. The reaction of the sodium salt of *E*-benzaldoxime with the copper(II), nickel(II), and zinc(II) chelates of 2-nitro-tetraphenylporphyrin (**1**, **2**, and **3** respectively) was investigated. Treatment of (2-nitro-5,10,15,20-tetraphenylporphyrinato)copper(II) **1** with the sodium salt of *E*-benzaldoxime (5-10 equivalents) in dry, freshly distilled dimethyl sulfoxide under an inert atmosphere at 60 °C for 1 to 2 hours afforded a 93% yield of the corresponding copper(II) 2-hydroxy-tetraphenylporphyrin **4** (Scheme I). Similar treatment of nickel(II) 2-nitro-tetraphenylporphyrin **2** gave nickel(II) 2-hydroxy-tetraphenylporphyrin **5** in 60% yield. The zinc(II) compound **3** did not react under these conditions.



1 M = Cu
2 M = Ni
3 M = Zn

4 M = Cu
5 M = Ni

Scheme I. i, sodium salt of *E*-benzaldoxime in Me_2SO, aqueous work-up.

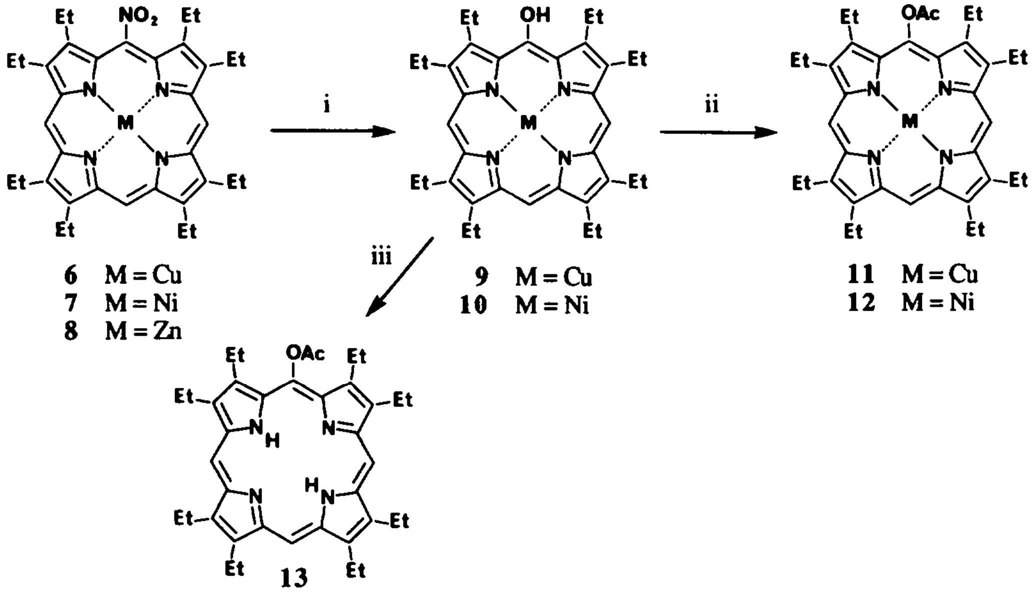
Optimum yields of the metallo-2-hydroxy-tetraphenylporphyrins, **4** and **5**, were achieved by the use of a large excess (10 equivalents) of the oxime anion nucleophile, which shortened the reaction time. The use of fewer equivalents of nucleophile and correspondingly longer reaction periods resulted in significantly lower yields.

The reaction of the copper(II) and nickel(II) chelates, **1** and **2**, therefore provides a very efficient entry to 2-hydroxy-tetraphenylporphyrins and, by subsequent alkylation,[10] 2-alkoxyporphyrins. This methodology represents a significant improvement over methods involving either oxidation of tetraphenylporphyrin with benzoyl peroxide,[2,10] or radical denitration of 3,3-dialkoxyoxy-2,3-dihydro-2-nitro-tetraphenylporphyrins and subsequent transformations.[11]

The reactivity of the different metalloporphyrins towards the benzaldoxime anion mirrors the effect of the central metal ion observed for the reaction of these metalloporphyrins with alkoxide nucleophiles, when both copper(II) 2-nitro-tetraphenylporphyrin **1** and nickel(II) 2-nitro-tetraphenylporphyrin **2** underwent facile reaction with the methoxide anion while the zinc(II) derivative **3** was unreactive.[17] Thus the relatively electronegative metal ions, copper(II) and nickel(II) can be seen as activating groups for nucleophilic reactions at the porphyrin periphery, akin in nature to an *ortho* or *para* electron withdrawing group in benzene chemistry.

***meso*-Hydroxyporphyrins.** It was envisaged that a similar displacement of a *meso*-nitro group by benzaldoxime anion would provide a synthesis of the *meso*-hydroxyporphyrins and their keto tautomers, the oxophlorins. The reaction of the sodium salt of *E*-benzaldoxime with metallo-5-nitro-octaethylporphyrins was therefore investigated.

Treatment of the copper(II) 5-nitro-octaethylporphyrin **6** in dry, freshly distilled dimethyl sulfoxide with the sodium salt of *E*-benzaldoxime (3 equivalents), under nitrogen at 55-60 °C for 1.5 hours, afforded copper(II) 5-hydroxy-octaethylporphyrin **9** in 89% yield (Scheme II). Similar treatment of nickel(II) 5-nitro-octaethylporphyrin **7** afforded nickel(II) 5-hydroxy-octaethylporphyrin **10** in 88% yield. However, treatment of zinc(II) 5-nitro-octaethylporphyrin **8** at temperatures up to 100 °C again failed to cause any reaction. The reactivity of the oxime nucleophile with *meso*-nitroporphyrins therefore corresponds to that observed with β-nitroporphyrins.



Scheme II. i, sodium salt of *E*-benzaldoxime in Me_2SO, aqueous work-up; ii, Ac_2O/pyridine iii, a H_2SO_4/CH_2Cl_2, b Ac_2O/pyridine.

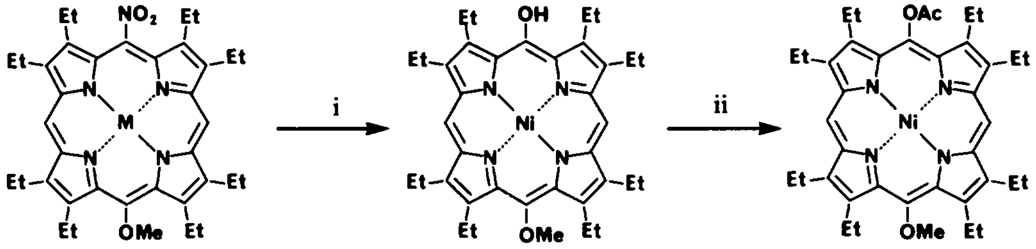
As the oxidation of *meso*-hydroxyporphyrins to the corresponding π-radical cations is known to be facile,[18] compounds **9** and **10** were converted to protected acetates by reaction with acetic anhydride and pyridine. In this way, copper(II) 5-acetoxy-octaethylporphyrin **11** and nickel(II) 5-acetoxy-octaethylporphyrin **12** were prepared in 97% and 99% yields, respectively.

As a further extension, the intermediate nickel(II) 5-hydroxy-octaethylporphyrin **10** was demetallated with concentrated sulfuric acid to afford 2,3,7,8,12,13,17,18-octaethyloxophlorin. As oxophlorins are easily oxidized in air, this compound was immediately converted by treatment with acetic anhydride and pyridine to the protected form, 5-acetoxy-octaethylporphyrin **13**, in an overall 68% yield from **10**. The fact that demetallation is readily achieved without either concomitant electrophilic sulfonation of the (activated) macrocyclic ring or oxidative decomposition of the system clearly increases the general utility of the hydroxylation methodology.

Other syntheses of oxophlorins from *meso*-unsubstituted porphyrins involve oxidative reagents such as thallium(III) trifluoroacetate[6] or benzoyl peroxide.[7] The high yielding nucleophilic method developed in the present work provides a complementary, non-oxidative approach to this biologically important structure.

Regiochemistry. As there are a number of sites on a nitroporphyrin at which nucleophilic attack could take place, it is highly desirable that the process actually be regiospecific. The reaction may involve either regiospecific displacement of the nitro group, by direct (*i.e.*, *ipso*) attack or attack at some other position followed by loss of nitrous acid from the resultant product, or it may be non-specific. In the above examples, there is no marker by which these three processes can be distinguished. Introduction of another substituent at the *meso*-position opposite that of the nitro group (i.e; 5,15-disubstitution) allows the specificity of the process to be determined.

The specific displacement of the nitro group in the substituted *meso*-nitroporphyrin **16** by an hydroxyl group showed the hydroxylation process involves a regiospecific *ipso*-attack (Scheme III).



14 M = Zn
15 M = 2H
16 M = Ni

17

18

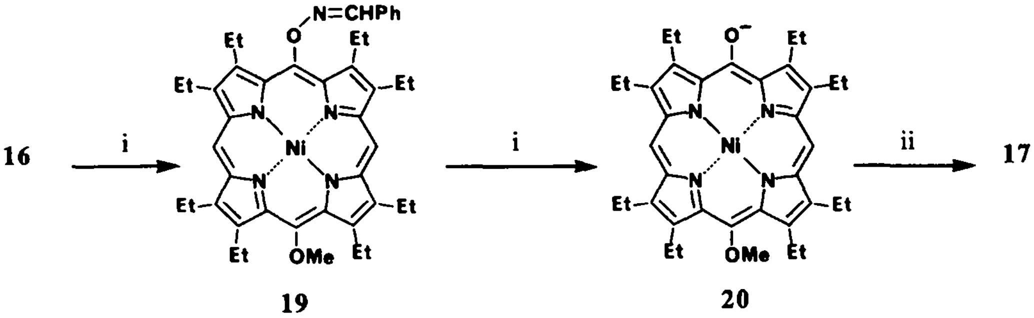
Scheme III. i, sodium salt of *E*-benzaldoxime in Me_2SO, aqueous work-up; ii, Ac_2O/pyridine.

The starting material for this reaction, (5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **16**, was synthesised in three steps from (5-nitro-2,3,7,8-12,13,17,18-octaethylporphyrinato)zinc(II) **8** as follows. Treatment of **8** in tetrahydrofuran with a solution of sodium methoxide in methanol according to the method of Gong and Dolphin,[14] followed by chromatography afforded (5-methoxy-15-nitro-octaethylporphyrinato)zinc(II) **14** in 23% yield. Demetallation with dry hydrogen chloride gave 5-methoxy-15-nitro-octaethylporphyrin **15** in 95% yield. The free base porphyrin was metallated with nickel acetate in refluxing *N,N*-dimethylformamide to give the nickel chelate **16** in 67% yield.

Treatment of a dry dimethyl sulfoxide solution of the nickel chelate **16** with the sodium salt of *E*-benzaldoxime (5 equivalents) under an inert atmosphere at 80 °C for two hours afforded the nickel(II) *meso*-hydroxy-octaethylporphyrin **17**. Again, protection of the hydroxyl group was achieved by heating the *meso*-hydroxyporphyrin **17** in a mixture of acetic anhydride and pyridine which gave the nickel(II) 5-acetoxy-15-methoxy-octaethylporphyrin **18** in 68% overall yield from **16**. The isomeric porphyrin, nickel(II) 5-acetoxy-10-methoxy-octaethylporphyrin was not detected.

The regiospecific outcome of this substitution reaction on the nitroporphyrin can be compared with the reaction of the oxime anion with the nitrobenzenes studied by Knudsen and Snyder.[15] An *ipso* displacement of the nitro group is found in each case.

Mechanism. The mechanism proposed[15] for the simpler nitrobenzene system appears likely to operate in the present case. The first step can be considered as an aromatic nucleophilic substitution, with *ipso* displacement of the nitro group by the oxime anion, which affords the oxime-substituted porphyrin **19**. A second equivalent of oxime anion then serves as a base, effecting the elimination of benzonitrile, with concomitant liberation of the porphyrin oxide **20**. Protonation on work-up yields the hydroxyporphyrin **17** (Scheme IV).



Scheme IV. i, sodium salt of *E*-benzaldoxime in Me_2SO; ii, H^+.

The electron-rich porphyrin oxide intermediates in this general sequence would be expected to be susceptible to further oxidation and this may explain the lower yields of hydroxyporphyrin obtained in the above reactions when fewer equivalents of nucleophile and correspondingly longer reaction times were employed.

While the same *ipso*-substitution mechanism is most likely to be operating in the reactions of the 2-nitroporphyrins, attack of the nucleophile on the β-pyrrolic position next to the carbon bearing the nitro group can give an identical hydroxyporphyrin product via a 2-nitro-3-oxychlorin followed by nitrous acid elimination. Further work on a labelled 2-nitroporphyrin is necessary to establish the exact mechanism in this particular case.

Conclusion

Highly efficient one-pot syntheses of both 2-hydroxy- and 5-hydroxy-porphyrins have been achieved by nucleophilic displacement of a nitro group by the anion of *E*-benzaldoxime. This method provides the first specific laboratory synthesis of oxophlorins from porphyrinic starting materials. The nucleophilic substitution reaction proceeds on nitroporphyrins activated by chelation to an electronegative metal ion; *i.e.*, both the copper(II) and nickel(II) chelates react smoothly while the corresponding zinc(II) chelates were found to be unreactive. In the case of the 5-nitroporphyrins, the displacement was shown to be regiospecific by the synthesis of (5-acetoxy-15-methoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)-nickel(II) **18** from the corresponding nitro-methoxyporphyrin **16**. This finding further illustrates that nitroporphyrins display similar electrophilic properties to much simpler nitro-arene systems.[11-13] The potential value of a simple non-oxidative method for the specific synthesis of the naturally occurring oxophlorins is obvious and is currently under investigation in our laboratory.

Experimental Section

Melting points were recorded on a Reichert hot-stage microscope and are uncorrected. All reagents and solvents were purchased from commercial sources and used as received unless otherwise noted. Light petroleum refers to the fraction of b.p. 65-70 °C, and was treated with concentrated sulfuric acid in the usual way and redistilled before use. Proton NMR spectra were recorded with a Bruker WM400 MHz spectrometer on samples dissolved in deuteriochloroform and are reported in units referenced to Me_4Si as internal standard. The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad are used throughout. Infrared spectra were recorded on a Digilab FTS 20/80 Fourier Transform spectrometer or on a Perkin-Elmer 221 spectrometer. Visible spectra were recorded on a Hitachi 150-20 spectrophotometer. Mass spectra were recorded on an A.E.I. MS 902 spectrometer at 70 eV. Column chromatography was performed on Merck zinc-free silica gel 60 (type 7754). Elemental analyses were performed by the Australian Microanalytical Service, Melbourne.

(2-Hydroxy-5,10,15,20-tetraphenylporphyrinato)copper(II) **4**

A solution of sodium methylsulfinylmethanide was prepared by stirring sodium hydride (50% suspension in oil, 0.024 g, 0.50 mmol) with dry, freshly distilled dimethyl sulfoxide (50 mL) at 75 °C under nitrogen for 30 min. *E*-Benzaldoxime (0.095 g, 0.92 mmol) was added and the resultant yellow mixture was cooled to 60 °C. (2-Nitro-5,10,15,20-tetraphenylporphyrinato)copper(II) **1** (0.103 g, 0.14 mmol) was added and the mixture was stirred at 60 °C for 1.5 h. The mixture was allowed to cool, diluted with dichloromethane (150 mL), washed with water (6 x 200 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed. The residue was chromatographed on a silica column (4 cm diameter, 200 g), protected from light, using 30% light petroleum in chloroform as eluant, and the resultant product recrystallized from dichloromethane/hexane to yield (2-hydroxy-5,10,15,20-tetraphenylporphyrinato)copper(II) **4** as a purple microcystalline solid (0.092 g, 93%), m.p. >350 °C (lit.,[2] >300 °C). Infrared spectrum (nujol) ν_{max} 3450 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 416 (log ε 5.50), 500 sh (3.61), 540 (4.20), 580 nm (3.72). Mass spectrum *m/z* 691 (M$^+$, 100%).

(2-Hydroxy-5,10,15,20-tetraphenylporphyrinato)nickel(II) **5**

(2-Nitro-5,10,15,20-tetraphenylporphyrinato)nickel(II) **2** (0.113 g, 0.157 mmol) was added to a solution of the sodium salt of *E*-benzaldoxime (21 mmol) in dimethyl sulfoxide (80 mL), prepared as described above, and the resulting mixture was stirred under nitrogen and in the dark at 60 °C for 2 h. Work-up as for **4** and recrystallization of the product from dichloromethane/hexane yielded (2-hydroxy-5,10,15,20-tetraphenylporphyrinato)nickel(II) **5** as a purple microcrystalline solid (0.065 g, 60%), m.p. >350 °C. Infrared spectrum (nujol) ν_{max} 3450 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 414 (log ε 5.28), 531 (4.10), 568 (3.73), 608 nm (3.07). ^{1}H NMR δ 7.64-7.71 (m, 9H, $H_{m,p}$ at $C_{5,10,15}$), 7.76-7.83 (m, 3H, $H_{m,p}$ at C_{20}), 7.90 (s, 1H, H_3), 7.94-8.06 (m, 8H, H_o), 8.56 and 8.71 (AB q, J_{AB} = 5 Hz, 2H, β-pyrrolic H), 8.67 and 8.72 (AB q, J_{AB} = 5 Hz, 2H, β-pyrrolic H), 8.70 and 8.73 (AB q, J_{AB} = 5 Hz, 2H, β-pyrrolic H). Mass spectrum *m/z* 686 (M$^+$, 100%). Anal. Calcd for $C_{44}H_{28}N_4NiO$: C,76.9; H, 4.1; N, 8.2. Found: H, 4.4; N, 7.7.

(5-Hydroxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **10**

A solution of sodium methylsulfinylmethanide was prepared by stirring sodium hydride (50% suspension in oil, 0.008 g, 0.17 mmol) to dry, freshly distilled dimethyl sulfoxide (60 mL) under nitrogen at 75 °C for 1 h. The solution was cooled to 55 °C, *E*-benzaldoxime (0.048 g, 0.46 mmol) was added and the mixture was stirred for 15 min. (5-Nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **7** (0.038 g, 0.060 mmol) was then added and the mixture was stirred under nitrogen at 55-60 °C for 1.5 h. The mixture was allowed to cool and then diluted with dichloromethane (200 mL), washed with water (7 x 200 mL) and with sodium dithionite solution (10%, 100 mL), dried over anhydrous sodium sulfate, filtered, and the solvent removed. The crude product was recrystallised from dichloromethane/light petroleum to yield (5-hydroxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **10** as violet cubes (0.032 g, 88%), m.p. >300 °C (lit.,[18] >300 °C). Infrared spectrum (nujol) ν_{max} 3450 br cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 407 (log ε 5.19), 524 (4.01), 557 nm (3.95). ^{1}H NMR δ 1.74 (m, 24H, CH_3), 3.24-4.61 (br m, 16H, CH_2). Mass spectrum *m/z* 606 (M$^+$, 100%), 605 (14), 591 (16).

(5-Acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **12**

A mixture of (5-hydroxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **10** (0.114 g, 0.19 mmol), acetic anhydride (2 mL) and pyridine (5 mL) was refluxed for 1 h, then cooled to 0 °C. Water (20 mL) was added cautiously, then the mixture was poured into dichloromethane (300 mL) and washed with dilute hydrochloric acid (1M, 2 x 250 mL), water (25 mL), dried over anhydrous, filtered, and the solvent removed. The crude acetoxy compound was purified by chromatography over neutral alumina (Grade III) using dichloromethane as eluant, followed by recrystallisation from dichloromethane/methanol to give (5-acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **12** as a purple needles (0.121 g, 99%), m.p. 231-232 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1762 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 402 (log ε 5.27), 524 (4.05), 558 nm (4.27). ^{1}H NMR δ 1.74 and 1.76 and 1.77 and 1.78 (4t, *J* = 7.8 Hz, each 6H, CH_3), 2.62 (s, 3H, CH_3CO), 3.58 (dq, J_{gem} = 14.3 Hz and J_{vic} = 7.8 Hz, 2H, CH_aH_b at $C_{3,7}$), 3.76 and 3.83 and 3.90 (each q, each 4H, CH_2 at $C_{2,8,12,13,17,18}$), 3.89 (dq, 2H, J_{gem} = 14.3 Hz and J_{vic} = 7.8 Hz, CH_aH_b at $C_{3,7}$), 9.49 (s, 1H, H_{15}), 9.52 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 648 (M$^+$, 100%), 606 (63), 590 (15). H.r.m.s. Calcd for $C_{38}H_{46}N_4O_2Ni$: *m/z* 648.2974. Found : *m/z* 648.2973.

(5-Acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)copper(II) **11**

(5-Nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)copper(II) **6** (0.044 g, 0.064 mmol) was added to a solution of the sodium salt of *E*-benzaldoxime (33 mmol) in dimethyl sulfoxide (50 mL), prepared as described above, and the resulting mixture was stirred under nitrogen and in the dark at 60 °C for 1.5 h. Work-up as for **10** and recrystallization of the product from dichloromethane/light petroleum yielded (5-hydroxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)copper(II) **9** as a purple microcrystalline solid (0.035 g, 89%). This hydroxyporphyrin was converted to (5-acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)copper(II) **11** by the foregoing acetylation procedure. Recrystallization of the product from dichloromethane/methanol gave purple needles (0.039 g, 97%) m.p. 240-242 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1760 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 407 (log ε 5.43), 528 (4.14), 559 nm (4.29). Mass spectrum *m/z* 653 (100%), 611 (42), 593 (60). H.r.m.s Calcd for $C_{38}H_{46}N_4O_2Cu$: *m/z* 653.2919. Found : *m/z* 653.2913.

5-Acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrin **13**

Concentrated sulfuric acid (18M, 5 mL) was added to a solution of (5-hydroxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **10** (0.044 g, 0.07 mmol) in dichloromethane (40 mL), and the mixture stirred for 2 h at room temperature. The reaction mixture was poured onto ice (100 g) and extracted with dichloromethane (2 x 100 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (400 mL), dilute aqueous sodium dithionite (1%, 400 mL), dried, and the solvent removed. The crude oxophlorin was heated in refluxing acetic anhydride (5 mL) and pyridine (5 mL) for 1 h, then water (10 mL) was added slowly to the cooled reaction mixture. Dichloromethane (200 mL) was added. The solution was washed with water (100 mL), dilute hydrochloric acid (1M, 4 x 200 mL), water (2 x 200 mL), dried, and the solvent removed. Recrystallization of the residue from dichloromethane/methanol gave 5-acetoxy-2,3,7,8,12,13,17,18-octaethylporphyrin **13** as purple needles (0.029 g, 68%), m.p. 211-213 °C. Infrared spectrum ($CHCl_3$) ν_{max} 3295, 1761 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 404 (log ε 5.48), 502 (3.97), 535 (3.75), 572 (3.72), 625 nm (3.26). ^{1}H NMR δ -3.53 (bs, 2H, 2 x NH), 1.81-1.94 (m, 24H, CH_3), 3.70 (m, 2H, CH_aH_b at $C_{3,7}$), 3.94-4.11 (m, 14H, CH_2 at $C_{2,8,12,13,17,18}$ and CH_aH_b at $C_{3,7}$), 9.92 (s, 1H, H_{15}), 10.08 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 592 (M^+, 100%), 550 (58), 534 (19). H.r.m.s. Calcd for $C_{38}H_{48}N_4O_2$: *m/z* 592.3777. Found : *m/z* 592.3777.

(5-Methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)zinc(II) **14**

This method is a modification of that of Gong and Dolphin.[14] To a suspension of sodium methoxide (5.94 g, 0.11 mol) in dry tetrahydrofuran (200 mL) and dry methanol (15 mL) was added a solution of (5-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)zinc(II) **8** (0.223 g, 0.35 mmol) in dry tetrahydrofuran (50 mL). The mixture was heated at reflux for 5 days in the dark. The reaction mixture was filtered through a pad of silica (100 g) and the solvent removed. The crude product was chromatographed on a silica column (4 cm diameter, 200 g) using 50% light petroleum in dichloromethane as eluant. The partially purified mixture was then separated by h.p.l.c. (Whatman Partisil M20 column) using dichloromethane/light petroleum (1:3, v/v) as eluant. The starting material (5-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)zinc(II) **8**) was recovered (0.069 g, 31%). The more polar product was recrystallized from dichloromethane/light petroleum to give (5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)zinc(II) **14** as a purple microcrystalline solid (0.053 g, 23%), m.p. >300 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1531, 1276, 1072 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 407 (log ε 4.48), 539 (4.13), 577 nm (4.48) [lit.,[14] (CH_2Cl_2) λ_{max} 408 (log ε 4.46), 502 sh (3.41), 539 (4.22), 577 nm (3.92)]. ^{1}H NMR δ 1.69 (t, J = 7.6 Hz, 6H, CH_3 at $C_{3,7}$), 1.84 (t, J = 7.6 Hz, 6H, CH_3 at $C_{13,17}$), 1.88 and 1.92 (2t, J = 7.6 Hz, each 6H, CH_3 at $C_{2,8,12,18}$), 3.72 (q, J = 7.6 Hz, 4H, CH_2 at $C_{3,7}$), 3.95 (dq, J_{vic} = 7.6 Hz, J_{gem} = 13.8 Hz, 2H, CH_aH_b at $C_{13,17}$), 4.07 (q, J = 7.6Hz, 8H, CH_2 at $C_{2,8,12,18}$), 4.16 (dq, J_{vic} = 7.6 Hz, J_{gem} = 13.8 Hz, 2H, CH_aH_b at $C_{13,17}$), 4.38 (s, 3H, OCH_3), 10.16 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 671 (100%), 641 (19), 626 (27), 596 (14).

5-Methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin **15**

Anhydrous hydrogen chloride was bubbled through a solution of (5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)zinc(II) **14** (0.053 g, 0.079 mmol) in dichloromethane (200 mL) for 5 min, followed by nitrogen for a further 15 min. The dichloromethane solution was washed with sucessively with water (2 x 200 mL), saturated sodium bicarbonate solution (2 x 200 mL), water (200 mL). The organic phase was dried and evaporated to dryness. The crude product was chromatographed on a silica column (4 cm diameter, 100 g) using 50% dichloromethane in light petroleum as eluant. Recrystallization of the product from dichloromethane/methanol gave 5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin **15** as a purple microcrystalline solid (0.046 g, 95%), m.p. >300 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1532, 1274, 1071 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 404 (log ε 5.16), 508 (4.19), 543 (3.66), 577 (3.75), 631 nm

(3.06) [lit.,[14] (CH_2Cl_2) λ_{max} 404 (log ε 5.15), 508 (4.19), 542 (3.66), 577 (3.79), 631 nm (3.09)]. ^1H NMR δ -3.14 (s, 1H, NH), -3.09 (s, 1H, NH), 1.67 (t, J = 7.6 Hz, 6H, CH_3 at $C_{3,7}$), 1.81 and 1.86 and 1.90 (3t, J = 7.6 Hz, each 6H, CH_3 at $C_{2,8,12,13,17,18}$), 3.67 (q, J = 7.6 Hz, 4H, CH_2 at $C_{3,7}$), 4.05 (q, J = 7.6 Hz, 12H, CH_2 at $C_{2,8,12,13,17,18}$), 4.45 (s, 3H, OCH_3), 10.14 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 609 (100%), 579 (16), 564 (35), 549 (18), 533 (10).

(5-Methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **16**

A mixture of 5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrin **15** (0.066 g, 0.11 mmol) and nickel acetate (0.0541 g, 0.22 mmol) in *N,N*-dimethylformamide (50 mL) was heated at reflux for 1 h and then allowed to cool. The reaction mixture was poured into dichloromethane (150 mL) and washed with water (5 x 250 mL), dried, and the solvent removed. The crude product was chromatographed on a silica column (4 cm diameter, 100 g) with 50% dichloromethane in light petroleum as eluant, and then recrystallised from dichloromethane/methanol to give (5-methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **16** as purple needles (0.048 g, 67%), m.p. 212 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1531, 1276, 1065 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 408 (log ε 5.19), 532 (4.05), 566.0 nm (4.09). ^1H NMR δ 1.49 (t, J = 7.6 Hz, 6H, CH_3 at $C_{3,7}$), 1.71 and 1.75 and 1.79 (3t, J = 7.6 Hz, each 6H, CH_3 at $C_{2,8,12,13,17,18}$), 3.46 (dq, J_{vic} = 7.6 Hz, J_{gem} = 13.8 Hz, 2H, CH_aH_b at $C_{3,7}$), 3.50 (dq, J_{vic} = 7.6 Hz, J_{gem} = 13.8 Hz, 2H, CH_aH_b at $C_{3,7}$), 3.75 and 3.82 and 3.86 (3q, J = 7.6 Hz, each 4H, CH_2 at $C_{2,8,12,13,17,18}$), 3.78 (s, 3H, OCH_3), 9.44 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 665 (M^+, 100%), 635 (26), 620 (40), 590 (9). H.r.m.s. Calcd for $C_{37}H_{45}N_5O_3Ni$: *m/z* 665.2873. Found : *m/z* 665.2877.

(5-Acetoxy-15-methoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **18**

(5-Methoxy-15-nitro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **16** (0.085 g, 0.13 mmol) was added to a solution of the sodium salt of *E*-benzaldoxime (1.3 mmol) in dimethyl sulfoxide (100 mL), prepared as described above, and the resulting mixture was stirred under nitrogen and in the dark at 70 °C for 2 h. The reaction mixture was allowed to cool and then poured into dichloromethane (200 mL) and washed with sodium dithionite solution (10%, 5 x 200 mL). The organic phase was dried and the solvent removed. The resultant crude hydroxyporphyrin **17** was heated in refluxing acetic anhydride (10 mL) and pyridine (10 mL) for 1 h. Work-up as for **10** and recrystallization of the product from dichloromethane/methanol yielded (5-acetoxy-15-methoxy-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) **18** as purple needles (0.056 g, 68%), m.p. 258 °C. Infrared spectrum ($CHCl_3$) ν_{max} 1762, 1277, 1081 cm^{-1}. Visible spectrum ($CHCl_3$) λ_{max} 410 (log ε 4.95), 531 (4.06), 564 nm (3.98). ^1H NMR δ 1.70 and 1.71 and 1.73 and 1.80 (4t, J = 7.6 Hz, each 6H, CH_3 at $C_{2,3,7,8,12,13,17,18}$), 3.50 (dq, J_{vic} = 7.6 Hz, J_{gem} = 14.1 Hz, 2H, CH_aH_b at $C_{3,7}$), 3.70 (dq, J_{vic} = 7.6 Hz, J_{gem} = 14.1 Hz, 2H, CH_aH_b at $C_{3,7}$), 3.72 and 3.79 (2q, J = 7.6 Hz, each 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.80 (q, J = 7.6 Hz, 4H, CH_2), 3.83 (dq, J_{vic} = 7.6 Hz, J_{gem} = 14.2 Hz, 2H, CH_aH_b at $C_{13,17}$), 3.86 (dq, J_{vic} = 7.6 Hz, J_{gem} = 14.2 Hz, 2H, CH_aH_b at $C_{13,17}$), 9.32 (s, 2H, $H_{10,20}$). Mass spectrum *m/z* 678 (M^+, 100%), 635 (46), 621 (20), 590 (11). H.r.m.s. Calcd for $C_{39}H_{48}N_4O_3Ni$ (M^+): *m/z* 678.3079. Found : *m/z* 678.3077; Calcd for $C_{37}H_{45}N_4O_2Ni$ (M^+-CH_3CO) *m/z* 635.2893. Found : *m/z* 635.2911.

Acknowledgements - We thank the Australian Research Grants Scheme for funding this research (to M.J.C.) and the Australian Government for Post-Graduate Research Awards (to L.G.K. and S.M.P.).

References

1. Clezy, P.S.; Nicol, A.W. *Aust. J. Chem.*, 1965, **11**, 1835; Jackson, A.H.; Kenner, G.W.; Smith, K.M. *J. Chem. Soc. C*, 1968, 302; Clezy, P.S.; Webb, N.W. *Aust. J. Chem.*, 1972, **25**, 2217.
2. Crossley, M.J.; Harding, M.M.; Sternell, S. submitted for publication; Harding, M.M.; Ph.D. Thesis, University of Sydney, 1986.
3. Crossley, M.J.; Harding, M.M.; Sternell, S. *J. Am. Chem. Soc.*, 1986, **108**, 3608.
4. Clezy, P.S. in `The Porphyrins' ed. Dolphin, D., Academic Press, New York, 1978, vol II, p. 103, and references contained therein.
5. O'Carra, P. in 'Porphyrins and Metalloporphyrins' ed. Smith, K.M., Elsevier, Amsterdam, 1975, p. 123, and references contained therein.

6. Barnett, G.H.; Hudson, M.F.; McCombie, S.W.; Smith, K.M. *J. Chem. Soc., Perkin Trans. I*, 1973, 691; Barnett, G.H.; Evans, B.; Smith, K.M. *Tetrahedron*, 1975, **31**, 2711.
7. Bonnett, R.; Dimsdale, M J.; Stephenson, G.F. *J. Chem. Soc. C*, 1969, 564; Bonnett, R.; Cornell, P.; McDonagh, A.F. *J. Chem. Soc.,Perkin Trans. I*, 1976, 794.
8. Bonnett, R.; Dimsdale, M.J. *Tetrahedron Lett.*, 1968, 731; *J. Chem. Soc.,Perkin Trans. I*, 1972, 2540.
9. Jackson, A.H.; Nagaraja Rao, K.R.; Wilkins, M. *J. Chem. Soc., Chem. Commun.*, 1982, 794; *J. Chem. Soc., Perkin Trans. I*, 1987, 307.
10. Callot, H.J. *Bull. Soc. Chim. Fr.*, 1974, 1492.
11. Catalano, M.M.; Crossley, M.J.; King, L.G. *J. Chem. Soc., Chem. Commun.*, 1984, 1537.
12. Crossley, M.J.; Gosper, J.J.; Wilson, M.G. *J. Chem. Soc., Chem. Commun.*, 1985, 1798.
13. Baldwin, J.E.; Crossley, M.J.; DeBernardis, J.F. *Tetrahedron*, 1982, **38**, 685.
14. Dolphin, D.; Gong, L. *Can. J. Chem.*, 1985, **63**, 406.
15. Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.*, 1974, **39**, 3343.
16. Catalano, M.M.; Crossley, M.J.; Harding, M.M.; King, L.G. *J. Chem. Soc., Chem. Commun.*, 1984, 1535.
17. King, L. G.; Ph.D. Thesis, University of Sydney, 1986;
18. Fuhrhop, J.-H.; Besecke, S.; Subramanian, J.; Mengerson, C.; Riesner, D. *J. Am. Chem. Soc.*, 1975, **97**, 7141.