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Syntheses of some β-substituted alkyne porphyrins related to protoporphyrin-IX [1]

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1 PERKIN

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β-Acetylporphyrins (*e.g.* 20, 35, 39) have been treated with Vilsmeier complex ($POCl_3$–DMF) to afford β-(1-chloro-2-formylvinyl)porphyrins (23, 36, 41); with an excess of KOH in methanol these compounds were transformed into the corresponding alkynylporphyrins (17, 37, 38). The bis-alkynyl-porphyrin 17 was transformed into the corresponding hemin 25 by treatment with iron(II) chloride.

In 1978, Arnold *et al.*[2] reported the first synthesis of an alkyne-substituted porphyrin–nickel(II) 5-ethynyl-2,3,7,8,12,13,17,18-octaethylporphyrin **1**; an intermediate was the corresponding 5-vinyloctaetylporphyrin (5-vinyl-OEP; **2**), prepared by Wittig methylenation of the corresponding aldehyde **3** or by Grignard addition followed by acid-catalysed dehydration. Compound **2** was treated with pyridinium hydrobromide perbromide to give the *cis*- and *trans*-nickel(II) 5-bromovinylporphyrins **4**. Treatment of these with sodium hydride gave **1** which slowly decomposed to 1,4-bis[5-(nickel octaethylporphyrinyl)]buta-1,3-diyne. Arnold and Nitschinsk[3] synthesized more alkyne porphyrins in 1992. The modified synthesis used the bromomethylene ylide to afford *trans*- **4** in one step from **3**, in 55% yield. Only trace amounts of the *cis*-isomer were observed. The dehydrobromination to the purple, oxidatively unstable **1** was carried out once again by using sodium hydride.

Anderson[4] also reported the synthesis of *meso*-alkynyl porphyrins. Porphyrin **5** was readily prepared in 14% yield from pyrrole and 3-trimethylsilylpropynal; use of Gunter–Mander conditions[5] enabled **6** to be obtained in 72% yield. The ester functionalized version, **7**, was synthesized analogously in 19% yield using a published[6] modification of the procedure, which involves deprotecting the dipyrrylmethane immediately before use. Treatment of **6** and **7** with tetrabutylammonium fluoride cleanly removed the TMS groups to give **8** and **9**, respectively. The UV–VIS absorption properties of the free-base and zinc(II) complexes of **5**–**9** were compared with those of standard porphyrins to show that alkynyl substituents red-shifted all the bands by about three times as much as aryl groups, and by about twice as much as vinyl groups.

The formation of the alkyne group has been extended to the porphyrin β-positions by Arnold and Nitschinsk.[3] The readily available 5,10,15,20-tetraphenylporphyrin (TPP) was explored first. The same series of steps was carried out, starting with the nickel complex of the aldehyde **10**. Bromomethylenation gave a *ca.* 2:1 mixture of *trans*- and *cis*-β-bromovinyl-NiTPP **11**; dehydrobromination of this as before led to the alkyne **12**, together with a small amount of the vinyl compound.

Published work[7] on functionalization of the ethyl groups in OEP enabled Arnold and Nitschinsk[3] to prepare the β-ethynylheptaethylporphyrin. OEP **13** was converted into to 2-(2′-bromovinyl)heptaethylporphyrin **14** using[7] NBS. Insertion of nickel and dehydrobromination led to alkyneporphyrin **15**. Therien and co-workers[8] also extended earlier work[9] to obtain β-alkynylporphyrins using palladium-catalysed cross-coupling of trimethylsilylethynylzinc chloride with zinc(II) 2-bromotetraphenylporphyrin.

Conjugation with the porphyrin apparently had a dramatic effect on the reactivity of the acetylene groups, making them more susceptible to nucleophilic attack. For example **8** reacted cleanly with diethylamine to give the mono-enamine **16**; the electron-releasing effect of the enamine group apparently prevented attack at the second triple bond because no bis-enamine was detected in the product. The porphyrin chromophore in **16** was significantly perturbed; the Soret band was red-shifted by 44 nm relative to **8** and the four Q bands coalesced to a single maximum at 615 nm.[4]

In connection with our studies on the spectroscopic and physiological properties of heme proteins reconstituted with unusual hemes,[10] we decided to synthesize the 3,8-bis-alkynyl analogue **17** of protoporphyrin-IX dimethyl ester **18**. We felt that reconstitution of the corresponding hemin dicarboxylic acid **24** into various apoproteins would yield interesting holoproteins with perturbed spectroscopic signatures and biological properties. Prior to our preliminary communication,[1] 3,8-diethynyldeuteroporphyrin IX dimethyl ester **17** and its hemin **24** had not been reported.

The first route attempted was reaction of zinc(II) 3,8-dibromodeuteroporphyrin IX dimethyl ester **26** with ethynyltrimethylsilane in the presence of a catalytic amount of bis(triphenylphosphine)palladium chloride in the hope of obtaining the zinc complex of 3,8-bis(trimethylsilylethynyl)-deuteroporphyrin IX dimethyl ester **27**. Subsequent manipulation should yield the desired 3,8-diethynyldeuteroporphyrin IX dimethyl ester **17**. Treatment of deuteroporphyrin IX dimethyl ester with pyridinium bromide perbromide gave 3,8-dibromodeuteroporphyrin IX dimethyl ester **19** in good yield. When zinc(II) 3,8-dibromodeuteroporphyrin IX dimethyl ester **26** was mixed with an excess of ethynyltrimethylsilane in the presence of a catalytic amount of bis(triphenylphosphine)palladium chloride, no product was detected. At higher temperatures, only decomposition products were observed.

Mironov *et al.*[11] reported that the reaction between acetylpyrroles **28** and $POCl_3$ in DMF gave a chlorovinyl derivative **29** which with subsequent alkali treatment led to the corresponding acetylenes **30**. We felt that this methodology could be applied to the synthesis of our proposed molecule 3,8-diethynyldeuteroporphyrin IX dimethyl ester **17**. In order to reach this goal, we needed 3,8-diacetyldeuteroporphyrin IX dimethyl ester **20** as our starting material. Copper(II) deuteroporphyrin IX dimethyl ester (**Cu21**) was treated with acetic anhydride and tin(IV) chloride, followed by treatment with acid to afford the 3,8-diacetyldeuteroporphyrin IX dimethyl ester **20** in *ca.* 65% yield.

We first studied the alkyne formation reaction on a model acetylpyrrole. When benzyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate **31** was treated with 1 equiv. of Vilsmeier complex ($POCl_3$–DMF), a new product was detected. It was identified as benzyl 4-(1-chlorovinyl)-3,5-dimethylpyrrole-2-carboxylate **32** from its ^1H NMR spectrum. Doublets at 5.20 and 5.62 ppm were assigned to the two geminal vinyl protons (CH_aH_b = ClR, J_{gem} 0.6 Hz). This chlorovinylpyrrole **32** in DMF was then

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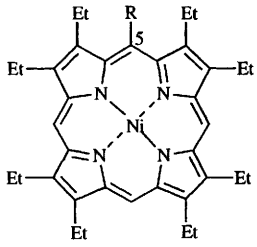
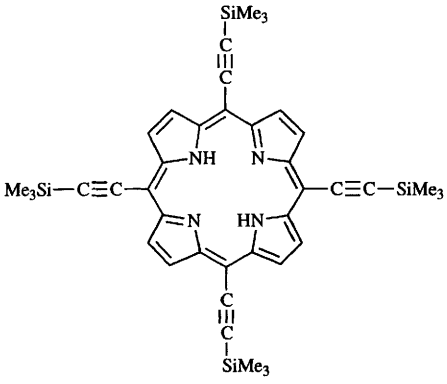


1 R = C≡CH
2 R = CH=CH_2
3 R = CHO
4 R = CH=CHBr



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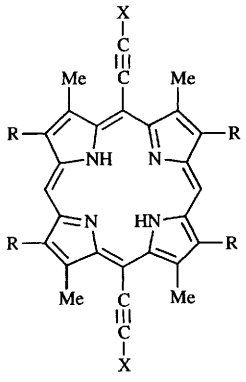
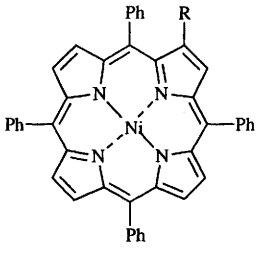
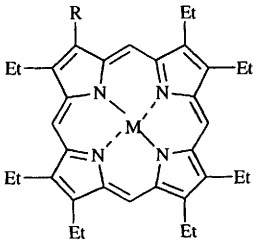


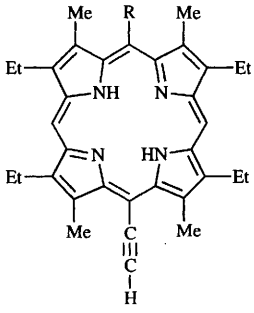
6 R = Et; X = $SiMe_3$
7 R = $CH_2CH_2CO_2Me$, X = $SiMe_3$
8 R = Et, X = H
9 R = $CH_2CH_2CO_2Me$, X = H



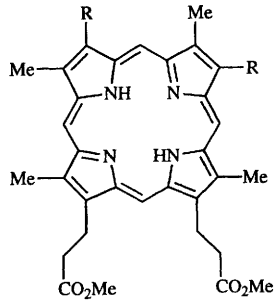
10 R = CHO
11 R = CH=CHBr
12 R = C≡CH



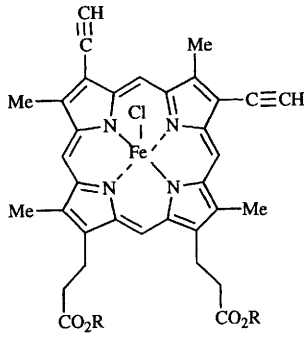
13 R = Et
14 R = CH=CHBr
15 R = C≡CH



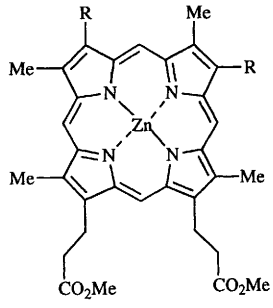
8 R = C≡CH
16 R = CH=$CHNEt_2$



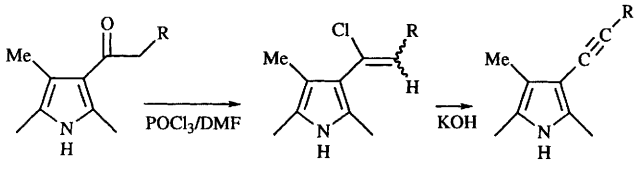
17 R = C≡CH
18 R = CH=CH_2
19 R = Br
20 R = COMe
21 R = H
22 R = CCl=CH_2
23 R = CCl=CHCHO



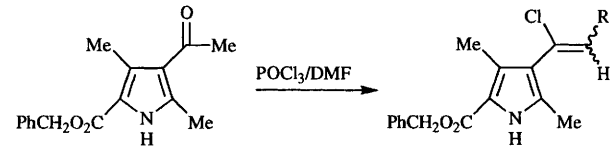
24 R = H
25 R = Me



26 R = Br
27 R = C≡C-$SiMe_3$

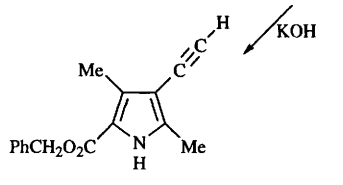


28 **29** **30**



31

32 R = H
33 R = CHO



34

treated with KOH to afford benzyl 4-ethynyl-3,5-dimethylpyrrole-2-carboxylate **34**. A singlet at 3.17 ppm was assigned to the ethynyl proton.

Neither 1 equiv. nor a slight excess of the Vilsmeier complex when added to the 3,8-diacetyldeuteroporphyrin IX dimethyl ester **20** in DMF at 0 °C gave a detectable reaction. Attempted reaction at 35 °C also failed. However, treatment of 3,8-diacetyldeuteroporphyrin IX dimethyl ester **20** with 12 equiv. of $POCl_3$ in DMF gave a new faster moving band. The ^1H NMR spectrum of the product formed showed that it was a mixture of

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several compounds. An increase in the amount of Vilsmeier complex used (16 equiv.) and a reaction time of 4 h gave two new bands neither of which (^{1}H NMR) represented the desired 3,8-bis-(1-chlorovinyl)deuteroporphyrin IX dimethyl ester **22**. With 16 equiv. of $POCl_3$ in DMF for longer periods, neither the starting material nor the second band were any longer apparent; only the first band was left. This yielded a red solid (λ_{max} 416, 510, 544, 578 and 632 nm; starting material **20**: λ_{max} 420, 514, 548, 584 and 638 nm). This product, in DMF, was treated with an excess of potassium hydroxide in methanol to give a bright red product, the ^{1}H NMR spectrum of which showed that it was the desired product 3,8-diethynyldeuteroporphyrin IX dimethyl ester **17**; the two ethynyl protons appear as two singlets at 4.20 and 4.21 ppm; high-resolution mass spectroscopy (HRMS) confirmed this conclusion (see Experimental section). The UV–VIS spectrum of this diethynylporphyrin has only a slight red shift (λ_{max} 408, 506, 542, 576 and 632 nm) compared with that of protoporphyrin IX dimethyl ester (λ_{max} 406, 504, 540, 574 and 630 nm).

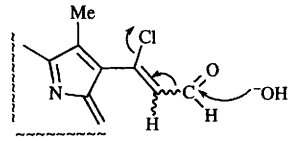
HRMS suggested a molecular formula of $C_{38}H_{36}Cl_2N_4O_6$ (requires: 714.2012; found: 714.2018) for the red solid isolated directly from the Vilsmeier reaction. The structure was therefore assigned as 3,8-bis(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester **23**. The ^{1}H NMR spectrum (doublets at 7.06, 7.38, 9.47 and 10.73 ppm) showed it to be a mixture of several geometrical isomers, depending upon the geometry of the formyl groups (relative to the chlorine atoms) on the vinyls. Further separation of these isomers **23** was not successful owing to the very close R_F values of all of the components.

We were surprised that the 3,8-bis(1-chloro-2-formylvinyl)-deuteroporphyrin IX dimethyl ester **23** was the major product in the reaction of 3,8-diacetyldeuteroporphyrin IX dimethyl ester **20** with $POCl_3$–DMF and also that it gave the desired diethynylporphyrin after being treated with KOH. The supposed product, 3,8-bis(1-chlorovinyl)deuteroporphyrin IX dimethyl ester **22**, was never detected in the reaction mixture, though **23** is presumably obtained from **22** *in situ* by formylation of the 1-chlorovinyl group, a reaction which has ample precedent.[12,13]

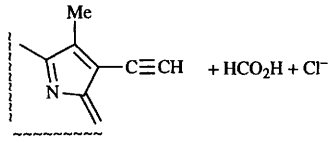
In order to establish whether the acetylpyrrole reaction sequence (**31**→**34**) proceeded in the same way in the presence of an excess of Vilsmeier reagent, the reactions were repeated using the 4-acetylpyrrole **31**, this time using an excess of $POCl_3$–DMF. Treatment of the acetylpyrrole **31** with 3 equiv. of $POCl_3$ in DMF gave a precipitate which, after purification, was identified as benzyl 4-(1-chloro-2-formylvinyl)-3,5-dimethylpyrrole-2-carboxylate **33** from its ^{1}H NMR spectrum. A doublet at 10.15 ppm is assigned to the aldehyde proton (*J* 7.5 Hz, O*H*CCH=), and another doublet at 6.08 ppm to the vinyl proton (*J* 7.5 Hz, OHCC*H*=). Treatment of compound **33** with KOH gave a product shown by ^{1}H NMR spectroscopy to be benzyl 3,5-dimethyl-4-ethynylpyrrole-2-carboxylate **34**; this confirmed the comparability of the chemistry in the pyrrole and porphyrin series.

We propose the mechanism in Scheme 1 for the conversion of the porphyrin **23** into the diethynylporphyrin **17**.

The above reactions were carried out with free-base porphyrins. Since reactions of unmetallated porphyrins in basic media often produce anions and oxidation products, we investigated whether use of metalloporphyrins could improve the yields. Treatment of copper(II) 3,8-diacetyldeuteroporphyrin IX dimethyl ester (**Cu20**) with an excess of $POCl_3$ in DMF gave three major bands. High resolution mass spectra showed that the mixture contained: (1) copper(II) 3,8-bis(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester (**Cu23**); (2) copper(II) 3- or 8-(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester; (3) copper(II) 3,8-bis(1-chlorovinyl)deuteroporphyrin IX dimethyl ester (**Cu22**). We concluded that Vilsmeier complex reacted with the copper(II) complex much more slowly than

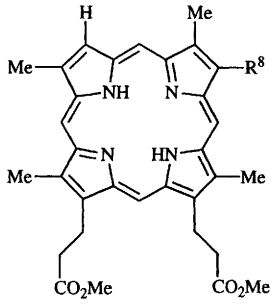


23

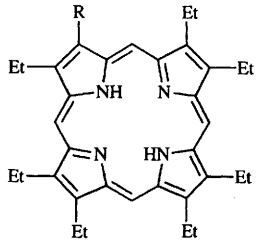


17

Scheme 1



35 R^8 = COMe
36 R^8 = CCl=CHCHO
37 R^8 = C≡CH



38 R = C≡CH
39 R = COMe
40 R = H
41 R = CCl=CHCHO
42 R = CH=CHNHBu

with the free-base porphyrin. Moreover, treatment with KOH and acidic demetallation failed to yield the desired diethynylporphyrin **17**. The metalloporphyrin strategy was therefore abandoned.

A monoethynylporphyrin was also synthesized from 8-acetyldeuteroporphyrin IX dimethyl ester **35**; reaction with an excess of $POCl_3$–DMF gave 8-(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester **36** in 69% yield, the ^{1}H NMR spectrum of which indicated that it was a mixture of *E*- and *Z*-isomers [doublets at 9.52 and 10.72 ppm were assigned to the aldehyde protons (*J* 7.5 Hz, O*H*CCH=) and those at 7.01 and 7.34 ppm to the vinyl protons for the two isomers (*J* 7.5 Hz, OHCC*H*=)]. The 69% yield in this reaction was much higher than the 30% yield observed for 3,8-bis(1-chloro-2-formylvinyl)porphyrin **23**. The 8-(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester **36** was treated with KOH to give 8-ethynyldeuteroporphyrin IX dimethyl ester **37** in 49% yield (again higher than the 26% yield for 3,8-diethynylporphyrin **17**). In the ^{1}H NMR spectrum, the ethynyl proton appeared as a singlet at 4.21 ppm.

Anderson reported that a *meso*-alkyne porphyrin reacted with diethylamine[4] to give the corresponding enamine **16**. Because of the two propionic esters present, 8-ethynyldeuteroporphyrin IX dimethyl ester **37** was hydrolysed to its corresponding dicarboxylic acid porphyrin and then refluxed with $BuNH_2$ in pyridine; no reaction took place at the acetylene group and the product mixture contained starting material and some propionic amides. In order to further investigate the reaction with amines, we synthesized a model ethynylporphyrin which did not possess the troublesome ester groups present in **17** and **37** namely, 2-ethynyl-3,7,8,12,13,17,18-heptaethylporphyrin **38**. This was synthesized in good yield from the corresponding 2-acetyl-3,7,8,12,13,17,18-heptaethylporphyrin

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39, itself obtained from 3,7,8,12,13,17,18-heptaethylporphyrin **40** by Friedel–Crafts acetylation. 2-(1-Chloro-2-formylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin **41** was obtained in 67% yield from the monoacetylporphyrin **39**, and the monoethynylheptaethylporphyrin **38** in 78% yield from the (1-chloro-2-formylvinyl)porphyrin **41**. 2-Ethynylheptaethylporphyrin **38** was also heated with $BuNH_2$ in toluene, but the desired product porphyrin **42** was not detected and starting material was recovered unchanged.

Since heme-apoprotein reconstitution studies require the iron complex of porphyrins, iron was inserted into **17** to give chloroiron(III) 3,8-diethynyldeuteroporphyrin IX dimethyl ester **25** in 92% yield. Purity of the product was confirmed by inspection of the low-spin ^1H NMR spectrum of hemin **25** [obtained by adding sodium cyanide to the hemin solution in CD_2Cl_2 and CD_3OD (see ref. 1 for a Figure)]. Hydrolysis to its corresponding hemin chloride **24** was accomplished in quantitative yield with KOH in water. Paramagnetic ^1H NMR experiments with various reconstituted heme proteins will be reported elsewhere.

Experimental

Mps were measured on a Thomas/Bristoline microscopic hot-stage apparatus and are uncorrected. Silica gel 60 (70–230 and 230–400 mesh, Merck) or neutral alumina (Merck; usually Brockmann Grade III, *i.e.* deactivated with 6% water) were used for column chromatography. Preparative thin layer chromatography was carried out on 20 × 20 cm glass plates coated with Merck G 254 silica gel (1 mm thick). Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 silica gel (pre-coated sheets, 0.2 mm thick). Reactions were monitored by TLC and spectrophotometry and were carried out under nitrogen and in the dark. ^1H NMR spectra were obtained in deuteriochloroform solution at 300 MHz using a General Electric QE300 spectrometer; chemical shifts are expressed in ppm relative to chloroform (7.258 ppm). Elemental analyses were performed at the Midwest Microlab, Ltd., Indiana, USA. Unless stated otherwise, electronic absorption spectra were measured in dichloromethane solution using a Hewlett-Packard 8450A spectrophotometer. Mass spectra were obtained at the Mass Spectrometry Facility, University of California, San Francisco, CA.

3,8-Dibromodeuteroporphyrin IX dimethyl ester 19

Pyridinium bromide perbromide (0.7 g) was added over a 5 min period to deuteroporphyrin IX dimethyl ester[14] **21** (0.4 g) in dichloromethane (30 cm^3). After 5 min the mixture was treated with acetone (15 cm^3) and after a further 5 min with cold water (20 cm^3); up to and during the addition of water the reaction mixture was vigorously stirred and cooled at 0 °C. The dichloromethane solution was separated, washed with water, dried (Na_2SO_4) and chromatographed on an alumina column (Brockmann Grade III), with 10% hexane in dichloromethane as eluent. The first fraction contained a mixture of the two isomeric monobromoporphyrins. The second fraction afforded the title compound (0.21 g, 41%), mp 271–273 °C (lit.,[15] mp 274–277 °C); λ_{max}/nm (CH_2Cl_2, relative absorbances) 402 (1.000), 502 (0.110), 534 (0.081), 570 (0.060) and 624 (0.044); $\delta_H(CDCl_3)$ −5.54 (s, 2 H, NH), 3.17 (m, 4 H, CH_2CH_2CO), 3.38, 3.42, 3.44, 3.51 (each s, 3 H, ring CH_3), 3.63, 3.64 (each s, 3 H, OCH_3), 4.28 (t, 4 H, CH_2CH_2CO), 9.38, 9.40, 9.60, 9.63 (each s, 1 H, *meso*-H); *m*/*z* 696 (100) and 622.9 (29).

Benzyl 4-(1-chlorovinyl)-3,5-dimethylpyrrole-2-carboxylate 32

A solution of benzyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate **31**[16] (579 mg) in DMF (3 cm^3) was chilled in an ice-bath and treated slowly with phosphorus oxychloride (0.2 cm^3). The resulting mixture was stirred at 0 °C for 15 min and then kept at room temperature until completion of the reaction (monitored by TLC). The mixture was then quenched with ice–water. The resulting precipitate was filtered off, washed with water, dried and chromatographed on silica gel with 25% ethyl acetate in cyclohexane as eluent to afford the title pyrrole (427 mg, 69%), mp 119–120.5 °C (Found: C, 66.4; H, 5.6; N, 4.9. $C_{16}H_{16}ClNO_2$ requires C, 66.42; H, 5.58; N, 4.84); $\delta_H(CDCl_3)$ 8.77 (s, 1 H, NH), 7.36 (m, 5 H, phenyl H), 5.62, 5.20 (each d, J_{gem} = 0.6, 1 H, CH_aH_b=ClR), 5.30 (s, 2 H, CO_2CH_2) and 2.36, 2.30 (each s, 3 H, 3- and 5-CH_3).

Benzyl 4-ethynyl-3,5-dimethylpyrrole-2-carboxylate 34

Potassium hydroxide (84 mg, 1.5 mmol) in water (0.1 cm^3) was added to a stirred solution of the pyrrole **32** (144 mg, 0.5 mmol) in DMF (1.5 cm^3). The reaction mixture was kept at 30–40 °C until completion of the reaction (*ca.* 1 h; TLC) after which it was diluted with dichloromethane, washed with water (× 3), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel eluting with 25% ethyl acetate in cyclohexane to give the title pyrrole (80 mg, 63%), mp 126.5–127.5 °C (Found: C, 75.8; H, 6.0; N, 5.6. $C_{16}H_{15}NO_2$ requires C, 75.86; H, 5.97; N, 5.53%); $\delta_H(CDCl_3)$ 8.65 (s, 1 H, NH), 7.35 (m, 5 H, phenyl H), 529 (s, 2 H, CO_2CH_2), 3.17 (s, 1 H, C≡CH) and 2.36, 2.32 (each s, 3 H, 3- and 5-CH_3).

Benzyl 4-(1-chloro-2-formylvinyl)-3,5-dimethylpyrrole-2-carboxylate 33

Phosphorus oxychloride (0.25 cm^3) was added slowly to a stirred solution of the acetylpyrrole **31** (226 mg) in DMF (1.8 cm^3) at 0 °C. The mixture was stirred at 0 °C for 10 min and then kept at room temperature until completion of the reaction (TLC). It was then diluted with dichloromethane and treated with aqueous sodium hydrogen carbonate. The organic layer was separated, washed with saturated brine (× 3), and then dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel with 25% ethyl acetate in cyclohexane as eluent to afford the title pyrrole (214 mg, 81%), mp 112.5–114.5 °C (Found: C, 64.0; H, 5.0; N, 4.4. $C_{17}H_{16}ClNO_3$ requires C, 64.34; H, 5.09; N, 4.42); $\delta_H(CDCl_3)$ 10.15 (d, *J* 7.5, 1 H, O*H*CCH=), 8.97 (s, 1 H, NH), 7.40 (m, 5 H, phenyl H), 6.08 (d, *J* 7.5, 1 H, OHCC*H*=), 5.32 (s, 2 H, CO_2CH_2) and 2.42, 2.39 (each s, 3 H, 3- and 5-CH_3).

3,8-Bis(1-chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester 23

Freshly distilled phosphorus oxychloride (0.4 cm^3) was added slowly to a stirred solution of 3,8-diacetyldeuteroporphyrin IX dimethyl ester[17] **20** (50 mg) in DMF (2.0 cm^3) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C for 0.5–1 h and then kept at room temperature for 6 h (monitored by TLC) to complete the reaction. It was then diluted with dichloromethane, washed vigorously with saturated aqueous sodium hydrogen carbonate until no CO_2 bubbles were apparent; after this it was washed with saturated brine (× 3), dried (Na_2SO_4) and evaporated. The residue was chromatographed on an alumina (Brockmann Grade III) column; the title compound was eluted as the most mobile band with dichloromethane. The appropriate eluates were combined and evaporated to give a mixture of the title compounds (17 mg, 30%; several geometrical isomers) which was then crystallized from dichloromethane–hexane; $\delta_H(CDCl_3)$ −3.55, −3.44 (each s, total 2 H, NH), 3.28 (t, 4 H, CH_2CH_2CO), 3.58–3.78 (many s, total 18 H, ring CH_3 and OCH_3), 4.35 (t, 4 H, CH_2CH_2CO), 7.06, 7.38 (each d, total 2 H, CCl=C*H*CHO), 9.47, 10.73 (each d, total 2 H, CCl=CHCHO), 9.99–10.27 (many s, total 4 H, *meso*-H) [Found (HRMS): 714.2018. $C_{38}H_{36}Cl_2N_4O_6$ requires 714.2012].

3,8-Diethynyldeuteroporphyrin IX dimethyl ester 17

Potassium hydroxide (16.0 mg, 3 equiv.) in a little methanol was added to a stirred solution of the porphyrin **23** (34 mg) in DMF (1.5 cm^3) at room temperature under nitrogen. The

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reaction mixture was kept at room temperature for 1–1.5 h until completion of the reaction (TLC) after which it was diluted with dichloromethane, washed with saturated brine (×3), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was chromatographed on an alumina column (Brockmann Grade III), with dichloromethane as eluent. The major fraction was collected and crystallized from dichloromethane–hexane to afford the title compound (73 mg, 26%), mp >226–228 °C (decomp.) (Found: C, 73.0; H, 5.8; N, 9.4. $C_{36}H_{34}N_4O_4$·0.5CH_3OH requires C, 72.72; H, 6.02; N, 9.30%); $\delta_H(CDCl_3)$ −4.36 (s, 2 H, NH), 3.22 (t, 4 H, CH_2CH_2CO), 3.53, 3.58, 3.67, 3.71 (each s, 3 H, ring CH_3), 3.64, 3.65 (each s, 3 H, OCH_3), 4.20, 4.21 (each s, 1 H, C≡CH), 4.33 (t, 4 H, CH_2CH_2CO), 9.75, 9.80, 9.99, 10.01 (each s, 1 H, *meso*-H); λ_{max}/nm (CH_2Cl_2) 410 (ε 166 400), 506 (18 200), 542 (14 900), 576 (11 000) and 632 (9 100) [Found: (HRMS): 586.2576. $C_{36}H_{34}N_4O_4$ requires 586.2580].

8-(1-Chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester 36

A stirred solution of 8-acetyldeuteroporphyrin IX dimethyl ester[18] **35** (20 mg) in DMF (1.5 cm^3) was treated dropwise with $POCl_3$ (0.2 cm^3) at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 6 h after which it was worked up as before. The residue was chromatographed on an alumina column (Brockmann Grade III), with dichloromethane as eluent, to afford the title porphyrin (15 mg, 69%); $\delta_H(CDCl_3)$ 10.72, 9.52 (each d, *J* 7.5, total 1 H, O*H*CCH= for two isomers), 10.12, 10.08, 10.05, 10.01, 10.00, 9.97, 9.96, 9.93 (each s, total 4 H, *meso*-H), 9.12, 9.06 (each s, total 1 H, 3-H), 7.34, 7.01 (each d, *J* 7.5, total 1 H, OHCC*H*=), 4.43, 4.27 (each m, 2 H, $CH_2CH_2CO_2$), 3.77–3.43 (many s, total 18 H, ring CH_3 and OCH_3), 3.25 (m, 4 H, $CH_2CH_2CO_2$) and −3.93, −4.03 (each s, total 2 H, NH) [Found (HRMS): 626.2271. $C_{35}H_{35}ClN_4O_5$ requires 626.2296].

8-Ethynyldeuteroporphyrin IX dimethyl ester 37

8-(1-Chloro-2-formylvinyl)deuteroporphyrin IX dimethyl ester **36** (13.6 mg) gave the title compound (6.0 mg, 49%) following the same procedure as described for compound **17**. It had mp 197–199 °C (Found: C, 71.4; H, 6.2; N, 9.8. $C_{34}H_{34}N_4O_4$·0.5H_2O requires C, 71.42; H, 6.17; N, 9.80%). $\delta_H(CDCl_3)$ 10.25, 10.04, 10.01, 9.99 (each s, 1 H, *meso*-H), 9.12 (s, 1 H, 3-H), 4.47, 4.33 (each t, 2 H, $CH_2CH_2CO_2$), 4.21 (s, 1 H, C≡CH), 3.76, 3.71, 3.69, 3.57 (each s, 3 H, ring CH_3), 3.67, 3.64 (each s, 3 H, OCH_3), 3.27 (m, 4 H, $CH_2CH_2CO_2$) and −3.95 (s, 2 H, NH); λ_{max}/nm (CH_2Cl_2) 402 (ε 183 100), 502 (18 100), 540 (19 600), 570 (12 900) and 624 (7200) [Found (HRMS): 562.2549. $C_{34}H_{34}N_4O_4$ requires 562.2580].

2-Acetyl-3,7,8,12,13,17,18-heptaethylporphyrin 39

A solution of methanol (7.0 cm^3) saturated with copper(II) acetate was added to a solution of heptaethylporphyrin[19] **40** (60 mg) in dichloromethane (25 cm^3). The reaction mixture was kept at reflux until completion of the reaction (monitored by TLC) after which it was evaporated under reduced pressure. A solution of the residue in dichloromethane was washed with water (×3), dried (Na_2SO_4) and evaporated. Recrystallization of the residue from dichloromethane–hexane gave copper(II) heptaethylporphyrin as a bright red solid, which was immediately used in the next reaction as follows. Acetic anhydride (4.0 cm^3) was added to a solution of the copper(II) heptaethylporphyrin in dichloromethane (20 cm^3) and the resulting mixture was cooled to 0 °C in an ice-bath and treated rapidly with anhydrous $SnCl_4$ (0.7 cm^3). After the reaction mixture had been stirred for 5 min at 0 °C it was poured into ice–water (100 cm^3). The organic layer was separated, washed with saturated brine (3 × 100 cm^3) and evaporated. The residue was dissolved in TFA containing 10% concentrated sulphuric acid (10 cm^3) and the mixture stirred at room temperature for 1 h to complete the demetallation. The mixture was then diluted with dichloromethane (50 cm^3), washed with saturated brine (3 × 100 cm^3) and evaporated. The residue was chromatographed on an alumina column (Brockmann Grade III), with dichloromethane as eluent, to give the title acetylporphyrin (42 mg, 65%), mp >300 °C; λ_{max}/nm (CH_2Cl_2, relative absorbances) 406 (1.000), 508 (0.110), 548 (0.121), 576 (0.111) and 636 (0.068); $\delta_H(CDCl_3)$ −3.63 (s, 2 H, NH), 1.97 (m, 21 H, CH_2CH_3), 3.42 (s, 3 H, $COCH_3$), 4.03 (q, 4 H, CH_2CH_3), 4.17 (m, 8 H, CH_2CH_3), 4.42 (q, 2 H, CH_2CH_3), 10.05 (s, 2 H, *meso*-H) and 10.18, 10.75 (each s, 1 H, *meso*-H) [Found (HRMS; EI): 548.3523. $C_{36}H_{44}N_4O$ requires 548.3515].

2-(1-Chloro-2-formylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin 41

The same procedure as described for compound **35** with 2-acetyl-3,7,8,12,13,17,18-heptaethylporphyrin (29 mg) gave the title compound (12 mg, 67%) as a mixture of two isomers; $\delta_H(CDCl_3)$ −3.68 (s, 2 H, NH), 1.92 (m, 21 H, CH_2CH_3), 4.05 (q, 4 H, CH_2CH_3), 4.19 (m, 10 H, CH_2CH_3), 7.10, 7.32 (each d, total 1 H, OHCC*H*=), 9.48, 10.74 (each d, total 1 H, O*H*CCH=) and 10.05–10.25 (many s, total 4 H, *meso*-H).

2-Ethynyl-3,7,8,12,13,17,18-heptaethylporphyrin 38

The same procedure as described for compound **17** with 2-(1-chloro-2-formylvinyl)-3,7,8,12,13,17,18-heptaethylporphyrin **41** (20 mg) gave the title compound (14 mg, 78%), mp >300 °C; λ_{max}/nm (CH_2Cl_2) 402 (ε 162 000), 506 (10 100), 542 (14 700), 568 (9600) and 622 (2000); $\delta_H(CDCl_3)$ −3.69 (s, 2 H, NH), 1.98 (m, 21 H, CH_2CH_3), 4.06 (q, 4 H, CH_2CH_3), 4.20 (m, 10 H, CH_2CH_3), 4.23 (s, 1 H, C≡CH) and 10.07, 10.10, 10.14, 10.36 (each s, 1 H, *meso*-H); [Found (HRMS; EI): 530.3412. $C_{36}H_{42}N_4$ requires 530.3409].

Chloroiron(III) 3,8-diethynyldeuteroporphyrin IX dimethyl ester 25

The diethynylporphyrin dimethyl ester **17** (20 mg) was dissolved in degassed chloroform. Acetonitrile (degassed) was heated to reflux for 0.5–1 h and then cooled to 50 °C. $FeCl_2$·xH_2O (2 equiv.) was dissolved in acetonitrile at 50 °C, after which the solution was cooled to 25–30 °C. The porphyrin solution was added to the ferrous chloride solution and the mixture was kept at 25–30 °C for 2 h when TLC showed the completion of iron insertion. The reaction mixture was washed with dilute brine (×2), dried (Na_2SO_4) and then, since TLC showed that the product was already very pure, evaporated. The residue was crystallized from dichloromethane–hexane to give the title hemin (21.3 mg, 92%). The low-spin ^1H NMR spectrum of the compound was obtained by adding sodium cyanide to the hemin solution in CD_2Cl_2 and CD_3OD; $\delta_H(CD_2Cl_2$ and $CD_3OD)$. 19.30, 17.30, 13.29, 10.29 (each s, 3 H, ring CH_3), 7.17, 6.32 (each t, 2 H, $CH_2CH_2CO_2$), 5.32 (s, solvent CH_2Cl_2), 3.99 (s, two CO_2CH_3 and solvent methanol OH overlapping), 3.30 (s, solvent methanol CH_3), 2.49, 0.21, −0.47, −1.30 (each s, 1 H, *meso*-H), 1.23 (s, 2 H, C≡CH) and 0.65, 0.53 (each t, 2 H, $CH_2CH_2CO_2$).

Acknowledgements

This work was supported by grants from the National Institutes of Health (HL 22252). Mass spectrometric analyses were performed by the University of California, San Francisco, Mass Spectrometry Facility (A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

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Paper 5/06906H
Received 18*th October* 1995
Accepted 29*th January* 1996

Published on 01 January 1996. Downloaded by University of Windsor on 30/10/2014 21:11:34.