Tetrahedron Vol 32, pp 2753 to 2756 Pergamon Press 1976 Printed in Great Britain

PYRROLES AND RELATED COMPOUNDS—XXXVI[1]

TRANSFORMATIONS OF PROTOPORPHYRIN-IX INTO HARDEROPORPHYRIN, PEMPTOPORPHYRIN, CHLOROCRUOROPORPHYRIN AND THEIR ISOMERS

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(*Received in the UK* 3 *May* 1976; *Accepted for publication* 10 *June* 1976)

Abstract—Treatment of protoporphyrin-IX dimethyl ester (**8b**) with 2 equiv of thallium(III) nitrate in methanol followed by chromatography affords good yields of a mixture of mono-acetal–mono-vinyl isomers (**11b** and **12b**) which can be converted into the corresponding (2-hydroxyethyl)-vinyldeuteroporphyrins (**13b** and **14b**) by hydrolysis and reduction with sodium borohydride. After separation by preparative TLC these compounds are transformed into isoharderoporphyrin trimethyl ester (**3b**) and harderoporphyrin trimethyl ester (**2b**) by treatment with CBr_4/Ph_3P (to afford the 2-bromoethyl derivatives), then sodium cyanide in 1-methylpyrrolidone (giving the 2-cyanoethyl compounds), followed by methanolysis. Formal syntheses of pemptoporphyrin dimethyl ester (**4b**) and its isomer (**5b**) are achieved by devinylation (resorcinol melt) of the haemins from the pure (2-hydroxyethyl)-vinyl isomers (**14b** and **13b**) respectively, followed by demetallation.

Controlled oxidation of protoporphydrin-IX dimethyl ester (**8b**) with osmium tetroxide gives starting material, mono-glycol–mono-vinyl isomers (**23b** and **24b**), and bis-glycol (**25b**); this mixture can be separated by column chromatography. Further separation of the mono-glycols through preparative TLC followed by treatment with sodium periodate gives pure samples of chlorocruoroporphyrin dimethyl ester (**6b**) and its isomer (**7b**).

In the TLC separations of unsymmetrically 2,4-substituted deuteroporphyrins studied, the 2-vinyl substituted isomers proved always to be the more polar (less mobile) components of the mixtures of isomers.

INTRODUCTION

In comparatively recent times, several 2 and/or 4 substituted derivatives of deuteroporphyrin-IX (**1a**) have been shown[2a] to be of biological importance. Prominent among these are harderoporphyrin (**2a**; found to occur in the Harderian gland of certain rodents,[3] and the porphyrinogen of which is an intermediate in protoporphyrin-IX metabolism[3b,4,5]), pemptoporphyrin (**4a**; a faecal metabolite[6]), and chlorocruoroporphyrin (**6a**; the porphyrin from the haem of the marine worm *Spirographis spallanzanii*[7]). In all cases, physical and spectroscopic data were only able to settle the gross structures for these compounds and it was left to total synthesis [2b] to establish the precise orientations of the 2 and 4 substituents; thus, for a time, the isomers **3**, **5** and **7** of the biologically important compounds **2**, **4** and **6** respectively assumed some importance. In the event, the natural isomers were shown to be those with the most highly degraded 2-substituent. So far as we are aware, no biological rationale has been attached to this conclusion which consumed many man-years of often innovative synthetic work.

In this paper we report less arduous synthetic approaches to compounds **2–7** from the readily available[8] protoporphyrin-IX (**8a**). The routes employ derivatisation of one of the pair of vinyl groups in the starting material (**8b**) followed by separation of the resulting monovinyl isomers by chromatographic methods; in all cases, the 2-vinyl substituted isomers proved to be the more polar (less mobile) component of the mixture.

DISCUSSION AND RESULTS

Part XXI[8] of this Series described the reaction of protoporphyrin-IX dimethyl ester (**8b**) with 3 equiv of thallium(III) nitrate in methanol, whereby a high yield of the 2,4-bis(dimethyl acetal) (**9b**) was obtained. The first equiv of the thallium reagent was consumed in formation of the thallium(III) complex which facilitated reaction of the other 2 equiv at the 2 and 4 vinyl groups; chelation of the porphyrin with thallium(III) imparts a high oxidation potential to the macrocyclic nucleus and thereby prevents reaction at the normally more reactive *meso*-positions.[9] Further transformations of the 2,4-bis(dimethyl acetal) (**9b**) led to a 37% overall yield of coproporphyrin-III tetramethyl ester (**10b**).

Treatment of protoporphyrin-IX dimethyl ester (**8b**) with only 2 equiv of thallium(III) nitrate, followed by a reductive/acidic work-up (see Ref. 8) gave a roughly equal mixture of starting material (**8b**), mono-acetal–mono-vinyl isomers (**11b** and **12b**), and bis-acetal (**9b**). The mono-acetal mixture was obtained in an overall yield of 36% (from **8b**) by simple column chromatography on alumina. The mono-acetals were separable by both TLC and high performance liquid chromatography (HPLC) on the analytical scale, and a 1:1 (approx) ratio of **11b** and **12b** was derived from integration of the peaks on the HPLC trace (254 nm detector); importantly, this confirmed that there was no preferential reactivity at either the 2 or 4 vinyls in **8b**. However, large scale separations of the mono-acetals (TLC or HPLC) were hampered by partial hydrolysis of the acetal functions to give the more polar formylmethyl side-chains, a consequence of the extended chromatography times required for bulk separation. Thus, the mono-acetal mixture was hydrolysed and then reduced with sodium borohydride to give a 78% yield of the (2-hydroxyethyl)-vinyl mixture (**13b** and **14b**). This was separated by open-tank (continuous elution) thick layer chromatography, the most polar (least mobile) band being shown from its subsequent transformations (*vide infra*) to be the 4 - (2 - hydroxyethyl) - 2 - vinylporphyrin (**14b**).

The separated isomers (**13b** and **14b**) were treated individually with carbon tetrabromide and triphenylphosphine and gave 87–90% yields of the corresponding (2-bromoethyl)-vinyl isomers (**15b** and **16b**) respectively. Attempts to carry out this reaction using thionyl bromide

(see Ref. 8) were unsatisfactory owing to formation of by-products arising from Markownikoff addition of hydrogen bromide across the vinyl group. Treatment of **15b** and **16b** with sodium cyanide in 1-methylpyrrolidone gave *ca* 70% yields of **17b** and **18b** which were methanolysed to afford 50–60% yields of isoharderoporphyrin trimethyl ester (**3b**) and harderoporphyrin trimethyl ester (**2b**) respectively. These compounds were satisfactorily identified by m.p., m.m.p., and comparative HPLC with authentic samples obtained from total synthesis.[4]

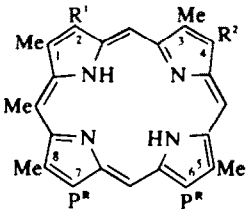
Formal syntheses of pemptoporphyrin dimethyl ester (**4b**) and isopemptoporphyrin dimethyl ester (**5b**) are possible merely by devinylation of the (2 - hydroxyethyl) - vinyl isomers (**14b** and **13b**) respectively. This is due to the fact that our earlier syntheses[10] of **4b** and **5b** used these (2-hydroxyethyl) deuteroporphyrins as intermediates, and treatment with mesyl chloride in pyridine (though thionyl chloride in dimethylformamide has since been shown[11] to be more efficient) gave the (2 - chloroethyl) - porphyrins (**19b** and **20b**); finally, treatment of the zinc(II) complexes of these with t-butoxide and then sulphuric acid in methanol gave the required vinylporphyrins (**4b** and **5b**).

Thus, treatment of the haemins of the (2 - hydroxyethyl) - vinyl isomers individually in a resorcinol melt gave moderate yields of the devinylated porphyrins (**21b** and **22b**) which were successfully identified with authentic material[10] by m.p., m.m.p. and HPLC analysis.

The precise mechanism of the resorcinol fusion devinylation procedure devised by Schumm[12] is still unclear. In an earlier paper[13] we reported the isolation of a resorcinol adduct (of unproven structure) and on the basis of this we put forward a possible mechanism which involved attachment of resorcinol to the vinyl group through a phenolic O atom. With hindsight we consider **26** to be a more likely structure† for the resorcinol adduct because, (i) attachment of the resorcinol to the porphyrin vinyl through *carbon* is chemically more attractive, and (ii) the adduct **26** possesses a proton suitably placed for intramolecular transfer to the porphyrin, thereby rationalisting, in part, the fact that resorcinol is the reagent of choice for this degradation.

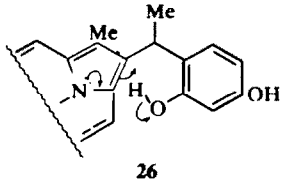
Two reports of the synthesis of chlorocruoro (*Spirographis*) porphyrin dimethyl ester (**6b**) and its isomer (**7b**) from protoporphyrin-IX dimethyl ester (**8b**) have recently appeared. The most celebrated of these is the conversion, via photoprotoporphyrins, described by Inhoffen *et al.*[14] More recently, a mixture of chlorocruoroporphyrin ester (**6b**) and its isomer (**7b**) obtained by partial oxidation of protoporphyrin-IX dimethyl ester with permanganate (see Ref. 15*a*) has been separated by TLC.[15b] Our approach, though basically similar, involved instead the treatment of protoporphyrin-IX with osmium tetroxide (see Ref. 16). The mono-glycol–mono-vinyl mixture (**23b** and **24b**) was readily separated from starting material and bis-glycol (**25b**) by column chromatography. Thick layer chromatography of the mono-glycols (overall yield 50% from **8b**) gave a good separation, the 4 - (1,2 - dihydroxyethyl) - 2 - vinyl isomer (**24b**) being the most polar (least mobile) component. Treatment of the separate isomers (**23b** and **24b**) with sodium periodate gave *ca* 80% yields of chlorocruoroporphyrin dimethyl ester (**6b**) and its isomer (**7b**) respectively. Compound **6b** was identified by m.p., m.p.p., and comparative HPLC with an authentic sample obtained[10] by total synthesis. Isospirographis porphyrin dimethyl ester (**7b**) was identified from its m.p., and by comparison with NMR and TLC data in the literature (e.g. Ref. 15).

†We thank Dr. F. M. Dean for this suggestion.



a: R = H
b: R = Me
V = CH=CH₂
P^R = CH₂CH₂CO₂R

1: R¹ = R² = H
2: R¹ = V, R² = P^R
3: R¹ = P^R, R² = V
4: R¹ = H, R² = V
5: R¹ = V, R² = H
6: R¹ = CHO, R² = V
7: R¹ = V, R² = CHO
8: R¹ = R² = V
9: R¹ = R² = $CH_2CH(OMe)_2$
10: R¹ = R² = P^R
11: R¹ = $CH_2CH(OMe)_2$, R² = V
12: R¹ = V, R² = $CH_2CH(OMe)_2$
13: R¹ = CH_2CH_2OH, R² = V
14: R¹ = V, R² = CH_2CH_2OH
15: R¹ = CH_2CH_2Br, R² = V
16: R¹ = V, R² = CH_2CH_2Br
17: R¹ = CH_2CH_2CN, R² = V
18: R¹ = V, R² = CH_2CH_2CN
19: R¹ = CH_2CH_2Cl, R² = H
20: R¹ = H, R² = CH_2CH_2Cl
21: R¹ = CH_2CH_2OH, R² = H
22: R¹ = H, R² = CH_2CH_2OH
23: R¹ = $CH(OH)CH_2OH$, R² = V
24: R¹ = V, R² = $CH(OH)CH_2OH$
25: R¹ = R² = $CH(OH)CH_2OH$



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EXPERIMENTAL

M.ps were measured on a microscopic hot-stage apparatus. Column chromatography was carried out on Fluka neutral alumina. TLC monitoring was performed on silica plates using 5% acetone in CH_2Cl_2 as eluant; preparative TLC was carried out on plates (1.5 mm thickness) of Merck GF 254 silica. HPLC separations were performed on a Waters Associates ALC 202-401 instrument with a 254 nm UV detector; 4 ft × ¼ in. of Corasil II was used and elutions were carried out with $CHCl_3$–cyclohexane mixtures. Visible absorption spectra (solns in $CHCl_3$) were measured on a Unicam SP 800 spectrophotometer, and ^1H NMR spectra were determined (usually in $CDCl_3$ with TMS as internal standard) with a Varian HA-100 instrument. Mass spectra (direct insertion probe, operating conditions 70 eV, 50 μA, source temp. *ca.* 200°) were measured using an A.E.I. MS 902 or MS 12 spectrometer. Light was excluded from all reactions.

2 - (2,2 - *Dimethoxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**11b**) *and* 4 - (2,2 - *Dimethoxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**12b**)

A soln of protoporphyrin-IX dimethyl ester[a] (590 mg) in CH_2Cl_2 (590 ml) was stirred vigorously during addition of thallium(III) nitrate trihydrate (977 mg; 2.2 equiv) in dry MeOH (200 ml) over 90 min. Shortly afterwards, thallium(I) nitrate was seen to precipitate, but the suspension was left stirring for 24 hr before treatment with SO_2 gas and briefly with HCl gas. After 5 min the mixture was diluted with CH_2Cl_2 (150 ml) and washed with H_2O (2 × 500 ml). The organic phase was dried (Na_2SO_4), evaporated to dryness, and the residue was chromatographed (alumina, Brockmann Grade III) using gradually increasing proportions of CH_2Cl_2 in toluene. Protoporphyrin-IX dimethyl ester was first eluted, then the desired isomeric mixture, and finally the bis-acetal. Evaporation of the eluates from the middle fraction gave a purple residue which was crystallised from CH_2Cl_2–n-hexane, giving 232 mg (36%) of the mono-acetal–mono-vinyl mixture. (Found: C, 70.2; H, 6.8; N, 8.9. $C_{38}H_{44}N_4O_6$ requires: C, 69.9; H, 6.8; N, 8.6%), λ_{max} 403 (ε 187,600), 502 (19,700), 537 (11,700), 571 (6600) and 625 nm (3900). The NMR spectrum was concentration dependent.[a]

2 - (2 - *Hydroxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**13b**) and 4 - (2 - *hydroxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**14b**)

(a) *Preparation.* The mono-acetal–mono-vinyl mixture from above (230 mg) dissolved in THF (110 ml) containing H_2O (4 ml) and conc HCl (1.5 ml) was refluxed for 10 min before being cooled and diluted with CH_2Cl_2 (100 ml) containing pyridine (10 ml). The mixture was washed successively with NaCl aq, $NaHCO_3$ aq, and finally H_2O. The organic phase was dried (Na_2SO_4), evaporated to dryness, and the residue in CH_2Cl_2 (50 ml) and pyridine (10 ml) was treated with $NaBH_4$ (1.3 g) in MeOH (25 ml) at 0°. While stirring, the mixture was allowed to attain room temp. before addition of glacial HOAc (3 ml). The soln was diluted with CH_2Cl_2, washed with H_2O, dried (Na_2SO_4), and then evaporated to dryness. The residue was taken up in 5% v/v H_2SO_4 in MeOH, stirred overnight in the dark, and then diluted with CH_2Cl_2 and washed with NaCl aq, $NaHCO_3$ aq, and finally H_2O. After drying (Na_2SO_4) the organic phase was evaporated and the residue chromatographed on alumina (Brockmann Grade V, elution with CH_2Cl_2). The porphyrin containing eluates were evaporated to dryness and the residue crystallised from CH_2Cl_2–n-hexane to give 255 mg (78%) of the required (2-hydroxyethyl)-vinyl mixture.

(b) *Separation of the isomers.* The foregoing mixture was separated by preparative TLC on silica. A soln of the isomers (10 mg) in CH_2Cl_2 (1 ml) was applied to the shorter edge of a 20 × 40 cm coated plate. This was then developed during 12 hr by continuous elution in a tank with the plate protruding *ca.* 3 cm above the top of the tank; the solvent mixture employed was 8% stabilised THF in $CHCl_3$. The bands were removed from the plate and the porphyrin was obtained by washing the silica with a soln of CH_2Cl_2 containing 2% MeOH. Evaporation of the eluates and crystallisation from CH_2Cl_2–n-hexane gave 3 mg of each isomer per plate. Plates were usually run one dozen at a time to give handleable amounts of material. The upper band (most mobile) contained the 2 - (2 - *hydroxyethyl*) - 4 - *vinylporphyrin* (**13b**), m.p. 218–220°. (Found: C, 70.8; H, 6.8; N, 9.2. $C_{36}H_{40}N_4O_5$ requires: C, 71.0; H, 6.6; N, 9.2%), λ_{max} 404 (ε 192,900), 504 (22,900), 538 (18,200), 574 (10,500) and 625 nm (2900). The compound was not sufficiently soluble in $CDCl_3$ for its NMR spectrum to be determined. The lower band (least mobile) contained the 4 - (2 - *hydroxyethyl*) - 2 - *vinylporphyrin* (**14b**), m.p. 208–210°. (Found: C, 70.0, 70.0; H, 6.6, 6.6; N, 9.1, 9.2. $C_{36}H_{40}N_4O_5 \cdot \frac{1}{2}H_2O$ requires: C, 70.0; H, 6.7; N, 9.1%), λ_{max} 404 (ε 191,800), 504 (22,700), 538 (18,000), 574 (10,300) and 625 nm (3000); the sample was not soluble enough in $CDCl_3$ for its NMR spectrum to be determined.

2 - (2 - *Bromoethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**15b**)

Compound **13b** (10 mg) in dry CH_2Cl_2 (5 ml) was treated with a soln of CBr_4 (85 mg) and triphenylphosphine (60 mg) in CH_2Cl_2 (1 ml) before being refluxed for 20 min with the reaction being monitored by TLC. The soln was filtered through a short column of alumina (Brockmann Grade II, elution with CH_2Cl_2) and the porphyrin containing eluates were evaporated. Crystallisation of the residue from CH_2Cl_2–n-hexane gave the *bromoethylporphyrin* (9.8 mg, 90%), m.p. 205–207°. (Found: C, 64.2; H, 5.9; N, 8.2. $C_{36}H_{40}BrN_4O_4$ requires: C, 64.4; H, 5.9; N, 8.3%), λ_{max} 401 (ε 177,700), 500 (15,100), 535 (11,800), 569 (7700), and 624 nm (4300); τ, 0.00, 0.14, 0.20, 0.30 (4 *meso*-H), 1.8–2.1 (m, C$\underline{H}$=CH$_2$), 3.7–4.1 (m, CH=C$\underline{H}_2$), 5.7 (m, C$\underline{H}_2$CH$_2$Br), 5.9 (m, 2 × C$\underline{H}_2$CH$_2$CO), 6.37 (2 × OMe), 6.52 (9H), 6.44 (3H) (4 × Me) and 6.8 (m, 2 × CH$_2$C$\underline{H}_2$CO).

4 - (2 - *Bromoethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**16b**)

This compound was similarly prepared from **14b** in 87% yield, crystallised from CH_2Cl_2–n-hexane, m.p. 197–199°. (Found: C, 64.2; H, 5.9; N, 8.1. $C_{36}H_{40}BrN_4O_4$ requires: C, 64.4; H, 5.9; N, 8.3%), λ_{max} 401 (ε 178,900), 500 (15,600), 535 (12,400), 569 (8100) and 624 nm (4700), τ, 0.08, 0.16, 0.31 (2H, 1H, 1H, 4-*meso*-H), 1.8–2.2 (m, C$\underline{H}$=CH$_2$), 3.6–4.0 (m, CH=C$\underline{H}_2$), 5.7 (m, CH$_2$CH$_2$Br), 6.0 (m, 2 × C$\underline{H}_2$CH$_2$CO), 6.36, 6.37 (2 × OMe), 6.58, 6.65, 6.67 (6H, 3H, 3H, 4 × Me) and 6.8 (m, 2 × CH$_2$C$\underline{H}_2$CO).

2 - (2 - *Cyanoethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**17b**)

Compound **15b** (30 mg) in 1-methylpyrrolidone (4 ml) was treated with powdered NaCN (120 mg) before being heated at 40° for 5 hr. The mixture was poured into 2% aq HOAc (200 ml) in a fume hood. The product was then dissolved in CH_2Cl_2 containing a little pyridine, and the organic phase was washed with H_2O, dried (Na_2SO_4), and then evaporated to dryness. After re-dissolving in CH_2Cl_2 (5 ml) the solution was treated with excess ethereal diazomethane and left to stand for 30 min before evaporation and chromatography of the residue on alumina (Grade III, elution with CH_2Cl_2). The major band was collected, evaporated to dryness and the residue was crystallised from CH_2Cl_2–n-hexane to give the *cyanoethylporphyrin* (20.2 mg; 72%), m.p. 235–237°. (Found: C, 72.1; H, 6.7; N, 11.6. $C_{37}H_{39}N_5O_4$ requires: C, 71.9; H, 6.4; N, 11.3%), λ_{max} 405 (ε 178,000), 503 (13,700), 536 (9900), 574 (6300), and 627 nm (4100), τ, −0.1, 0.01, 0.13, 0.50 (4 *meso*-H), 1.4–1.9 (m, C$\underline{H}$=CH$_2$), 3.5–3.85 (m, CH=C$\underline{H}_2$), 5.7 (m, 2 × C$\underline{H}_2$CH$_2$CO), 6.1 (m, C$\underline{H}_2$CH$_2$CN), 6.29 (2 × OMe), 6.44, 6.48, 6.51 (6H, 3H, 3H, 4 × Me), 6.6 (m, 2 × CH$_2$C$\underline{H}_2$CO), and 7.00 (m, CH$_2$C$\underline{H}_2$CN).

4 - (2 - *Cyanoethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**18b**)

This compound was prepared in a similar manner from **16b** in 69% yield. It was crystallised from CH_2Cl_2–n-hexane, m.p. 203–205°. (Found: C, 72.0; H, 6.7; N, 11.5. $C_{37}H_{39}N_5O_4$ requires: C, 71.9; H, 6.4; N, 11.3%), λ_{max} 405 (ε 186,900), 503 (14,400), 536 (10,300), 574 (6300) and 627 nm (4300), τ, 0.23, 0.30, 0.36, 0.66 (4 *meso*-H), 1.8–2.2 (m, C$\underline{H}$=CH$_2$), 3.7–4.1 (m, CH=C$\underline{H}_2$), 5.8 (m, 2 × C$\underline{H}_2$CH$_2$CO), 6.3 (m, C$\underline{H}_2$CH$_2$CN), 6.42, 6.44 (2 × OMe), 6.63, 6.70, 6.88 (6H, 3H, 3H, 4 × Me), 7.0–7.4 (m, 2 × CH$_2$CH$_2$CO and CH$_2$CH$_2$CN).

4,6,7 - *Tris*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**2b**), '*Harderoporphyrin trimethyl ester*'

Compound **18b** (5 mg) in saturated methanolic HCl (2 ml) was set aside overnight before neutralisation with aq ammonia. CH_2Cl_2 was added and the soln was washed with H_2O, dried (Na_2SO_4), and then evaporated to dryness. The residue was chromatographed on alumina (Grade V, elution with CH_2Cl_2) and the porphyrinic eluates were evaporated. Crystallisation of the residue from CH_2Cl_2–n-hexane gave the porphyrin (3 mg, 60%), m.p. 200–202° (lit.[4] 203–204°). The product showed no depression of the m.p. when admixed with authentic material and was shown to be identical with an authentic sample by comparative HPLC.

2,6,7 - *Tris*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**3b**), '*Isoharderoporphyrin trimethyl ester*'

This compound was similarly prepared in 50% yield from **17b**. It crystallised from CH_2Cl_2–n-hexane, m.p. 211–213° (lit.[4] 216–218°) which was undepressed upon admixture with authentic material. Comparative HPLC confirmed the identity of this product.

2 - (2 - *Hydroxyethyl*) - 6,7 - *bis*(2-*methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**21b**)

Compound **13b** (45 mg) in pyridine (2 ml) and HOAc (50 ml) was treated with a freshly made soln of $FeSO_4$ (aq satd, 2 ml) and then NaCl (50 mg). The mixture was refluxed under N_2 for 10 min when metallation was shown to be complete by spectrophotometry. The solution was poured into H_2O, extracted with CH_2Cl_2, and the organic phase was dried (Na_2SO_4) and then evaporated to dryness. The residual haemin was recrystallised from CH_2Cl_2–n-hexane (42 mg). It was then intimately ground with resorcinol (3 g), heated at 160° (oil bath) for 30 min, cooled, and then treated with HOAc (100 ml) and pyridine (2 ml). To this soln was added $FeSO_4$ in conc HCl (satd, 5 ml) and the mixture was refluxed under N_2 for 10 min. It was then poured into H_2O, extracted with CH_2Cl_2 which was dried (Na_2SO_4) and evaporated to dryness. The residue was set aside overnight in 5% v/v H_2SO_4 in MeOH (30 ml), poured into NaCl aq, extracted with CH_2Cl_2, and this was washed with $NaHCO_3$ aq and H_2O before being dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on alumina (Grade V, elution with CH_2Cl_2) and the porphyrinic eluates were evaporated to give a residue which was crystallised from CH_2Cl_2–n-hexane. Yield 14 mg (30%), m.p. 208–209° (lit.[10] 210–212°). The m.p. was undepressed upon admixture with an authentic sample, with which the product was identical by HPLC analysis.

4 - (2 - *Hydroxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**22b**)

This compound was similarly prepared in 37% yield from **14b**. It was crystallised from CH_2Cl_2–n-hexane and had m.p. 214–216° (lit.[10] 215–217°) which was undepressed upon admixture with authentic material. Comparative HPLC confirmed the identity of the product.

2 - (1,2 - *Dihydroxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**23b**) and 4 - (1,2 - *dihydroxyethyl*) - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**24b**)

(a) *Preparation.* Protoporphyrin-IX dimethyl ester (220 mg) in dioxan (35 ml) was treated with osmium tetroxide (100 mg) in ether (10 ml) containing pyridine (0.2 ml), and was then left with stirring for 48 hr during formation of a black ppt. The suspension was then refluxed with a soln of Na_2SO_3 (1 g) in H_2O (10 ml) for 75 min. The suspension was then filtered and poured into CH_2Cl_2 (200 ml) and extracted with H_2O. The organic phase was dried (Na_2SO_4), evaporated, and the residue was chromatographed on alumina (Grade V, elution with 5% v/v acetone in $CHCl_3$). Two mobile bands were obtained; the first contained starting material and the second the required isomeric mixture which was crystallised from CH_2Cl_2–n-hexane to give 115 mg (50%). A small amount of bis-glycol (**25b**) was left in the column.

(b) *Separation of the isomers.* The isomeric mixture (10 mg) was applied to the narrow side of a 20 × 40 cm silica-coated plate which was then developed in 8% v/v stabilised THF in CH_2Cl_2, two developments usually being sufficient to afford a good separation. The yield of each isomer per plate averaged 3.5 mg; 10–12 plates were run at a time. The upper (most mobile) band afforded 2 - (1,2 - *dihydroxyethyl*) - 4 - *vinyldeuteroporphyrin* - IX *dimethyl ester* (**23b**), m.p. 201–203°, from CH_2Cl_2–n-hexane. (Found: C, 68.3, 68.4; H, 6.4, 6.4; N, 8.8, 8.8. $C_{36}H_{40}N_4O_6 \cdot \frac{1}{2}H_2O$ requires: C, 68.2; H, 6.5; N, 8.8%), λ_{max} 405 (ϵ 183,500), 504 (14,000), 539 (12,900), 574 (7400) and 627 nm (4200). The compound was highly insoluble and a satisfactory NMR spectrum could not be obtained. The lower (least mobile) band afforded 4 - (1,2 - *dihydroxyethyl*) - 2 - *vinyldeuteroporphyrin* - IX *dimethyl ester* (**24b**), m.p. 193–195° from CH_2Cl_2–n-hexane. (Found: C, 68.3; H, 6.4; N, 8.7. $C_{36}H_{40}N_4O_6 \cdot \frac{1}{2}H_2O$ requires: C, 68.2; H, 6.5; N, 8.8%), λ_{max} 405 (ϵ 178,000), 504 (13,200), 539 (12,200), 574 (6900) and 627 nm (3900). The compound was not sufficiently soluble for its NMR spectrum to be determined.

2 - *Formyl* - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 4 - *vinylporphin* (**6b**), '*Chlorocruoro* (Spirographis) *porphyrin dimethyl ester*'

Compound **23b** (100 mg) in THF (60 ml) was treated with sodium periodate (1 g) in H_2O (10 ml). The mixture was stirred for 24 hr before being poured into H_2O and CH_2Cl_2. The organic phase was washed with H_2O, dried (Na_2SO_4), and then evaporated to dryness to give a residue which was chromatographed on alumina (Grade III, elution with $CHCl_3$). The porphyrin containing eluates were evaporated and crystallisation from CH_2Cl_2–MeOH gave the product, 77 mg (82%) with m.p. 276–278° (lit.[14] 278°). Admixture with an authentic sample[10] caused no depression of the m.p.: HPLC comparison with the same authentic sample confirmed the identity of the product.

4 - *Formyl* - 6,7 - *bis*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**7b**), '*Isospirographis porphyrin dimethyl ester*'

This compound was similarly prepared from **24b** in 78% yield. It was crystallised from CH_2Cl_2–MeOH with m.p. 226–228° (lit.[14] 225–227°). HPLC indicated no contamination of the product with **6b**.

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