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PYRROLES AND RELATED COMPOUNDS—XXXV[1]

A STEPWISE, GENERAL SYNTHESIS OF UNSYMMETRICALLY SUBSTITUTED PORPHYRINS[2]

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Dedicated to Prof. Dr. Hans Herloff Inhoffen on the occasion of his 70th birthday.

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Abstract—Using a new, general approach involving the stepwise progression through pyrrole, dipyrrole, tripyrrole, to tetrapyrrole, followed by cyclisation of the resulting *a,c*-biladiene by the copper salt method, syntheses of isocoproporphyrin tetramethyl ester (**1b**), coproporphyrin-III tetramethyl ester (**24**), protoporphyrin-IX dimethyl ester (**26**), 2,4,6,7-tetrakis(2-methoxycarbonylethyl)-5-methoxycarbonylmethyl-1,3,8-trimethylporphin (**29**) (the ester of the pentacarboxylic porphyrin recently associated with haem metabolism), rhodoporphyrin-XV dimethyl ester (**27**) and 2,4,7-triethyl-6-methoxycarbonyl-1,3,5,8-tetramethylporphin (**28**), are described.

The route employs condensation of unsymmetrically substituted pyrromethanes with 2-formyl-5-methylpyrroles to give crystalline and fully characterised tripyrrene salts in high yield. These are then condensed with a second mole of a different 2-formyl-5-methylpyrrole to give very high yields of *a,c*-biladiene dihydrobromides; cyclisation with copper(II) chloride in dimethylformamide gives copper(II) porphyrins which are demetallated in trifluoroacetic acid containing sulphuric acid to give high overall yields of the corresponding metal free porphyrins.

Haem and most of the tetrapyrrolic macrocycles related to its biosynthesis possess an element of symmetry. Positions 5 and 8 and positions 6 and 7 (Fischer numeration) in rings C and D have identical pairs of substituents. This circumstance was employed by Hans Fischer in his classical synthesis[3] of protoporphyrin-IX, and the convenience has been accepted in the majority of subsequent syntheses in this area.[4] In recent years, however, exploration of the biosynthetic pathway to haem[5] has revealed the participation, as intermediates, of porphyrinogens corresponding to unsymmetrical porphyrins. Thus, for example, the "sub-uroporphyrins" bearing seven, six, and five carboxylic acids no longer retain the C–D symmetry.[6] Moreover, specifically ^{13}C, ^{14}C and ^{2}H labelled porphyrins, required for studies of biosynthesis[5] and the binding of haem to globins,[7] are generally unsymmetrical.

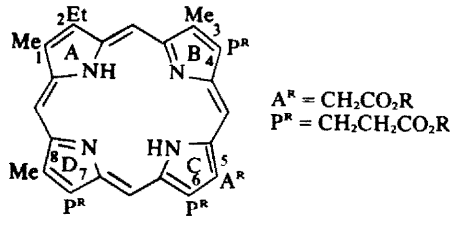
In the chlorophyll field symmetry is not encountered, and the classical methods of synthesis are inadequate. In this connection, we have already devised and employed new methods involving stable open-chain tetrapyrrolic precursors of the macrocycle,[8] notably the *b*-oxobilane method.[9] Versatile as this is, it has the drawback of requiring high experimental skill. We now describe a more efficient method and exemplify it in several instances related to haem, chlorophyll-*a*, and the biosynthesis of the *Chlorobium* chlorophylls.

The method is based on the cupric-catalysed cyclisation of *a,c*-biladienes,[10] which has recently been employed and improved by Clezy *et al.*[11] Our contribution is to show how such unsymmetrically substituted tetrapyrrolic intermediates can be readily constructed by adapting methods already developed by us for our previous syntheses. Owing to the unavailability of unsymmetrically substituted 1′,8′-dimethyl-*a,c*-biladienes, previous workers have tended to rely upon the corresponding *b*-bilenes for preparation of complex porphyrins by the copper salt method; even then, if safeguards are not built into rings A and D of the *b*-bilene, side-reactions[12] become troublesome.

Thus, condensation of an acetoxymethylpyrrole with a 2-unsubstituted pyrrole yields[13] a benzyl t-butyl pyrromethane-5,5′-dicarboxylate. Hydrogenolysis frees the 5-position for condensation with a 2-formylpyrrole under acidic conditions which nonetheless permit retention of the t-butyl ester. The resulting key intermediate, a tripyrrene, which is fully characterised, is then treated, after acidolysis of the t-butyl protecting group, with another 2-formylpyrrole, yielding the 1′,8′-dimethyl-*a,c*-biladiene. Subsequent to the appearance of our preliminary publication,[2] Gossauer has communicated[14] the synthesis of a porphyrin using a similar sequence of reactions.

Our first specific example is a synthesis of isocoproporphyrin, which is found in the faeces of patients suffering from symptomatic cutaneous hepatic porphyria, and in rats with porphyria induced by hexachlorobenzene poisoning.[15a] By consideration of results from an ingenious lanthanide shift NMR study, the original structural proposal was amended[15b] in favour of (**1a**); meanwhile, a total synthesis of the incorrectly assigned structure was completed[16] and the product was shown to be different from natural isocoproporphyrin. Though we were developing the present porphyrin synthesis for other applications,[17] we considered that a good test of the generality of the new approach would be a synthesis of isocoproporphyrin tetramethyl ester (**1b**); a successful synthesis would also serve to confirm the new structural proposal[15b] and the reasoning which led to its suggestion.

Condensation of the acetoxymethylpyrrole (**2**) with the 2-unsubstituted pyrrole (**3**) in acetic acid containing a catalytic amount of toluene p-sulphonic acid[13] gave a good yield of the pyrromethane (**4a**) which was hydrogenated over palladised charcoal to afford the carboxylic acid (**4b**). This was condensed in the presence of toluene p-sulphonic acid with the 2-formyl-5-methylpyrrole (**5**) and



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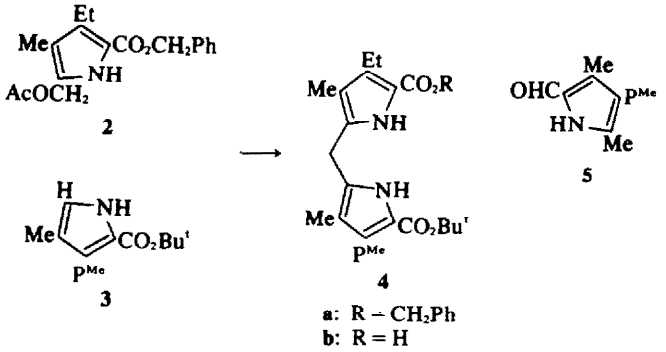
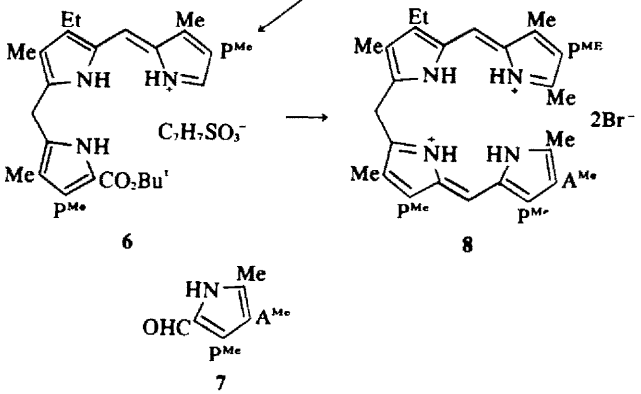
a: R = H
b: R = Me



2 **3** **4** **5**

a: R = CH_2Ph
b: R = H



6 **8**

7

gave an 80% yield of the tripyrrene,[18] isolated as its toluene p-sulphonate (**6**). The remaining t-butyl ester protecting group was cleaved in trifluoroacetic acid–hydrobromic acid in the presence of the 2-formyl-5-methylpyrrole (**7**) and gave an 89% yield of the *a,c*-biladiene di-hydrobromide (**8**). Cyclisation[10,11] with copper(II) chloride in dimethylformamide gave the copper(II) complex of the required porphyrin which was demetallated in trifluoroacetic acid containing 5% sulphuric acid to give a 30% yield of isocoproporphyrin tetramethyl ester (**1b**).

The NMR spectrum of the synthetic material (**1b**) was virtually identical with that already published[15a] for the natural material; the TLC behaviour was identical with that of a sample of natural material kindly supplied by Dr. Elder, and the synthetic substance (recrystallised from methylene chloride–n-hexane) possessed a melting point (182–183°, corr.) only slightly higher than that of the natural compound crystallised from the same system. The mixed m.p. showed no depression and together with superimposable high performance liquid chromatography traces confirmed fully the proposed[15b] structure for isocoproporphyrin (**1a**). However, satisfactory m.ps could only be obtained in evacuated capillaries; on a Kofler hot-stage only partial melting (*ca.* 175–177°) was observed with both the natural and synthetic esters. Shortly after the publication of our preliminary report[2] of the synthesis of (**1b**), we were informed by Prof. Clezy of his own independent synthesis of the same molecule. His material, however, recrystallised from methylene chloride–methanol, melted fairly cleanly on a Kofler hot-stage some 10° higher than the natural ester and our own synthetic sample. Though both synthetic samples were identical by TLC, the differential m.p. behaviour (due to different crystalline modifications) has been confirmed in both laboratories following an exchange of samples. After recrystallisation of the Liverpool sample from methylene chloride–methanol, its m.p. is raised to 193–195° with slight softening around 183°. There is some evidence (Experimental) that the higher melting form is partially hydrated, but neither in Prof. Clezy's laboratory nor our own has it been possible to generate the low-melting form by recrystallisation of high-melting material from methylene chloride–n-hexane.

The Experimental contains full details of the syntheses of five other porphyrins using this general approach. Only

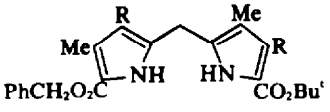
brief comments on the individual examples are therefore given here.

Coproporphyrin-III tetramethyl ester (**24**) *and protoporphyrin-IX dimethyl ester* (**26**). The tripyrrene hydrobromides (**12** or **13**) were obtained by condensation of the appropriate pyrromethane [obtained by hydrogenolysis of (**9**) or (**10**)] with the 2-formyl-5-methylpyrrole (**5**). These were in turn condensed with a second mole of the same formylpyrrole (**5**) to give the *a,c*-biladiene dihydrobromides (**19** or **20**). Cyclisation as described above followed by demetallation gave coproporphyrin-III tetramethyl ester (**24**; identified by comparison with authentic material) or the 2,4-bis(2-chloroethyl)porphyrin (**25**), a well-characterised intermediate in all of our earlier syntheses[19] of protoporphyrin-IX. Treatment of the zinc(II) chelate of **25** with t-butoxide in t-butyl alcohol gave a good yield of protoporphyrin-IX dimethyl ester after treatment with 5% sulphuric acid in methanol.

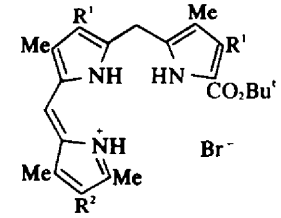
At first sight, the strategy of condensing two molecules of the same 2-formyl-5-methylpyrrole (**5**) in separate steps might appear to be unnecessary, and under normal circumstances the intermediacy of the tripyrrenes (**12** or **13**) could be avoided by one-step condensation of two molecules of formylpyrrole with a 5,5′ doubly deprotected pyrromethane. However, the coproporphyrin-III was required for biosynthetic studies[20] in which a carbon label is to be sited in the propionic side-chain in ring C. Furthermore, the protoporphyrin-IX was required[21] to bear a ^2H_3C group at position 5 (in ring C) for contact shift NMR studies of haems and haemoproteins (*cf.* Ref. 7). Both of these additional features render the required porphyrin unsymmetrical in the C–D portion and necessitate a general approach. The stepwise nature of the synthesis through tripyrrenes also facilitates the economical addition of the sub-unit bearing the novel (labelled) atoms at the tripyrrole → tetrapyrrole stage.

2,4,6,7 - *Tetrakis*(2 - *methoxycarbonylethyl*) - 5 - *methoxycarbonylmethyl* - 1,3,8 - *trimethylporphin* (**29**) (*pentamethyl ester of "pentacarboxylic porphyrin" in the "sub-uroporphyrin" series*). We recently described preliminary results of an investigation[22] concerning the biosynthesis of the *Chlorobium* chlorophylls from *Chloropseudomonas ethylicum*. It transpired that the porphyrinogen derivative of the pentacarboxylic acid of porphyrin (**29**) was required in order to substantiate the pathway which we have proposed for the biosynthesis of the majority of the (660) chlorophylls; for this reason, we embarked upon the synthesis of **29** via the tripyrrene method. Simultaneously, Professor Jackson reported[6] that the pentacarboxylic porphyrinogen in normal haem metabolism is the same porphyrinogen derived from the pentacarboxylic acid of **29**; moreover, he described[6] the synthesis of **29** and its successful identification with naturally derived pentacarboxylic ester from rats.

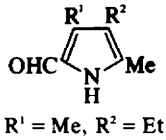
Treatment of the tripyrrene hydrobromide (**12**) with the



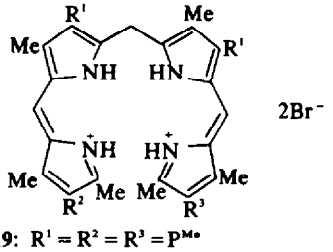
9: R = P^{Me}
10: R = CH_2CH_2Cl
11: R = Et



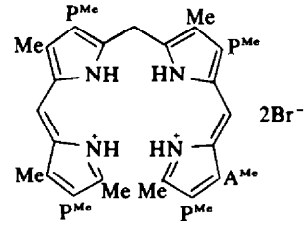
12: R′ = R″ = P^{Me}
13: R′ = CH_2CH_2Cl; R″ = P^{Me}
14: R′ = Et; R″ = P^{Me}
15: R′ = R″ = Et



16: R′ = Me, R″ = Et
17: R′ = A^{Me}, R″ = P^{Me}
18: R′ = Me, R″ = CO_2Me



19: R′ = R″ = R‴ = P^{Me}
20: R′ = CH_2CH_2Cl; R″ = R‴ = P^{Me}
21: R′ = Et; R″ = P^{Me}; R‴ = CO_2Me
22: R′ = R″ = Et; R‴ = CO_2Me



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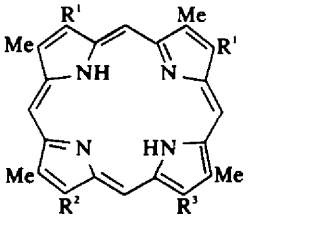
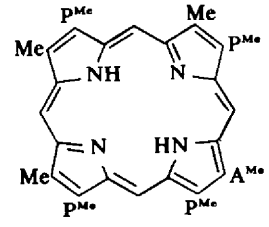


24: R′ = R″ = R‴ = P^{Me}
25: R′ = CH_2CH_2Cl, R″ = R‴ = P^{Me}
26: R′ = V; R″ = R‴ = P^{Me}
27: R′ = Et; R″ = P^{Me}; R‴ = CO_2Me
28: R′ = R″ = Et; R‴ = CO_2Me



29

2-formyl-5-methylpyrrole (**17**) in trifluoroacetic and hydrobromic acids gave the *a,c*-biladiene salt (**23**), which was cyclised with copper(II) chloride in dimethylformamide; demetallation of the resultant copper(II) porphyrin gave a good yield of the penta carboxylic ester (**29**) which was successfully identified with the material described by Jackson.[6]

Rhodoporphyrin-XV dimethyl ester (**27**) *and* 2,4,7 - *triethyl* - 6 - *methoxy* - *carbonyl* - 1,3,5,8 - *tetramethylporphin* (**28**). We considered it necessary to test the route by synthesis of rhodo-type porphyrins because the terminal rings in the intermediate *a,c*-biladiene (eventually rings C and D in the porphyrin) would be electronically dissimilar. While it has been demonstrated[10,11] that *a,c*-biladienes with either electron releasing or electron withdrawing substituents in the terminal rings can be cyclised by the copper salt method, the situation in which there is an imbalance of electron density in the terminal rings had not been investigated.

Hydrogenation of pyrromethane (**11**) followed by condensation with the 2-formyl-5-methylpyrrole (**5** or **16**) gave the tripyrrene hydrobromides (**14** or **15**) respectively. These were further treated, as described earlier, with pyrrole (**18**) and gave good yields of the respective *a,c*-biladienes (**21** or **22**). Cyclisation with copper(II) chloride in dimethylformamide followed by demetallation gave rhodoporphyrin-XV dimethyl ester (**27**) (satisfactorily identified with a sample prepared[23] from chlorophyll-*a*) and 2,4,7-triethyl-6-methoxycarbonyl-1,3,5,8-tetramethylporphin (**28**) in yields comparable with those of the other porphyrins synthesised herein.

EXPERIMENTAL

M.ps were measured on a microscopic hot-stage apparatus. Unless otherwise stated, chromatographic purifications were carried out on Fluka neutral alumina (Brockmann Grade III). 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 temperatures *ca.* 200°) were measured using an A.E.I. MS 902 or MS 12 spectrometer.

Pyrroles

Benzyl 3-*ethyl*-4,5-*dimethylpyrrole*-2-*carboxylate*. 3-Methylhexan-2,4-dione[24] (256 g) in glacial AcOH (1 l) was treated dropwise with the oxime prepared[25] from dibenzyl malonate (650 g) in HOAc (200 ml) with concomitant addition of aliquots of an intimate mixture of Zn powder (320 g) and anhyd. NaOAc (320 g) over 1.5 hr at such a rate that the mixture was maintained at 60–70°. The mixture was then heated under reflux for 1 hr before being poured onto iced H_2O (15 l). After extraction with $CHCl_3$(2 l), the organic phase was washed with H_2O, dried (Na_2SO_4), and evaporated to give a brown oil which crystallised when triturated with light petroleum, yield 125 g (35%), m.p. 88–90° (Lit.[26] 89–90°). τ, 0.83 (NH), 2.68, 4.72 ($C_6H_5{\cdot}CH_2$), 7.26(q), 8.91(t) (CH_2CH_3), and 7.90, 8.11 (4,5-Me).

Benzyl 5-*acetoxymethyl*-3-*ethyl*-4-*methylpyrrole*-2-*carboxylate* (**2**). The foregoing pyrrole (2 g) in HOAc (40 ml) and Ac_2O (1 ml) was treated portionwise over 2.5 hr with $Pb(OAc)_4$ (3.65 g) before being stirred overnight at room temp. H_2O (200 ml) was added slowly and the white ppt was filtered off, washed with H_2O, and dried. Recrystallisation from ether-hexane gave the *acetoxymethylpyrrole* (2.25 g; 92%), m.p. 111–112°. (Found: C, 68.34; H, 6.61; N, 4.58. $C_{18}H_{21}NO_4$ requires: C, 68.55; H, 6.71; N, 4.44%), τ, 0.95 (NH), 2.62, 4.71 ($C_6H_5{\cdot}CH_2$), 5.00 (CH_2O), 7.26(q), 8.89(t) (CH_2CH_3), 7.95, 7.97 (4-Me and COMe).

Benzyl 4 - (2 - *benzyloxycarbonylethyl*) - 3 - *benzyloxycarbonylmethyl* - 5 - *methylpyrrole* - 2 - *carboxylate*. Ethyl 4(2 - ethoxycarbonylethyl) - 3 - ethoxycarbonylmethyl - 5 - methylpyrrole - 2 - carboxylate[27] (2 g) in benzyl alcohol (60 ml) containing Na (60 mg) was heated at 100° *in vacuo* (15 mm Hg) during 5 hr. After standing overnight at room temp. solid CO_2 was added and the benzyl alcohol removed *in vacuo* (1 mm Hg). The resultant brown oil was chromatographed (elution with toluene–methylene chloride) and evaporation of the appropriate eluates (TLC monitoring) gave a pale yellow solid. Recrystallisation from methylene chloride–hexane gave the *pyrrole* as white needles (2.3 g; 74%), m.p. 100–101°. (Found: C, 72.95; H, 6.22; N, 2.81. $C_{32}H_{31}NO_6$ requires: C, 73.12; H, 5.95; N, 2.67%), τ, 0.11 (NH); 2.70(5 H), 2.74(10 H)(3 *Ph*·CH_2); 4.82, 4.96, 4.98 (3 Ph·CH_2); 6.16 (CH_2); 7.18–7.64 (m) (CH_2CH_2); and 7.84 (5-Me).

Benzyl 4 - (2 - *methoxycarbonylethyl*) - 3 - *methoxycarbonylmethyl* - 5 - *methylpyrrole* - 2 - *carboxylate*. The foregoing pyrrole (1.5 g) suspended in MeOH (20 ml) containing conc. HNO_3 (2 drops) was stirred at 60° overnight. Methylene chloride (30 ml) and H_2O (20 ml) were added and the organic phase was washed with H_2O (20 ml), $NaHCO_3$ aq (20 ml), then H_2O (20 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a white solid which was recrystallised from CH_2Cl_2–hexane–ether to give the *pyrrole* (930 mg; 85%) as white needles, m.p. 111–113° (Lit.[28] 113–116°). τ, 1.0 (NH); 2.67, 4.77 (Ph.CH_2); 6.23 (CH_2); 6.40, 6.46 (2 OMe); 7.2–7.74 (m)(CH_2CH_2); and 7.82 (5-Me).

2 - *Formyl* - 4 - (2 - *methoxycarbonylethyl*) - 3 - *methoxycarbonylmethyl* - 5 - *methylpyrrole* (**17**). The foregoing pyrrole (900 mg) in THF (25 ml) and Et_3N (2 drops) was hydrogenated at room temp. and atmospheric pressure over Pd–C (10%, 90 mg) until uptake of H_2 was complete (*ca.* 1 hr). The catalyst was filtered off on Celite and the filtrate was evaporated to dryness to give a pink solid which was recrystallised from THF-hexane to give the pyrrole-2-carboxylic acid (650 mg; 95%). This was dissolved in TFA (10 ml) and kept under N_2 for 30 min before evaporation of the solvent. CH_2Cl_2 and H_2O were added and the organic phase was washed with $NaHCO_3$ aq, H_2O, and then dried (Na_2SO_4) before concentration to a volume of *ca* 10 ml. This soln was added dropwise to dry CH_2Cl_2 (50 ml) containing the complex formed from allowing $POCl_3$ (2.5 g) and DMF (1.2 g) to stand in dry ether (70 ml) during 30 min. Na_2CO_3 aq (150 ml of 1 N) was added slowly and the heterogeneous mixture refluxed with vigorous stirring during 1 hr. The organic phase was separated, washed with H_2O, brine, and then dried (Na_2SO_4). Evaporation gave a residue which was chromatographed (elution with CH_2Cl_2). A slow running yellow fraction was collected and evaporation of the eluates gave a yellow solid which was recrystallised from CH_2Cl_2–hexane to give the *formylpyrrole* (200 mg; 33%) as pale pink needles, m.p. 78–78.5°. (Found: C, 58.12; H, 6.40; N, 5.29. $C_{13}H_{17}NO_5$ requires: C, 58.42; H, 6.41; N, 5.24%), τ, −0.10 (NH); 0.53 (CHO); 6.32 (CH_2); 6.37, 6.42 (2 OMe); 7.2–7.68 (CH_2CH_2); 7.77 (5-Me).

2 - *Formyl* - 3 - (2 - *methoxycarbonylethyl*) - 4 - *methoxycarbonylmethyl* - 5 - *methylpyrrole* (**7**), the isomer of the compound above, was similarly prepared from benzyl 3 - (2 - methoxycarbonylethyl) - 4 - methoxycarbonylmethyl - 5 - methylpyrrole - 2 - carboxylate[29] (5 g) by hydrogenation, decarboxylation, and then formylation. The *formylpyrrole* (2.1 g; 58%) was obtained as pale yellow crystals from MeOH, m.p. 111–112°. (Found: C, 58.19; H, 6.21; N, 5.23. $C_{13}H_{17}NO_5$ requires: C, 58.42; H, 6.41; N, 5.24%), τ, −0.1 (NH); 0.46 (CHO); 6.35, 6.38 (2 OMe); 6.60 (CH_2); 6.97(t), 7.42 (t) (CH_2CH_2); and 7.72 (5-Me).

Methyl 5-*formyl*-2,4-*dimethylpyrrole*-3-*carboxylate* (**18**), (with Dr. M. J. Sutton). $POCl_3$ (25 ml) in dry CH_2Cl_2 (140 ml) was added to DMF (25 ml). The soln was warmed to 35° during 30 min and then cooled to 0° in an ice bath. Methyl 2,4-dimethylpyrrole-3-carboxylate (8.7 g) in dry CH_2Cl_2 (160 ml) was added dropwise over 5 min with stirring, and the soln was then stirred for a further 5 min at 0° before being refluxed for 30 min. The mixture was cooled to room temp. and $NaHCO_3$ (250 g) in H_2O (800 ml) was added cautiously. After being stirred vigorously overnight, the soln was poured into H_2O (500 ml) and extracted with CH_2Cl_2 (3 × 250 ml). The organic extracts were washed with H_2O (3 × 250 ml), dried (Na_2SO_4), evaporated, and the residual cream solid was crystallised from CH_2Cl_2–n-hexane to give the

formylpyrrole (9.3 g; 93%) as white needles, m.p. 173–173.5°. (Found: C, 59.7; H, 6.1; N, 7.8. $C_9H_{11}NO_3$ requires: C, 59.7; H, 6.1; N, 7.7%), τ, 0.38 (CHO), 6.22 (OMe), 7.44, 7.48 (2,4-Me).

Compounds **5** and **16** were prepared in a similar fashion from the corresponding 2-unsubstituted pyrroles.

Pyrromethanes

Benzyl 5' - t - butoxycarbonyl - 4 - ethyl - 4' - (2 - methoxycarbonylethyl) - 3,3' - dimethylpyrromethane - 5 - carboxylate (**4a**). Compound **3**[30] (1.73 g) in AcOH (90 ml) was treated with compound **2** (1.7 g) and then toluene p-sulphonic acid hydrate (75 mg) before being stirred under N_2 at 40° during 4 h. The mixture was poured into H_2O, extracted with CH_2Cl_2, washed with $NaHCO_3$ aq., H_2O, and then dried (Na_2SO_4). Evaporation gave an oil which was chromatographed, the product being eluted with EtOAc–toluene (1:1). The appropriate eluates were evaporated and the resultant oil was dried to a brittle foam under high vacuum. Yield 2.0 g (71%), τ, 1.15, 1.32 (2 × NH br); 2.72, 4.79 (C_6H_5·CH_2); 6.24 (CH_2); 6.39 (OMe); 7.05(t), 7.54(t) ($CH_2CH_2CO_2Me$); 7.30(q), 8.94(t)(CH_2CH_3); 8.08 (2 × Me); 8.51 (Bu').

5' - t - Butoxycarbonyl - 4 - ethyl - 4' - (2 - methoxycarbonylethyl) - 3,3' - dimethylpyrromethane - 5 - carboxylic acid (**4b**). The foregoing pyrromethane (2.0 g) in THF (70 ml) containing triethylamine (0.2 ml) and 10% Pd–C (270 mg) was hydrogenated at room temp. and atm. pressure until uptake of H_2 had ceased. After filtration through Celite, the filtrate was evaporated and the *product* recrystallised from THF–hexane to give 1.6 g (95%) of white crystals, m.p. (decomp.), (Found: C, 63.77; H, 7.41; N, 6.37. $C_{23}H_{32}N_2O_6$ requires: C, 63.87; H, 7.46; N, 6.48%), τ, −1.60, −0.85 (2 × NH br); 6.18 (CH_2); 7.03 (t), 7.55 (t), 6.37 ($CH_2CH_2CO_2Me$); 7.24 (q), 8.85 (t) (CH_2CH_3); 7.90, 7.98 (2 × Me); 8.85 (Bu').

5' - t - Butoxycarbonyl - 3,4' - di(2 - methoxycarbonylethyl) - 3',4 - dimethylpyrromethane - 5 - carboxylic acid. Catalytic hydrogenation of compound **9**[30] (1 g) similarly gave the *pyrromethane acid* (820 mg; 97%) as pale pink prisms from THF–heptane, m.p. 163.5–165.5 (dec.), (Found: C, 61.49; H, 7.12; N, 5.83. $C_{25}H_{34}N_2O_8$ requires: C, 61.21; H, 6.99; N, 5.71%), τ, −1.22, −0.77 (2 × NH br); 6.13 (CH_2); 6.33, 6.35 (2 × OMe); 6.92–7.80 (2 × CH_2CH_2CO); 7.70, 7.90 (2 × Me); 8.45 (Bu').

Tripyrrenes

t - Butyl 1,4,6 - tri(2 - methoxycarbonylethyl) - 1',2,3,5 - tetramethyltripyrrene - a - 6' - carboxylate hydrobromide (**12**). The foregoing pyrromethane acid (400 mg) and compound **5** (170 mg) in CH_2Cl_2 (100 ml) were stirred with a soln of toluene *p*-sulphonic acid hydrate (388 mg; 2.5 equiv) in MeOH (5 ml) during 30 min. (The reaction was followed spectrophotometrically: a sample of the neat mixture was placed in a 10 mm cell and the side of the 492 nm absorption, which was well off scale, was observed until it broadened no further). The soln was washed with Na_2CO_3 aq (100 ml) and the organic phase was dried (Na_2SO_4) and then evaporated to dryness. Dry CH_2Cl_2 (50 ml) was added, followed by dry HBr gas which was passed through the brown soln until it became red (5 sec). Quantities of dry benzene (2 × 50 ml) were added and then evaporated in order to azeotrope unwanted H_2O and HBr. The resulting solid was recrystallised from CH_2Cl_2–ether to give the *tripyrrene hydrobromide* (480 mg; 82%) as bright red microprisms, m.p. 175–182° (decomp.). (Found: C, 58.35; H, 6.51; N, 5.78. $C_{35}H_{48}BrN_3O_8$ requires: C, 58.49; H, 6.73; N, 5.85%), λ_{max} 492 nm (ε 85,000), τ −3.31, −3.22 (2 × NH^+); −0.28 (NH); 2.89 (methine-H); 5.63 (CH_2); 6.34 (2 × OMe); 6.35 (OMe); 6.8–7.9(m)(3 × CH_2CH_2CO); 7.28, 7.67, 7.72, 7.93 (4 × Me); 8.42 (Bu').

The following tripyrrenes were prepared in a similar way:

t - Butyl 4,6 - di(2 - chloroethyl) - 1 - (2 - methoxycarbonyl) - 1',2,3,5 - tetramethyltripyrrene - a - 6' - carboxylate hydrobromide (**13**), from benzyl 5' - t - butoxycarbonyl - 3,4' - di(2-chloroethyl) - 3',4 - dimethylpyrromethane - 5 - carboxylate (**10**)[19] (600 mg) by debenzylation and then condensation with compound **5** (215 mg). After recrystallisation from ether, 378 mg (50%) of bright red microcrystals of the *tripyrrene hydrobromide*, m.p. >160° (dec.) were obtained. (Found: C, 54.54, 54.37; H, 6.18, 6.11; N, 6.30. $C_{31}H_{42}BrCl_2N_3O_4 \cdot \frac{1}{2}H_2O$ requires: C, 54.67; H, 6.32; N, 6.17%), λ_{max} 486 nm (ε 92,000); τ, −3.40, −3.28 (2 × NH^+), −0.32 (NH); 2.91 (methine-H); 5.69 (CH_2); 6.35 (OMe); 7.31, 7.69, 7.73, 7.90 (4 × Me); 6.41(t), 6.68(t), 6.90(t), 7.14(t), 7.31(t), 7.52(t) (2 × CH_2CH_2Cl and CH_2CH_2CO); 8.43(Bu').

t - Butyl 4,6 - diethyl - 1 - (2 - methoxycarbonylethyl) - 1',2,3,5 - tetramethyltripyrrene - a - 6' - carboxylate hydrobromide (**14**), by hydrogenolysis of compound **11**[31] (425 mg) and condensation with compound **5** (168 mg). The *tripyrrene hydrobromide* was obtained as red microcrystals (347 mg; 63%) from CH_2Cl_2–ether, m.p. >165° (dec.), (Found: C, 61.65; H, 7.28; N, 6.79 $C_{31}H_{44}BrN_3O_4$ requires: C, 61.78; H, 7.36; N, 6.97%), λ_{max} 490 nm (ε 91,000); τ, −3.28, −3.18 (2 × NH^+), −0.99 (NH); 2.89 (methine-H); 5.67 (CH_2); 6.31 (OMe); 7.10–7.66 (m)(2 × CH_2CH_3 and CH_2CH_2CO); 7.28, 7.66, 7.72, 7.92 (4 × Me); 8.40 (Bu'); 8.88(t), 8.96(t) (2 × CH_2CH_3).

t - Butyl 1,4,6 - triethyl - 1',2,3,5 - tetramethyltripyrrene - a - 6' - carboxylate hydrobromide (**15**), by hydrogenolysis of compound **11**[31] (460 mg) and condensation with compound **16** (134 mg). The *tripyrrene hydrobromide* was obtained as bright red microcrystals (268 mg; 50%) from CH_2Cl_2–ether, m.p. >165° (decomp.), (Found: C, 63.66; H, 8.05; N, 7.59. $C_{29}H_{42}BrN_3O_2$ requires: C, 63.96; H, 7.77; N, 7.72%), λ_{max} 490 nm (ε 88,000); τ, −3.18 (2 NH^+); −0.19 (NH); 2.90 (methine-H); 5.67 (CH_2); 7.26(q) (CH_2CH_3); 7.29 (Me); 7.52(m) (2 × CH_2CH_3); 7.68, 7.72; 7.92 (3 × Me); 8.40 (Bu'); 8.74–9.06 (m) (3 × CH_2CH_3).

t - Butyl 3 - ethyl - 1,6 - di(2 - methoxycarbonylethyl) - 1',2,4,5 - tetramethyltripyrrene - a - 6' - carboxylate toluene-p-sulphonate (**6**), from compound **4b** (788 mg) and compound **5** (381 mg). In this case the Na_2CO_3 wash did not afford the tripyrrene free base and the *tripyrrene toluene-p-sulphonate* (1.09 g; 80%) was obtained from CH_2Cl_2–ether, m.p. >135° (decomp.), (Found: C, 63.60; H, 7.05; N, 5.56. $C_{40}H_{53}N_3O_9S$ requires: C, 63.89; H, 7.10; N, 5.59%), λ_{max} 489 nm (ε 97,000); τ, −3.02. −2.82 (2 NH^+); −0.36 (1 NH); 2.13 (d) (*o*-Ph); 2.87 (d)(*m*-Ph); 2.97 (methine-H); 5.80 (CH_2); 6.36, 6.38 (2 × OMe); 7.01 (t), 7.16–7.62 (m, 8 H) (2 × $CH_2CH_2CO_2Me$ and CH_2CH_3); 7.56, 7.66, 7.72, 7.98, 8.01 (5 × Me); 8.50 (Bu'); 8.83 (t) (CH_2CH_3).

1',8'-Dimethyl-a,c-biladienes

3 - Ethyl - 1,6,7 - tri(2 - methoxycarbonylethyl) - 8 - methoxycarbonylmethyl - 1',2,4,5,8' - pentamethyl - a,c - biladiene dihydrobromide (**8**). Compound **6** (500 mg) was stirred in TFA (4 ml) for 5 min before addition of compound **7** (217 mg) in MeOH (7 ml) and then 45% HBr/HOAc (2 ml). After stirring for 30 min, ether (100 ml) was added dropwise with continued stirring. The *a,c-biladiene dihydrobromide* was filtered off and washed well with ether to give 525 mg (89%) of red-brown crystals, m.p. >150° (decomp.). (Found: C, 55.43; H, 6.13; N, 6.28. $C_{41}H_{54}Br_2N_4O_8$ requires: C, 55.28; H, 6.11; N, 6.29%), λ_{max} 453 (ε 26,500) and 519 nm (243,000); τ, −3.60, −3.40 (2 H), −3.21 (4 × NH br); 2.43, 2.89 (2 × methine-H); 4.77 (CH_2 bridge); 6.29, 6.33, 6.36, 6.40, 7.27 (6 H), 7.66, 8.09, and 8.11 (9 × Me); 6.50 (CH_2CO_2Me); 6.80–7.56 (m) (3 × $CH_2CH_2CO_2Me$ and CH_2CH_3); 8.83 (t) (CH_2CH_3).

1,3,5,8 - Tetra(2 - methoxycarbonylethyl) - 1',2,4,6,7,8' - hexamethyl - a,c - biladiene dihydrobromide (**19**) was similarly prepared from compounds **12** and **5**; when filtered from the ether solution it became gummy upon exposure to air. The material was therefore not fully characterised, and the bright red crystals of *a,c*-biladiene were stored under ether prior to cyclisation to porphyrin.

3,5 - Di(2 - chloroethyl) - 1,8 - di(2 - methoxycarbonylethyl) - 1',2,4,6,7,8' - hexamethyl - a,c - biladiene dihydrobromide (**20**) was similarly prepared from compounds **13** (145 mg) and **5** (48 mg in MeOH (2.5 ml)) using TFA (1.4 ml) and 45% HBr/HOAc (0.7 ml). Yield 164 mg (90%) of red-brown crystals, m.p. >150° (decomp.). (Found: C, 52.55; H, 5.66; N, 6.64. $C_{37}H_{48}Br_2Cl_2N_4O_4$ requires: C, 52.68; H, 5.74; N, 6.64%), λ_{max} 454 (ε 26,700) and 566 nm (224,000); τ, −3.54, −3.48, −3.34 (2H) (4 × NH br); 2.85 (2 × methine-H); 4.78 (CH_2 bridge); 6.34 (2 × OMe); 6.76–7.05 (6 H, m), 7.10–7.34 (4 H, m), 7.51 (4 H, t) (2 × CH_2CH_2Cl and 2 × CH_2CH_2CO); 7.28 (6H), 7.56 (6H), 7.60, 8.01 (6 × Me).

4,6 - Diethyl - 8 - methoxycarbonyl - 1 - (2 - methoxycar-

bonylethyl) - 1',2,3,5,7,8' - *hexamethyl* - a,c - *biladiene dihydrobromide* (**21**) was prepared from compounds **14** (250 mg) and **18** (75.5 mg in MeOH (5 ml)) using TFA (2.0 ml) and 45% HBr/HOAc (1 ml). Yield, 244 mg (79%) of red-brown crystals, m.p. >150° (decomp.). (Found: C, 53.84, 53.99; H, 6.28, 6.12; N, 7.24. $C_{35}H_{46}Br_2N_4O_4 \cdot 2H_2O$ requires: C, 53.71; H, 6.44; N, 7.16%), λ_{max} 450 (ϵ 25,300) and 517 nm (206,000); τ, −3.98, −3.39 (2H), −3.22 (4 × NH br); 2.75, 2.86 (2 × methine-H); 4.24 (CH_2 bridge); 6.14, 6.35 (2 × OMe); 7.08 (7-Me); 7.16–7.62 (m) (2 × CH_2CH_3 and CH_2CH_2CO); 7.30, 7.39, 7.66, 7.74, 8.06 (5 × Me); 8.85 (t), 9.32 (t) (2 × CH_2CH_3).

1,4,6 - *Triethyl* - 8 - *methoxycarbonyl* - 1',2,3,5,7,8' - *hexamethyl* - a,c - *biladiene dihydrobromide* (**22**) was similarly prepared from compounds **15** (95 mg) and **18** (32 mg in MeOH (2.5 ml)) using TFA (0.8 ml) and 45% HBr/HOAc (0.38 ml). Yield, 108 mg (90%) of red-brown crystals, m.p. >150° (decomp.). (Found: C, 57.75; H, 6.55; N, 8.28. $C_{33}H_{44}Br_2N_4O_4$ requires: C, 57.56; H, 6.44; N, 8.14%), λ_{max} 450 (ϵ 28,400) and 517 nm (207,000); τ, −4.00, −3.39, −3.26, −3.18 (4 × NH); 2.75, 2.88 (2 × methine-H); 4.75 (CH_2 bridge); 6.14 (OMe); 7.08 (7-Me); 7.16–7.72 (m) (3 × CH_2CH_3); 7.32, 7.39, 7.69, 7.75, 8.05 (5 × Me); 8.86 (t), 8.91 (t), 9.33 (t) (3 × CH_2CH_3).

1,4,6,8 - *Tetra*(2 - *methoxycarbonylethyl*) - 7 - *methoxycarbonylmethyl* - 1',2,3,5,8' - *pentamethyl* - a,c - *biladiene dihydrobromide* (**23**) was likewise prepared from compounds **12** (125 mg) and **17** (50 mg in MeOH (1 ml)) using TFA (1 ml) and 45% HBr/HOAc (0.5 ml). Yield, 150 mg (91%). Two recrystallisations from CH_2Cl_2—ether gave red prisms, m.p. >150° (decomp.). (Found: C, 53.23, 53.44; H, 5.92, 5.99; N, 5.90, 5.77. $C_{43}H_{56}Br_2N_4O_{10} \cdot H_2O$ requires: C, 53.42; H, 6.05; N, 5.79%), λ_{max} 453 (ϵ 36,300) and 526 nm (162,000); τ, −3.8 to −3.1 (4 × NH br); 2.53, 2.86 (2 × methine-H); 4.79 (CH_2 bridge); 6.17 (CH_2CO); 6.29, 6.34 (6 H), 6.42, 6.60 (5 × OMe); 6.8–8.1 (m) (4 × CH_2CH_2CO); 7.27 (6 H), 7.65, 7.73, 8.03 (5 × Me).

Porphyrins

2 - *Ethyl* - 4,6,7 - *tri*(2 - *methoxycarbonylethyl*) - 5 - *methoxycarbonylmethyl* - 1,3,8 - *trimethylporphin*, "*Isocoproporphyrin tetramethyl ester*", (**1b**). Compound **8** (263 mg) was added to a solution of copper(II) chloride (1.3 g) in DMF (20 ml) kept at 145°. The mixture was stirred during 4 min and then poured into H_2O, extracted with CH_2Cl_2, and the organic phase was washed three times with H_2O before being dried (Na_2SO_4). After evaporation, the residue (copper(II) complex of required porphyrin) was treated with H_2SO_4 (0.5 ml) in TFA (9.5 ml) with vigorous stirring during 20 min before being poured into H_2O and extracted with $CHCl_3$. The organic phase was washed with $NaHCO_3$ aq and then H_2O, dried (Na_2SO_4) and then evaporated to dryness. The residue was set aside overnight in 5% w/v H_2SO_4 in MeOH before being poured into NaOAc aq and extracted with CH_2Cl_2. The organic phase was washed with $NaHCO_3$ aq, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed (elution with CH_2Cl_2) and evaporation of the red eluates gave a residue which was crystallised from CH_2Cl_2–n-hexane to give *isocoproporphyrin tetramethyl ester* (68 mg; 30%), m.p. 182–183° (sealed capillary).† When recrystallised from CH_2Cl_2—MeOH, the material had m.p. 193–195° (heated hot-stage). The compound (ex. CH_2Cl_2–n-hexane) was identical by TLC and m.m.p. with a sample of natural material (m.p. 180–182°) supplied by Dr. G. H. Elder. It was also identical by TLC with a sample subsequently synthesised by Prof. P. S. Clezy, and the m.p. and m.m.p. of the sample from CH_2Cl_2–MeOH confirmed its identity. (Found: (ex. CH_2Cl_2–n-hexane) C, 67.84; H, 6.72; N, 7.78. $C_{40}H_{46}N_4O_8$ requires: C, 67.59; H, 6.52; N, 7.88%. Found: (ex. CH_2Cl_2–MeOH) C, 66.67, 66.61; H, 6.52, 6.45; N, 7.82. $C_{40}H_{46}N_4O_8 \cdot \frac{1}{2}H_2O$ requires: C, 66.73; H, 6.74; N, 7.78%), λ_{max} 398 (ϵ 198,000), 493 (14,300), 526 (9,600), 559 (6800), and 609 nm (4500); λ_{max} in $CHCl_3$ containing 5% TFA, 403 (ϵ 400,000), 543 (16,200), and 582 nm (7600), τ‡, −0.99 (2H), 0.01 (2H) (4 × *meso*-H); 4.60 (CH_2CO_2Me); 5.44–5.86 (m) (3 × $CH_2CH_2CO_2Me$); 6.04 (q)(CH_2CH_3); 6.26, 6.34, 6.36, 6.40 (4 × OMe); 6.42, 6.46, 6.50 (3 × Me); 6.54–6.90 (m) (3 × $CH_2CH_2CO_2Me$); 8.18 (t) (CH_2CH_3).

2,4,6,8 - *Tetra*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin*, "*Coproporphyrin*-III *tetramethyl ester*", (**24**). This compound was similarly prepared from compound **19** (about 125 mg) using copper(II) chloride (700 mg) in DMF (10 ml) at 165° during 4 min. After demetallation, the product was obtained as red microneedles (30 mg; 24% from compound **12**) from CH_2Cl_2–MeOH and had m.p. 150–154, remelting 178–182° (Lit.[32] 150–155, 179–182°). The material was identical with an authentic sample. (Found: C, 67.30; H, 6.49; N, 8.11. Calc. for $C_{40}H_{46}N_4O_8$: C, 67.59; H, 6.52; N, 7.88%), λ_{max} 400 (ϵ 158,600), 497 (13,700), 531 (9100), 567 (5950), 592 (1300), and 620 nm (4300); τ, 0.03, 0.05, 0.10 (2H) (4 *meso*-H); 5.5–5.8 (m) (4 × $CH_2CH_2CO_2Me$); 6.33, 6.37 (6H), 6.38 (4 × OMe); 6.6–6.9 (m) (4 × $CH_2CH_2CO_2Me$); 6.42, 6.46, 6.47, 6.50 (4 × Me).

2,4 - *Di*(2 - *chloroethyl*) - 6,7 - *di*(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**25**) was similarly prepared from compound **20** (67 mg) using copper(II) chloride (850 mg) in DMF (15 ml) at 145° for 4 min. After demetallation using 5% H_2SO_4 in TFA (10 ml) for 20 min the product was obtained from CH_2Cl_2–MeOH as deep red crystals (24 mg; 46%), m.p. 216–218° (Lit.[33] 216–217°). The material was identical with an authentic sample[33] and was transformed into protoporphyrin-IX dimethyl ester (**26**) in 65% yield as previously described.[33]

2,4 - *Diethyl* - 6 - *methoxycarbonyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin*, "*Rhodoporphyrin*-XV *dimethyl ester*", (**27**) was likewise prepared from compound **21** (59 mg) using copper(II) chloride (560 mg) in DMF (10 ml) at 145° during 4 min. The product was demetallated in H_2SO_4 (1 ml) and TFA (9 ml). Crystallisation from CH_2Cl_2–MeOH gave 13 mg (29%) of red-brown needles, m.p. 264–266° (Lit.[34] 268°), τ, −0.90, 0.04, 0.21, 0.25 (4 × *meso*-H); 5.57, 6.32 (2 × OMe); 6.14, 6.46, 6.49, 6.56 (4 × Me), 5.68 (t), 6.72 (t) (CH_2CH_2CO); 5.86–6.30 (m), 8.19 (t) (2 × CH_2CH_3); 14.14 (2 × NH br).

2,4,7 - *Triethyl* - 6 - *methoxycarbonyl* - 1,3,5,8 - *tetramethylporphin* (**28**) was similarly prepared from compound **22** (108 mg) in DMF (10 ml) containing copper(II) chloride (530 mg) at 145° for 4 min. After demetallation, etc. the *product* was obtained as red-brown needles (30 mg; 38%) from CH_2Cl_2–MeOH, with m.p. >300°. (Found: C, 75.36; H, 7.09; N, 11.16. $C_{32}H_{36}N_4O_2$ requires: C, 75.56; H, 7.13; N, 11.02%), λ_{max} 403 (ϵ 224,000), 503 (11,200), 541 (16,800), 564 (9800), 620 nm (2400); in $CHCl_3$ + 5% TFA, λ_{max} 406 (ϵ 400,000), 548 (14,500), and 594 nm (11,500), τ, −1.10, −0.18, 0.10 (2H) (4 × *meso*-H); 5.64 (OMe); 5.75–6.25 (m), 8.00–8.35 (m) (3 × CH_2CH_3); 6.10, 6.42 (6H), 6.53 (4 × Me).

2,4,6,7 - *Tetra*(2 - *methoxycarbonylethyl*) - 5 - *methoxycarbonylmethyl* - 1,3,8 - *trimethylporphin* (**29**) was similarly prepared from compound **23** (80 mg) in DMF (12 ml) containing copper(II) chloride (450 mg) at 165° during 4 min. After demetallation, etc. the *product* was recrystallised from CH_2Cl_2–MeOH to give red microneedles (25 mg; 38%), m.p. 214–215.5°. The porphyrin was satisfactorily identified by TLC, m.p. and m.m.p. with a sample of authentic material supplied by Prof. Jackson. (Found: C, 65.31; H, 6.34; N, 7.43. $C_{42}H_{48}N_4O_{10}$ requires: C, 65.61; H, 6.29; N, 7.29%), λ_{max} 400 (ϵ 189,800), 500 (13,800), 534 (9600), 568 (6700), 595 (1200) and 622 nm (3700); τ, −0.10 (2H), 0.02 (2H) (4 × *meso*-H); 4.96 (CH_2CO_2Me); 5.4–5.9 (m), 6.56–6.92 (m) (4 × CH_2CH_2CO); 6.24, 6.32, 6.34 (6H), 6.38 (5 × OMe); 6.40, 6.41, 6.47 (3 × Me).

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†See text for a fuller discussion of the m.p. behaviour of **1b**.

‡Concentration 0.04 M in $CDCl_3$. The spectrum showed concentration dependence.

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