Synthetic and Biosynthetic Studies of Porphyrins. Part 10.[1] Syntheses of Porphyrins with Acetic, Propionic, and Butyric Acid Side-chains for Biosynthetic Studies

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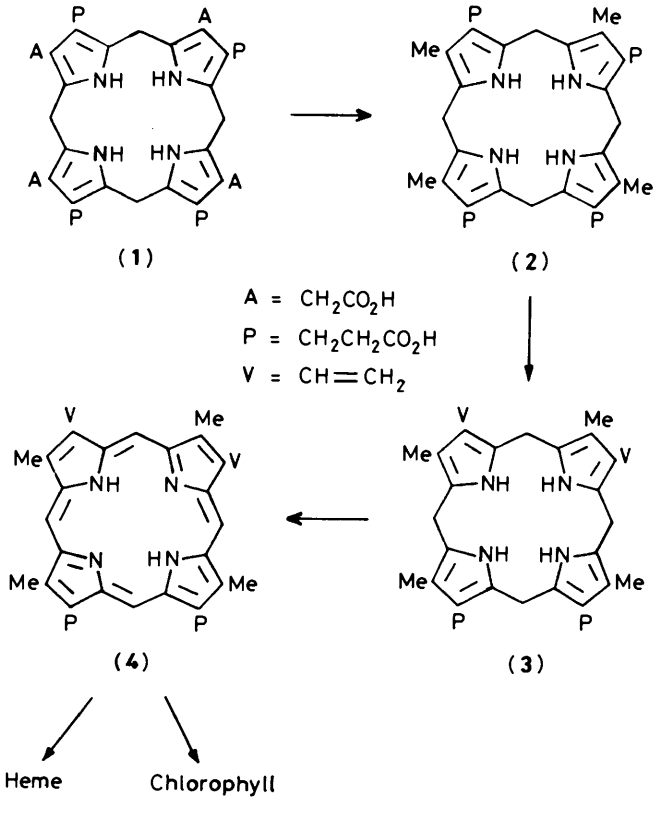
In connection with studies of substrate specificity of uroporphyrinogen decarboxylase and coproporphyrinogen oxidase, enzymes in the heme and chlorophyll biosynthetic pathways, and heme oxygenase, an enzyme involved in the catabolism of hemes, we have synthesized a number of new porphyrins substituted with acetic, propionic, and butyric side-chains, using the *a,c*-biladiene route; one porphyrin was also prepared by the MacDonald pyrromethane approach. In one of the *a,c*-biladiene cyclizations, *meso*-chlorinated porphyrins were formed as minor by-products, but this side-reaction was suppressed by carefully drying the copper(II) chloride used in this stage, or by use of copper(II) acetate as an alternative oxidant.

Of all the enzymes in the heme and chlorophyll biosynthetic pathways uroporphyrinogen decarboxylase is perhaps the least demanding in terms of its substrate specificity. Its normal role is to catalyze the decarboxylation of the acetic side-chains of uroporphyrinogen-III (**1**) to coproporphyrinogen-III (**2**), *via* intermediate hepta-, hexa-, and penta-carboxylic porphyrinogens.[2] This series of reactions appears to occur in a preferential 'clockwise' pattern, starting with the acetic acid residue on the D-ring of uroporphyrinogen-III. However, the enzyme will also decarboxylate all the various 'type-IX' isomeric intermediates (14 in all), as well as the isomeric porphyrinogens of the I, II, and IV series. We have also shown that a number of unnatural substrates containing acetic acid side-chains, but no propionic acid side-chains, are decarboxylated by uroporphyrinogen decarboxylase, *e.g.* even the octa-acetic analogue.[3] Some 30 substrates for the enzyme are now known, but all those tested so far have only contained methyl, ethyl, vinyl, acetic, or propionic side-chains. In the present study we have synthesized analogues containing two butyric acid side-chains or one butyric and one propionic side chain, rather than two propionic acid side-chains (one each on the C and D rings of the porphyrinogen), as it was of interest to discover whether or not a longer side-chain at these positions would affect the efficiency of uroporphyrinogen decarboxylase and of the other later enzymes in the biosynthetic and catabolic pathways.

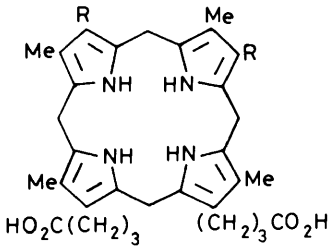


Scheme 1.

In contrast to uroporphyrinogen decarboxylase, coproporphyrinogen oxidase [which catalyzes the oxidative conversion of two propionic acid side-chains of coproporphyrinogen-III to the vinyl groups of protoporphyrinogen-IX (**3**)], has a much higher substrate specificity;[4] for example, only isomer -IV of the three coproporphyrinogen isomers is also a substrate and, moreover, the enzyme will not tolerate other bulky or polar groups in positions neighbouring the propionic acid to be degraded. Again, we were interested to know whether or not the C- and D-ring propionate groups could be replaced by the larger butyrate side-chains.

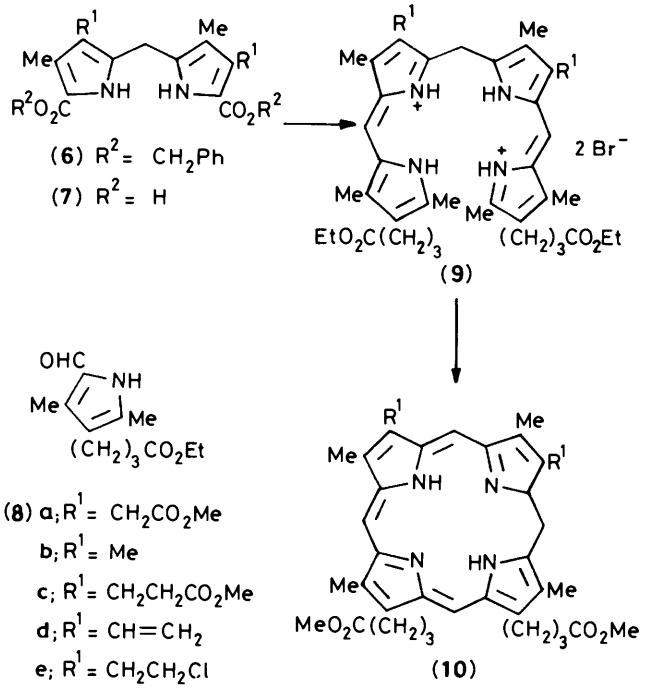
Heme oxygenase is the enzyme which is responsible for ring-opening of hemes to produce biliverdins. The microsomal system consists of a heme oxidizing enzyme and a NADPH-cytochrome reductase. The oxidation step is selective only to the α-position in protoheme, and in a large number of hemes bearing vicinal propionic acid side-chains in rings C and D of the heme. It was recently shown[5] that introduction of butyric acid side-chains in place of propionic acid groups caused a 50% decrease in substrate activity toward heme oxygenase, while the 6,7-diacetic acid analogue of protoheme was completely inactive as a substrate. Several porphyrins described in this paper were designed to further probe the substrate specificity of heme oxygenase, in particular with regard to the presence of one butyric acid and one propionic acid side-chain in the ring C,D region, and whether or not the presence of butyric side-chains in a type-III protoheme would suppress further or enhance the substrate specificity in heme catabolism.

Our primary targets were the diacetic and dipropionic porphyrinogen-6,7-dibutyric derivatives (**5a**) and (**5c**), the former being intended as a substrate for uroporphyrinogen decarboxylase, and the latter for coproporphyrinogen oxidase.



(5) a; R = CH_2CO_2H
b; R = Me
c; R = $CH_2CH_2CO_2H$
d; R = $CH{=}CH_2$

The expected products from the enzymic reactions would be the hexamethyl-dibutyric porphyrinogen (**5b**) and the divinyl-dibutyric porphyrinogen (**5d**), respectively. The porphyrin dimethyl ester (**10d**) related to (**5d**) has previously been synthesized from protoporphyrin-IX;[6] syntheses of the appropriate related porphyrins (**10a—e**), (**17**), (**18**), (**23**), and (**24**), were therefore initiated following variants of the *a,c*-biladiene route[7,8] and using the strategies outlined in Schemes 2 and 3. In the case of (**10a—c**) a pyrromethane (**7**) corresponding to the A,B rings of the porphyrin was converted into the required intermediate *a,c*-biladiene (**9**) by condensation with two mol equiv. of a formylpyrrole (**8**) corresponding to the C and D rings of the porphyrins (**10**). For the type-III porphyrin (**17**) a



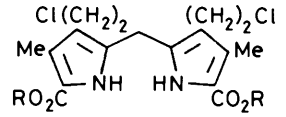
(6) R^2 = CH_2Ph
(7) R^2 = H

(8) a; R^1 = CH_2CO_2Me
b; R^1 = Me
c; R^1 = $CH_2CH_2CO_2Me$
d; R^1 = $CH{=}CH_2$
e; R^1 = CH_2CH_2Cl

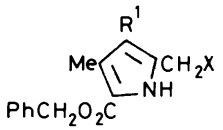
Scheme 2.

symmetrical pyrromethane (**11**) was obtained by self-condensation of the pyrrole (**13d**) in the presence of Montmorillonite clay catalyst.[9]

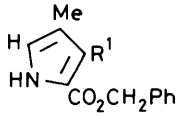
The pyrroles required for the synthesis of the pyrromethanes were prepared by established methods as indicated in the Experimental section; the formylpyrrole (**8**) was prepared by a more recently developed method.[10] The pyrromethanes (**6**) were synthesized by coupling the appropriate 2-acetoxymethyl-pyrroles (**13**) [prepared by lead tetra-acetate oxidation of the corresponding 2-methylpyrroles (**12**)] with the 2-unsubstituted pyrroles (**14**) in acetic acid containing a catalytic amount of toluene-*p*-sulphonic acid.[10] [Recently, we have shown that these unsymmetrical coupling reactions can be effected in much better yields and without concomitant formation of any by-products (*e.g.* symmetrical pyrromethanes) by use of Montmorillonite clay as catalyst].[9]



(11) R = CH_2Ph
(15) R = H

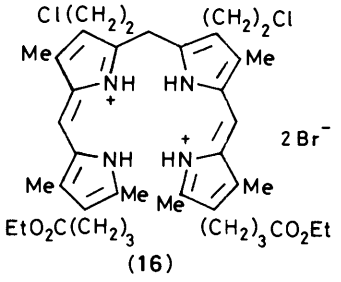


(12) X = H
(13) X = OAc



(14)

a; R^1 = CH_2CO_2Me
b; R^1 = Me
c; R^1 = $CH_2CH_2CO_2Me$
d; R = CH_2CH_2Cl



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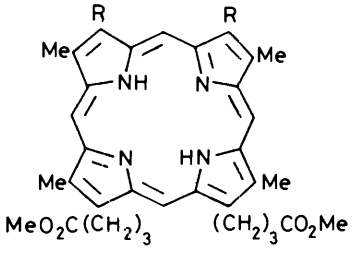
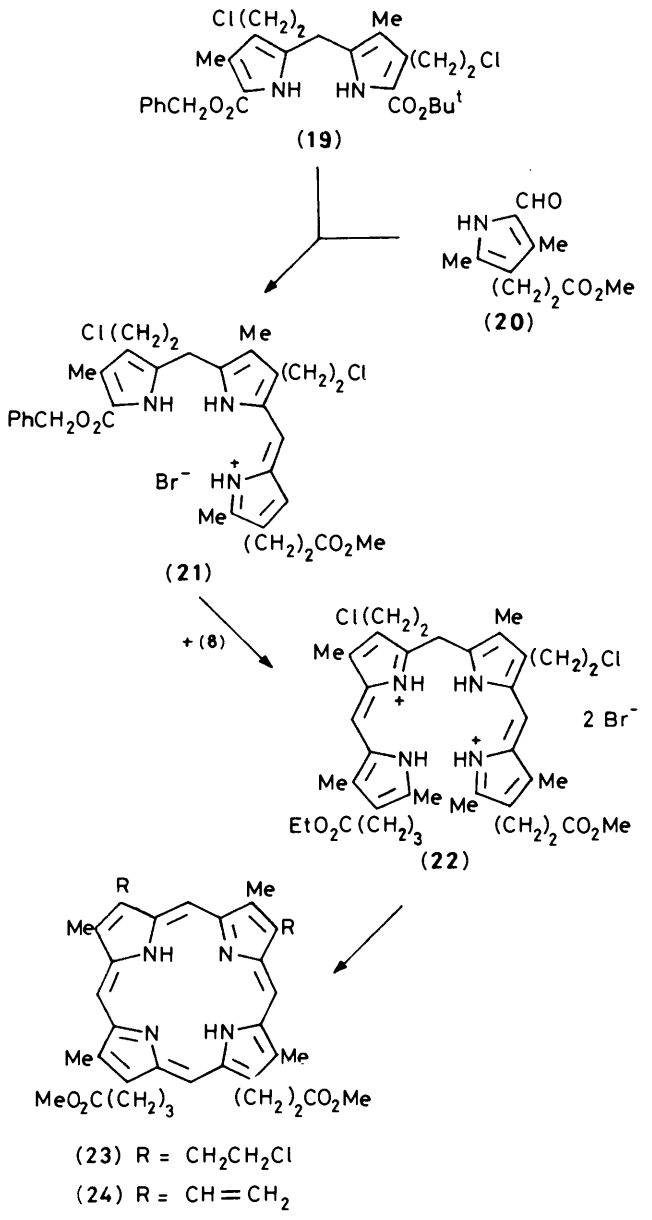


(17) R = CH_2CH_2Cl
(18) R = $CH{=}CH_2$

Hydrogenolysis of the pyrromethane benzyl esters (**6**) and (**11**) was then achieved over palladium–carbon to afford the corresponding pyrromethanecarboxylic acids (**7**) and (**15**). Each of the latter was, in turn, condensed with 2 mol equiv. of the 2-formylpyrrole (**8**) in presence of hydrogen bromide in acetic acid, and the corresponding *a,c*-biladiene dihydrobromides (**9**) and (**16**) were formed in *ca.* 75% yield. When heated with copper(II) chloride or copper(II) acetate in dimethylformamide at 160 °C for 5 min, the *a,c*-biladienes gave the copper com-

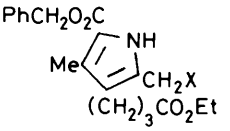


Scheme 3.

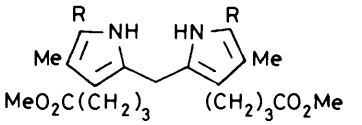
plexes of the required porphyrins (**10a**—**c**,**e**) in good yield, and demetallation was effected in 15% sulphuric acid in trifluoroacetic acid. The f.d. mass spectrum of the first porphyrin to be prepared (**10b**) [using copper(II) chloride], however, revealed that it was contaminated with a minor impurity, thought to be a *meso*-chloroporphyrin from its molecular weight. This was confirmed by chromatographic separation of the impurity, followed by spectral analyses. The visible absorption spectrum was of the 'phyllo'-type indicating *meso*-substitution, and the n.m.r. spectrum showed a multiplet in the *meso*-proton region (*ca.* 10 p.p.m.), and this was indicative of the formation of an isomeric mixture of *meso*-chlorinated porphyrins. Further work showed that the formation of these impurities could be obviated by careful drying of the copper(II) chloride before use, or by using copper(II) acetate instead of the chloride. The *meso*-chlorination reaction is presumably a consequence of oxidative formation of chlorine atoms in the presence of water at the relatively high temperatures used in the cyclization reaction. No previous reports of the formation of these *meso*-chloro derivatives in the *a*,*c*-biladiene (or the related *b*-bilene) routes to porphyrins have appeared; they may well have been formed in small amounts but have only come to light as a result of the routine use of more sensitive analytical and spectroscopic techniques.

The syntheses of the divinylporphyrins (**10d**), (**18**), and (**24**) could not be carried out directly from vinylpyrroles, and the vinyl groups were introduced *via* intermediate chloroethylpyrroles (**13d**) and (**14d**), and the bischloroethylpyrromethanes (**6e**) and (**11**), the latter being obtained from 2 mol equiv. of the pyrrole (**13d**). The mixed butyric/propionic acid porphyrin (**24**) was synthesized by the 'clockwise' tripyrrene/*a*,*c*-biladiene route,[8] as outlined in Scheme 3. The pyrromethane (**19**) was treated with trifluoroacetic acid, followed by formylpyrrole (**20**) and HBr gas to give the benzyltripyrrenecarboxylate hydrobromide (**21**). This tripyrrene was then deprotected and treated with formylpyrrole (**8**) to give a 70% yield of the unsymmetrical *a*,*c*-biladiene (**22**). Cyclization with copper(II) acetate in dimethylformamide (DMF) in the usual way gave the corresponding copper(II) porphyrin which was demetallated (TFA–H_2SO_4) to give the porphyrin (**23**). Dehydrochlorination, as previously described, then afforded the porphyrin (**24**) in good yield.

The bischloroethylporphyrin (**10e**) was also synthesized by the MacDonald route[11] from the pyrromethane (**7e**) and the diformylpyrromethane (**26c**) in dichloromethane–methanol using toluene-*p*-sulphonic acid as catalyst, followed by addition



(**25**) **a**; X = H
b; X = Br



(**26**) **a**; R = CO_2CH_2Ph
b; R = CO_2H
c; R = CHO

of zinc(II) acetate and aeration.[12] The precursor (**26a**) of the diformylpyrromethane (**26c**) was prepared by self-condensation (in hot methanol) of the 2-bromomethylpyrrole (**25b**) derived from the 2-methylpyrrole (**25a**) by direct bromination in ether; hydrogenolysis of the benzyl esters of the pyrromethane (**26a**) followed by decarboxylation and formylation with benzoyl chloride–dimethylformamide then afforded the diformylpyrromethane (**26c**).

The yield of porphyrin (**10e**) obtained in the MacDonald route (10%) was, however, much lower than by the *a*,*c*-biladiene route. It was dehydrohalogenated with pyridine–potassium hydroxide[13] to form the required divinylporphyrin (**10d**) after re-esterification with methanol–sulphuric acid.

Biosynthetic studies with the porphyrinogens (**5a**) and (**5c**), and heme oxygenase experiments with the hemes from porphyrins (**18**) and (**24**) are well in hand and the results will be reported elsewhere.

Experimental

M.p.s were measured on a hot-stage apparatus, and are uncorrected. ^{1}H N.m.r. spectra were measured in deuteriochloroform solution at 360 MHz (Nicolet NT-360 or Bruker WP 360 spectrometer) or at 90 MHz (Varian EM-390 or Perkin-Elmer 90 spectrometer) with tetramethylsilane as internal standard. Electronic absorption spectra were measured, in dichloromethane or chloroform solution, using a Hewlett-Packard 8450A or Pye-Unicam SP 800 spectrophotometer. Mass spectra

were determined with a Varian CH5D double focussing instrument; electron impact spectra were measured at 70 eV and 50 μA, the source temperature being maintained in the region 200—220 °C. Field desorption spectra were measured at wire currents increasing from 10—20 μA and at source temperatures in the range 50—150 °C. Elemental analyses were performed at the Berkeley Microchemical Analysis Laboratory, UC Berkeley, or in Cardiff using a Technicon instrument.

Reactions were monitored, wherever possible by t.l.c. and/or spectrophotometry. H.p.l.c. was also used to assess the purity of products, especially porphyrins, and occasionally to separate minor impurities. Silica gel 60 (Merck, 70—230 mesh) or alumina (Merck) were used for column chromatography, and preparative t.l.c. was carried out on 20 × 20 cm glass plates coated with Merck GF 254 silica gel (1 mm thick). Analytical t.l.c. was performed using Merck silica gel 60 F 254 pre-coated sheets (0.2 mm). Organic solutions were dried over anhydrous sodium sulphate or magnesium sulphate and usually evaporated to dryness on a rotary evaporator.

Pyrromethanes

Dibenzyl 3,3′-Bis-(3-methoxycarbonylpropyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylate (**26a**).—Benzyl 4-(3-methoxycarbonylpropyl)-3,5-dimethylpyrrole-2-carboxylate (**25a**)[10] (4.9 g) in ether (150 ml) was treated dropwise with bromine (0.85 ml) in ether (50 ml) during 5 min, and stirred at 20 °C for 1.5 h. The solvent was evaporated off and the residual pink solid (**25b**) was taken up in methanol (35 ml) and heated under reflux for 4 h. The solution was allowed to cool overnight at 0 °C and the product which had crystallized out was filtered off, washed with cold methanol, and recrystallized from hot methanol to give the required *pyrromethane* (3.2 g, 70%), m.p. 138—139 °C (Found: C, 69.1; H, 6.7; N, 4.3. $C_{37}H_{42}N_2O_8$ requires C, 69.15; H, 6.5; N, 4.5%); δ 2.22 (s, 6 H, 2 × Me), 1.70 (t, 4 H, 2 × CH_2), 2.15 and 2.45 (each m, 4 H, CH_2CH_2), 3.55 (s, 6 H, 2 × OMe), 3.82 (s, 2 H, CH_2), 5.20 (s, 4 H, 2 × CH_2Ph), 7.30 (s, 10 H, 2 × Ph), and 9.00 (br s, 2 × NH).

5,5′-Diformyl-3,3′-bis-(2-methoxycarbonylpropyl)-4,4′-dimethylpyrromethane (**26**).—The foregoing pyrromethane dibenzyl ester (**26a**) (3.0 g) in tetrahydrofuran (50 ml) containing triethylamine (0.1 ml) and 10% palladized charcoal (300 mg) was hydrogenated at room temperature and atmospheric pressure until uptake of hydrogen ceased. The catalyst was filtered off on Celite and the solvent was evaporated to give the dicarboxylic acid (**26b**), m.p. 165 °C (decomp.), δ 2.20 (s, 6 H, 2 × Me), 3.70 (s, 6 H, 2 × OMe), 3.80 (s, 2 H, CH_2), and 1.80 and 2.4—2.65 (each m, 12 H, 2 × $CH_2CH_2CH_2$). Without further purification, this material (1.8 g) was heated under reflux in dimethylformamide (12 ml) for 15 min before being cooled to 0 °C and treated with freshly distilled benzoyl chloride (3 ml) while the reaction temperature was maintained < 5 °C. Benzene (20 ml) was then added to the reaction mixture and the precipitated solid was filtered off, dissolved in 50% aqueous methanol containing sodium hydrogen carbonate (1.5 g), and warmed on a hot water-bath for 15 min, and then stirred overnight at room temperature to hydrolyse the intermediate imine salt. The crude product was filtered off the crystallized from aqueous methanol to afford the *diformylpyrromethane* (960 mg) as fluffy needles, m.p. 184—185 °C (Found: C, 64.1; H, 6.8; N, 6.2. $C_{23}H_{30}N_2O_6$ requires C, 64.15; H, 6.7; N, 6.5%); δ 2.10 (s, 6 H, 2 × Me), 3.30 (s, 6 H, 2 × OMe), 3.95 (s, 2 H, CH_2), 2.25—1.90 (m, 12 H, 2 × $CH_2CH_2CH_2$), and 9.90 (s, 2 H, 2 × CHO).

Dibenzyl 3,3′-Bis-(2-chloroethyl)-4,4′-dimethylpyrromethane-5,5′-dicarboxylate (**11**).—The acetoxymethylpyrrole (**13d**)[14] (5 g) in acetic acid (100 ml) containing toluene-*p*-sulphonic acid (140 mg) was stirred at 40—45 °C under nitrogen for 4 h. The mixture was poured into water and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate, water, and then dried and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade III, elution with dichloromethane), and evaporation of the appropriate eluates gave the *pyrromethane* (2.83 g, 70%), m.p. 95—96 °C (lit.,[9] m.p. 95—97 °C), after recrystallization from dichloromethane–hexane; δ 2.25 (s, 6 H, 2 × Me), 2.80 and 3.45 (t, 2 H, CH_2CH_2Cl), 3.85 (s, 2 H, CH_2), 5.20 (s, 4 H, 2 × CH_2Ph), 7.20 (s, 10 H, 2 × Ph), and 9.85 (br s, 2 H, 2 × NH).

Dibenzyl 3,3′,4,4′-Tetramethylpyrromethane-5,5′-dicarboxylate (**6b**).—The acetoxymethylpyrrole (**13b**)[15] (4 g) in dichloromethane (100 ml) was stirred with Montmorillonite clay (20 g) for 75 min and the mixture then filtered and the clay washed with dichloromethane. Evaporation of the combined filtrates gave the *pyrromethane* (2.80 g, 90%), m.p. 176—177 °C (Found: C, 73.65; H, 6.3; N, 5.8. $C_{29}H_{30}N_2O$ requires C, 74.05; H, 6.4; N, 5.95%); δ 1.90 (s, 6 H, 2 × Me), 2.30 (s, 6 H, 2 × Me), 3.80 (s, 2 H, CH_2), 5.20 (s, 4 H, 2 × CH_2Ph), 7.30 (s, 10 H, 2 × Ph), and 9.10 (br s, 2 H, 2 × NH).

a,c-*Biladienes*

1,8-Bis-(3-ethoxycarbonylpropyl)-4,6-bis-(2-methoxycarbonylmethyl)-1,2,3,5,7,8′-hexamethyl-a,c-biladiene Dihydrochloride (**9a**).—The pyrromethane (**7a**) (320 mg) was stirred in trifluoroacetic acid (5 ml) at 20 °C for 15 min under nitrogen. The formylpyrrole (**8**)[10] (380 mg) in dry methanol (10 ml) was then added, followed by HBr in acetic acid (45%; 3 ml), and the mixture was stirred at 20 °C for 30 min during precipitation of a red solid. Dry ether (50 ml) was added dropwise to complete precipitation and the product was filtered off, washed with dry ether, and air dried to afford the a,c-*biladiene salt* (510 mg, 70.5%) as a brick-red solid, m.p. > 300 °C (Found: C, 56.55; H, 6.1; N, 6.0. $C_{43}H_{58}Br_2N_4O_8$ requires C, 56.7; H, 6.3; N, 6.1%); δ 1.27 (t, 6 H, 2 × $CO_2CH_2CH_3$), 1.80, 2.25, and 2.50 (each t, 4 H, 2 × $CH_2CH_2CH_2$), 2.10, 2.33, 2.40, and 2.80 (each s, 3 H, 4 × Me), 3.40 and 3.70 (each s, 3 H, OMe), 4.20 (m, 4 H, 2 × CH_2CH_3), 5.20 (s, 2 H, CH_2), 7.25 and 7.10 (each s, 1 H, CH), and 13.20, 13.25, 13.35, and 13.40 (each br s, 1 H, 4 × NH); $\lambda_{max.}$ 450 (ε 55 000) and 525 nm (95 000).

1,8-Bis-(3-ethoxycarbonylpropyl)-4,5-bis-(2-methoxycarbonylethyl)-1′,2,3,5,7,8′-hexamethyl-a,c-biladiene Dihydrobromide (**9c**).—This compound was prepared from the pyrromethane (**7c**) (490 mg), trifluoroacetic acid (6 ml), and the formylpyrrole (**8**) (535 mg) in methanol (15 ml) and HBr in acetic acid (45%; 5 ml) in the same manner as the preceding *a,c*-biladiene. Ether (50 ml) was added to give the a,c-*biladiene salt* (755 mg, 71%) as a brick-red solid, m.p. > 300 °C (Found: C, 56.4; H, 6.8; N, 5.8. $C_{45}H_{62}Br_2N_4O_8$ requires C, 57.1; H, 6.55; N, 5.9%); δ 1.27 (t, 6 H, 2 × CH_2CH_3), 1.8, 2.25, 2.5, and 2.75 (each m, 20 H, 2 × CH_2CH_2CO and 2 × $CH_2CH_2CH_2CO$), 2.00, 2.25, 2.30, and 2.35 (s, 3 H, 4 × Me), 2.50 (s, 6 H, 1′,8′-Me), 3.25 and 3.40 (s, 3 H, OMe), 4.20 (q, 4 H, CH_2CH_3), 5.25 (s, 2 H, CH_2), 7.10 and 7.20 (s, 2 H, 2 × –CH=), 13.15 (s, 2 H, 2 × NH), and 13.30 and 13.35 (s, 1 H, 2 × NH); $\lambda_{max.}$ 450 (ε 40 200) and 525 nm (78 500).

4,6-Bis-(2-chloroethyl)-1,8-bis-(3-ethoxycarbonylpropyl)-1′,2,3,5,7,8′-hexamethyl-a,c-biladiene Dihydrobromide (**9e**).—This compound was similarly prepared in 80% yield from the pyrromethane (**7e**) (500 mg) and formylpyrrole (**8**) (635 mg). It formed brick-red prisms, m.p. > 300 °C (Found: C, 54.5; H, 6.5; N, 6.2. $C_{41}H_{56}Br_2Cl_2N_4O_4$ requires C, 54.7; H, 6.3; N, 6.2%); δ

1.27 (t, 6 H, 2 × CH_2CH_3), 1.80, 2.23, 3.0—3.2, and 3.6 (each m, 20 H, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CH_2$), 2.05 (s, 3 H, Me), 2.30 (s, 9 H, 3 × Me), 2.75 (s, 6 H, 2 × Me), 4.20 (q, 4 H, 2 × CH_2CH_3), 5.20 (s, 2 H, CH_2), 7.15 and 7.25 (s, 2 H, 2 × –CH=), and 13.25, 13.36, 13.34, and 13.50 (each s, 1 H, 4 × NH); $\lambda_{max.}$ 450 (ε 41 000) and 525 nm (80 000).

1,8-*Bis*-(3-*ethoxycarbonylpropyl*)-1′,2,3,4,5,6,7,8′-*octamethyl*-a,c-*biladiene Dihydrobromide* (**9b**).—The pyrromethane (**6b**) was quantitatively debenzylated by hydrogenation in tetrahydrofuran containing triethylamine and 10% palladized charcoal, as described above in the synthesis of compound (**26b**). The resulting pyrromethane-5,5′-dicarboxylic acid (**7b**) (370 mg) was dissolved in trifluoroacetic acid (3 ml) and stirred for 15 min before addition of formylpyrrole (**7**) (600 mg) in methanol (15 ml). The mixture was stirred for 3 min, HBr in acetic acid (31%; 3 ml) was added, and stirring was continued for a further 30 min under nitrogen at room temperature. Ether (50 ml) was then added dropwise and the resulting precipitate was filtered off, washed with cold ether, and then dried to give the a,c-*biladiene salt* (770 mg, 75%) as dark red crystals, m.p. >330 °C (Found: C, 58.1; H, 6.6; N, 7.0. $C_{39}H_{54}Br_2N_4O_4$ requires C, 58.35; H, 6.8; N, 7.0%), δ 1.40 (t, 6 H, 2 × CH_2CH_3), 1.8, 2.25, 2.30, and 2.70 (s, 6 H, 8 × Me), 1.8, 2.25, and 2.50 (m, 6 H, $CH_2CH_2CH_2$), 4.10 (q, 4 H, 2 × CH_2CH_3), 5.20 (s, 2 H, CH_2), and 13.25 and 13.70 (br s, 2 H, 4 × NH); $\lambda_{max.}$ 450 (ε 89 100) and 526 nm (99 800).

4,5-*Bis*-(2-*chloroethyl*)-1,8-*bis*-(3-*ethoxycarbonylpropyl*)-1′,2,3,6,7,8′-*hexamethyl*-a,c-*biladiene Dihydrobromide* (**16**).—This *a,c*-biladiene was similarly prepared using the pyrromethane-5,5′-dicarboxylic acid (**15**) (330 mg) obtained by catalytic debenzylation of the pyrromethane (**11**), formylpyrrole (**8**) (420 mg) in methanol (10 ml), trifluoroacetic acid (3 ml), and HBr in acetic acid (31%; 2 ml). The a,c-*biladiene* was obtained as deep red crystals (550 mg, 72%), m.p. >300 °C (Found: C, 54.8; H, 6.2; N, 6.3. $C_{41}H_{56}Br_2Cl_2N_4O_4$ requires C, 54.7; H, 6.3; N, 6.2%); δ 1.50, 2.35, and 2.50 (each m, 20 H, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CH_2$), 2.35, 2.75, and 3.25 (each s, 6 H, 6 × Me), 4.20 (q, 4 H, 2 × CH_2CH_3), 5.25 (s, 2 H, CH_2), 7.20 (s, 2 H, 2 × –CH=), and 13.30 and 13.50 (each br s, 2 H, 4 × NH); $\lambda_{max.}$ 448 (ε 38 900) and 512 nm (77 200).

4,6-*Bis*-(2-*chloroethyl*)-1-(3-*ethoxycarbonylpropyl*)-8-(2-*methoxycarbonylethyl*)-1′,2,3,5,7,8′-*hexamethyl*-a,c-*biladiene Dihydrobromide* (**22**).—Tripyrrene hydrobromide (**21**)[8] (444 mg) in trifluoroacetic acid (10 ml) was stirred for 10 min under nitrogen before addition of formylpyrrole (**8**) (176 mg) in methanol (10 ml). HBr in acetic acid (31%; 3 ml) was then added and the mixture was stirred for a further 30 min. Precipitation of the product had begun, and this was finished by dropwise addition of ether (50 ml) and cooling to 0 °C. The a,c-*biladiene* was filtered off, washed with cold ether, and was collected as deep red crystals (415 mg, 70%), m.p. >300 °C (Found: C, 53.6; H, 6.0; N, 6.3. $C_{39}H_{52}Br_2Cl_2N_4O_4$ requires C, 53.7; H. 6.0; N, 6.4%); δ 1.30 (t, 3 H, CH_2CH_3), 1.70, 2.50, 2.75, 3.05, 3.15, and 3.60 (each m, 18 H, 2 × CH_2CH_2Cl, CH_2CH_2CO, and $CH_2CH_2CH_2CO$), 2.28, 2.30, 2.32, 2.35, 2.73, and 2.75 (each s, 3 H, 6 × Me), 5.25 (s, 2 H, CH_2), 3.75 (s, 3 H, OMe), 4.20 (q, 2 H, CH_2CH_3), 7.20 (s, 2 H, 2 × –CH_2=), and 13.30, 13.35, 13.40, and 13.55 (each s, 1 H, 4 × NH); $\lambda_{max.}$ 450 (ε 54 900) and 522 nm (95 000).

Porphyrins

2,4-*Bismethoxycarbonylmethyl*-6,7-*bis*-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethylporphyrin* (**10a**).—The *a,c*-biladiene (**9a**) (350 mg) was added to a solution of copper(II) acetate (2.0 g) in dimethylformamide (30 ml) which had previously been heated to 145 °C. The mixture was stirred for 5 min and then poured into water (100 ml) and extracted with dichloromethane (3 × 100 ml). The organic extracts were washed with water (100 ml), dried, and then evaporated to dryness to give a dark residue which was stirred with sulphuric acid in trifluoroacetic acid (20%; 20 ml) for 30 min and then poured into water and extracted with chloroform (3 × 100 ml). The organic phase was separated, washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness. The residue was taken up in 5% sulphuric acid in methanol (25 ml) and kept overnight at 20 °C in the dark. The resulting solution was poured into aqueous sodium acetate (10%; 100 ml) and extracted with dichloromethane (3 × 50 ml). The organic extracts were washed with water, dried, and evaporated to dryness to give a residue which was taken up in dichloromethane and chromatographed on alumina (Brockmann Grade III, elution with dichloromethane). The porphyrinic fraction was collected, evaporated to dryness, and the residue was recrystallized from dichloromethane–methanol to give the *porphyrin* (66 mg, 25%) as deep purple needles, m.p. 134—135 °C (Found: M^+, *m/z* 710.343. $C_{40}H_{46}N_4O_8$ requires *M*, 710.340); δ −3.98 (s, 2 H, 2 × NH), 2.65, 2.75, and 4.05 (m, each 4 H, $CH_2CH_2CH_2CO$), 3.65, 3.67, 3.80, and 3.82 (each s, 3 H, 4 × Me), 3.76 and 3.78 (each s, 6 H, 4 × OMe), 4.90 and 5.00 (s, 2 H, 2 × CH_2CO), and 9.95, 10.00, 10.02, and 10.12 (s, 1 H, 4 × *meso*-H); $\lambda_{max.}$ 399 (170 000), 495 (14 000), 530 (10 200), 570 (7 100), and 620 nm (5 250).

2,4-*Bis*-(2-*methoxycarbonylethyl*)-6,7-*bis*-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethylporphyrin* (**10c**).—This compound was prepared from the *a,c*-biladiene dihydrobromide (**9c**) (280 mg) as described above, using copper(II) acetate (2 g) in dimethylformamide (15 ml). After work-up and chromatography the *porphyrin* (70 mg, 32%) crystallized as purple needles, m.p. 138—140 °C (Found: C, 68.2; H, 6.75; N, 7.6. $C_{42}H_{50}N_4O_8$ requires C, 68.3; H, 6.8; N, 7.6%); δ −3.75 (s, 2 H, 2 × NH), 2.60, 2.75, 3.27, 4.20, and 4.50 (each m, 4 H, 2 × CH_2CH_2CO and 2 × $CH_2CH_2CH_2CO$), 3.70, 3.72, 3.74, and 3.75 (each s, 3 H, 4 × Me), 3.70 and 3.73 (s, 6 H, 4 × OMe), 10.06 (s, 3 H, 3 × *meso*-H), and 10.25 (s, 1 H, *meso*-H); $\lambda_{max.}$ 400 (ε 180 000), 495 (14 700), 530 (10 900), 565 (6 500), and 618 nm (5 200).

2,4-*Bis*-(2-*chloroethyl*)-6,7-*bis*-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethylporphyrin* (**10e**).—(*a*). The *a,c*-biladiene (**9e**) (150 mg) was cyclized with copper(II) acetate (1.5 g) in hot dimethylformamide, as described above, and gave the *porphyrin* (**10e**) (30 mg, 26%) as purple needles, m.p. 180—181 °C (from dichloromethane–hexane) (Found: C, 65.8; H, 6.4; N, 8.0. $C_{38}H_{44}Cl_2N_4O_4$ requires C, 65.9; H, 6.4; N, 8.1%); δ −3.75 (s, 2 H, 2 × NH), 2.65, 2.75, 4.15, 4.30, and 4.55 (each m, 4 H, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CH_2CO$), 3.64, 3.65, 3.67, and 3.68 (each s, 3 H, 4 × Me), 3.74 and 3.75 (each s, 3 H, 2 × OMe), 10.10 (s, 2 H, 2 × *meso*-H), and 10.05 and 10.20 (each s, 1 H, 2 × *meso*-H); $\lambda_{max.}$ 400 (ε 177 000), 495 (14 900), 530 (10 500), 565 (7 800), and 620 nm (6 000).

(*b*). In a similar preparation, but using copper(II) chloride dihydrate (1.5 g) in place of the corresponding diacetate for cyclization of the *a,c*-biladiene salt (**9e**), two porphyrins were obtained and separated by chromatography. The first product was the required bis-(2-chloroethyl)porphyrin (**10e**) (12 mg, 10%), identical in all respects with the product from procedure (*a*). The second was a *meso*-chloroporphyrin (15 mg, 12%), which formed purple needles from dichloromethane–hexane; δ −3.50 (br s, 2 H, 2 × NH); 2.55, 2.75, 4.05, 4.50 (m, 20 H, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CH_2CO$), 3.50 and 3.52 (each s, 3 H, 2 × OMe); 9.65, 9.75, and 10.10 (each s, 1 H, 3 × *meso*-H).

(*c*). *MacDonald method.* The diformylpyrromethane (**26c**) (45 mg) and the pyrromethanedicarboxylic acid (**7e**) (40 mg) were dissolved in dichloromethane (50 ml) and treated with toluene-*p*-sulphonic acid (150 mg) dissolved in methanol (10 ml). The mixture was stirred at 20 °C for 24 h in the dark, and then treated with a saturated solution of zinc(II) acetate in methanol (25 ml). After being stirred for a further 15 h at 20 °C without exclusion of light, the solution was evaporated to dryness to give a residue which was taken up in 5% sulphuric acid in methanol (50 ml). The solution was kept at 20 °C overnight and then poured into water (100 ml), made just alkaline with dilute aqueous ammonium hydroxide, and extracted with dichloromethane. The organic extracts were washed with water, dried, and evaporated to dryness to give a residue which was chromatographed on alumina (Brockmann Grade III, elution with dichloromethane). The porphyrinic band was collected, evaporated to dryness, and then recrystallized from dichloromethane–hexane to give the porphyrin (**10e**) (8 mg, 11%), m.p. 180—181 °C, identical with the material described in procedure (*a*).

6,7-*Bis*-(3-*methoxycarbonylpropyl*)-1,2,3,4,5,8-*hexamethylporphyrin* (**10b**).—The *a,c*-biladiene (**9b**) (500 mg) was cyclized, as described for compound (**10a**) using copper(II) acetate (5 g) in refluxing dimethylformamide (20 ml), and afforded the *porphyrin* (150 mg, 40%), m.p. 323—325 °C, after recrystallization from dichloromethane–methanol (Found: C, 72.9; H, 7.15; N, 9.5. $C_{36}H_{42}N_4O_4$ requires C, 72.27; H, 7.1; N, 9.4); δ −3.75 (s, 2 H, 2 × NH), 2.65, 2.75, and 4.15 (each m, 4 H, 2 × $CH_2CH_2CH_2CO$), 3.60 and 3.65 (each s, 9 H, 6 × Me), 3.75 (s, 6 H, 2 × OMe), 10.05 and 10.10 (each s, 1 H, 2 × *meso*-H), and 10.20 (s, 2 H, 2 × *meso*-H); $\lambda_{max.}$ 408 (ε 169 250) 496 (12 950), 530 (9 250), 566 (6 200), and 620 nm (4 700).

2,3-*Bis*-(2-*chloroethyl*)-6,7-*bis*-(3-*methoxycarbonylpropyl*)-1,4,5,8-*tetramethylporphyrin* (**17**).—This porphyrin was obtained in 38% yield, following the procedure described above, employing the *a,c*-biladiene (**16**) (400 mg), copper(II) acetate (4 g), and dimethylformamide (15 ml). The *porphyrin* was obtained as fine red crystals, m.p. 197—199 °C (from dichloromethane–methanol) (Found: C, 66.2; H, 6.5; N, 8.0. $C_{38}H_{44}Cl_2N_4O_4$ requires C, 66.0; H, 6.4; N, 8.1%); δ −3.75 (s, 2 H, 2 × NH); 2.15, 2.25, 4.10, 4.30, and 4.45 (each m, 4 H, 2 × CH_2CH_2Cl and 2 × $CH_2CH_2CH_2CO$), 3.60 and 3.65 (each s, 6 H, 4 × Me), 3.75 (s, 6 H, 2 × OMe), 10.00 and 10.25 (each s, 1 H, 2 × *meso*-H), and 10.10 (s, 2 H, 2 × *meso*-H); $\lambda_{max.}$ 406 (ε 184 800), 498 (15 200), 568 (8 400), and 622 nm (6 300).

2,4-*Bis*-(2-*chloroethyl*)-6-(2-*methoxycarbonylethyl*)-7-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethylporphyrin* (**23**).—This compound was similarly obtained from the *a,c*-biladiene (**22**) (300 mg) in dimethylformamide (10 ml) containing copper(II) acetate (3 g). After recrystallization from dichloromethane–methanol, the *porphyrin* was obtained as red crystals (80 mg, 35%), m.p. 199—201 °C (Found: C, 65.7; H, 6.3; N, 8.2. $C_{37}H_{42}Cl_2N_4O_4$ requires C, 65.6; H, 6.2; N, 8.3%); δ −3.75 (s, 2 H, 2 × NH), 2.65, 2.75, 3.30, 4.10, 4.50, and 4.60 (m, 18 H, 2 × CH_2CH_2Cl, 2 × CH_2CH_2CO, and 2 × $CH_2CH_2CH_2CO$), 3.5—3.75 (m, 18 H, 4 × Me and 2 × OMe), 10.05 (s, 2 H, 2 × *meso*-H), and 10.10 and 10.15 (each s, 1 H, 2 × *meso*-H); $\lambda_{max.}$ 406 (ε 176 500), 498 (14 950), 532 (10 600), 568 (7 800), and 622 nm (5 840).

6,7-*Bis*-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethyl*-2,4-*divinylporphyrin* (**10d**).—The foregoing bis-(2-chloroethyl)-porphyrin (**10e**) (20 mg) was heated under reflux in boiling pyridine (25 ml) under nitrogen for 10 min before addition of aqueous sodium hydroxide (10%; 5 ml). The mixture was heated under reflux for a further 2 h and then cooled and treated with aqueous acetic acid (25%; 10 ml). The mixture was evaporated to dryness, using toluene (25 ml) as a 'chaser'. The residue was taken up in 5% sulphuric acid in methanol (25 ml), kept overnight at 20 °C, and then poured into water and neutralized with aqueous sodium acetate. The porphyrin ester was extracted with dichloromethane, and the extract washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness. The residue was taken up in dichloromethane and chromatographed on alumina (Brockmann grade III, elution with dichloromethane). The porphyrinic fractions were evaporated and the residue was recrystallized from dichloromethane–methanol to give the *vinylporphyrin* (14 mg, 78%), m.p. 219—220 °C (lit.,[6] 219—221 °C); δ −3.78 (s, 2 H, 2 × NH), 2.60—2.65, 2.72—2.76, and 4.12—4.17 (m, 4 H, 2 × $CH_2CH_2CH_2CO$), 3.73, 3.75 (s, 3 H, OMe), 6.15—6.40 (m, 4 H, =CH_2), 8.20—8.30 (m, 2 H, CH=), and 10.00, 10.10, 10.11, and 10.12 (each s, 1 H, 4 × *meso*-H); $\lambda_{max.}$ 400 (ε 180 000), 500 (14 400), 533 (11 600), 570 (6 800), and 624 nm (5 600).

6,7-*Bis*-(3-*methoxycarbonylpropyl*)-1,4,5,8-*tetramethyl*-2,3-*divinylprophyrin* (**18**).—This porphyrin was prepared using the same method as described for porphyrin (**10d**) (40 mg), from the bis-(2-chloroethyl)porphyrin (**17**). It was crystallized from dichloromethane–hexane to give the *porphyrin* (27 mg, 75%), m.p. 254—256 °C (Found: C, 74.0; H, 6.8; N, 9.1. $C_{38}H_{42}N_4O_4$ requires C, 73.8; H, 6.8; N, 9.05%); δ −3.65 (s, 2 H, 2 × NH), 2.60, 2.75, and 4.10 (each m, 4 H, 2 × $CH_2CH_2CH_2CO$), 3.60 and 3.70 (s, 6 H, 4 × Me), 3.75 (s, 6 H, 2 × OMe), 6.15 and 5.35 (dd, 2 H, 2 × =CH_2), 8.25 (m, 2 H, -CH=), 10.05 (s, 2 H, 2 × *meso*-H), and 10.20 and 10.30 (each s, 1 H, 2 × *meso*-H); $\lambda_{max.}$ 414 (ε 167 300), 506 (14 600), 542 (12 150), 576 (7 800), and 630 nm (6 100).

6-(2-*Methoxycarbonylethyl*)-7-(3-*methoxycarbonylpropyl*)-1,3,5,8-*tetramethyl*-2,4-*divinylporphyrin* (**24**).—Likewise, the bis-(2-chloroethyl)porphyrin (**23**) was dehydrochlorinated to give the title *porphyrin* (38 mg, 70%), m.p. 213—215 °C (from dichloromethane–hexane) (Found: C, 73.6; H, 6.8; N, 9.4. $C_{37}H_{40}N_4O_4$ requires C, 73.5; H, 6.7; N, 9.3%); δ −3.60 (s, 2 H, 2 × NH), 2.65, 2.75, and 4.65 (each m, 2 H, $CH_2CH_2CH_2CO$), 4.10 and 3.50 (t, 2 H, CH_2CH_2CO), 6.15 and 6.35 (dd, 2 H, 2 × =CH_2), 8.30 (m, 2 H, 2 × CH=), 10.05 (s, 2 H, 2 × *meso*-H), and 10.10 and 10.15 (each s, 1 H, 2 × *meso*-H); $\lambda_{max.}$ 418 (ε 168 200), 504 (13 400), 540 (11 100), 576 (6 500), and 630 nm (5 000).

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