Tetrahedron. Vol. 32, pp 275 to 283. Pergamon Press 1976. Printed in Great Britain

PYRROLES AND RELATED COMPOUNDS—XXXIV[1]

ACRYLIC ESTERS IN THE PORPHYRIN SERIES

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(*Received in the UK 5 August 1975; Accepted for publication 9 September 1975*)

Abstract—Treatment of imidazolylporphyrins (**12**) with sodium borohydride in methanol affords high yields of the corresponding hydroxymethylporphyrins (**14**) which can be oxidised with chromium trioxide in pyridine to give high yields of formylporphyrins (**11**). When heated with methyl hydrogen malonate in pyridine, good yields of porphyrin *trans*-acrylic esters (**15**) are produced; a milder method involving reaction of the formylporphyrin (**11a**) with a phosphonium ylid (**20**) or better, a phosphonate ester (**21**), gives good yields of the porphyrin *trans*-acrylic ester (**16a**).

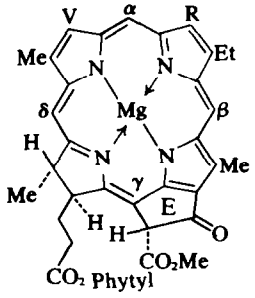
Porphyrin β-keto-esters (e.g. **8b**) are reduced with sodium borohydride in methanol, to give the 6-hydroxypropionate ester (**17b**); prolonged treatment with borohydride results in over-reduction at the 7-propionate side-chain. The hydroxypropionate porphyrin (**17b**) is readily dehydrated to give a high yield of the porphyrin *trans*-acrylic ester (**15b**). Methods for the magnesiation and preparation of β-keto-ester and *trans*-acrylic ester porphyrin 7-propionic acids are described; hydrolysis of porphyrin β-keto-esters (e.g. **8b**) can be controlled such that only the propionic function is hydrolysed. However, prolonged alkaline hydrolysis and re-esterification furnishes a mixture of 2-vinylrhodoporphyrin-XV dimethyl ester (**9b**) and the 2-vinyl-6-acetylporphyrin (**18b**). The latter porphyrin can also be prepared by treatment of the acid chloride (**10b**) from 2-vinylrhodoporphyrin-7-methyl ester with sodio di-t-butyl malonate, followed by treatment with trifluoroacetic acid.

INTRODUCTION

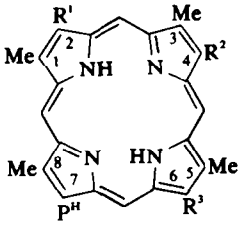
Though studies with mutants have given[2] some clear indications of the structures of certain intermediates in the biosynthesis of chlorophylls $-a$ and $-b$ (**1**) from protoporphyrin-IX (**2c**), in almost all cases these proposals and suggestions need to be verified by feeding experiments with labelled precursors. In recent years, our primary interest in chlorophyll biosynthesis has centered on the formation, from the 6-propionic side-chain, of the so-called "isocyclic" ring ("E"). We[3] and others[4] have suggested that this intriguing cyclisation might take place through the intermediacy of porphyrin β-keto-esters such as **3**, or more correctly, through the magnesium complex of **3**. However, there is no absolute necessity that β-keto-esters must be on the metabolic pathway to the chlorophylls, and other routes can be readily visualised.

The main support for magnesium β-keto-esters as biosynthetic intermediates comes from two widely different sources; most recently, two purely chemical methods[5,6] for transformation of the acyclic β-keto-esters into phaeoporphyrins have been described, the second of these (which involves[6] photo-oxidative cyclisation using thallium(III) salts) being remarkably efficient. Perhaps the most persuasive evidence in favour of biological significance for β-keto-esters is the reported isolation[7] of such compounds (after demetallation) from a *Chlorella* mutant; in the complex mixture obtained from these mutants, spectroscopic identification was also made of porphyrins with acrylic (e.g. **4b,c**) and hydroxypropionic (**5b,c**) groups. It is not clear, however, whether these compounds are actually on the biosynthetic pathway, or whether they are side-products in the particular mutant, or even artefacts of the chemical processing; this analysis might also be applied to the β-keto-esters.

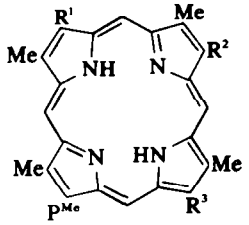
Parts XXVIII[5] and XXIX[8] of this Series describe the development of efficient methods for synthesis of



1: Chlorophyll-*a*; R = Me
Chlorophyll-*b*; R = CHO



2: $R^3 = P^H$
3: $R^3 = COCH_2CO_2Me$
4: $R^3 = CH{=}CHCO_2Me$
5: $R^3 = CH(OH)CH_2CO_2Me$
6: $R^3 = CHO$
7: $R^3 = H$
a: $R^1 = R^2 = Et$
b: $R^1 = V$; $R^2 = Et$
c: $R^1 = R^2 = V$
$P^R = CH_2CH_2CO_2R$
$V = CH{=}CH_2$



8: $R^3 = COCH_2CO_2Me$
9: $R^3 = CO_2Me$
10: $R^3 = COCl$
11: $R^3 = CHO$
12: $R^3 = CON{-}CH{=}CH{-}N{=}CH$
13: $R^3 = CO_2H$
14: $R^3 = CH_2OH$
15: $R^3 = CH{=}CHCO_2Me$
16: $R^3 = CH{=}CHCO_2Bu^t$
17: $R^3 = CH(OH)CH_2CO_2Me$
18: $R^3 = CH(OAc)CH_2CO_2Me$
19: $R^3 = COMe$

porphyrin β-keto-esters bearing other peripheral substituents in an array of possible biological significance. In the present paper we report synthetic approaches to similarly substituted porphyrin acrylic esters, together with solutions to the problem of magnesiation and the more delicate requirement that the acrylic ester or β-keto-ester must be maintained in the protected form while the 7-propionic side-chain must be as the free-acid. We also describe an efficient method for transformation of porphyrin β-keto-esters into acrylic esters by way of the biologically interesting hydroxypropionate side-chain.

Syntheses of porphyrin acrylic esters

Acrylic porphyrins have been synthesised before; with only one exception[9] (in which an acrylic pyrrole was carried through to porphyrin) all approaches have utilised Knoevenagel-type condensations of formylporphyrins. Acrylates can also be prepared by application of the Wittig reaction; we have successfully employed both the classical Knoevenagel method as well as the less drastic Wittig approach using a formylporphyrin and a phosphonium ylid or a phosphonate ester. The necessary formylporphyrins have in the past been obtained by electrophilic substitution of peripherally unsubstituted haemins with dichloromethyl ethyl ether[10] or by degradation of vinylporphyrins with oxidants such as osmium tetroxide.[11] Owing to the relative inaccessibility of peripherally unsubstituted porphyrins, we chose to approach the formylporphyrins from the corresponding porphyrins bearing nuclear carboxyl groups. As in our β-keto-ester work,[5,8] this choice was influenced by the availability of rhodoporphyrins, both from synthetic[12] and natural[13] sources.

Direct reduction of the porphyrin acid chlorides (**10a,b**) with lithium tri(t-butoxy)aluminohydride[14] or sodium trimethoxy borohydride[15] gave erratic and unacceptably low yields (10–30%) of the required formylporphyrins (**11a,b**). The corresponding 6-imidazolylporphyrins (**12a,b**) [obtained by treatment of the 6-carboxylic acids (**13a,b**) with carbonyl di-imidazole] were completely unreactive towards these two reducing agents at low temperatures.

The less direct approach to the aldehydes (**11a,b**) via the corresponding hydroxymethylporphyrins (**14a,b**) was next investigated; treatment of the acid chlorides (**10a,b**) with sodium borohydride, sodium trimethoxy borohydride, or lithium tri(t-butoxy)aluminohydride gave 40–70% yields of the required products (**14a,b**). Reduction of the less sensitive imidazolylporphyrins (**12a,b**) proved to be much more efficient and reproducible, 70–80% yields of the hydroxymethylporphyrins (**14a,b**) being obtained at room temperature with sodium trimethoxy borohydride or lithium tri(t-butoxy)aluminohydride. The best method, however, involved treatment of the imidazolides (**12a,b**) with excess sodium borohydride in methanol–chloroform at 0° during 30 min, and gave 85–90% yields. Oxidation of the products (**14a,b**) with chromium trioxide in pyridine[16] at room temperature gave an 85% yield of the formylporphyrins (**11a,b**) [68% overall from the porphyrin free acids (**13a,b**)].

Condensation of the formylporphyrins with methyl hydrogen malonate in pyridine at 80° for 12 hr and then at reflux for a further 12 hr gave, after chromatography, the acrylate di-esters (**15a,b**), in 75% yield. As might be expected, the 16·5 Hz coupling constant for the vinylic protons in the acrylate side-chains showed them to be the *trans* isomers.

We considered differential hydrolysis of the ester functions† in these acrylates to be an unrealistic objective; the acrylic ester propionic acid porphyrin (**4b**) (the magnesium complex of which would be required for feeding experiments) and its di-hydro-derivative (**4a**) were therefore prepared by hydrolysis of the formylporphyrins (**11a,b**) to give the propionic acids (**6a,b**), followed by Knoevenagel condensation as before to give **4a,b** in 65–70% yield. All spectroscopic data was compatible with the formulations of the propionic acids; they were insoluble, difficult to crystallise, and appeared from combustion analysis to be hydrated.

As mentioned earlier, the Wittig reaction is a very efficient method for preparation of acrylates, and since we anticipated synthesising other acrylic porphyrins with sensitive side-chains (e.g. as in chlorophyll-*c*[17]), we investigated this route, even though the Knoevenagel approach had furnished satisfactory results. Treatment of the formylporphyrin (**11a**) with the ylid (**20**) at room temperature during 24 hr gave a 60% yield of the porphyrin t-butyl acrylate (**16a**).

A higher yield (78%) of **16a** was obtained when the formylporphyrin (**11a**) was treated at 0° with the phosphonate ester (**21**). When **16a** was treated with trifluoroacetic acid and then diazomethane, it afforded the porphyrin *trans*-acrylate (**15a**) described above, and possessed the same m.p. as a sample prepared by Fischer[18] from pyrroporphyrin-XV (**7a**) *via* the formylporphyrin (**6a**).

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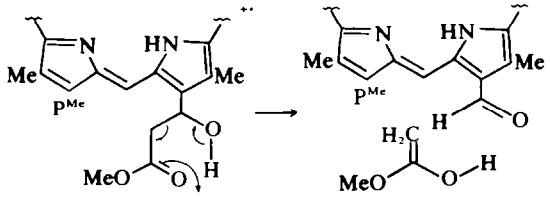
Having stocks of porphyrin β-keto-esters available, we also investigated the transformation of these into the corresponding acrylic derivatives. Reaction of the 2-vinyl-6-β-keto-ester (**8b**) with an excess of sodium borohydride in methanol afforded a 65% yield of the required 6-hydroxypropionate porphyrin (**17b**), together with a second, more polar compound. The NMR spectrum of **17b** showed the methyl ester of the propionate side-chain in the normal position (τ 6·3), but that of the hydroxypropionate side-chain was at higher field, and could not be distinguished from the nuclear Me groups. The mass spectrum was consistent with the formulation **17b**, and showed a prominent peak due to loss of water. However, the base peak in the spectrum corresponded to formylporphyrin, presumably arising from a retro-aldol type of fragmentation:



†All potential metabolic precursors of the chlorophylls after magnesium protoporphyrin-IX and before formation of the phytyl ester on the 7-side-chain must necessarily possess a propionic *acid* side-chain at position-7, but the 6-side-chain (whatever its nature) must be protected as the corresponding methyl ester.

The more polar product obtained from these reactions predominated when reaction times were extended, and could be obtained in 47% yield after chromatography. Due to its involatility, a satisfactory mass spectrum could not be obtained, and its polarity indicated that it might be a diol, derived from further reduction of **17b**. The NMR spectrum indicated the structure **22** with the propionic ester reduced. No signal was observed in the "normal" methyl ester region (τ 6·3–6·4) and a two proton multiplet (τ 7·1) corresponding to the central methylene of a 7-(3-hydroxypropyl) side-chain was present. The proposed structures **17b** and **22** were further confirmed by conversion into their acetates **18b** and **23** respectively, by treatment with acetic anhydride in pyridine, and all spectroscopic and analytical data were in accord with the proposed structures.

Esters are not normally reduced with sodium borohydride under the conditions employed herein. The reduction can be rationalised in terms of an intramolecular hydride transfer, as depicted in **25**. Molecular models show that this does not involve strain in the porphyrin macrocycle, nor any unfavourable non-bonded interactions in the 12-membered ring through which the hydride transfer occurs. A sample of 2-vinylrhodoporphyrin-XV dimethyl ester (**9b**) was subjected to similar reductive conditions; reaction was observed, though considerably slower than with the β-keto-ester (**8b**). Chromatography gave recovered starting material together with a highly polar compound, identified by NMR and combustion analysis as **24**, an isomer of the compound **14b** described above. This ester reduction presumably also involves hydride transfer from a borane-type complex of the 6-ester carbonyl.

Treatment of the hydroxypropionate porphyrin (**17b**) with phosphoryl chloride in pyridine gave a 79% yield of the *trans*-acrylic ester (**15b**), identical with the material prepared by the Knoevenagel condensation.

Magnesium insertion into porphyrin β-keto-esters and acrylates

All biosynthetic precursors of the chlorophylls after protoporphyrin-IX contain magnesium.[2] Thus, insertion of magnesium without unwanted transformations of possible precursors is a necessary prerequisite before feeding experiments can be carried out. The three most often used methods are, (i) "magnesium viologen", magnesium hexapyridyl di-iodide or magnesium 4,4'-dipyridyl, in dry pyridine at reflux,[19] (ii) *n*-propoxymagnesium bromide in n-propanol and tetrahydrofuran at 70°[20] and (iii) magnesium perchlorate in refluxing pyridine.[21]

It transpired that the n-propoxymagnesium bromide method was satisfactory for magnesiation of porphyrin β-keto-esters, though in our hands it did effect transesterification of the propionate ester (Experimental). However, this transesterification was no drawback since the next stage before feeding was always alkaline hydrolysis of the propionic ester (*vide infra*). In the case of porphyrin acrylates, transesterification of the acrylic side-chain would also be expected and this would yield a compound bearing a *n*-propyl acrylic ester which could not be expected to be incorporated into the chlorophylls. Thus, other methods for magnesiation were investigated.

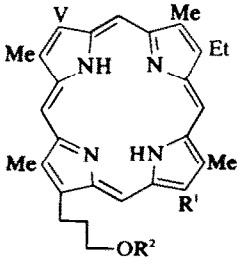
Of the three methods developed by Corwin[19] the magnesium hexapyridyl di-iodide route appeared to be the most promising. The method involves the preparation of magnesium iodide etherate (by refluxing a solution of iodine in dry ether with excess magnesium), which is dried, quenched with pyridine to give a yellow precipitate, and this slowly dissolves in excess added pyridine. In practice it was found that the precipitate could be readily solubilised by addition of a few drops of methanol to the suspension in pyridine. The porphyrin is then added and magnesiation is complete within one hour.

When this procedure was applied to the *meso*-tritiated (*vide infra*) porphyrin acrylic ester (**4b**), the isolated magnesium complex was found to have lost some 90% of its initial radioactivity. This loss has been shown[22] to be due to an unexpectedly facile electrophilic substitution reaction involving protons from the added dry methanol, and the development of this for *meso*-deuteration of porphyrins and metalloporphyrins has been outlined elsewhere.[23] It was also shown[22,23] that this method of magnesiation also accomplished hydrolysis of methyl esters within the molecule, possibly via iodide assisted cleavage.[24]

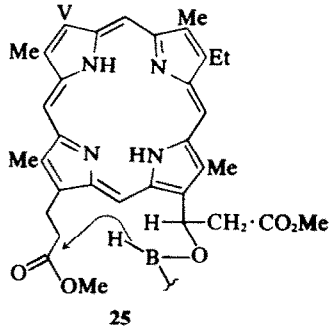
Erratic results were experienced with the "magnesium viologen" reagent. However, methoxymagnesium bromide and *t*-butoxymagnesium bromide, although insoluble in their parent alcohols (in contrast to the *n*-propoxymagnesium bromide case) proved extremely soluble in pyridine. These pyridine solutions converted the acrylic (and other) porphyrins into their magnesium complexes quantitatively. In practice, methoxymagnesium bromide was used for the acrylic porphyrin (**4b**), and magnesium was inserted with loss of only 10–15% of radioactivity.

Hydrolyses of porphyrin β-keto-esters

Specific alkaline hydrolysis of the propionate ester in porphyrin β-keto-esters (**8**) should be possible by virtue of the formation of the enolate anion of the keto-ester side-chain, thereby protecting the carbomethoxy function from nucleophilic attack; this should apply both to the free porphyrin or its magnesium complex. The magnesium complexes were chosen for trial experiments, so that in experiments with radioactive β-keto-esters, the hyd-



22: $R^1 = CH(OH)\cdot CH_2CO_2Me$; $R^2 = H$
23: $R^1 = CH(OAc)\cdot CH_2CO_2Me$; $R^2 = Ac$
24: $R^1 = CO_2Me$; $R^2 = H$



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rolysis step could immediately precede the feeding experiment. Since the magnesium complexes of the keto-esters were prepared using *n*-propoxymagnesium bromide, the C-7 propionate side-chain was present as the *n*-propyl ester. Hydrolysis of the 2-ethyl-6-β-keto-ester magnesium complex with M/10 methanolic potassium hydroxide was complete (propionic side-chain only) in 6–7 hr at room temperature. Even after 15 hr the visible absorption spectrum of the enolate was unchanged; acidification and treatment with diazomethane afforded the 2,4-diethyl-β-keto-ester (**8a**). Total hydrolysis of the β-keto-ester (**8b**) was achieved by refluxing for 10 hr in M KOH in methanol–pyridine. After acidification, work-up, and esterification (CH_2N_2), the product was shown to be a mixture of the expected 6-acetylporphyrin (**19b**) and 2-vinylrhodoporphyrin-XV dimethyl ester (**9b**), the latter produced by a retro-Claisen type of reaction. Only a low yield of the acetyl compound **19b** was obtained and hence a comparison sample was obtained by treatment of the acid chloride (**10b**) with sodio di-*t*-butyl malonate, followed by treatment with trifluoroacetic acid. The acetyl compound **19b** was obtained in 30% yield, was fully characterised, and was shown to be identical with the sample prepared by hydrolysis of the 2-vinyl-6-β-keto-ester. The analogous 2-ethyl-6-acetylporphyrin (**19a**) was similarly prepared.

Preliminary feeding experiments with tritiated acrylates and β-keto-esters

Tritiated β-keto-esters were prepared by total synthesis via the *b*-oxobilane method and the appropriate rhodoporphyrin.[12] The tritium was incorporated at the oxophlorin stage, using the method already described[25] for deuteration at the *meso*-position opposite the oxophlorin carbonyl group, but using tritio- instead of deuteroacetic acid as exchange reagent.

The *meso*-tritiated acrylic porphyrin (**4b**) was prepared from natural starting materials. Phaeophytin-*a* was degraded[13] to afford methyl phaeophorbide-*a* which was tritiated at the δ-position† using tritioacetic acid (cf. Ref. 26); this labelled material was then transformed efficiently[13] into 2-vinylrhodoporphyrin-XV dimethyl ester (**9b**), and from there, as described above, into the magnesium complex of **4b**.

Results from the feeding of the magnesium complexes of tritium labelled acrylic porphyrin (**4b**) and the β-keto-esters (**3**) to an isolated chloroplast system[27] from mustard seedlings are confusing, erratic, and are not amenable to any logical interpretation. We consider that the unsatisfactory conclusion to this investigation is due to two main factors; (i) the choice of tritium as the radioactive label, particularly so in this case because it is located in the *meso*-position from which recent work has shown it to be readily exchanged, and (ii) the choice of a plant system for incubation of the large macrocyclic precursors.

Recent studies of the *Chlorobium* chlorophylls[28] and vitamin B_{12} biosynthesis[29] have revealed that bacterial systems are capable of incorporating macrocyclic precursors such as uroporphyrinogen-III to levels as high as 5%. Our future work on the biosynthesis of the isocyclic ring in chlorophylls will therefore focus on the feeding of carbon labelled precursors to bacterial systems producing bacteriochlorophyll-*a*.

†In theory (*cf* Ref. 26) most natural chlorins should undergo ready exchange at the δ-position. However, the other chlorin (purpurin-7 trimethyl ester) which is an intermediate in the transformation of phaeophytin-*a* into 2-vinylrhodoporphyrin-XV dimethyl ester, underwent exchange at a slow rate, presumably owing to the effect of the electron-withdrawing γ-oxalyl substituent.

EXPERIMENTAL

M.ps were measured on a hot-stage apparatus. Unless otherwise stated, neutral alumina (Merck; Brockmann grade III) was used for all chromatographic separations. Reactions were followed by TLC as described in earlier parts of this Series. Electronic absorption spectra were determined (solutions in CH_2Cl_2) with a Unicam SP 800 spectrophotometer, ^1H NMR spectra (solutions in $CDCl_3$ with TMS as internal standard) with a Varian HA-100 instrument, and mass spectra with an A.E.I. MS 902 or MS 12 spectrometer (at 50 μA and 70 eV; direct insertion probe with source temperature *ca.* 200–220°).

4 - *Ethyl* - 6 - *hydroxymethyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**14b**)

(a) *From the imidazolide* (**12b**) *and sodium borohydride.* 4 - Ethyl - 6 - (imidazolyl - 1 - carbonyl) - 7 - (2 - methoxycarbonylethyl) - 1,3,5,8 - tetramethyl - 2 - vinylporphin[8] (516 mg) in dry $CHCl_3$ (75 ml) was cooled to 0° and treated with an ice cold soln of $NaBH_4$ (1 g) in MeOH/$CHCl_3$ (150 ml; 1:1). The reaction was monitored by spectrophotometry, the characteristic[30] rhodo spectrum of the imidazolide being replaced by an aetio-type spectrum. After 1 hr at 0° the excess $NaBH_4$ was decomposed by stirring with acetone (50 ml) for 30 min; the mixture was washed with H_2O (2 × 500 ml), the organic phase dried (Na_2SO_4) and the solvents then evaporated to dryness to give a residue which was chromatographed on alumina (grade V) (elution with CH_2Cl_2 containing *ca.* 1% MeOH). A minor band was first eluted, and the porphyrin isolated from this was shown to be identical with **9b**. Further elution and evaporation of the red eluates gave a residue which was crystallised from CH_2Cl_2/*n*-hexane to give the *hydroxymethylporphyrin* (411 mg; 90%) as brown microneedles, m.p. 258–60°. (Found: C, 71·2; H, 6·6; N, 10·1. $C_{33}H_{36}N_4O_3 \cdot H_2O$ requires: C, 71·45; H, 6·6; N, 10·4%); NMR (in TFA) τ, −1·33 (1H, s), −0·06 (3H, s) 4 *meso*-H; 1·70 (1H, m), 3·49 (2H, m) $CH{=}CH_2$; 3·52 (2H, s) CH_2OH; 5·32 (2H, t), 6·66 (2H, t), 6·26 (3H, s) $CH_2CH_2CO_2Me$; 6·14, 6·16, 6·20, 6·22 (4 Me); 5·72 (2H, q), 8·16 (3H, t) CH_2CH_3. λ_{max} 402 (ε 197,100), 505 (12,100), 541 (13,200), 571 (8300) and 626 nm (2400); in CH_2Cl_2 + 1% TFA, 407 (ε 321,400), 554 (16,800) and 600 nm (7400), *m/e* 536 (100%), 519 (9), 463 (21), m* 400 (536 → 463).

(b) *From the acid chloride* (**10b**) *and sodium trimethoxyborohydride.* Compound **13b**[5] (85 mg) was treated with oxalyl chloride (5 ml) for 30 min before evaporation to dryness, final traces of the reagent being removed at 0·1 mm Hg. The acid chloride **10b** was dissolved in THF (20 ml) with stirring and cooled to 0° before addition, dropwise over 5 min, of sodium trimethoxyborohydride (200 mg; 10 equiv) in dry THF (10 ml). Stirring was continued for a further 20 min at 0°, the mixture was then diluted with CH_2Cl_2 (50 ml), washed with H_2O (2 × 250 ml), dried (Na_2SO_4), and evaporated to dryness to give a residue which was chromatographed on alumina (grade V) (elution with CH_2Cl_2). A trace of porphyrin was first eluted and identified as **11b**. Further elution gave the hydroxymethylporphyrin, and after the eluates were evaporated, the residue was crystallised from CH_2Cl_2/*n*-hexane to give 64 mg (70%), identical in all respects with the material described in (a) above.

4 - *Ethyl* - 6 - *formyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**11b**)

(a) The foregoing hydroxymethylporphyrin (400 mg) in dry pyridine (16 ml) was added to a soln of CrO_3 (270 mg; 3·3 equiv) in dry pyridine (28 ml). The soln was stirred in darkness during 24 hr, being monitored by spectrophotometry with the change from aetio- to rhodo-type being distinct. The mixture was added to H_2O (500 ml) and extracted with $CHCl_3$ (3 × 100 ml). The organic extracts were combined, washed with H_2O (2 × 500 ml), dried (Na_2SO_4), and evaporated to dryness to give a residue which was chromatographed on alumina (grade V) (elution with CH_2Cl_2). The

formylporphyrin was eluted first and crystallised from CH_2Cl_2/*n*-hexane to give purple prisms (320 mg; 86% on consumed starting material), m.p. 245–7°. (Found: C, 73·9; H, 6·55; N, 10·4. $C_{33}H_{34}N_4O_3$ requires: C, 74·1; H, 6·4; N, 10·5%); τ (0·08 M), −1·06 (1H, s) CHO; 0·18 (1H, s), 0·73 (1H, s), 1·03 (2H, s) 4 *meso*-H; 2·16 (1H, m), 3·98 (2H, m) $CH{=}CH_2$; 6·13 (2H, t), 7·06 (2H, t), 6·64 (3H, s) $C\underline{H}_2CH_2CO_2Me$; 6·42, 6·79, 6·83, 6·94, (4 Me); 6·53 (2H, q), 8·48 (3H, t) $CH_2C\underline{H}_3$; λ_{max} 413 (ϵ 183,000), 519 (7200), 561 (20,000), 581 (13,100) and 637 nm (1400); in CH_2Cl_2 + 1% TFA, 416 (ϵ 260,100), 565 (10,900) and 617 nm (11,500), *m/e* 524 (100%), 461 (21).

Further elution of the column with CH_2Cl_2 containing 1% MeOH furnished, after evaporation and crystallisation from CH_2Cl_2/*n*-hexane, starting hydroxymethylporphyrin (25 mg).

(b) *From the acid chloride* (**10b**) *and lithium tri-(t-butoxy)aluminohydride.* Compound **13b**[5] (37 mg) was treated with oxalyl chloride (5 ml) for 2 hr at room temp before evaporation to dryness (final traces removed at 0·1 mm Hg). The residue was cooled to −78° in THF (2 ml) under N_2. Lithium tri-(*t*-butoxy)aluminohydride (13 mg; 1·1 equiv) in dry THF was added, dropwise with stirring, over a period of 5 min. The soln was stirred at −78° for 30 min, poured onto ice, and then extracted with $CHCl_3$ (30 ml). The organic phase was washed with water (100 ml), dried (Na_2SO_4) and evaporated to give a residue which was chromatographed (elution with CH_2Cl_2). A large amount of polar material was left on the top of the column, but evaporation of the red eluates and recrystallisation from CH_2Cl_2/*n*-hexane gave the formylporphyrin (7 mg; 15%), identical in all respects with the material prepared in (a) above.

(c) *From the acid chloride* (**10b**) *and sodium trimethoxyborohydride.* Compound **13b**[5] (50 mg) was treated with oxalyl chloride as described above. The dry acid chloride in THF (20 ml) was cooled, with stirring in an atmosphere of N_2, to −78° before treatment, dropwise over a period of 5 min with a soln of sodium trimethoxyborohydride (45 mg; 6 equiv) in dry THF (5 ml); stirring was continued at −78° for 40 min before quenching of the reaction by pouring onto ice. The mixture was extracted with chloroform which was washed with H_2O, dried (Na_2SO_4), and evaporated to dryness, giving a residue which was chromatographed (elution with CH_2Cl_2). Evaporation of the red eluates and crystallisation from CH_2Cl_2/*n*-hexane gave the formylporphyrin (18 mg; 36%), identical with the material described in (a) above.

2,4 - *Diethyl* - 6 - *hydroxymethyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**14a**)

2,4 - Diethyl - 6 - (imidazolyl - 1 - carbonyl) - 7 - (2 - methoxycarbonylethyl) - 1,3,5,8 - tetramethylporphin[8] (200 mg) in dry, ice cold $CHCl_3$ (50 ml) was added to an ice cold soln of $NaBH_4$ (1 g) in $CHCl_3$/MeOH (100 ml; 1:1). After stirring for 30 min at 0°, acetone (50 ml) was added and stirring was continued for a further 30 min. H_2O (500 ml) was added and the organic phase thoroughly washed, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on alumina (grade V) (elution with CH_2Cl_2); a small amount (15 mg; 8%) of a mobile band was recovered and identified as **9a** by absorption spectrum, TLC, m.p. and m.m.p. comparison with authentic material. Further elution with CH_2Cl_2 containing a small amount (<1%) of MeOH and evaporation of the eluates gave a residue which was crystallised from CH_2Cl_2/*n*-hexane to give the *hydroxymethylporphyrin* (140 mg; 84%) as tiny brown microneedles, m.p. 260–268° dec (lit.[31] 290°); τ, (0·025 M), 0·0 (3H, s), 0·12 (1H, s) 4 *meso*-H; 4·17 (2H, s) CH_2OH; 5·90m, 6·95t, 6·62s, $CH_2CH_2CO_2Me$; 5·50, 5·52, 5·56, 5·58 (4 Me); 6·10m, 8·22q (2 × CH_2CH_3), *m/e* 538 (100%), 522 (92), 507 (10) and 565 (18). λ_{max} 399 (ϵ 158,500), 448 (11,600), 533 (7900), 567 (5800) and 623 nm (3300); in CH_2Cl_2 + 1% TFA, 404 (ϵ 307,100), 549 (14,500) and 593 nm (5600).

2,4 - *Diethyl* - 6 - *formyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**11a**)

The foregoing hydroxymethylporphyrin (145 mg) in pyridine (10 ml) was added to a soln of CrO_3 (90 mg; 3·1 equiv) in pyridine (5 ml) and the soln was stirred at room temp for 36 hr. After dilution with CH_2Cl_2 and washing with H_2O (2 × 250 ml) the organic extract was dried (Na_2SO_4), evaporated to dryness (last traces of pyridine removed at 0·1 mm Hg), and the residue was chromatographed on alumina (grade V) (elution with CH_2Cl_2). The required porphyrin was eluted first, followed by a small amount (est. 2–3%) of unreacted starting material. Evaporation of the main eluates and crystallisation of the residue from CH_2Cl_2/*n*-hexane gave purple prisms (123 mg; 85%) of the formylporphyrin, m.p. 257–8° (lit.[10] 242°); τ (0·05 M), −1·24 (1H, s) CHO; −0·36 (1H, s), 0·40 (1H, s), 0·50 (2H, s) 4 *meso*-H; 5·95 (2H, t), 6·94 (2H, t), 6·62 (3H, s) $C\underline{H}_2CH_2CO_2Me$; 6·49 (6H, s), 6·73 (3H, s), 6·74 (3H, s) 4 Me; 6·30 (4H, m), 8·31 (6H, m), $2CH_2C\underline{H}_3$; λ_{max} 412 (ϵ 169,300), 515 (7700), 556 (15,600), 578 (9900) and 638 nm (1700); in CH_2Cl_2 + 1% TFA, 415 (ϵ 283,000), 560 (11,600) and 610 nm (9500), *m/e* 536 (100%), 521 (9), 477 (4), 463 (19), m* 400 (536 → 463), 506 (536 → 521).

2,4 - *Diethyl* - 6 - *formyl* - 7 - (2 - *carboxyethyl*) - 1,3,5,8 - *tetramethylporphin* (**6a**)

The foregoing formylporphyrin methyl ester (70 mg) in THF (20 ml) was treated with conc HCl (5 ml) and water (0·1 ml) at room temp during 24 hr before being diluted with CH_2Cl_2 (200 ml) and added to water (500 ml) containing pyridine (50 ml). The organic phase was washed, separated, and washed again with H_2O (500 ml). It was dried (Na_2SO_4) and evaporated to very small volume, leaving the porphyrin acid dissolved in a little pyridine. Approx. 3 volumes of MeOH were added and the porphyrin was filtered off and recrystallised from THF/*n*-heptane to give the required *porphyrin carboxylic acid* (55 mg; 80%) as purple prisms, which decomposed *ca.* 280–90°. (Found: C, 72·6; H, 6·6; N, 10·2. $C_{32}H_{34}N_4O_3 \cdot \frac{1}{2}H_2O$ requires: C, 72·3; H, 6·6; N, 10·5%); τ, in TFA, −1·68, −1·54, −1·06, −0·88, −0·81 (each 1H, s) 4 *meso*-H and CHO; 5·44 (2H, t), 6·60 (2H, t) $CH_2CH_2CO_2H$; 5·92 (3H, s), 6·31 (3H, s), 6·34 (6H, s) 4 Me; 5·82 (4H, q), 8·24 (6H, t) 2 × CH_2CH_3. λ_{max} (in pyridine) 415 (ϵ 168,900), 519 (7000), 562 (18,800), 583 (12,800) and 637 nm (1300); in CH_2Cl_2/TFA (4:1), 415 (ϵ 220,400), 555 (10,900) and 620 nm (11,700).

4 - *Ethyl* - 6 - *formyl* - 7 - (2 - *carboxyethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**6b**)

This compound was similarly prepared from the corresponding **11b**, and was obtained (85% on *ca.* 100 mg scale) from THF/*n*-heptane at 0° as purple prisms, m.p. >300°. (Found: C, 73·0; H, 6·5; N, 10·4. $C_{32}H_{32}N_4O_3 \cdot \frac{1}{2}H_2O$ requires: C, 72·6; H, 6·3; N, 10·6%); τ, (in TFA), −1·61, −1·48, −0·98, −0·86, −0·81 (each 1H, s) 4 *meso*-H and CHO; 1·84 (1H, m), 2·57 (2H, m) $CH{=}CH_2$; 5·46 (2H, t), 6·65 (2H, t) $CH_2CH_2CO_2H$; 5·94, 6·30, 6·32, 6·38, (4 Me); 5·83 (2H, q), 8·26 (3H, t) CH_2CH_3. λ_{max} (in pyridine), 416 (ϵ 124,100), 520 (6200), 562 (14,100), 583 (10,900) and 637 nm (2300); in CH_2Cl_2/TFA (4:1), 415 (ϵ 170,800), 567 (7800) and 620 nm (9400).

4 - *Ethyl* - 7 - (2 - *methoxycarbonylethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**15b**)

Compound **11b** (118 mg) in pyridine (8 ml) was heated under N_2 with methyl hydrogen malonate (1·2 ml) during 12 hr at 80° and then at 110° during a further 12 hr. The mixture was diluted with CH_2Cl_2 (250 ml), washed with sat $NaHCO_3$ aq, and then H_2O, dried (Na_2SO_4) and then evaporated to dryness. The residue was chromatographed (elution with CH_2Cl_2) and evaporation of the red eluates followed by crystallisation from CH_2Cl_2/MeOH gave the *porphyrin acrylic ester* (85 mg; 76%) as tiny purple plates, m.p. 250–1°. (Found: C, 73·3; H, 6·5; N, 9·6. $C_{36}H_{38}N_4O_4$ requires: C, 73·2; H, 6·5; N, 9·5%), τ, (in TFA), −1·02 (1H, s), −0·96 (1H, s), −0·92 (2H, s) 4 *meso*-H; 0·51 (1H, d, J = 16·5 Hz), 2·76 (1H, d), 5·87 (3H, s) $CH{=}CH{\cdot}CO_2Me$; 1·80 (1H, m), 3·55 (2H, m) $CH{=}CH_2$; 5·39 (2H, t), 6·81 (2H, t), 6·30 (3H, s) $CH_2CH_2CO_2Me$; 6·15 (3H, s), 6·26 (3H, s), 6·36 (6H, s) 4 Me; 5·82 (2H, q), 8·14 (3H, t) CH_2CH_3. λ_{max} 413 (ϵ 163,700), 513 (8100), 555 (19,500), 576 (12,600) and 642 nm (1500); in CH_2Cl_2 + 1% TFA, 414 (ϵ 261,800), 560 (13,500) and 610 nm (9700), *m/e* 590 (100%), 577 (21), 551 (24), 534 (21), 517 (31).

2,4 - *Diethyl* - 7 - (2 - *methoxycarbonylethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethylporphin* (**15a**)

This compound was similarly prepared from 2,4 - diethyl - 6 - formyl - 7 - (2 - methoxycarbonylethyl) - 1,3,5,8 - tetramethylpor-

phin (50 mg), and gave the porphyrin acrylic ester (40 mg; 77%) as purple prisms, m.p. 267–9° (lit.[18] 261°) from CH_2Cl_2/*n*-hexane. (Found: C, 72·65; H, 6·7; N, 9·5. Calc. for $C_{36}H_{40}N_4O_4$: C, 72·95; H, 6·8; N, 9·45%); τ, (in TFA), −1·12, −1·03, −0·93, −0·92 (4 *meso*-H); 0·48 (1H, d, J = 16·5 Hz), 2·72 (1H, d), 5·85 (3H, s) CH=CH·CO_2Me; 5·46 (2H, t), 6·80 (2H, t), 6·36 (3H, s) $CH_2CH_2CO_2$Me; 6·30 (9H, s), 6·12 (3H, s) 4 Me; 5·80 (4H, q), 8·21 (6H, t) CH_2CH_3. λ_{max} 413 (ϵ 150,900), 510 (10,100), 549 (15,800), 575 (9700) and 636 nm (2600); in CH_2Cl_2 + 1% TFA, 411 (ϵ 260,100), 556 (15,000) and 604 nm (8400), *m/e* 592 (100%), 580 (16), 577 (17), 519 (31).

4 - *Ethyl* - 7 - (2 - *carboxyethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**4b**)

4 - Ethyl - 6 - formyl - 7 - (2 - carboxyethyl) - 1,3,5,8 - tetramethyl - 2 - vinylporphin (30 mg) in pyridine (1·25 ml) was heated under nitrogen with methyl hydrogen malonate (0·3 ml) for 12 hr at 75–80° and then for a further 12 hr at 110°. The mixture was cooled to −5° and kept at this temp for 24 hr, after which the *porphyrin* was collected by filtration and washed with MeOH and ether. The porphyrin carboxylic acid was recrystallised from THF/*n*-heptane, giving purple prisms (19 mg; 60%), m.p. >300°. (Found: C, 71·8; H, 6·2; N, 9·7. $C_{35}H_{36}N_4O_4 \cdot \frac{1}{2}H_2O$ requires: C, 71·8; H, 6·4; N, 9·6%). τ, (in TFA), −1·18 (1H, s), −1·01 (3H, s) 4 *meso*-H; 0·46 (1H, d, J = 16·5 Hz), 2·70 (1H, d), 5·80 (3H, s) CH=CH·CO_2Me; 1·72 (1H, m), 3·42 (2H, m) CH=CH_2; 5·31 (2H, t), 6·67 (2H, t) $CH_2CH_2CO_2H$; 6·08, 6·18, 6·21, 6·28 (4 Me), 5·74 (2H, q), 8·15 (3H, t) CH_2CH_3. λ_{max} (in pyridine), 417 (ϵ 127,200), 515 (9000), 557 (17,000), 579 (12,100) and 646 nm (2000); in CH_2Cl_2/TFA (4:1), 415 (ϵ 245,000), 561 (12,700) and 612 nm (9600).

Treatment of the mother liquors from the crystallisation with excess ethereal diazomethane followed by chromatography on alumina (elution with CH_2Cl_2) afforded **15b** (9 mg; 30%), identical with the material described above.

2,4 - *Diethyl* - 7 - (2 - *carboxyethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethylporphin* (**4a**)

This compound was similarly prepared from 2,4 - diethyl - 7 - (2 - carboxyethyl) - 6 - formyl - 1,3,5,8 - tetramethylporphin (32 mg) and gave the acrylate porphyrin propionic acid (22 mg; 63%) as lustrous purple microprisms, m.p. 270–285°C (dec) from THF/*n*-heptane. τ, (in TFA), −1·16 (1H, s), −1·02 (1H, s), −0·92 (2H, s); 0·50 (1H, d, J = 16·5 Hz), 2·71 (1H, d), 5·85 (3H, s) CH=CH·CO_2Me; 6·13 (3H, s), 6·30 (9H, s) 4 Me; 5·35 (2H, t) 6·80 (2H, t) $CH_2CH_2CO_2H$; 5·80 (4H, q), 8·20 (6H, t) CH_2CH_3; λ_{max} (in pyridine) 416 (ϵ 153,100), 511 (8400), 551 (12,700), 579 (8400) and 640 nm (2400); in CH_2Cl_2/TFA (4:1), 409 (ϵ 249,100), 555 (11,400) and 603 nm (6100).

t-*Butoxycarbonylmethylenetriphenylphosphonium bromide*

t-Butyl bromoacetate (28·5 g) in dry benzene (100 ml) was stirred with triphenylphosphine (43 g; 1 equiv) in dry benzene (100 ml) under nitrogen during 18 h. The product was filtered off, washed with dry benzene, and then dried, yield, 65 g (97%), m.p. 177°.

t-*Butoxycarbonylmethylenetriphenylphosphorane* (**20**)

The foregoing phosphonium salt (5 g) in water (100 ml) and a few drops of phenolphthalein was stirred with benzene while 2M NaOH was added dropwise until the soln remained slightly pink in colour. The benzene layer, after separation, was washed with water, dried (Na_2SO_4) and evaporated to give an oil which solidified on scratching to give a pale yellow solid. After washing with ether, a colourless solid (2·2 g) was obtained and this was used without further purification.

t-*Butoxycarbonylmethyldiethylphosphonate* (**21**)

A mixture of freshly distilled triethylphosphite (4·98 g; 0·03 mole) and t-butyl bromoacetate (5·85 g; 0·03 mole) was heated under N_2 at 100° for 10 min and then at 140° for 3 hr. Distillation afforded the product, (5·5 g; 73%), b.p. 90–92° (0·15 mm Hg); τ, 5·84 (4H, doublet, J_{P-H} 9 Hz of quartets J 7 Hz) CH_2CH_3; 7·13 (2H, d, J 22 Hz) CH_2; 8·51 (9H, s) Bu^t; and 8·64 (6H, t) CH_2CH_3.

6 - trans - 2 - *t* - *Butoxycarbonylvinyl* - 2,4 - *diethyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin* (**16a**)

(a) *Using the phosphonium ylid.* To 2,4 - diethyl - 6 - formyl - 7 - (2 - methoxycarbonylethyl) - 1,3,5,8 - tetramethylporphin (100 mg; 0·00019 mole) in dry benzene (20 ml) and THF (few drops) **20** (140 mg; 0·00038 mole) was added in dry benzene (10 ml). The mixture was stirred for 24 hr, then poured into water and extracted with CH_2Cl_2 which was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on alumina (Brockmann Grade V; elution with methylene chloride). Evaporation of the mobile red eluates and recrystallisation of the residue from chloroform–methanol gave the *acrylic ester porphyrin* (70 mg; 60%), m.p. 242–244°. (Found: C, 72·4; H, 7·3; N, 8·8. $C_{39}H_{46}N_4O_4 \cdot \frac{1}{2}H_2O$ requires: C, 72·7; H, 7·3; N, 8·7%); τ, (in TFA)†, −1·02, −0·98, −0·86 (2H), 4-*meso*-H; 0·40 (1H, d, J 17 Hz) and 2·69 (1H, d, J 17 Hz) CH=CH·CO, 5·4–5·9 (8H, m) CH_2–Ar, 6·08 (3H, s) CO_2Me, 6·27 (12H, s) 4 Me, 8·18 (6H, t) CH_2CH_3 and 8·38 (s), Bu^t, λ_{max} 412 (ϵ 151,000), 509 (10,800), 548 (15,800), 574 (9400) and 633 nm (3000); in $CHCl_3$ + 5% TFA, λ_{max} 411 (ϵ 257,000), 555 (15,100) and 602 nm (9000), ν_{max} (KBr), 1740, 1695 and 1610 cm^{-1}, *m/e* (%), 634 (26), 577 (35) and 533 (100).

The NMR sample was evaporated to dryness and treated with excess ethereal diazomethane; after chromatography and crystallisation from methylene chloride–methanol, the product was shown, in the usual ways, to be identical with **15a** described above.

(b) *Using the phosphonate ester.* Sodium hydride (4·4 mg 60%, 0·00011 mole) was washed with pentane and then suspended in dry benzene under N_2. The mixture was cooled to 0° and **21** (27·7 mg, 0·00011 mole) added with further stirring at 0° for 10 min and then at 25° for 30 min. 2,4 - Diethyl - 6 - formyl - 7 - (2 - methoxycarbonylethyl) - 1,3,5,8 - tetramethylporphin (54 mg, 0·0001 mole) was added and the mixture was stirred at 40° during 16 hr before being poured into water, extracted with chloroform, washed with water and then dried (Na_2SO_4). After evaporation, the residue was chromatographed on alumina (Brockmann Grade V, elution with chloroform) and the red eluates were evaporated to dryness and the residue was crystallised from chloroform–heptane, giving 50 mg (78%) of the required product, identical in all respects with the material described in (a).

δ-[^{3}H]-*Methyl phaeophorbide*-a‡. $CH_3CO_2{}^3H$ (prepared from tritiated water (0·4 ml; *ca.* 2 Ci) and Ac_2O (2·0 g) by heating at 100° for 3 hr) was added to a soln of methyl phaeophorbide-*a* (1·0 g) in pure chloroform (4·0 ml) in an ampoule. The ampoule was flushed with N_2, sealed, and then immersed in an oil bath stabilised at 55° during 7·5 days. The ampoule was then opened, the contents flushed into a flask, and then evaporated to dryness, giving crude methyl phaeophorbide-*a* which was used directly in subsequent experiments.

δ-[^{3}H]-*Purpurin-7 trimethyl ester.* The foregoing crude product in pyridine (150 ml) and ether (250 ml) was cooled with a steady stream of air. KOH (20 g) in *n*-propanol (25 ml) was added and the bright green soln was stirred during 30 min before being extracted with water (5 × 100 ml), the ether layer being discarded. The aqueous extracts were combined and acidified with conc. H_2SO_4 (30 ml) and then extracted with CH_2Cl_2 (3 × 100 ml) which was dried (Na_2SO_4) and treated with excess ethereal diazomethane during 30 min. After evaporation the residue was chromatographed on alumina (Brockmann Grade IV, elution with methylene chloride). The crude purpurin-7 trimethyl ester obtained by evaporation was not purified further.

†The compound was only slightly soluble in most NMR solvents. In TFA with repeated scanning, diminution of the singlet *t*-butyl resonance (τ 8·38) was readily observed. The sample was worked up for the dimethyl ester (**15a**).

‡As mentioned in the text, tritiated porphyrin acrylic esters were prepared by tritiation of methyl phaeophorbide-*a* followed by degradation to 2-vinylrhodoporphyrin-XV using literature methods (cf. Ref. 13). All reactions were first optimised in the corresponding deuteriated series.[32] A gradual decrease in activity was noted as progress was made through the tritiated series and hence such labels in *meso* positions are suspect (see text).

δ-[^{3}H]-2-*Vinylrhodoporphyrin*-XV *dimethyl ester.* The foregoing crude purpurin-7 trimethyl ester in collidine (250 ml) was heated at 180–185° during 2·5 hr. After cooling, the collidine was removed *in vacuo* and the residue was chromatographed on alumina (Brockmann Grade III) eluting with methylene chloride. The porphyrin containing eluates were evaporated and the residue crystallised from CH_2Cl_2–MeOH, giving the required porphyrin (300 mg; 33% from methyl phaeophorbide-*a*), activity 59·3 Ci/mole.

δ - [^{3}H] - 4 - *Ethyl* - 6 - *formyl* - 7(2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin.* The foregoing 2-vinylrhodoporphyrin-XV dimethyl ester (145 mg) was "diluted" with inactive 2-vinylrhodoporphyrin-XV dimethyl ester (340 mg) (to give theoretical activity of 17·6 Ci/mole) and dissolved in pyridine (250 ml). KOH (20 g) in MeOH (200 ml) was added and the mixture was refluxed for 3 hr. After cooling, the soln was added to water (1 l.) and acidified with conc. H_2SO_4 (25 ml). The precipitated porphyrin dicarboxylic acid was filtered off on a bed of Celite and washed with MeOH before removal of the porphyrin by washing with 5% (v/v) H_2SO_4 in MeOH and storage in the dark for 12 hr. The soln was added to water and extracted with CH_2Cl_2 (3 × 100 ml). The organic extracts were washed with water (2 × 500 ml), dried (Na_2SO_4) and evaporated to dryness. This crude rhodoporphyrin-XV half-acid was dissolved in THF (100 ml) and added to a soln of N,N'-carbonyldi-imidazole (1 g) in CH_2Cl_2 (100 ml). The soln was refluxed during 1 hr and then evaporated to give the crude imidazolide, which was chromatographed on alumina (Grade V, elution with CH_2Cl_2). The eluates were evaporated and the residue was dissolved in chloroform (20 ml) and cooled to 0°. $NaBH_4$ (1 g) in chloroform (50 ml) and MeOH (50 ml) at 0° was added to the porphyrin soln and the mixture stirred at 0° for 1 hr. Acetone (50 ml) was added and stirring was continued for a further 30 min. The soln was washed with water (3 × 250 ml), dried (Na_2SO_4), and evaporated to dryness to give a residue which was chromatographed on alumina (Grade V, elution with CH_2Cl_2). Work-up of the eluates gave firstly 2-vinylrhodoporphyrin-XV dimethyl ester (11 mg) and then the required tritiated hydroxymethylporphyrin (331 mg, 73% from 2-vinylrhodoporphyrin-XV dimethyl ester), both identical with authentic samples.

The hydroxymethylporphyrin (311 mg) in pyridine (12 ml) was added to a solution of chromium trioxide (225 mg) in dry pyridine (22 ml) and the mixture was stirred at room temp during 18 hr. Methylene chloride (200 ml) was added and the soln was washed with water (2 × 500 ml), dried (Na_2SO_4), and evaporated, last traces of pyridine being removed at 0·1 mm Hg. The residue was chromatographed on alumina (Grade V, elution with CH_2Cl_2). The required formylporphyrin was first eluted, followed by unchanged hydroxymethylporphyrin. Evaporation of the respective eluates and recrystallisation of the residues from CH_2Cl_2–MeOH furnished the hydroxymethylporphyrin (29 mg) and the required formylporphyrin (253 mg; 89% based on material consumed; activity 13·2 Ci/mole).

δ - [^{3}H] - 4 - *Ethyl* - 7 - (2 - *carboxyethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin.* The foregoing formylporphyrin (98 mg) was hydrolysed in pure THF (30 ml) and water (0·2 ml) containing conc. HCl (5 ml). CH_2Cl_2 (100 ml) and pyridine (20 ml) were added and the soln was washed with water (2 × 250 ml). The organic extracts were dried (Na_2SO_4) and evaporated to give a residue which was recrystallised from THF–*n*-heptane, giving the required porphyrin acid (79 mg; 83%). The mother liquors were esterified with excess ethereal diazomethane and purified by chromatography, giving recovered starting formylporphyrin (14 mg; 9%).

The porphyrin acid (79 mg) in dry pyridine (4·1 ml) was added to methyl hydrogen malonate (0·5 ml) and the mixture heated at 70°, in an atmosphere of N_2 during 15 hr. The temp was then raised to 108° and heating continued during a further 6 hr. The soln was cooled to −5° and stored at this temp for 24 hr. The required crystalline acrylate porphyrin acid was filtered off, washed with MeOH and recrystallised from THF–*n*-heptane, (66 mg: 78%; activity 11·3 Ci/mole).

δ - [^{3}H] - 4 - *Ethyl* - 7 - (2 - *carboxyethyl*) - 6 - (trans - 2 - *methoxycarbonylvinyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin magnesium complex.* The foregoing acrylate porphyrin acid (11·5 mg) in dry pyridine (2 ml) was added to a solution of dry methoxymagnesium bromide (3·0 g) in dry pyridine (4 ml) and the mixture heated at 106° in an atmosphere of dry N_2, during 30 min. At the end of this time, spectrophotometry indicated complete metalation of the porphyrin. The soln was diluted with CH_2Cl_2 (10 ml) and washed with 5% aqueous citric acid (50 ml), then with water (2 × 50 ml), and the organic extracts were dried (Na_2SO_4), and evaporated *in vacuo.* The residue was 'chased out' several times with dry THF and then recrystallised from THF–*n*-heptane, giving the required Mg-complex (11 mg; 95%), activity 7·3 Ci/mole. The NMR spectrum of the Mg-complex, in trifluoroacetic acid, was identical with inactive acrylate porphyrin acid and hence further purification was not attempted.

Methoxymagnesium bromide. Mg turnings (750 mg), EtBr (15 ml) and dry ether (30 ml) were refluxed together under N_2 during 1 hr, after which the Mg was completely in soln. Excess solvent was removed by evaporation under a steady stream of dry N_2, and then at 0·1 mm Hg. Dry MeOH (30 ml) was added and after complete reaction (5 min) the excess MeOH was removed *in vacuo* and the MeOMgBr thoroughly dried at 0·1 mm Hg.

t-Butoxymagnesium bromide was prepared in an analogous manner, using dry t-BuOH in place of dry MeOH.

Protoporphyrin-IX *di-n-propyl ester*

(a) *From protoporphyrin*-IX *dimethyl ester after magnesiation with n-propoxy-magnesium bromide.* A soln of EtMgBr was prepared by refluxing a mixture of Mg (0·25 g), dry ether (15 ml), and dry EtBr (4 ml). After dissolution of the metal, the soln was evaporated at 60° under N_2. The residue was treated with cold, dry *n*-propanol (20 ml) and then heated to 70° before addition of protoporphyrin-IX dimethyl ester[33] (50 mg). Heating under N_2 was continued for 1 hr, by which time the visible spectrum of a portion indicated complete metallation. Ether (200 ml) was added to the cooled mixture, which was then washed with water (200 ml) then a soln containing ammonium acetate (10 g) and di-sodium phosphate (10 g) in water (200 ml), and finally with saturated brine (100 ml). The organic layer was evaporated *in vacuo*, and the residue dried at 0·1 mm Hg and then dissolved in CH_2Cl_2 (100 ml). Trifluoroacetic acid (5 ml) was added and the soln was washed with water (3 × 100 ml) and dried ($MgSO_4$). After evaporation, the residue was chromatographed on alumina (Grade III, elution with CH_2Cl_2) and the porphyrin recrystallised from CH_2Cl_2–*n*-hexane, giving purple plates (41 mg; 74%), m.p. 201–203°, of the required *di-n-propyl ester.* (Found: C, 74·2; H, 7·1; N. 8·8. $C_{40}H_{46}N_4O_4$ requires: C, 74·3; H, 7·2; N, 8·7%); *τ*, (0·06 M), 0·20, 0·25, 0·31, 0·40 (4-*meso*-H), 2·02 (m), 3·95 (m) $2CH{=}CH_2$; 5·80 (t), 6·86 (t), 6·00 (t), 8·48 (m), 9·23 (t) $2CH_2CH_2CO_2CH_2CH_2CH_3$; 6·59, 6·93 (9H) 4 Me. λ_{max} 405 (*ε* 193,000), 504 (15,300), 538 (11,300), 574 (6600) and 629 nm (4900); in CH_2Cl_2 + 5% TFA, λ_{max} 410 (*ε* 415,000), 553 (5500) and 598 nm (7800).

(b) *From acid catalysed transesterification.* Protoporphyrin-IX dimethyl ester[33] (40 mg) was stirred overnight with a mixture of dry *n*-propanol (20 ml) and conc. H_2SO_4 (1·0 ml). The resulting soln was added to ether (250 ml) and washed with water (2 × 250 ml) and saturated brine (250 ml). After drying (Na_2SO_4) and evaporation, the residue was chromatographed and recrystallised as in (a). The di-*n*-propyl ester (37 mg; 88%) was obtained as purple plates, m.p. 202–204°; no depression was observed upon admixture with the sample prepared in (a).

Reaction of 4 - *ethyl* - 6 - (*methoxycarbonylacetyl*) - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin with diazomethane* (*cf* Ref. 6)

The 2-vinyl-*β*-keto-ester[8] (50 mg) in CH_2Cl_2 (50 ml) at 0° was treated with ethereal diazomethane (40 ml prepared from 5 g of "Diazald") and then kept at 0–5° in the dark for 3 days. The soln was evaporated and the residue chromatographed (Grade III alumina, elution with CH_2Cl_2) to afford the *enol ether* from the major mobile band, recrystallised from CH_2Cl_2–*n*-hexane to give purple needles (32 mg; 61%), m.p. 197–199° (with softening at *ca.* 180°). (Found: C, 71·4; H, 6·5; N, 9·0. $C_{37}H_{46}N_4O_5$ requires: C, 71·6; H, 6·5; N, 9·0%); *τ*, (0·08M), −0·06, −0·03, 0·12, 0·23 (4 *meso*-H); 2·0 (m), 4·11 ($CH{=}CH_2$); 5·66 (t), 6·80 (t), 6·36

($CH_2CH_2CO_2CH_3$); 6·04, 6·13, 6·33, 6·54, 6·60 (6H) (4 Me and 2 OMe); 6·1 (q), 8·22 (t) (CH_2CH_3).

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

Compound **8b**[8] (47 mg) in CH_2Cl_2 (25 ml) was treated with an ice cold soln of $NaBH_4$ (0·65 g) in dry MeOH (25 ml). The soln was stirred at room temp for 5 min before addition of acetone (10 ml) followed by AcOH (2 ml). The mixture was diluted with $CHCl_3$ (50 ml) and washed with water (2 × 100 ml) before drying (Na_2SO_4) of the organic phase. Evaporation and chromatography of the residue on alumina (Grade V, elution with CH_2Cl_2) gave a small fore-run of **15b** and **9b**. The major, slower running band was evaporated and the residue crystallised from MeOH to give the *hydroxypropionate porphyrin* (30·5 mg; 65%) as purple needles, m.p. 239–241° (Found: C, 71·2; H, 6·6; N, 9·4. $C_{36}H_{40}N_4O_5$ requires: C, 71·0; H, 6·6; N, 9·2%); τ, (0·03M), −0·26, −0·02, 0·09, 0·15 (4 *meso*-H); 1·81(m), 3·82(m) ($CH{=}CH_2$); 3·36(m) (CHOH); 5·78 (t), 6·84 (t), 6·37 ($CH_2CH_2CO_2CH_3$); 6·06 (q), 8·22 (t) (CH_2CH_3); 6·44 (6H), 6·46, 6·51 and 6·58 (4 Me and OMe), λ_{max} 402 (ϵ 197,000), 502 (11,800), 540 (12,000), 569 (6600) and 626 nm (2100); in CH_2Cl_2 + 5% TFA λ_{max} 408 (ϵ 349,000), 553 (15,900) and 599 nm (6500), *m/e* (%), 608 (77), 590 (85), 634 (100) and 461 (35).

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

The foregoing hydroxypropionate porphyrin (18 mg) was stirred at 50–60° for 20 min with a mixture of pyridine (1·5 ml) and Ac_2O (0·5 ml) before dilution with MeOH (20 ml) and evaporation to dryness (finally at 0·1 mm Hg). Chromatography on alumina (Grade III, elution with CH_2Cl_2) gave a single porphyrin; evaporation of the eluates and crystallisation from CH_2Cl_2–*n*-hexane gave fine red needles, (16·5 mg; 86%), m.p. 211–212°. (Found: C, 70·3; H, 6·55; N, 8·8. $C_{38}H_{42}N_4O_6$ requires: C, 70·1: H, 6·5; N, 8·6%); τ, (0·03 M), −0·41, −0·10 (2H), −0·04 (4 *meso*-H); 1·90 (m), 3·90 (m) ($CH{=}CH_2$); 2·20 (t), 7·75, 6·0 (m), 6·26 [CH(OCOCH$_3$)$CH_2CO_2CH_3$]; 5·53 (t), 6·69 (t), 6·36 ($CH_2CH_2CO_2CH_3$); 6·0 (m), 8·16 (t) (CH_2CH_3); 6·36 (6H), 6·41, 6·44 (4 Me), λ_{max} 402 (ϵ 182,000), 503 (10,500), 540 (12,100), 570 (6400) and 627 nm (1600); in CH_2Cl_2 + 5% TFA, λ_{max} 408 (ϵ 351,000), 553 (14,500) and 602 nm (6700), *m/e* (%), 622 (100), 590 (75) and 579 (58).

Dehydration of **17b** *to give* **15b**. Compound **17b** (26 mg) was stirred at 50° for 15 min with dry pyridine (2·5 ml) and $POCl_3$ (0·4 ml). The mixture was added cautiously to MeOH (10 ml), diluted with $CHCl_3$ (50 ml) and then washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on alumina (Grade III, elution with CH_2Cl_2) and evaporation of the porphyrinic eluates followed by crystallisation from $CHCl_3$–MeOH gave the *trans*-acrylate (20 mg; 79%) as sparingly soluble needles, m.p. 254–255°, and this was fully identified with the material described above.

4 - *Ethyl* - 6 - (1 - *hydroxy* - 2 - *methoxycarbonylethyl*) - 7 - (3 - *hydroxypropyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**22**)

Compound **8b**[8] (95 mg) was dissolved in CH_2Cl_2 (80 ml) and a soln of $NaBH_4$ (0·8 g) in water (2·5 ml) and MeOH (75 ml) was added. The soln was stirred at room temp for 2 hr before treatment with acetone (5 ml) and then AcOH (1 ml). The soln was washed with water (2 × 500 ml) and the organic layer evaporated after addition of a little ethereal diazomethane. The residue was chromatographed on alumina (Grade V, elution with CH_2Cl_2 containing 2% of acetone). The first porphyrin eluted was the hydroxypropionate ester which was isolated and recrystallised from CH_2Cl_2–MeOH (13·5 mg; 14%). The major slow-running band contained the major product; evaporation and crystallisation from THF–*n*-heptane gave the *porphyrin diol* (39 mg; 43%) as small red-brown needles, m.p. 213–216°. (Found: C, 72·0; H, 7·0; N, 9·9. $C_{35}H_{40}N_4O_4$ requires: C, 72·4; H, 6·9; N, 9·65%); τ (0·03 M), 0·10, 0·13, 0·37, 0·51 (4 *meso*-H), 1·9 (m), 3·9 (m), ($CH{=}CH_2$); 3·9 (m) (CHOH); 6·1 (m), 7·06 (m), 6·1 (m) ($CH_2CH_2CH_2OH$); 6·1 (m), 8·29 (t) (CH_2CH_3); 6·56, 6·58, 6·60, 6·67, 6·86 (4 Me and OMe), λ_{max} 401 (ϵ 173,000), 501 (10,900), 538 (10,900), 570 (6400) and 625 nm (2300); in CH_2Cl_2 + 5% TFA, 407 (ϵ 369,000), 551 (15,000) and 598 nm (5900).

6 - (1 - *Acetoxy* - 2 - *methoxycarbonylethyl*) - 4 - *ethyl* - 7 - (3 - *acetoxypropyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**23**)

The foregoing porphyrin diol (25 mg) was heated at 60–70° with a mixture of pyridine (1·5 ml) and Ac_2O (0·5 ml). The mixture was evaporated at 0·1 mm Hg and the residue was chromatographed on alumina (Grade III, elution with CH_2Cl_2). A single porphyrin was obtained and recrystallisation from CH_2Cl_2–*n*-hexane gave the *diacetate* (22·5 mg; 74%) as small red prisms, m.p. 189·5–191°. (Found: C, 70·15; H, 6·6; N, 8·3. $C_{39}H_{44}N_4O_6$ requires: C, 70·5; H, 6·7; N, 8·4%); τ (0·04 M), −0·41, −0·10, −0·08, −0·03 (4 *meso*-H); 1·82 (m), 3·86 (m) ($CH{=}CH_2$); 2·56 (t), 7·75 ($CHOCOCH_3$); 5·57 (t), 6·72 (m), 5·64 (t), 7·99 ($CH_2CH_2CH_2OCOCH_3$); 6·32, 6·37, 6·38, 6·42, 6·47 (4 Me and OMe), λ_{max} 402 (ϵ 174,000), 502 (10,200), 539 (11,800), 570 (6600) and 626 nm (2000); in CH_2Cl_2 + 5% TFA, λ_{max} 408 (ϵ 339,000), 551 (13,800) and 598 nm (6600).

4 - *Ethyl* - 7 - (3 - *hydroxypropyl*) - 6 - *methoxycarbonyl* - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**24**)

Compound **9b**[13] (100 mg) in chloroform (100 ml) was treated with a soln of $NaBH_4$ (0·5 g) in cold MeOH (30 ml). After stirring for 3 hr more $NaBH_4$ (0·4 g) was added and a similar addition was made after a further 3 hr stirring. The mixture was stirred overnight, washed with water (3 × 200 ml) and the organic layer was evaporated to dryness. The residue was chromatographed on alumina (Grade V). Elution with CH_2Cl_2 afforded starting material (63 mg) from CH_2Cl_2–*n*-hexane. Further elution with $CHCl_3$ containing 1% MeOH gave a second porphyrin. Evaporation of the eluates and crystallisation of the residue from THF–*n*-heptane gave the *hydroxypropylporphyrin* (24 mg; 68%) as small purple plates, m.p. >300°. (Found: C, 74·0; H, 6·8; N, 10·5. $C_{33}H_{36}N_4O_3$ requires: C, 73·85; H, 6·8; N, 10·4%); τ in CF_3CO_2D, −1·70, −1·09, −0·96, −0·92 (4 *meso*-H); 1·8 (m), 3·5 (m) ($CH{=}CH_2$); 5·43 (6-CO_2Me); 5·94 (5-Me); 6·23, 6·27 (6H), 6·32 (1,3,8-Me and OMe); 5·7 (m), 8·20 (t) (CH_2CH_3); 5·7 (m), 6·65 (m) and 5·7 (m) ($CH_2CH_2CH_2OH$), λ_{max} 406 (ϵ 199,000), 514 (8200), 559 (17,900), 577 (9700) and 635 nm (900); in CH_2Cl_2 + 5% TFA, λ_{max} 412 (ϵ 289,000), 559 (11, 800) and 610 nm (9600), *m/e* 536 (100), 521 (10), 492 (11), 491 (1), 268 (7).

6 - *Acetyl* - 2,4 - *diethyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethylporphin*, "6 - *acetylpyrroporphyrin*-XV *methyl ester*" (**19a**)

Compound **13a**[5] (55 mg) was stirred at room temp for 1 hr with CH_2Cl_2 (3 ml) and oxalyl chloride (3 ml). The green soln was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2 (3 ml) and dry benzene (20 ml) which was evaporated to dryness. The residual **10a** was dissolved in CH_2Cl_2 (4·0 ml).

A soln of sodio t-butyl malonate was prepared by stirring under N_2 a mixture of di-t-butyl malonate (110 mg; 5 equiv) and sodium hydride (50% dispersion, 24 mg) at room temp for 5 min. To this was added the porphyrin acid chloride soln and the mixture was stirred for 15 min at room temp. The mixture was partitioned with $CHCl_3$ (50 ml) and 1% HCl aq (50 ml), the organic layer was washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed on alumina (Grade V), elution with CH_2Cl_2 affording a minor fore-run containing rhodoporphyrin-XV dimethyl ester (an impurity in the preparation of the 7-methyl ester 6-carboxylic acid). Elution with CH_2Cl_2–MeOH (20:1) gave an intense narrow band of β-keto-diester, leaving a little porphyrin acid on the column. The porphyrinic eluates were evaporated and the residue taken up in TFA (7·5 ml) and set aside for 30 min at room temp. The soln was evaporated to dryness and the residue was dissolved in CH_2Cl_2 and washed with water (2 × 100 ml). The organic layer was evaporated and the residue chromatographed on alumina (Grade III, elution with CH_2Cl_2) to afford a single band which was collected and evaporated to dryness. Crystallisation of the residue from $CHCl_3$–MeOH gave the acetylporphyrin (12 mg; 22%) as purple prisms, m.p. 274–276° (lit.[34] 278°); τ, (0·05M), −0·66, −0·9, 0·20, 0·23 (4 *meso*-H); 5·70 (t), 6·97 (t), 6·40 ($CH_2CH_2CO_2CH_3$); 6·1 (m),

8·25 (t) ($2CH_2CH_3$); 6·27, 6·49 (6H), 6·60 (4 Me); 6·78 ($COCH_3$), *m/e* (%), 550 (100), 477 (26).

6 - *Acetyl* - 4 - *ethyl* - 7 - (2 - *methoxycarbonylethyl*) - 1,3,5,8 - *tetramethyl* - 2 - *vinylporphin* (**19b**)

(a) *From the corresponding β-keto-ester.* Compound **8b** (70 mg) was refluxed under N_2 at 60–65° for 20 hr with pyridine (35 ml) and KOH (4 g) in MeOH (35 ml). AcOH (7 ml) was then added and heating continued for 15 min before dilution with $CHCl_3$ (100 ml) and washing with water (3 × 100 ml). The organic layer was dried ($MgSO_4$), treated with excess ethereal diazomethane, and evaporated to dryness. The residue was chromatographed on alumina (Grade III, elution with CH_2Cl_2) and the porphyrin containing eluates were concentrated and chromatographed on silica thick plates (1·5 mm). Two developments in CH_2Cl_2–acetone (100:1) gave two clear bands, from which the porphyrins were extracted using $CHCl_3$. After separate chromatography of each band on alumina (Grade V, elution with CH_2Cl_2) and crystallisation from CH_2Cl_2–MeOH, the porphyrin from the TLC band with higher R_f was 2-vinylrhodoporphyrin-XV dimethyl ester (20 mg; 27%), m.p. 269–271°, identified by comparison with an authentic sample. The porphyrin with lower R_f was the expected acetyl compound (12 mg; 16%) which formed purple plates, m.p. 259–261°.

(b) *From the corresponding carboxylic acid.* This preparation was conducted exactly as described above for the analogous **19a** using the following: 2-vinylrhodoporphyrin-7-methyl ester (75 mg), oxalyl chloride (5 ml), di-t-butyl malonate (200 mg) and sodium hydride dispersion (35 mg) in dry THF (8 ml). The keto-diester was isolated chromatographically (Grade V), and decomposed with TFA (10 ml). The acetylporphyrin was finally purified by chromatography on alumina (Grade III) and then recrystallised from CH_2Cl_2–MeOH, giving purple plates (24 mg; 31%), m.p. 260–262°, mixed m.p. with the sample from (a), 259–262°. (Found: C, 74·6; H, 6·7; N, 10·2. $C_{34}H_{36}N_4O_3$ requires: C, 74·4; H, 6·6; N, 10·2%); τ (0·03M), −0·62, 0·15, 0·28 (2H) (4 *meso*-H); 2·0 (m), 3·85 (m) ($CH{=}CH_2$); 5·68 (t), 6·96 (t), 6·35 ($CH_2CH_2CO_2Me$); 6·10 (q), 8·24 (t) (CH_2CH_3); 6·26, 6·53 (6H), 6·72 (4 Me); 6·72 ($COCH_3$), λ_{max} 409 (ε 176,000), 513 (7400), 554 (15,400), 578 (9100) and 632·5 nm (500); in CH_2Cl_2 + 5% TFA, λ_{max} 414 (ε 245,000), 561 (10,500) and 611 (9000).

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