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Synthetic and Biosynthetic Studies of Porphyrins

III. Structures of the Intermediates between Uroporphyrinogen-III and Coproporphyrinogen-III: Synthesis of Fourteen Heptacarboxylic, Hexacarboxylic, and Pentacarboxylic Porphyrins Related to Uroporphyrin-III

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Four heptacarboxylic, six hexacarboxylic, and four pentacarboxylic porphyrins related to uroporphyrin-III by decarboxylation of one, two, or three of the acetic acid side chains have been synthesised as their methyl esters by application of the MacDonald or *b*-oxobilane methods, as appropriate. Comparison (mixed mp, "mixed" nmr spectra, and hplc) of the synthetic materials with the methyl esters of hepta-, hexa-, and pentacarboxylic porphyrins isolated from natural sources showed that the structures of the latter corresponded to the D-ring methyl, the DA-dimethyl, and the DAB-trimethyl analogs of uroporphyrin-III. Because the naturally occurring porphyrins arise by oxidation of intermediate porphyrinogens, we conclude that the enzymic decarboxylation of uroporphyrinogen-III to coproporphyrinogen-III takes place in a preferred sequential clockwise fashion (both in normal and abnormal metabolism) starting with the acetic acid moiety on the D-ring and followed by those on the A, B, and C rings.

The nature of the key intermediates in the biosynthesis of haem and chlorophyll from aliphatic precursors was elucidated some 25 years ago (*1*) (Scheme 1). More recently evidence has been obtained that in plants δ-aminolevulinic acid (ALA) is synthesised from glutamate (*2*) in contrast to the mammalian pathway from glycine and succinate. Intensive studies of the formation of uroporphyrinogen-III from porphobilinogen (PBG) *via* di-, tri-, and tetrapyrrolic open chain intermediates have now led to the conclusion that the D-ring of uroporphyrinogen-III (**1a**) is reversed during the cyclisation of an unrearranged tetrapoyrrole with alternating acetic and propionic side chains formed by head-to-tail condensation of four PBG units. (*3, 4*). It has also become clear that uroporphyrinogen-III is the point at which the vitamin B_{12} pathway branches from the porphyrin pathway (*3c, 4, 5*).

Our own earlier work has been concerned with the development of new methods for synthesising porphyrins required for biosynthetic studies, and the first two papers in this series were concerned with porphyrins related to coproporphyrinogen-III (**16a**) and protoporphyrin-IX (**17**) in the later stages of haem biosynthesis (*6, 7*). The present paper is, however, specifically concerned with the nature of the intermediates (*8*) produced in the enzymic decarboxylation of uroporphyrinogen-III (**1a**) to coproporphyrinogen-III (**16a**).

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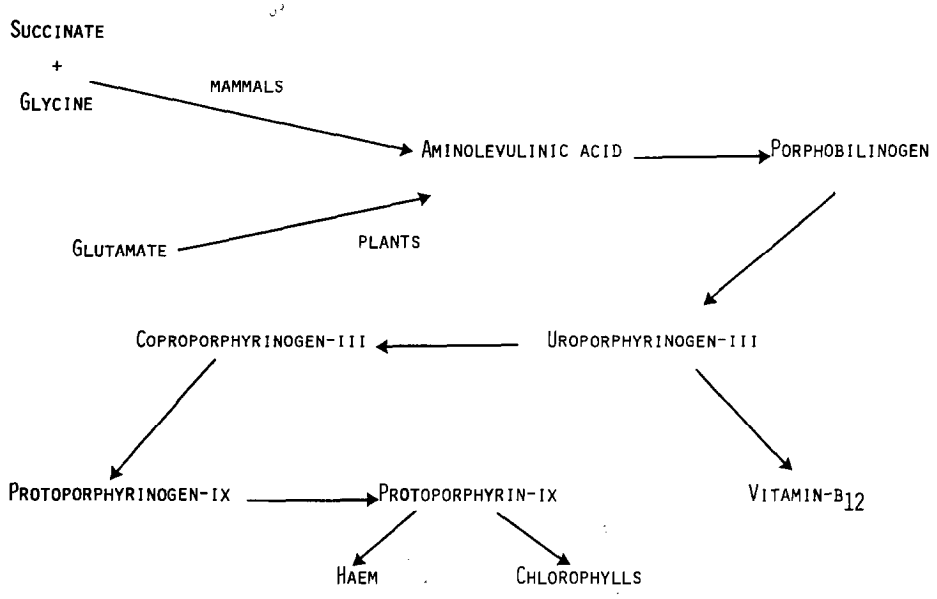


SCHEME 1. Outline of tetrapyrrole biosynthesis from aliphatic precursors. (The structures of the intermediate porphyrinogens are shown in Table 1.)

In normal metabolism, whether in mammals or in plants, only small amounts of free porphyrins can be detected; and it is clear that haem and chlorophyll syntheses occur very rapidly without accumulation of significant amounts of intermediates (*9*). There are a few exceptions to this general rule, notably the occurrence of *turacin* (copper uroporphyrin-III) as the red colouring material of turaco feathers, and of "ooporphyrin" (protoporphyrin-IX) as the colouring material of brown egg shells. More important, from the present point of view, in various genetic or acquired disorders of haem metabolism (*porphyrias*) (*10*) relatively large amounts of free porphyrins may be excreted in the urine, or faeces; circulation of free porphyrins in the bloodstream may also lead to photosensitivity, and hence to skin lesions. In man, for example, the total porphyrin excretion rate is of the order of 50–100 μg/day or less; whereas porphyric patients may excrete several milligrams per day, and the urine is coloured red.

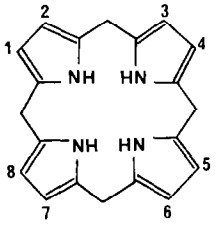
Small amounts of metal-free porphyrins with two to eight carboxylic side chains are also formed in *in vitro* biosynthetic experiments in which ALA or PBG is incubated with tissue systems such as liver homogenates, red cell haemolysates, photosynthetic bacteria, and plant material (*10–15*).These by-products consist mainly of uroporphyrin-III (**1b**), a heptacarboxylic porphyrin, phyriaporphyrin (*11*) (previously known as "pseudouroporphyrin" (*14*) or "porphyrin-208") (*15a*), coproporphyrin-III (**16b**), and protoporphyrin-IX (**17**); traces of hexa-, penta-, and tricarboxylic porphyrins can also be detected, as well as the presence of "type-I" porphyrins with four to eight carboxyl groups. These results led to the suggestion that the biosynthesis of protoporphyrin-IX (**17**) involves a stepwise decarboxylation (*11*) of uroporphyrinogen-III (**1a**). In the first four steps the

enzyme uroporphyrinogen decarboxylase catalyses the decarboxylation of the four acetic acid side chains, and the next two steps involve the successive oxidative decarboxylation of the two propionic acid side chains on rings A and B by coproporphyrinogen oxidative decarboxylase.

In theory there are 24 (factorial 4) possible pathways between uroporphyrinogen-III (**1a**) and coproporphyrinogen-III (**16a**), depending upon the order in which the four acetic acid side chains are decarboxylated (see Table 1). Our specific interest was to discover whether the natural process involved a random sequence

TABLE 1

STRUCTURES OF PORPHYRINOGENS AND PORPHYRINS[a]



Name	Structure number	1	2	3	4	5	6	7	8
Uroporphyrinogen-III	1	A[b]	P	A	P	A	P	P	A
Heptacarboxylic porphyrinogens	2	Me	P	A	P	A	P	P	A
	3	A	P	Me	P	A	P	P	A
	4	A	P	A	P	Me	P	P	A
	5	A	P	A	P	A	P	P	Me
Hexacarboxylic porphyrinogens	6	Me	P	Me	P	A	P	P	A
	7	A	P	Me	P	Me	P	P	A
	8	A	P	A	P	Me	P	P	Me
	9	Me	P	A	P	A	P	P	Me
	10	Me	P	A	P	Me	P	P	A
	11	A	P	Me	P	A	P	P	Me
Pentacarboxylic porphyrinogens	12	Me	P	Me	P	Me	P	P	A
	13	A	P	Me	P	Me	P	P	Me
	14	Me	P	A	P	Me	P	P	Me
	15	Me	P	Me	P	A	P	P	Me
Coproporphyrinogen-III	16	Me	P	Me	P	Me	P	P	Me
Protoporphyrinogen-IX	17	Me	V	Me	V	Me	P	P	Me
Dehydroisocopro-porphyrinogen	(54)	Me	V	Me	P	A	P	P	Me
Uroporphyrinogen-I	(55)	A	P	A	P	A	P	A	P
Coproporphyrinogen-I	(56)	Me	P	Me	P	Me	P	Me	P

[a] The porphyrinogens are indicated in the text by the suffix **a** after the number. The corresponding porphyrin permethyl esters are indicated by the suffix **b** after the number.

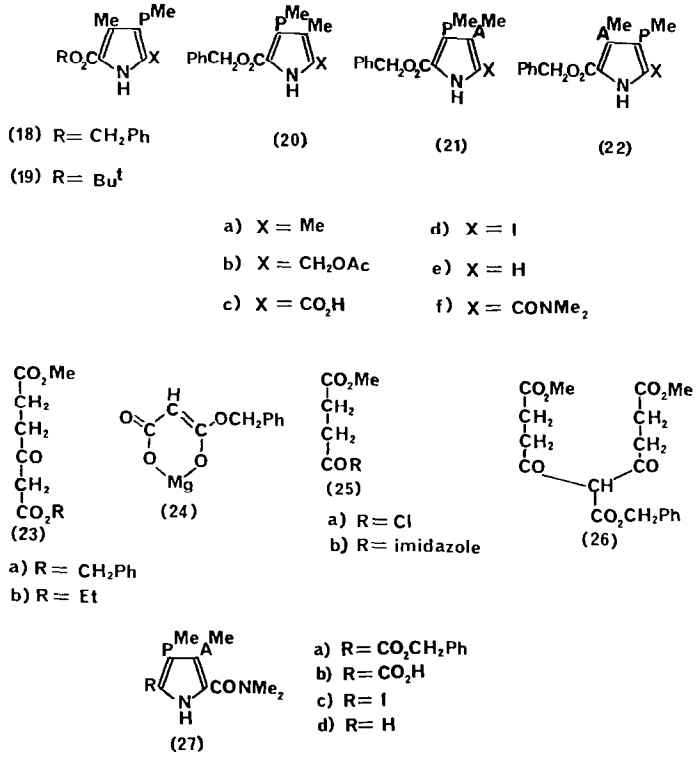
[b] A, CH_2CO_2H; P, $CH_2CH_2CO_2H$; V, $CH = CH_2$.

of decarboxylations or whether there was a preferred (or even specific) pathway. For this purpose we needed to isolate the naturally occurring hepta-, hexa-, and pentacarboxylic porphyrins and to compare them directly with materials synthesised by rational methods. In that it was known that the unnatural type-II and -IV uroporphyrinogens are also metabolised (*16*) as well as the type-I and -III isomers, it seemed likely that all of the isomeric type-III intermediate porphyrinogens would also be substrates for uroporphyrinogen decarboxylase (even if the natural process involved a specific pathway). We decided to synthesise all 14 related porphyrins (as described below) so that we could not only compare them with the natural materials, but also carry out kinetic and biosynthetic experiments with the corresponding porphyrinogens.

The amounts of intermediate porphyrins excreted in normal metabolism, or obtainable from *in vitro* biosynthetic experiments, are relatively small. However, while porphyrias are relatively rare diseases (*10*) and many of the abnormalities are genetic in origin (owing to a disturbance of one, or other, of the enzymes of the porphyrin pathway), porphyrias may also be induced, or potentiated, by chemical agents (e.g., chlorinated hydrocarbons, steroids, barbiturates, and other drugs). The biochemical analogies between hexachlorobenzene-induced porphyria and symptomatic cutaneous hepatic porphyria have been known for many years (*17*). Both are hepatic porphyrias characterised by different degrees of uroporphyrinogen decarboxylase deficiency in which relatively large amounts of porphyrins with 8-, 7-, 6-, 5-, and 4-carboxylic acid side chains are produced, the relative amounts of each porphyrin produced may vary with the severity of the disease, or the length and degree of poisoning (*18, 19*). Hexachlorobenzene-poisoned rats thus provided a convenient model system for our studies, and the octa-, hepta-, hexa-, penta-, and tetracarboxylic porphyrins excreted in the faeces were isolated as their methyl esters and separated by preparative high pressure liquid chromatography (*20*). The composition of the individual fractions, as well as the crude mixture, was confirmed by use of field desorption mass spectrometry (*20*). Porphyrins usually give only molecular ions using this technique (unless very labile side chains are present); and it is particularly convenient for analysis of column fractions, because the emitter wire can be dipped directly into the eluate. From about 100 mg of crude porphyrin mixture some 10–15 mg of each of the octa-, hepta-, hexa-, and pentacarboxylic porphyrin esters was obtained. They were all shown to be of the "type-III" series, because hot acidic decarboxylation in a sealed tube afforded coproporphyrin-III (**16b**), shown chromatographically to contain very little of the type-I isomer, in accord with earlier results obtained by other workers. The structures of the hepta-, hexa-, and pentacarboxylic esters were then determined by spectroscopic methods (cf. Ref. (*8*)) and by comparisons with the synthetic porphyrins prepared as described below.

SYNTHETIC STRATEGY

All of the 14 possible type-III hepta-, hexa-, and pentacarboxylic porphyrins were synthesised from dipyrrylmethane intermediates, either by the MacDonald or *b*-oxobilane routes (*21–23*). The MacDonald route (from diformyl pyrrome-



SCHEME 2. Pyrroles and other intermediates required for construction of the dipyrrylmethanes used in the various porphyrin syntheses.

thanes and pyrromethane dicarboxylic acids)[2] was utilised wherever possible, but one of the pyrromethanes must be symmetrical to avoid the formation of isomeric mixtures. The five pyrroles (**18a–22a**) required for these syntheses (Scheme 2) were prepared by modifications of well-established methods as indicated under Experimental. Attempts to prepare methyl benzyl ketoadipate (**23a**) (needed for the synthesis of pyrrole (**22a**)) by direct acylation of the magnesium complex (**24**) of the monobenzyl ester of malonic acid with the monomethyl ester monoacid chloride (**25a**) derived from succinic acid unfortunately led to the formation of considerable amounts of the diacyl product (**26**); when the imidazolide (**25b**) was used instead of the acid chloride, the monoacyl derivative (**23a**) was formed but in rather low yield (*26, 27*). We, therefore, reverted to the use of the more conventional procedure in which the acid chloride (**25a**) was condensed with the magnesium derivative of diethyl malonate; the product was hydrolysed to the methylethyl β-keto adipic ester (**23b**) and then selectively transesterified to the desired benzyl methylester (**23a**) by heating with benzyl alcohol in the absence of a catalyst (*28–30*).

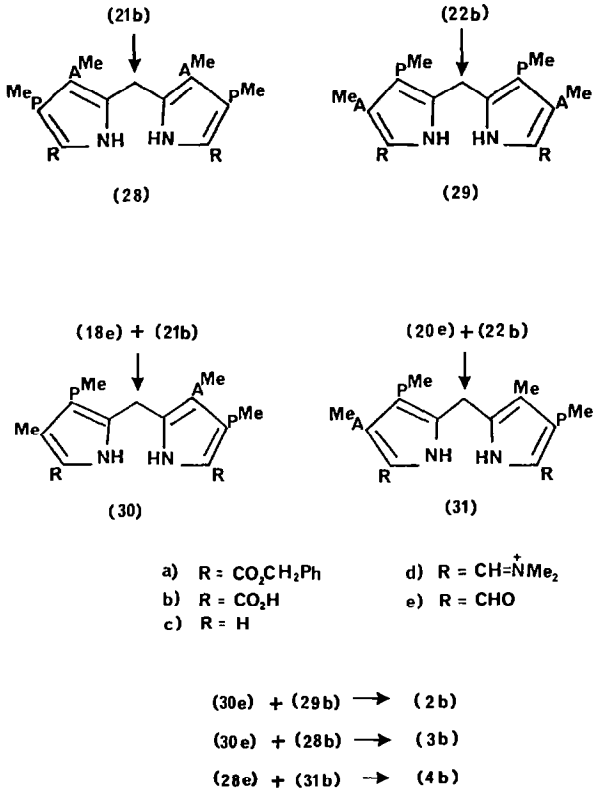
All of the pyrromethane syntheses were carried out by coupling appropriate α-acetoxymethyl pyrroles (**18b–22b**) with α-free pyrroles (**18e–21e**) under mildly

[2] In the original method the di-free pyrromethanes were utilised (*24*), but as we showed some years ago the corresponding dicarboxylic acids may serve equally well (*25*).

acidic conditions, the former being derived from the parent α-methyl pyrroles (**18a–21a**) by treatment with one equivalent of lead tetraacetate. The α-free pyrroles, however, were prepared by trichlorination of the α-methyl pyrroles (**18b–21b**) followed by mild alkaline hydrolysis to the corresponding α-carboxylic acids (**18c–21c**); the latter were iodinatively decarboxylated in presence of bicarbonate, and hydrogenolysis of the intermediate iodopyrroles (**18d–21d**) then afforded the desired α-free pyrroles (**18e–21e**). The pyrrole amide (**27d**) utilised as an intermediate in all the *b*-oxobilane syntheses was prepared from the pyrrole carboxylic acid (**21c**) *via* the corresponding acid chloride and dimethylamide (**27a**). The latter was hydrogenolysed over palladium chloride to the corresponding carboxylic acid (**27b**), which was then iodinatively decarboxylated. Hydrogenolysis of the resulting iodo amide (**27c**) then gave the required pyrrole amide (**27d**) (Scheme 2).

HEPTACARBOXYLIC PORPHYRINS

The heptacarboxylic porphyrin esters (**2b**), (**3b**), and (**4b**) with methyl groups on rings A, B and C, respectively, were all synthesised, by adaptation of the MacDonald method, from appropriate diformyl pyrromethanes and pyrromethane dicarboxylic acids (Scheme 3). The two symmetrical pyrromethanes dibenzyl



SCHEME 3. Syntheses of three type-III heptacarboxylic porphyrins (**2b**), (**3b**), and (**4b**) by the MacDonald route.

esters (**28a**) and (**29a**) were synthesised by self-condensation of the acetoxymethyl pyrroles (**21b**) and (**22b**), respectively, in methanolic hydrochloric acid. (*31*). Both pyrromethanes were obtained in good yield and compared well with those obtained by slightly different procedures.

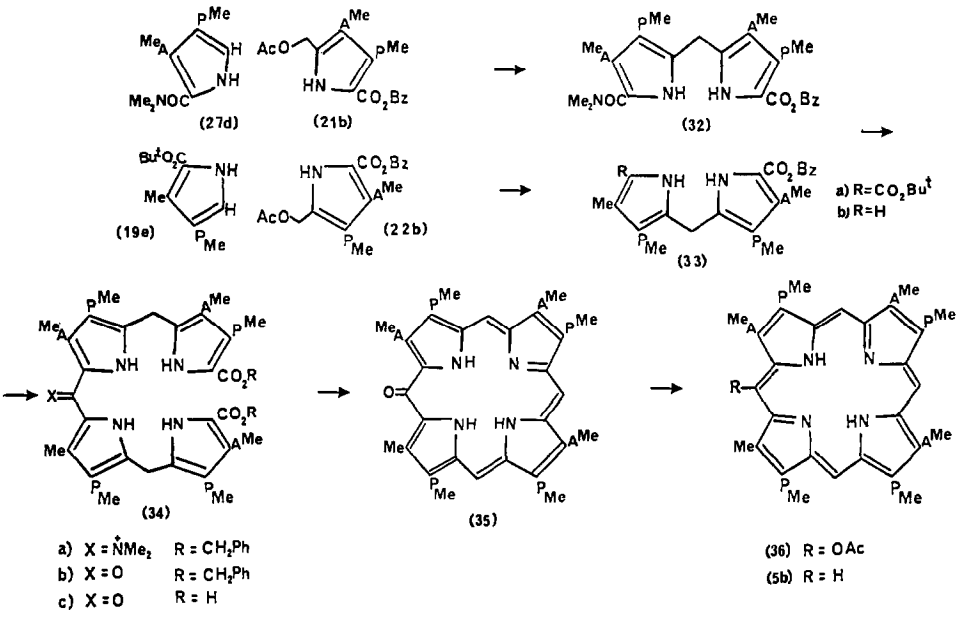
The unsymmetrical pyrromethane dibenzyl ester (**30a**) required for the synthesis of both the A- and B-ring methylheptacarboxylic porphyrins was synthesised by condensation of the acetoxymethyl pyrrole (**21b**) with the α-free pyrrole (**18e**) in methanol containing toluenesulphonic acid (*32*). The product crystallised in good yield directly from the reaction mixture and was hydrogenolysed over palladium–charcoal to the corresponding dicarboxylic acid (**30b**). The latter was then converted into the diformyl pyrromethane (**30e**) by treatment with trimethylorthoformate and trifluoroacetic acid (*33*).

Condensation of the symmetrical pyrromethane dicarboxylic acid (**29b**) (obtained by hydrogenolysis of the corresponding dibenzyl ester (**29a**)) with the unsymmetrical diformyl pyrromethane (**30e**) in methanol and dichloromethane containing a catalytic amount of *p*-toluenesulphonic acid then gave the A-ring methyl porphyrin heptamethyl ester (**2b**) in good yield after addition of zinc acetate and aeration (*34*). A similar condensation of the unsymmetrical diformyl pyrromethane (**30e**) with the symmetrical pyrromethane dicarboxylic acid (**28b**) (isomeric with (**29b**)) gave the B-ring methyl porphyrin heptamethyl ester (**3b**) also in good yield.

In the case of the A-ring isomer (**2b**) it would also have been possible to carry out the MacDonald synthesis with the diformyl pyrromethane (**29e**) corresponding to rings CD of the porphyrin; however this was not such a convenient procedure owing to the difficulty of decarboxylating the intermediate dicarboxylic acid (**29b**) which resulted in lower overall yields of the diformyl pyrromethane (**29e**). Similarly, an alternative method could have been used for the synthesis of the B-ring methylheptacarboxylic porphyrin (**3b**) viz. from pyrromethanes corresponding to rings AB and CD. However, the symmetrical pyrromethane (**29a**) is not as accessible as its isomer (**28a**) owing to the lengthy synthesis required for the precursor pyrrole (**22a**) compared with the isomer (**21a**).

The C-ring methyl porphyrin heptacarboxylic ester (**4b**) was synthesised in a similar manner to the A and B ring methyl isomers (**2b**) and (**3b**) from the symmetrical diformyl pyrromethane (**28e**) and the unsymmetrical pyrromethane diacid (**31b**). The latter was prepared by *p*-toluenesulphonic acid-catalysed condensation of the acetoxymethyl pyrrole (**22b**) and the α-free pyrrole (**20e**). The conversion of the pyrromethane dicarboxylic acid (**28b**) to the diformyl derivative (**28e**) proved unexpectedly difficult, in contrast to analogous reactions carried out in these laboratories (*6, 7*); eventually it was found that decarboxylation of the diacid (**28b**) could only be achieved by heating in refluxing dimethylformamide. After cooling, the resulting di-α-free pyrromethane (**28c**) was then formylated by addition of benzoyl chloride, followed by hydrolysis of the intermediate imine salt (*36*) (**28d**). Similar difficulties have also been reported by the Cambridge group (*37*), who found that decarboxylation was more rapid in boiling diethyl formamide, or by heating to 180°C with dimethylformamide in a Carius tube.

The ring-D methylheptacarboxylic porphyrin (**5b**) could not be synthesised by the MacDonald route owing to the lack of any element of symmetry, and the *b*-



SCHEME 4. Synthesis of the ring-D methylheptacarboxylic porphyrin (**5b**) by the *b*-oxobilane route.

oxobilane route was selected instead (Scheme 4). Based on experience with related syntheses in Cardiff (*6*, *7*), and earlier in Liverpool (*23*), we decided to synthesise the two pyrromethanes (**32**) and (**33a**) as precursors of the *b*-oxobilane (**34b**). Of the eight possible ways of synthesising the porphyrin via a *b*-oxobilane, this particular strategy was chosen so that the oxo-linkage was formed by electrophilic substitution α- to the peripheral methyl group (on the putative D-ring of the final porphyrin); substitution α- to a peripheral acetic or propionic ester side chain is less favourable for steric reasons (and possibly also for electronic reasons in the case of the acetic ester side chain).

The pyrromethane amide (**32**) corresponding to the AB rings of the final porphyrin was synthesised from the α-free pyrrole amide (**27d**) and the acetoxymethyl pyrrole (**21b**), while the pyrromethane t-butyl ester (**33a**) was prepared in a similar manner from the α-free pyrrole t-butyl ester (**19e**) and the isomeric acetoxymethyl pyrrole (**22b**). Brief treatment of the pyrromethane t-butyl ester (**33a**) with cold trifluoroacetic acid gave the corresponding α-free pyrromethane (**33b**), which was coupled in dichloromethane with the phosphorylchloride complex of the pyrromethane amide (**32**). After chromatographic purification the resulting imine salt (**34a**) was hydrolysed to the *b*-oxobilane dibenzyl ester (**34b**). Hydrogenolysis of the benzyl esters afforded the dicarboxylic acid (**34c**), which underwent trichloroacetic acid-catalysed decarboxylation and cyclisation with trimethyl orthoformate in dichloromethane, followed by aerial oxidation to give the oxophlorin (**35**). Acetylation with acetic anhydride in pyridine then afforded the corresponding acetoxyporphyrin (**36**), hydrogenation of which followed by reoxidation gave the desired ring D methylheptacarboxylic porphyrin-heptamethyl ester (**5b**) in moderate overall yield.

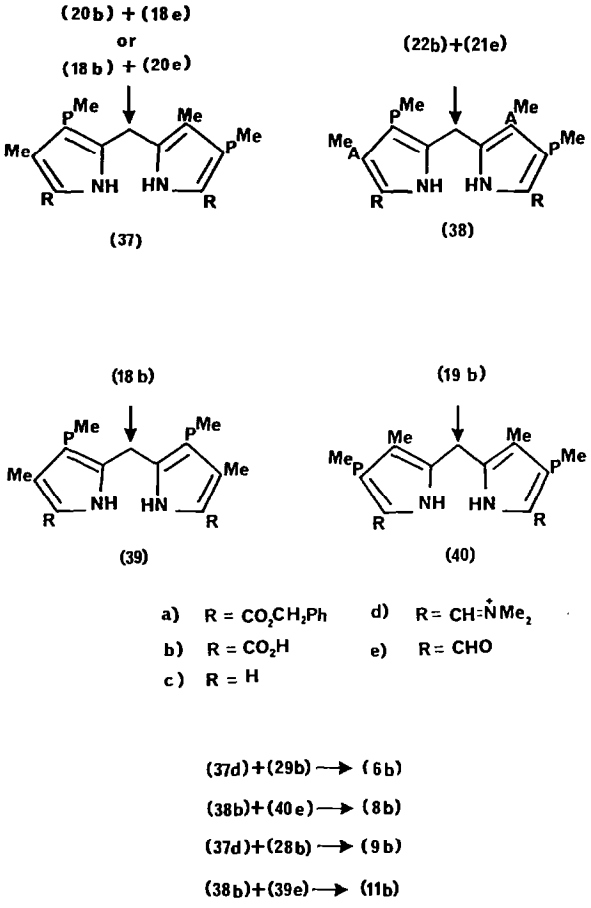
Mixed mp determinations of the naturally derived ester with all four heptacarboxylic porphyrin esters suggested that the natural product was the ring D methyl isomer (**5b**), but the results were not completely unequivocal. Careful comparisons of the nmr spectra of the synthetic and natural compounds, especially the precise pattern of the *meso*-proton resonances, also led to the same conclusion; but the picture was complicated by small differences in the overall appearance of the spectra of the synthetic D-ring methyl isomer (**5b**) and the natural product, presumably due to concentration effects. Final confirmation of the structure of the natural product was obtained by mixing equal amounts of the synthetic and natural materials and carrying out titrations with the shift reagent, Eu (fod-d_9)$_3$, and measuring the nmr spectrum after each addition (*38*). The 'mixed nmr' spectrum has been recorded elsewhere (*8*) and showed that only 1 compound was present, whereas in corresponding titrations with mixtures of isomeric compounds up to 8 *meso*-proton resonances and 16 methyl resonances were observed (rather than 4 and 8, respectively).

In a parallel series of investigations the Cambridge group (*37*) showed that a heptacarboxylic porphyrin isolated from incubations of PBG with chicken red cell haemolysates also has the same structure as the porphyrin which we isolated from the faeces of poisoned rats. They synthesised three of the four isomers by the MacDonald route in a manner somewhat similar to our syntheses, but the D-ring methyl isomer was prepared by the biladiene route. Clezy's group (*39*) in Australia has also independently synthesised these four heptacarboxylic porphyrins, three of them by the MacDonald route; but interestingly the D-ring methyl isomer (**5b**) was synthesised by the *b*-oxobilane route. However, the oxo-linkage in the Australian synthesis was at the position corresponding to the γ-*meso*-position in the porphyrin rather than the δ-position as in our synthesis. The properties of the synthetic compounds prepared in Australia, Cambridge, and Cardiff were all reasonably in accord with each other.

HEXACARBOXYLIC PORPHYRINS

Similar approaches were adopted towards these porphyrins as with the heptacarboxylic analogs described above, the availability of pyrrolic and dipyrrolic intermediates as well as the degree of symmetry of the required porphyrins dictating the precise routes. The unsymmetrical pyrromethane dibenzyl ester (**37a**) was prepared either from the acetoxymethyl pyrrole (**20b**) and the α-free pyrrole (**18e**), or from the isomeric pyrroles (**18b**) and (**20e**), respectively. Conversion to the diformyl pyrromethane (**37e**) was readily achieved by hydrogenolysis of the benzyl groups followed by trifluoroacetic acid-catalysed decarboxylation, and formylation with trimethylorthoformate. This diformyl pyrromethane (**37e**) was then utilised in a MacDonald-type synthesis of the two dimethyl porphyrin hexacarboxylic esters (**6b**) and (**9b**) by acid-catalysed condensation with the symmetrical pyrromethane dicarboxylic acids (**29b**) and (**28b**), respectively (Scheme 5).

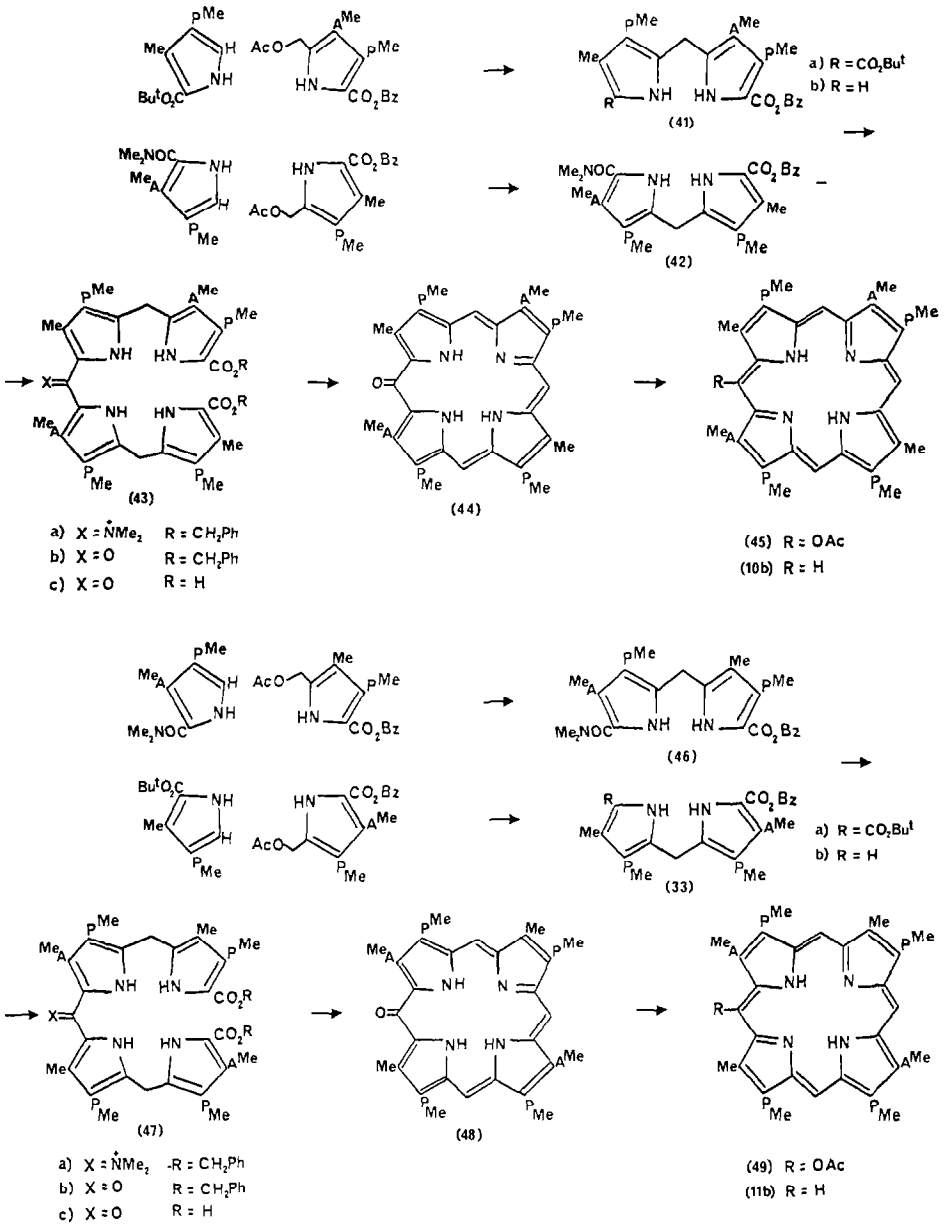
The unsymmetrical pyrromethane (**38a**) bearing two acetic and two propionic



SCHEME 5. Syntheses of four type-III hexacarboxylic porphyrins (**6b**), (**7b**), (**8b**), and (**9b**) by the MacDonald route.

ester side chains was synthesised from the acetoxymethyl pyrrole (**22b**) and the α-free pyrrole (**21e**), and condensed with the diformyl pyrromethane (**39e**) to give the hexacarboxylic porphyrin (**11b**) with methyl groups on rings C and D; the diformyl pyrromethane (**39e**) was prepared from the corresponding dicarboxylic acid (**39b**) both by the trimethylorthoformate, and the phosphorylchloride–dimethylformamide methods. The isomeric diformyl pyrromethane (**40e**) was also synthesised from the dibenzyl ester (**40a**) by hydrolysis of the diacid (**40b**) followed by decarboxylation and formylation in a similar manner. Condensation of this diformyl pyrromethane (**40e**) with the same unsymmetrical pyrromethane dicarboxylic acid (**38b**) as used above, then gave the hexacarboxylic porphyrin ester (**8b**) with methyl groups on rings A and D (Scheme 5).

The other two hexacarboxylic porphyrins (**7b**) and (**10b**) were synthesised by application of the *b*-oxobilane method, as shown in Schemes 6 and 7; the precise routes were selected on the same principles as outlined above, and it will be noted that the same readily accessible pyrrole amide (**27d**) was utilised in each of these



SCHEMES 6, 7. Syntheses of two type-III hexacarboxylic porphyrins (**10b**) and (**11b**) by the *b*-oxobilane route.

syntheses as in the ring D heptacarboxylic porphyrin (**5b**) preparation (Scheme 4). The yields of each of the required pyrromethanes were generally good, although (**41a**) was low melting and only crystallised very slowly; the pyrromethane (**33a**) required as precursor for the CD rings was the same as that used for the synthesis of the D-ring methyl heptacarboxylic porphyrin (**5b**). The overall yield of the

hexacarboxylic porphyrin (**7b**) with methyl groups on rings A and C was good, but the synthesis of (**10b**) was less satisfactory largely owing to a slower reaction and a poor yield (26% at best) at the oxobilane stage; attempts to improve this by using 1,2-dichloroethane as solvent and using a higher reaction temperature were not successful.

As outlined in our preliminary report (*8*) of this work the nmr spectral behaviour of the naturally derived hexacarboxylic porphyrin hexamethylester (**8b**) uniquely distinguished it from the other five isomers. For example, three of the *meso*-proton resonances moved rapidly downfield (*40*) on titration with the shift reagent Eu(fod-d_9)$_3$, whereas only two of the four *meso*-proton resonances are affected in the same way in each of the other isomers. These results are in accord with our earlier studies (*38*) of the four coproporphyrin tetramethyl esters and isocoproporphyrin tetramethyl ester, which showed that the shift reagent is chelated by pairs of neighbouring ester side chains thus causing a marked downfield shift of the resonance of the *meso*-proton between the two groups. Mixed mp determinations with the synthetic materials confirmed the structure (**8b**) deduced from the nmr spectral titrations of the naturally derived material. Titrations with shift reagent were also carried out with all six synthetic isomers, and these were in accord with predictions and likewise confirmed that the natural hexacarboxylic porphyrin had the two methyl groups on rings A and D.

PENTACARBOXYLIC PORPHYRINS

Three of the four porphyrin pentacarboxylic esters were synthesised by variations of the MacDonald route, as shown in Scheme 8. Thus the porphyrin

(31b)+(39e) ⟶ (15b)

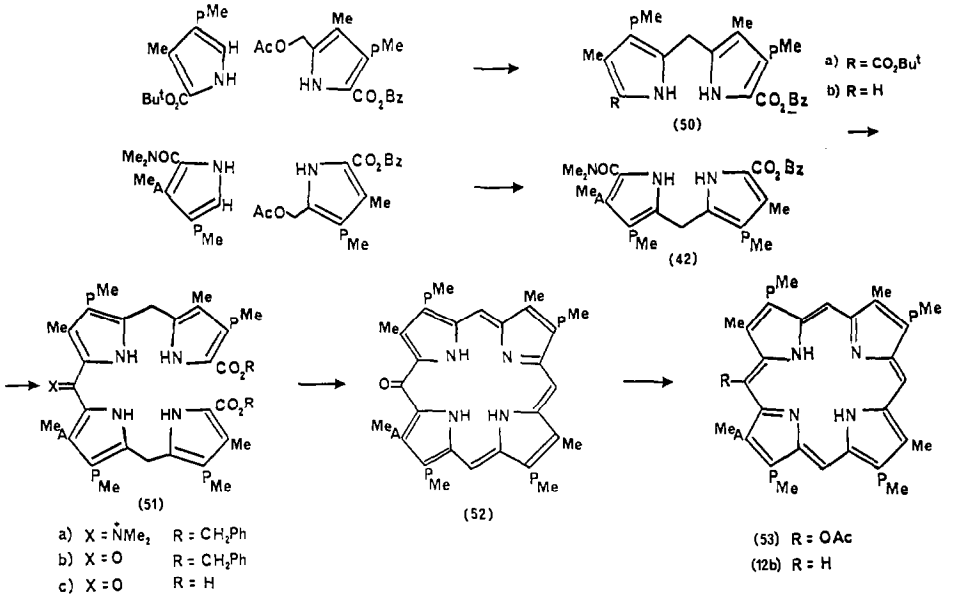
(30b)+(39e) ⟶ (14b)

(30b)+(40e) ⟶ (13b)

SCHEME 8. Syntheses of three type-III pentacarboxylic porphyrins (**13b**), (**14b**), and (**15b**) by the MacDonald route.

(**15b**) with methyl groups on rings B, C, and D was synthesised from pyrromethanes (**31b**) and (**39e**) which had been utilised previously in syntheses of the C-ring methyl heptacarboxylic porphyrin (**4b**) (Scheme 3) and the CD dimethylhexacarboxylic porphyrin (**11b**) (Scheme 5), respectively. The pyrromethane diester (**30a**) required for both the trimethyl porphyrins was the same as that required (cf. Scheme 3) for the AB rings of the ring-A methylheptacarboxylic porphyrin (**2b**). Hydrogenolysis then afforded the corresponding diacid (**30c**) which was condensed with the diformyl pyrromethanes (**39e**) and (**40e**) (cf. Scheme 5) to give the pentacarboxylic porphyrins (**14b**) and (**13b**), respectively.

The remaining pentacarboxylic porphyrin (**12b**) was finally synthesised by the *b*-oxobilane route, as shown in Scheme 9. The pyrromethane t-butyl ester (**50a**) was prepared by both possible methods from the acetoxymethyl pyrroles (**19b**)



SCHEME 9. Synthesis of the type-III pentacarboxylic porphyrin (**12b**) (with a D-ring acetic acid side chain) by the *b*-oxobilane route.

and (**20b**) and the α-free pyrroles (**19e**) and (**20e**), respectively, while the pyrromethane amide (**42**) corresponding to the CD rings of the desired porphyrin had been prepared previously (*cf.* Scheme 6) for the synthesis of the hexacarboxylic porphyrin (**7b**). Trifluoroacetic acid-catalysed deesterification and decarboxylation followed by condensation of the α-free pyrromethane (**50b**) with the phosphorylchloride-activated pyrromethane amide (**42**) proceded well, and after hydrolysis of the intermediate imine salt (**51a**) the *b*-oxobilane (**51b**) was obtained in good yield. Conversion to the oxophlorin (**52**) and thence to the porphyrin (**12b**) via the acetoxyporphyrin (**53**) was achieved in a manner analogous to the previous syntheses, good yields being obtained at each stage.

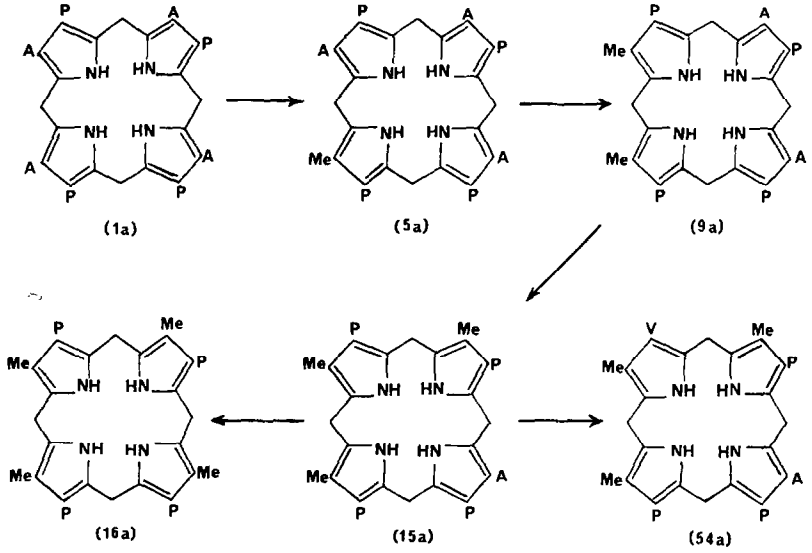
The nmr spectral titrations of the naturally derived pentacarboxylic porphyrin pentamethyl ester had narrowed its structure down to two of the four possibilities (**13b**) and (**14b**), as two of the four *meso*-proton resonances moved rapidly to low field on addition of Eu(fod-d_9)$_3$ shift reagent, whereas only one proton resonance is so affected in the other two isomers (**12b**) and (**15b**). Mixed mp determinations with the two synthetic porphyrins (**13b**) and (**14b**) and the naturally derived porphyrin showed that the natural product (**13b**) had retained an acetic acid residue on the C ring.

The four type-III pentacarboxylic porphyrins have also been synthesised by the Australian group (*39*), three by the MacDonald method, and the fourth by the *b*-oxobilane route, as in their correponding heptacarboxylic porphyrin synthesis; the physical characterisations of these materials were very similar to those of the compounds synthesised in Cardiff and they were also compared directly. It is interesting to note again that in Clezy's *b*-oxobilane synthesis the oxo-linkage was

at the position corresponding to the γ-*meso* bridge in the final porphyrin, whereas ours corresponded to the δ-position.

CONCLUSIONS

The porphyrins excreted in the faeces of the poisoned rats are derived by oxidation of the corresponding porphyrinogens which are intermediates between uroporphyrinogen-III (**1a**) and coproporphyrinogen-III (**16a**) in the biosynthesis of haem. Their structures indicate that the decarboxylation of uroporphyrinogen-III (**1a**) is a clockwise process (Scheme 10), starting with the D-ring acetic acid and



SCHEME 10. Preferred natural pathway from uroporphyrinogen-III (**1a**) to coproporphyrinogen-III (**2a**) and the formation of dehydroisocoproporphyrinogen (**54a**).

proceeding by sequential degradation of the acetic acid groups on rings A, B, and C. Supporting evidence for the specific involvement of the heptacarboxylic porphyrinogen (**5a**) is provided by the fact that the heptacarboxylic porphyrin (**5b**) isolated by the Cambridge group (*37*) from haemolysates is identical with the porphyrin we obtained from poisoned rat faeces; moreover, we have subsequently demonstrated (*41*) that the heptacarboxylic porphyrin excreted by patients with symptomatic porphyria has the same structure, and Clezy (*39*) has also reported a similar finding.

The structure assigned to the pentacarboxylic porphyrinogen (**13a**) is also in accord with its involvement as the branch point (*19, 38, 42*) for formation of dehydroisocoproporphyrinogen (**54**) and its congeners (Scheme 10); the corresponding porphyrins (**55**) accumulate in the faeces both of the poisoned rats and of symptomatic porphyric patients and form a major part of the excreted tetracarboxylic porphyrin fraction, the other component being the "normal" metabolite

coproporphyrin-III (**16a**). The formation of dehydroisocoproporphyrinogen (**54**) has been shown to be due to impairment of the decarboxylase activity of the uroporphyrinogen decarboxylase, so that the pentacarboxylic porphyrinogen (**15a**) accumulates (*19, 42*); the latter is then partly transformed by coproporphyrinogen oxidative decarboxylase into dehydroisocoproporphyrinogen (**54a**) and partly decarboxylated in the normal manner into coproporphyrinogen-III (**16a**) by uroporphyrinogendecarboxylase.

Alternative explanations for our results are that the porphyrins isolated from porphyric faeces are formed by a different process from the normal metabolic pathway, and/or that they accumulate because the corresponding porphyrinogens are metabolised at a slower rate than the isomers. However, the remarkable "clockwise" nature of the process we have discovered provides the simplest explanation, and could be accounted for by association of the uroporphyrinogen-III (**1a**) with the active site on the enzyme followed by a series of 90° rotations in the course of which each of the acetic acid side chains is decarboxylated in turn. It is not yet known for certain whether uroporphyrinogen decarboxylase is a single enzyme with only one active site (*43*), or a complex with more than one active site; although the former possibility seems more likely. However, it is of interest that Akhtar has recently shown the stereochemistry of the decarboxylation process (*44*).

Using red cell haemolysate preparations, we have also found that all of the 14 possible intermediate porphyrinogens (**2a**)–(**15a**) are metabolised (*41, 45*) to coproporphyrinogen-III (**16a**), although the rates of the decarboxylations vary from substrate to substrate (some preliminary results of these studies have already been published). It is also interesting to note in the present context that the abnormal metabolite uroporphyrinogen-I (**55**) is metabolised by both possible routes, through the two isomeric type-I hexacarboxylic porphyrinogens, to coproporphyrinogen-I (**56**) both *in vivo* (in porphyrics) and *in vitro* (in a chicken red cell haemolysate preparation). As the unnatural type-II and type-IV uroporphyrinogens are also substrates (*16*) for uroporphyrinogen decarboxylase, there are probably over 30 substrates for this enzyme, assuming that all the type-II and -IV intermediate hepta-, hexa-, and pentacarboxylic porphyrinogens are also substrates.

The apparent preference for a specific decarboxylation process in the metabolism of the normal metabolite uroporphyrinogen-III is thus even more striking in view of the apparent versatility of uroporphyrinogen decarboxylase in being capable of metabolising so many substrates. The reason for the preference may be due to the unsymmetrical nature of uroporphyrinogen-III) (**1a**) (compared with its isomers) so that the initial enzyme–substrate complex is formed in a specific manner, and the D-ring acetic acid group is specifically decarboxylated in the first stage. We then suggest that the substrate remains complexed to the enzyme as it rotates, so that the other three acetic acid residues are successively decarboxylated at the active site in a clockwise manner (assuming that there is only one enzyme and only one active site). If on the other hand the intermediate porphyrinogens dissociate from the enzyme into the cytoplasm, then they may not recomplex with the enzyme in a specific manner; and further decarboxylations

may give rise to other isomeric porphyrinogens. Experiments to test this hypothesis are in progress, and careful hplc analyses of porphyrins produced in both normal and abnormal metabolism as well as in *in vitro* experiments with red cell haemolysates have indeed shown (*46*) that small amounts of other isomeric porphyrins may also be formed in addition to those derived from the preferred route. We conclude that these arise by "leakage" from the enzyme–substrate complex, as indicated above. The fact that the uroporphyrinogen decarboxylase can metabolise all the alternative substrates as well as those on the preferred pathway is presumably a consequence of the vital importance of porphyrins in the life processes of most living organisms; and thus, even if the enzyme becomes slightly impaired (due to genetic defects or poisoning), abnormal metabolites can still be transformed to coproporphyrinogen-III.

EXPERIMENTAL

All melting points were recorded using a Kofler hot stage and are uncorrected.

Infrared spectra were recorded on a Pye-Unicam S.P. 200 G spectrophotometer and were calibrated using a polystyrene film. Ultraviolet and visible spectra were measured on a Pye-Unicam S.P. 800 spectrophotometer using a holmium filter as standard.

Nuclear magnetic resonance spectra were determined with Perkin–Elmer R14, 100 MHz and R32, 90 MHz spectrometers, using tetramethylsilane as internal reference.

Mass spectra were determined on a Varian CH5D instrument with a combined field desorption–field ionisation electron impact source. Electron impact spectra were measured at 70 e.v. and 50 μA, the source temperature being in the range 200–220°C; field desorption spectra were measured at wire currents increasing from 10–20 mA, and at source temperatures in the range 50–150°C.

Elemental microanalyses were performed on a Technicon instrument. Reactions were monitored wherever possible by tlc on silica gel, or alumina, plates, visualising the spots by iodine, Ehrlich's reagent, or by uv fluorescence as appropriate. Ultraviolet/visible spectroscopy was also widely used in monitoring reactions especially in preliminary trial runs. In the later phases of the work high pressure liquid chromatography was also used to monitor the extent of reactions, to assess the purity of the products, and in some cases was also used preparatively to separate mixtures of products.

Methyl-5-methyl-4,6-dioxoheptanoate

Magnesium turnings (13 g, 0.54 mol), absolute methanol (20 ml), and carbon tetrachloride (1 ml) were mixed together. When the vigorous reaction started to die down small portions of methanol were added to a total of about 150 ml at such a rate as to maintain vigorous refluxing and the mixture was then boiled for an additional 1 hr. The excess of methanol was removed on a rotary evaporator and the last traces were removed by azeotropic distillations with dry benzene (4 × 50 ml).

The pure white solid (magnesium methoxide) was taken up in dry ether (300 ml). Into this suspension was slowly stirred 3-methyl-pentan-2,4-dione (57 g, 0.5 mmol) in dry ether (150 ml) and stirred for 2 hr and then boiled for 1 hr under reflux. After cooling to −20°C 3-carbomethoxypropionyl chloride (75 g, 0.5 mol) in dry ether (100 ml) was slowly stirred in. The mixture was then stirred at room temperature overnight.

Sulphuric acid (25%, 150 ml) was added to the mixture, the light yellow ether solution was decanted off, and the aqueous layer extracted with ether (2 × 100 cm^3). The ether extracts were filtered and then washed with ammonium hydroxide (25%, 6 × 30 ml) to complete cleavage of acetyl group, then with water and dried ($MgSO_4$). The ether was removed under vacuum and the yellow–orange residue after distillation under vacuum gave methyl 5-methyl-4,6-dioxoheptanoate (33.5 g, 0.18 mol; 36%) as a pale yellow oil, bp 80–81°C/0.3 mm.

ν_{max} (film), 1750 (methyl ester C=O), 1740 (keto C=O), 1710 (keto C=O) cm^{-1}.

τ ($CDCl_3$), 6.00 (1H, s, $CO.C(CH_3)=CO\mathit{H}$); 6.30 (1H, q, $CO.CH(CH_3).CO$); 6.40 (3H, s, OCH_3); 7.3 (4H, m, $COCH_2CH_2CO_2C_3$); 7.90 (3H, s, $COCH_3$); 8.25 (3H, s, $CO(CH_3)C=COH$); 8.80 (3H, d, $COCH(C\mathit{H}_3)CO$.

Oximino Dibenzyl Malonate

Dibenzyl malonate (284 g, 1.0 mol) in glacial acetic acid (180 ml) was stirred during the slow addition of sodium nitrite (190 g, 2.75 mol) in water (350 ml), the temperature being maintained below 10°C during the addition. The mixture was then stirred overnight at room temperature. Ether (3 × 250 ml) was added and the organic layers were separated and the combined extracts washed with sodium hydrogen carbonate solution (10%) until effervescene stopped, then with water (2 × 250 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave an oil that could be crystallised from ethylene chloride/light petroleum (256.7 g, 0.82 mol, 82%), mp 65–66°C.

ν_{max} (nujol), 3330 (broad OH), 1750 (ester C=O), 1625 (C=N) cm^{-1}.

τ ($CDCl_3$), 2.60 (1OH, s, 2 × $\mathit{Ph}.CH_2$); 4.62 (2H, s, $PhC\mathit{H}_2$); 4.70 (2H, s, $Ph.C\mathit{H}_2$); 7.81 (1H, s, $NO\mathit{H}$).

Benzyl Hydrogen Malonate

Thionyl chloride (85 ml, 139 g, 1.17 mol) was added dropwise to a solution of malonic acid (100 g, 0.96 mol) in tetrahydrofuran (300 ml) and the reaction mixture refluxed for 2 hr. Benzyl alcohol (134 ml, 135.4 g, 1.25 mol) was then added dropwise with stirring over a period of 1 hr. The reaction mixture was refluxed for 2 hr and then allowed to stand overnight at room temperature. The solvent was removed under reduced pressure and the oily residue was treated with 10% aqueous sodium bicarbonate (3 × 400 ml). The mixture was extracted with ether (2 × 150 ml) and then the aqueous solution was cooled and acidified with 6 *N* hydrochloric acid (pH 2–3) and extracted with ether (4 × 150 ml). The ether extracts were dried ($MgSO_4$) and then solvent was removed under reduced

pressure giving the required product as an oil which crystallised from carbon tetrachloride as a white powder (131.7, 0.68 mol, 58%), mp 46–48°C.

Found: C, 62.00; H, 5.20; $C_{10}H_{10}O_4$ requires C, 61.86; H, 5.15.

τ ($CDCl_3$ 0.90 (1H, s, CO_2H); 2.67 (5H, s, $PhCh_2O$); 4.82 (2H, s, $PhCH_2O$); 6.55 (2H, s, $COCH_2CO$).

MS *m/e* (%); FD M^+ 194 (100%).

Methyl 5-Benzyloxycarbonyl-4-oxopentanoate (**23a**)

(*i*) *Magnesium comlex procedure*. A solution of isopropyl bromide (90 g, 0.73 mol) in tetrahydrofuran (750 ml) was added to magnesium turnings (21.6 g, 0.9 mol). The reaction was initiated with slight warming and the remainder of the solution was added at such a rate to keep the reaction mixture in gentle refluxing. After the addition the mixture was left standing overnight and decanted to yield a clear solution. (The concentration of the Grignard solution was estimated by adding a portion (1 ml) of the above solution into water (50 ml) and then 5×10^{-2} *M* sulphuric acid (20 ml). This solution was boiled for 5 min then cooled and titrated against 0.1 *M* sodium hydroxide using methyl orange as an indicator. A typical experiment yielded 1 *M* concentration of Grignard.)

The Grignard solution (0.6 mol, e.g., 600 ml) was added dropwise to a stirred solution of benzyl hydrogen malonate (58.2 g, 0.3 mol) in tetrahydrofuran (100 ml) cooled in ice water. When the evolution of gas had ceased, the solution was stirred at room temperature for 1 hr. 3-Methoxycarbonylpropionyl chloride (45.2 g, 0.3 mol) in tetrahydrofuran (400 ml) was added dropwise to a stirred suspension of the above magnesium complex cooled to −10°C. Stirring was continued for a further 2 hr and the solution was then hydrolysed by pouring ito 5% sulphuric acid (1 liter). The organic layer was separated and the aqueous layer thoroughly extracted with ether. The combined organic layers were washed with 5% aqueous sodium bicarbonate solution followed by a saturated sodium chloride solution and dried ($MgSO_4$). Removal of the solvent in a rotary evaporator gave an oil which was distilled under reduced pressure to yield benzyl methyl-3-keto adipate (22 g, 0.084 mol, 28%), bp 150–152°C at 0.1 mm Hg.

Found: C, 63.60; H, 6.05; $C_{14}H_{16}O_5$ requires C, 63, 64; H, 6.05.

ν_{max} (film), 1740 and 1710 (esters C=O), 1725 (keto C=O) cm^{-1}.

τ ($CDCl_3$), 2.60 (5H, s, $PhCH_2O$); 4.80 (2H, s, $PhCH_2O$); 6.33 (3H, s, OCH_3); 6.45 (2H, s, $COCH_2CO$); 7.14 and 7.40 (each 2H, t, $COCH_2CH_2CO$).

MS *m/e* (%); FD M^+ 264 (100%).

(*iia*) *N,N'-Thionyl diimidazole*. A solution of thionyl chloride (12.8 ml, 21.35 g, 0.31 mol in tetrahydrofuran (100 ml)) was added dropwise to a stirred solution of imidazole (82.5 g, 1.25 mol) as well in tetrahydrofuran (600 ml). The precipitate of imidazole chlorohydrate appeared immediately, stirring was continued for a further 15 min, and then the solution was filtered and the residue washed with tetrahydrofuran to give a clear pale green filtrate.

(*iib*) *Imidazolide*. A solution of methyl hydrogen succinate (39.6 g, 0.3 mol) in tetrahydrofuran (200 ml) was added to the solution of *N,N'*-thionyl diimidazole. The stirring was continued for a further 15 min.

(*iic*) *Keto ester.* A solution of the imidazolide was added dropwise to a stirred suspension of the magnesium complex of benzyl hydrogen malonate (i) over a period of 2 hr at room temperture. The mixture was stirred for a further 2 hr and then hydrolysed by pouring into 4% hydrochloric acid (1.5 liter). The organic layer was separated and the aqueous layer thoroughly extracted with ether and the combined organic layers were washed with 5% aqueous sodium bicarbonate solution followed by a saturated aqueous solution of sodium chloride. After drying ($MgSO_4$), the solvent was removed in a rotary evaporator and the residual oil was fractionally distilled under reduced pressure to yield the required methyl-5-benzoxy carbonyl-4-oxopentanoate (33.26 g, 0.126 mol, 42%). Properties were as in (i).

(*iii*) A mixture of methyl 5-ethoxycarbonyl-4-oxopentanoate (**23b**) (67 g, 0.33 mol) and benzyl alcohol (53.5 g, 0.5 mol) was heated under reflux at 165–170°C for 4 hr under reduced pressure (water pump). The reaction mixture was fractionally distilled under reduced pressure giving the required β-keto ester (75.2 g, 0.29 mol, 86.3%). Properties were as in (i) and (ii).

Methyl 5-Benzoxycarbonyl-3-oximino-4-oxopentanoate

Methyl-5-benzoxycarbonyl-4-oxopentanoate (264 g, 1 mol) in glacial acetic acid (200 ml) was stirred during the slow addition of sodium nitrite (190 g, 2.75 mol) in water (350 ml), the temperature being maintained below 10°C during the addition. The mixture was then stirred overnight at room temperature. The mixture was extracted with ether (3 × 200 ml) and the combined extracts were washed with 10% aqueous sodium bicarbonate solution until effervescence stopped then with water (3 × 200 ml) and dried ($MgSO_4$). Removal of the solvent gave the required oxime as a white solid (237.6 g, 0.92 mol, 92%), mp 85–86°C.

ν_{max} (nujol), 3300 (N–OH); 1700 and 1740 (esters C=O); 1700 (keto C=O) cm^{-1}.

τ ($CDCl_3$), −0.16 (1N, s, NO*H*); 2.65 (5H, s, *Ph*CH_2O); 4.68 (2H, s, PhCH_2O); 6.35 (3H, s, OCH_3); 6.40 (2H, t, $COCH_2CH_2CO_2CH_3$); 7.35 (2H, t, $COCH_2$-$CH_2CO_2CH_3$).

Benzyl 3-(2-Methoxycarbonyl-ethyl)-4,5-dimethylpyrrole-2-carboxylate (**20a**)

Oximino dibenzyl malonate (124 g, 0.4 mol) in glacial acetic acid (300 ml) was run during 45–60 min into a vigorously stirred mixture of sodium acetate (80 g), acetic acid (500 ml), methyl 5-methyl-4,6-dioxoheptanoate (74.5 g, 0.4 mol), and zinc dust (20 g). During the addition, zinc dust (50 g) was added in small portions and the temperature was kept at 65–70°C by cooling the reaction mixture flask in ice water. The cooling bath was removed after the addition of the oxime and when the temperature rise ceased the mixture was slowly heated to 95–97°C (water bath) during 2 hr, stirring being continued. The hot solution was decanted from excess zinc into well-stirred ice and water (15 liter) and the zinc washed with hot 50% acetic acid. A white solid was filtered after 12 hr, washed with hot water, and recrystallised from chloroform–petrol (40–60°) giving the pyrrole as a white powder (55.5 g, 0.15 mol). The mother liquor was concentrated on a rotary

evaporator, the remaining oil was chromatographed on alumina (Merck, neutral, Brockmann Grade III) eluting with methylene chloride–petrol (40–60°C) (1 : 19, v/v) giving a second crop of the desired pyrrole (13.5 g, 0.036 mol; total yield 46.5%), mp 95–95.5°C (lit. (*47*) mp 95–96°C).

Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.7; H, 6.7, N, 4.5. Found: C, 68.6; H, 6.6; N, 4.6.

ν_{max} (nujol), 3310 (NH); 1740 and 1680 (C=O esters).

τ ($CDCl_3$), 1.15 (1H, s, *NH*); 2.65 (5H, s, *Ph*CH_2O); 4.75 (2H, s, PhCH_2O); 6.40 (3H, s, OCH_3); 6.98 (2H, t, CH_2CHCO); 7.53 (2H, t, CH_2CH_2CO); 7.85 (3H, s, CH_3); 8.08 (3H, s, CH_3).

Ethyl-5-methyl-4-iodo-3-carbethoxymethyl Pyrrole-2-carboxylate

A suspension of ethyl-5-methyl-4-carboxylic acid 3-carbethoxymethyl pyrrole-2-carboxylate (18 g, 0.064 mol) in methanol (500 ml) was treated with 10% aqueous sodium bicarbonate (230 ml) and the mixture heated until a colourless solution was obtained. The solution was vigorously stirred, then kept at 60°C and a solution of iodine (19.2 g, 0.076 mol) and potassium iodide (31.6 g, 0.190 mol) in methanol (200 ml) and water (100 ml) was added dropwise, at such a rate that the iodine colour ws discharged between drops (2 hr). After keeping the solution at 60°C for a further 3 hr, water (1 liter) was slowly added and the product precipitated out. Then it was diluted to 5 liter, cooled to 0°C, filtered, the precipitate washed with water and dried in a vacuum desicator. It was recrystallised from methylene chloride–petrol (40–60°C) giving the iodo pyrrole (21.9 g, 0.060 mol, 94%), mp 120–121°C (lit. (*48*) 116–119°C).

ν_{max} (nujol), 3310 (NH); 1750 and 1680 (esters C=O) cm^{-1}.

τ ($CDCl_3$), 0.63 (1H, s, N*H*); 5.72 (2H, q, OCH_2CH_3); 5.84 (2H, q, OCH_2CH_3); 6.22 (2H, s, CH_2CO_2); 7.74 (3H, s, 5-CH_3); 8.00 (3H, t, OCH_2CH_3); 8.06 (3H, t, OCH_2CH_3).

Ethyl-5-methyl-3-carbethoxymethyl Pyrrole-2-carboxylate

Ethyl-5-methyl-4-iodo-3-carbethoxymethyl pyrrole-2-carboxylate (16.1 g, 0.044 mol) was dissolved in a solution of 1.5% sodium acetate in ethanol (200 ml). This solution was hydrogenated over Adams platinum catalyst (20 mg) at room temperature and atmospheric pressure. When the uptake of hydrogen finished the catalyst was filtered off through celite and the solution evaporated to dryness in a rotary evaporator. The yellow residue was partitioned between ethyl acetate (100 ml) and water (100 ml), the organic layer dried over magnesium sulphate and filtered. The solvent was removed and the resulting oil crystallised on standing at room temperature and was recrystallised from aqueous methanol giving the desired pyrrole as a colourless precipitate (9.62 g, 0.040 mol, 91.5%), mp 90–92°C (lit (*35*) mp 91–92°C).

ν_{max} (nujol), 3330 (NH), 1730, 1670, and 1650 (ester C=O) cm^{-1}.

τ ($CDCl_3$), 0.8 (1H, s, N*H*); 4.5 (1H, d, 4-*H*); 5.68 (2H, q, OCH_2CH_3); 5.82 (2H, q, OCH_2CH_3); 6.20 (2H, s, CH_2CO); 7.74 (3H, s, 5-CH_3), 8.68 (3H, t, OCH_2CH_3); 8.84 (3H, t, OCH_2CH_3).

Ethyl-5-methyl-4-formyl-3-carbethoxymethyl Pyrrole-2-carboxylate

N,N-Dimethyl formamide (3.1 ml, 2.93 g, 0.040 mol) was added dropwise to a stirring solution of phosphorus oxychloride (3.7 ml, 6.15 g, 0.040 mol) in dry ether (15 ml) under nitrogen. The temperature of the reaction mixture was kept below 5°C throughout the addition. After the addition the mixture was stirred for 30 min at room temperature. The complex separated as a viscous oil. To the complex in ether and methylene chloride (20 ml) was added dropwise ethyl-5-methyl-3-carbethoxymethyl pyrrole-2-carboxylate (8.03 g, 0.033 mol) in methylene chloride (25 ml) at 5°C. The stirred mixture was then refluxed for 4 hr and cooled to room temperature. Removal of the solvent in a rotary evaporator gave an oily residue that was treated with aqueous sodium acetate (16.4 g, 0.2 mol, in 300 ml of water). The mixture was stirred vigorously for 20 min at 100°C and 20% aqueous sodium carbonate was added to raise the reaction mixture's pH to 8. The formyl pyrrole was filtered and dried in a vacuum dessicator and recrystallised from methylene chloride–petrol (40–60°C) (8.5 g, 0.031 mol, 95.6%), mp 160–161°C (lit. (*49*) mp 153–154°C).

ν_{max} (nujol), 3270 (NH), 1740 and 1690 (ester C=O), 1680 (aldehyde C=O) cm^{-1}.

τ ($CDCl_3$), −0.18 (1H, s, N*H*); 0.04 (1H, s, CO*H*); 5.70 (2H, q, OCH_2CH_3); 5.82 (2H, s, CH_2CO); 5.84 (2H, q, OCH_2CH_3); 7.55 (3H, s, 5-CH_3); 8.70 (3H, t, OCH_2CH_3); 8.75 (3H, t, OCH_2CH_3).

Ethyl-5-methyl-4-(2-ethoxycarbonylvinyl)-3-ethoxycarbonylmethyl Pyrrole-2-carboxylate

A mixture of ethyl-5-methyl-4-formyl-3-ethoxycarbonylmethyl pyrrole-2-carboxylate (28.3 g, 0.106 mol), ethyl hydrogen malonate (28.4 g, 0.215 mol), piperidine (31.5 ml, 27.1 g, 0.318 mol), and absolute alcohol (300 ml) was refluxed for 72 hr. Water was then added to the reaction mixture until the solution became cloudy, and was left overnight in the refrigerator. The white crystalline precipitate was collected, washed well with hot water, and dried *in vacuo*. The product was recrystallised from aqueous ethanol to give ethyl-5-methyl-4-carbethoxyvinyl-3-carbethoxymethyl pyrrole-2-carboxylate (30.3 g, 0.09 mol, 85%), mp 84–85°C (lit. (*49*) mp 88–89°C).

ν_{max} (nujol), 3280 (NH), 1795 (ester C=O), 1712, 1675, and 1670 (ester C=O) cm^{-1}.

τ ($CDCl_3$), 0.28 (1H, s, N*H*); 2.37 (1H, d, C*H*=CHCO); 4.03 (1H, d, CH=C*H*CO); 5.8 (6H, m, 3 × $-OCH_2CH_3$); 6.05 (2H, s, $-CH_2CO$); 7.68 (3H, s, $-CH_3$); 8.73 (9H, m, 3 × OCH_2CH_3).

Ethyl-5-methyl-4-(2-ethoxycarbonylethyl)-3-ethoxy-carbonylmethylpyrrole-2-carboxylate

Ethoxy-5-methyl-4-(2-ethoxycarbonylvinyl)-3-ethoxy carbonylmethyl pyrrole-2-carboxylate (13.5 g, 0.040 mol) was dissolved in absolute ethanol (200 ml) and triethylamine (three drops). This solution was hydrogenated over 10% palladium

on charcoal (0.5 g) at room temperature and atmospheric pressure. The disappearance of the uv absorption at 312 nm showed the reaction was complete; the mixture was filtered through Celite, and the solvent evaporated off in a rotary evaporator to give the required pyrrole as an oil. It crystallised from aqueous ethanol as needles (12.8 g, 0.038 mol, 95%), mp 61–61.5°C (lit. (*49*) mp 63–64°C).

ν_{max} (nujol), 3300 (NH), 1730 (ester C=O), 1675 (ester C=O).

τ ($CDCl_3$), 0.83 (1H, s, N*H*); 5.84 (6H, m, 3 × OCH_2CH_3); 6.23 (2H, s, —CH_2CO); 7.32 (2H, t, —CH_2—CH_2CO); 7.63 (2H, t, CH_2CH_2CO); 8.75 (9H, m, 3 × OCH_2CH_3).

Benzyl-5-methyl-4-(2-benzyloxycarbonylethyl)-3-benzyl Oxycarbonylmethyl Pyrrole-2-carboxylate

Sodium (0.1 g, 0.004 mol) was warmed to solution in distilled benzyl alcohol (100 ml). Ethyl-5-methyl-4-(2'-ethoxycarbonyl-ethyl)-3-(ethoxycarbonylmethyl) pyrrole-2-carboxylate (10 g, 0.030 mol) was added to the warm solution and the mixture was vigorously stirred and heated at 90°C for 8 hr under reduced pressure (water pump). Solid carbon dioxide was added to neutralise the solution and benzyl alcohol removed under vacuum (0.1 mm at 100°C). The residue was crystallised from ethanol–water and recrystallised from *n*-heptane to give the pyrrole tribenzylester (10.4 g, 0.020 mol, 67%), mp 94–95°C (lit. (*150*) mp 92–93°C).

ν_{max} (nujol), 3285 (NH), 1730, 1670 (esters C=O).

τ($CDCl_3$), 1.18 (1H, s, N*H*); 2.72 (5H, s, *Ph*CH_2O); 2.75 (1OH, s, 2 × *Ph*CH_2O); 4.83 (2H, s, PhCH_2O); 4.98 (2H, s, PhCH_2O); 5.00 (2H, s, PhCH_2O); 6.20 (2H, s, · CH_2CO); 7.34 (2H, t, CH_2CH_2CO); 7.60 (2H, t, · CH_2CH_2CO); 7.90 (3H, s, 5 · CH_3).

Benzyl-5-methyl-4-(2'-carboxyethyl)-3-carboxymethyl pyrrole-2-carboxylate

A solution of ethyl-5-methyl-4-(2'-ethoxycarbonylethyl)-3-ethoxycarbonylmethyl pyrrole-2-carboxylate (15 g, 0.040 mol) in benzyl alcohol (100 ml) was added to a warm solution of sodium (2.3 g, 0.1 mol) in benzyl alcohol (115 ml). The mixture was heated first for 1 hr with stirring at 95°C, and then 3 hr under a water pump vacuum. Benzyl alcohol was removed under vacuum (0.1 mm at 100°C). Water (150 ml) was added to the residue and stirred overnight to get a clear solution then extracted with ether (2 × 100 ml). The aqueous layer was acidified (pH 1–2) with 10% hydrochloric acid and the precipitated dried *in vacuo* and recrystallised from acetone *n*-heptane (10.2 g, 0.030 mol, 73.4%), mp 212–214°C (lit. (*50*) mp 217–218°C).

ν_{max} (nujol), 3300 (NH and HO (broad), 1740 and 1680 (C=O) cm^{-1}.

τ ($CDCl_3$), 0.33 (1H, s, N*H*); 0.90 (2H, br, 2 × CO_2H; 2.70 (5H, s, *Ph*CH_2O); 4.80 (2H, s, PhCH_2O; 6.17 (2H, s, CH_2CO); 7.36 (2H, t, CH_2CH_2CO); 7.53 (2H, t, CH_2CH_2CO); 7.85 (3H, s, 5-CH_3).

Benzyl-5-methyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl Pyrrole-2-carboxylate (**22a**)

(i) Sodium (0.14 g, 0.006 mol) was dissolved in absolute methanol (100 ml) and then benzyl-5-methyl-4-(2′-benzyloxycarbonylethyl)-3-(benzyloxycarbonylmethyl) pyrrole-2-carboxylate (2 g, 0.004 mol) was added and the solution heated in a water bath under nitrogen for 45–55 min. The reaction mixture was neutralised by adding solid carbon dioxide and then poured into ice water (400 ml) giving the required pyrrole as a white precipitate (1.72 g, 0.005 mol, 77%), mp 118–119°C (lit. (*50*) mp 113–116°C).

(ii) Benzyl-5-methyl-4-(2-carboxyethyl)-3-carboxymethyl pyrrole-2-carboxylate (10 g, 0.029 mol) was dissolved in 10% hydrogen chloride in methanol (250 ml) and left overnight in the dark at room temperature. The solvent was removed in a rotary evaporator, more methanol was added and removed in the same way. The oily residue crystallised from *n*-hexane as white needles (9.9 g, 0.027 mol), mp 117–118°C (lit. (*50*) mp 113–116°C).

ν_{max} (nujol), 3280 (N—H), 1730, 1710, and 1670 (ester C=O).

τ ($CDCl_3$), 1.00 (1H, s, N*H*); 2.64 (5H, s, *Ph*CH_2O); 2.74 (2H, s, PhCH_2O); 6.20 (2H, s, CH_2CO); 6.39 (3H, s, OCH_3); 6.45 (3H, s, OCH_3); 7.31 (2H, t, CH_2CH_2CO); 7.58 (2H, t, CH_2CH_2CO); 7.83 (3H, s, 5-CH_3).

Benzyl-5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl Pyrrole-2-carboxylate (**22b**)

Benzyl-5-methyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl pyrrole-2-carboxylate (5 g, 0.013 mol) was stirred in glacial acetic acid (50 ml) at 20°C as lead tetraacetate (7.13 g, 0.016 mol) was added in portions. The solution was stirred overnight and poured into ice water (1 liter). The white precipitate was filtered, washed with hot water, and recrystallised from methylene chloride–petrol (40–60°C) giving the required pyrrole (4.3 g, 0.010 mol, 77%), mp 116–117°C (lit. (*51*) mp 111–112°C).

ν_{max} (nujol), 3320 (NH), 1723 and 1670 (C=O).

τ ($CDCl_3$) 0.55 (1H, s, N*H*); 2.57 (5H, s, *Ph*CH_2O); 2.68 (2H, s, PhCH_2O); 2.90 (2H, s, —CH_2OCO); 6.15 (2H, s, CH_2CO); 6.32 (3H, s, OCH_3); 6.38 (3H, s, OCH_3); 7.18 (2H, t, CH_2CH_2CO); 7.50 (2H, s, CH_2CH_2CO); 7.92 (3H, s, $OCOCH_3$).

Benzyl-5-methyl-4-acetyl-3-(2′-methoxycarbonylethyl)pyrrole-2-carboxylate

Benzyl-5-methoxycarbonyl-2-oximino-3-oxopentanoate (171.5 g, 0.5 mol) in glacial acetic acid (250 ml) was added slowly into a vigorously stirred mixture of acetyl acetone (51.5 ml, 50 g, 0.5 mol) in glacial acetic acid (500 ml), anhydrous sodium acetate (150 g), and zinc dust (30 g). Simultaneously zinc (100 g) was added at such a rate as to keep the temperature about 70°C. After the addition the mixture was heated at 90–95°C for 2 hr then cooled to about 50°C and decanted from zinc into well-stirred ice water (15 liter) and the remaining zinc washed with hot 50% acetic acid (200 ml), and left overnight. A white solid was filtered, washed

with hot water, and recrystallised from aqueous ethanol giving the required *pyrrole* (94.33 g, 0.275 mol, 55%), mp 101–103°C.

Found: C, 65.8; H, 5.9; N, 4.3. $C_{19}H_{21}O_5N$ requires C, 66.4; H, 6.1; N, 4.1.

ν_{max} (nujol), 3300 (NH), 1730 and 1630 (esters C=O), 1750 (keto C=O).

τ ($CDCl_3$), 0.43 (1H, s, N*H*); 2.63 (5H, s, *Ph*CH_2O); 4.68 (2H, s, Ph.C*H*$_2$O); 6.38 (3H, s, OC*H*$_3$); 6.60 (2H, t, C*H*$_2$$CH_2CO$); 7.45 (2H, t, CH_2C*H*$_2$CO); 7.50 (3H, s, COC*H*$_3$); 7.55 (3H, s, 5-C*H*$_3$).

MS *m/e* (%); FD M^+ 343 (100).

Benzyl-5-methyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (**21a**)

Benzyl-5-methyl-4-acetyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (27.05 g, 0.079 mol) was dissolved in absolute methanol (150 ml) and a solution of thallium (III) nitrate (31.6 g, 0.118 mol) in absolute methanol (300 ml) was added and then concentrated nitric acid (1.5 ml). The solution was stirred for 3 days at 20°C, the precipitate of thallium (I) nitrate was filtered off, and the solution poured into ice water (10 liters). The pink solid that precipitated was filtered and recrystallised from aqueous methanol giving the desired *pyrrole* (25.34 g, 0.086 mol, 86%), mp 78–79°C (lit. (*52*) mp 78.5–79.5°C).

Found: C, 63.8; H, 6.3; N, 3.9. $C_{20}H_{23}NO_6$ requires C, 64.3; H, 6.2; N, 3.8.

ν_{max} (nujol), 3310 (NH), 1745, 1735, and 1675 (ester C=O) cm^{-1}.

τ $CDCl_3$), 0.95 (1H, s, *NH*); 2.65 (5H, s, *Ph*CH_2O); 4.75 (2H, s, PhC*H*$_2$CO); 6.40 (3H, s, OC*H*$_3$); 6.45 (3H, s, OC*H*$_3$); 6.64 (2H, s, C*H*$_2$CO); 7.05 (2H, t, C*H*$_2$$CH_2CO$); 7.55 (2H, t, CH_2C*H*$_2$CO); 7.87 (3H, s, OC*H*$_3$).

MS *m/e* (%); FD M^+ 373 (100).

Benzyl-5-acetoxymethyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (**21b**)

Benzyl - 5 - methyl - 4 - methoxycarbonylmethyl - 3 - (2 - methoxycarbonylethyl)pyrrole-2-carboxylate (5 g, 0.013 mol) was stirred in glacial acetic acid (50 ml) at room temperature as lead tetraacetate (7.13 g, 0.016 mol) was added in portions. The solution was stirred overnight and poured into ice water (1 liter). The white precipitate was filtered, washed with hot water, and dissolved in methylene chloride. The solution was washed with water, dried, and the solvent evaporated off in a rotary evaporator and recrystallised from methylene chloride–petrol (40–60°C) giving the required pyrrole (5.17 g, 0.012 mol, 92%) mp 104–105°C (lit. (*53*) mp 107–108°C).

Found: C, 61.0; H, 6.0; N, 3.0. $C_{22}H_{25}NO_8$ requires C, 61.3; H, 5.8; N, 3.3.

ν_{max} (nujol), 3250 (NH); 1730 and 1660 (ester C=O) cm^{-1}.

τ ($CDCl_3$), 0.65 (1H, s, N*H*); 2.58 (5H, s, *Ph*CH_2CO); 4.57 (2H, s, PhC*H*$_2$CO); 4.95 (2H, s, 5-C*H*$_2$OCO); 6.30 (3H, s, OC*H*$_3$); 6.37 (3H, s, OC*H*$_3$); 6.45 (2H, s, 4-C*H*$_2$CO); 6.97 (2H, t, C*H*$_2$$CH_2CO$); 7.47 (2H, t, CH_2C*H*$_2$CO); 7.95 (3H, s, CH_3CO_2).

Benzyl 5-carboxylic acid 4-Methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (**21c**)

Sulphuryl chloride (6 ml, 10.02 g, 0.074 mol) was added dropwise to a stirred solution of benzyl-5-methyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (6 g, 0.016 mol) in dry ether (200 ml) keeping the temperature below 20°C. The mixture was stirred at room temperature (protected from moisture) until a sample of 2 ml (solvent evaporated off in a rotary evaporator at room temperature) showed a complete transformation to benzyl-5-trichloromethyl - 4 - methoxycarbonylethyl - 3 - (2′ - methoxycarbonyl - ethyl)pyrrole-2-carboxylate (60 hr). (τ ($CDCl_3$), 0.53 (1H, s, N*H*); 2.62 (5H, s, *Ph*CH_2O); 4.67 (2H, s, Ph.C*H*$_2$O); 6.13 (2H, s, C*H*$_2$CO); 6.34 (3H, s, OC*H*$_3$); 6.41 (3H, s, OC*H*$_3$); 7.02 (2H, t, C*H*$_2$$CH_2CO$); 7.43 CH_2C*H*$_2$CO).

Ether was removed to give an orange oil which was dissolved in dioxane (50 ml). A solution of 10% aqueous sodium acetate (100 ml) was added and the mixture stirred at 70°C for 1.5 hr and left stirring overnight at room temperature. Ether (2 × 200 ml) was added and the combined organic layers were extracted with 10% aqueous sodium carbonate (3 × 100 ml). Traces of ether were removed from the aqueous solution under reduced pressure at room temperature and then hydrochloric acid (concd) was added until pH 1–2. A fine white solid precipitated, which was filtered, washed with hot water, and dried. It was recrystallised from chloroform–petrol (40–60°C) to give needles, mp 123–125°C (4.84 g, 0.012 mol, 75%).

Found: C, 59.3; H, 5.1; N, 3.7. $C_{20}H_{21}NO_8$ requires C, 59.6; H, 5.2; N, 3.5.

ν_{max} (nujol), 3200 (NH and OH (broad)), 1760, 1740, and 1720 (esters C=O), 1690 (acid C=O) cm^{-1}.

τ ($CDCl_3$), 0.20 (1H, s, CO_2*H*); 1.63 (1H, s, N*H*); 2.61 (5*H*, *s*, $PhCH_2O$); 4.65 (2H, s, PhC*H*$_2$O); 6.10 (2H, s, C*H*$_2$CO); 6.31 (3H, s, OC*H*$_3$); 6.38 (3H, s, OC*H*$_3$); 6.98 (2H, t, C*H*$_2$$CH_2CO$); 7.48 (2H, t, CH_2C*H*$_2$CO).

Benzyl-5-N,N-dimethylamido-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (**21f**)

5-Benzyl-5-carboxylic acid 4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (3.2 g, 0.0086 mol) was dissolved in freshly distilled thionyl chloride (10.7 ml) and the solution heated at 45°C for 60 min. The excess of thionyl chloride was removed in a rotary evaporator at room temperature to give the desired product benzyl-5-chlorocarbonyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate.

τ ($CDCl_3$), −0.40 (1H, s, N*H*); 2.49)5H, s, *Ph*CH_2O); 4.63 (2H, s, PhC*H*$_2$O); 6.15 (2H, s, C*H*$_2$CO); 6.32 (3H, s, OC*H*$_3$); 6.40 (3H, s, OC*H*$_3$); 7.00 (2H, t, C*H*$_2$$CH_2CO$); 7.50 (2H, t, CH_2C*H*$_2$CO).

This was dissolved in dry benzene (100 ml) and dimethylamine gas (generated by boiling 30% w / v aqueous solution) was passed through the solution for 30 min at room temperature. The resulting pale yellow solution was washed with water (2 × 100 ml), 5% hydrochloride acid (3 × 100 ml), and finally water again (2 × 100 ml). The benzene solution was dried over $MgSO_4$, filtered, and solvent evaporated off

in rotary evaporator. The resulting yellowish solid was recrystallised from methylene chloride–petrol (40–60°C) giving the desired *pyrrole* (3.0 g, 0.007 mol, 78%), mp 132–134°C.

Found: C, 61.2; H, 6.2; N, 6.8. $C_{22}H_{26}N_2O_7$ requires C, 61.4; H, 6.1, N, 6.5.

ν_{max} (nujol), 3200 (NH); 1740, 1700 (esters C=O), 1620 (amide C=O) cm^{-1}.

τ ($CDCl_3$), 0.58 (1H, s, N*H*); 2.61 (5H, s, P*h*CH_2O); 4.70 (2H, s, PhCH_2O); 6.35 (3H, s, OCH_3); 6.37 (2H, s, CH_2CO); 6.40 (3H, s, OCH_3); 7.00 (6H, s, N (CH_3)$_2$); 7.03 (2H, t, CH_2CH_2CO), 7.50 (2H, t, CH_2CH_2CO).

5-N,N-Dimethylamido-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylic acid (**27b**)

Benzyl - 5 - *N,N* - dimethylamido - 4 - methoxycarbonylmethyl - 3 - (2 - methoxycarbonylethyl)pyrrole-2-carboxylate (7 g, 0.016 mol) was dissolved in tetrahydrofuran (200 ml) and triethylamine (0.5 ml). The solution was hydrogenolysed over 10% palladium charcoal (0.2 g) at room temperature and atmospheric pressure. When the hydrogen uptake was complete the mixture was filtered through Celite and the solvent evaporated off in rotary evaporator to give the required acid as a white powder. It was dissolved in chloroform (200 ml) and then extracted with 10% aqueous sodium carbonate (3 × 100 ml). To the aqueous solution was added hydrochloric acid (concd) to pH 1–2, and the desired *pyrrole* was obtained as a white precipitate (5.12 g, 0.015 mol, 90%), mp 198–200°C.

Found: C, 52.8; H, 5.7; N, 8.1. $C_{15}H_{20}N_2O_7$ requires C, 53.0; H, 5.9; N, 8.2.

ν_{max} (nujol), 3200 (NH), 2500–3500 (broad OH), 1740, 1650 (esters C=O), 1620 (acid C=O) cm^{-1}.

τ ($CDCl_3$-$DSOd_6$), −1.27 (1H, s, N*H*); 5.60 (1H, br, Co_2H); 6.40 (6H, s, 2 × OCH_3); 6.45 (2H, s, CH_2CO); 7.02 (6H, s, N (CH_3)$_2$); 7.04 (2H, t, CH_2CH_2CO); 7.45 (2H, t, CH_2CH_2CO).

5-Iodo-4-(2-methoxycarbonylethyl)-3-methoxymethyl-2-N,N-dimethylamido Pyrrole (**27c**)

To a suspension of 5-*N,N*-dimethylamido-4-methoxymethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylic acid (6.8 g, 0.020 mol) in methanol (20 ml) was added to 10% aqueous sodium bicarbonate (65 ml) and the mixture heated until a colourless solution was obtained. The solution was vigorously stirred and kept at 65°C and a solution of iodine (6 g, 0.023 mol), and potassium iodide (12 g, 0.072 mol) in methanol (50 ml) and water (150 ml) was added dropwise, at such a rate that the iodine colour was discharged between drops. After the addition the solution was kept at 65°C for a further 2 hr, water (2 liter) was added, and the product precipitated off. It was left in the refrigerator overnight, filtered, and washed with hot water. The white precipitate was recrystallized from methylene chloride–petrol (40–60°C) giving the *iodopyrrole* (7.2 g, 0.017 mol, 86%), mp 129–131°C.

Found: C, 39.7; H, 4.4; N, 6.9. $C_{14}H_{19}N_2O_5I$ requires C, 40.0; H, 4.5; N, 6.6.

ν_{max} (nujol), 3200 (NH), 1730 (ester C=O), 1640 (amide C=O) cm^{-1}.

τ ($CDCl_3$), 0.15 (1H, s, N*H*); 6.31 (6H, s, 2 × OCH_3); 6.38 (2H, s, CH_2CO); 6.95 (6H, s, CON (CH_3)$_2$); 7.42 (4H, m, CH_2CH_2CO).

4-(2'Methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-N,N-dimethylamido Pyrrole (**27d**)

5 - Iodo - 4 - (2'methoxycarbonylethyl) - 3 - methoxycarbonylmethyl - 2 - *N,N* - dimethylamido pyrrole (2.8 g, 0.007 mol) was dissolved in a solution of 3% sodium acetate in methanol (150 ml). This solution was hydrogenated over Adams platinum catalyst (15 mg) at 20C and 760 mm. When the uptake of hydrogen was complete the catalyst was filtered off through Celite and the solution evaporated to dryness in a rotary evaporator. The yellow residue was partitioned between ethyl acetate (100 ml) and water (100 ml), the organic layer washed with 10% aqueous sodium carbonate (100 ml), water (100 ml), dried over magnesium sulphate, and filtered. The solvent was removed on a rotary evaporator and the resulting oil was crystallised from aqueous methanol giving the required *pyrrole* (1.82 g, 0.006 mol, 88%) as white needles, mp 70–73°C.

Found: C, 57.0; H, 6.7; N, 9.2. $C_{14}H_{20}N_2O_5$ requires C, 56.8; H, 6.8; N, 9.5.

ν_{max} (nujol), 3200 (NH), 1730 (ester C=O), 1590 (amide C=O) cm^{-1}.

τ ($CDCl_3$), 0.42 (1H, s, N*H*); 3.45 (1H, d, 5-*H*); 6.35 (6H, s, 2 × OCH_3); 6.40 (2H, s, CH_2CO); 6.98 (6H, s, CON (CH_3)$_2$); 7.35 (4H, m, CH_2CH_2CO).

Benzyl-5-iodo-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (**21d**)

Benzyl-5-carboxylic acid-4-methoxycarbonylmethyl-3-(2-methoxycarbonyl-ethyl)pyrrole-2-carboxylate (11.2 g, 0.028 mol) was dissolved in methanol (30 ml) and a solution of 10% aqueous sodium bicarbonate (70 ml) was added and the mixture heated at 65°C until a colourless solution was obtained. The solution was then stirred at the same temperature as a solution of potassium iodide (13.9 g, 0.084 mol) and iodine (7.0 g, 0.028 mol) in methanol (40 ml) and water (125 ml) was added dropwise, so that the iodine colour was discharged between drops. After the addition the last traces of iodine disappeared after stirring for a further 90 min at 65°C. A white precipitate separated from the reaction mixture, ice water to 1 liter was added, and the mixture was left overnight in the refrigerator. The white solid was filtered off and washed with hot water giving the desired *iodo pyrrole* (12 g, 0.025 mol, 89%). It was recrystallised from chloroform–petrol (60–80°C) to give crystals, mp 103–105°C.

Found: C, 47.10; H, 4.20; N, 2.90. $C_{19}H_{20}O_6N$ requires C, 47.01; H, 4.12, N, 2.89.

ν_{max} (nujol), 3210 (NH), 1743 and 1650 (esters C=O) cm^{-1}.

τ ($CDCL_3$), 0.40 (1H, s, N*H*); 2.65 (5H, s, *Ph*-CH_2O); 4.68 (2H, s, PhCH_2O); 6.32 (3H, s, OCH_3); 6.40 (3H, s, OCH_3); 6.52 (2H, s, CH_2CO); 6.95 (2H, t, CH_2CH_2CO); 7.48 (2H, t, CH_2CH_2CO).

Benzyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (**21c**)

Benzyl-5-iodo-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (10 g, 0.021 mol) was dissolved in 3% anhydrous sodium acetate in methanol (200 ml) and hydrogenated over Adams platinum catalyst (20 mg) at 20°C/760 mm. After the hydrogen uptake had finished the catalyst was filtered off through Celite and the methanolic solution evaporated to dryness in a rotary evaporator. The resulting residue was partitioned between ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and washed with 10% aqueous sodium carbonate (100 ml), 10% aqueous sodium thiosulphate (100 ml), water (2 × 50 ml), and dried over magnesium sulphate. Ethyl acetate was removed on a rotary evaporator and the clear oil was crystallised from aqueous methanol giving the required *pyrrole* (6.12, 0.017 mol, 83%), mp 64–65°C (lit. (*53*) mp 60–63°C).

Found: C, 63.70; H, 5.82; N, 3.89. $C_{19}H_{21}O_6N$ requires C, 63.51; H, 5.85; N, 3.90.

ν_{max} (njuol), 3212 (NH), 1740 and 1650 (esters C=O) cm^{-1}.

τ($CDCl_3$), 0.48 (1H, s, N*H*); 2.65 (5H, s, *Ph*CH_2O); 3.22 (1H, d, 5-*H*); 6.35 (3H, s, OCH_3); 6.41 (3H, s, OCH_3); 6.52 (2H, s, CH_2CO); 6.97 (2H, s, CH_2CH_2CO); 7.47 (2H, s, CH_2CH_2CO).

Pyrromethanes

Dibenzyl-4,4'-di-(2-methoxycarbonylethyl)-3,3'-dimethyl pyrromethane-5, 5'-dicarboxylate (**40a**). Benzyl-5-acetoxymethyl-4-methyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (5 g, 13.5 mmol) was dissolved in dry methanol (50 ml) and concentrated hydrochloric acid (3 ml) and heated under reflux for 8 hr under nitrogen. The reaction mixture was left overnight in the refrigerator and then the precipitate was filtered off and dissolved in methylene chloride (100 ml). The solution was washed with water (100 ml), decolourised (charcoal), and filtered through Celite. Methylene chloride was distilled off under vacuum and the residue recrystallised from methylene chloride–light petrol (bp 60–80°C), giving the desired *pyrromethane* (3.3 g, 5.4 mmol, 80%), mp 90–91°C.

Found: C, 68.5; H, 6.0; N, 4.3. $C_{35}H_{38}N_2O_8$ requires C, 68.4; H, 6.2; N, 4.6.

τ ($CDCl_3$), 0.80 (2H, s, 2 × *NH*); 2.70 (10 H, s, 2 × *Ph*CH_2O); 4.77 (4H, s, 2 × PhCH_2O); 6.23 (2H, s, 2'-CH_2-2); 6.40 (6H, s, 2 × OCH_3); 7.00 (4H, t, 2 × CH_2CH_2CO); 7.57 (4H, t, 2 × CH_2-CH_2CO); 8.07 (6H, s, 3, 3'CH_3).

MS *m/e* (%); FD M^+ 614 (100).

4,4'-Di-(2-methoxycarbonylethyl)-3,3'-dimethyl pyrromethane-5,5'-dicarboxylic acid (**40b**). Dibenzyl-4,4'-di-(2-methoxycarbonylethyl)-3,3'-dimethyl pyrromethane-5,5'-dicarboxylate (5 g, 8 mmol) was dissolved in tetrahydrofuran (150 ml) containing triethyl amine (five drops). This solution was hydrogenolyzed over 10% palladium on charcoal (0.2 g) at 20°C and 760 mm. When the hydrogen uptake ceased the mixture was filtered through Celite and evaporated to dryness under reduced pressure to yield the required pyrromethane-5,5'-dicarboxylic acid (3.3 g, 7.6 mmol; 95%), mp 182–183°C.

τ($CDCl_3$-$DMSOd_6$), −1.05 (2H, s, 2 × N*H*), 3.55 (2H, br 2 × CO_2H); 6.38 (2H, s, 2′-CH_2-2); 6.43 (6H, s, 2 × OCH_3); 7.10 (4H, t, 2 × CH_2CH_2CO); 7.60 (4H, t, 2 × CH_2CH_2CO); 8.07 (6H, s, 2 × CH_3).

5,5′-Diformyl-4,4′-di-(2-methoxycarbonylethyl)-3,3′-dimethyl pyrromethane (**40e**). Finely ground pyrromethane-5,5′-dicarboxylic acid (1.1 g, 2.53 mmol) was added in small portions to trifluoroacetic acid (5 ml) and the mixture stirred for 5 min at 40°. The solution was then cooled to 0°C and triethylorthoformate (1.4 ml) was added. The mixture was kept at 0°C for 10 min and then stirred into ice water (80 ml). The precipitate was filtered off and then added to a mixture of ethanol (10 ml) and aqueous 1 *M* ammonium hydroxide (20 ml), the product was filtered off after stirring for 10 min and recrystallised from chloroform–petrol (40–60°C) giving the desired *pyrromethane* (0.5 g, 1.21 mmol; 48%), mp 214–216°C.

Found: C, 62.7; H, 6.3; N, 6.7. $C_{21}H_{26}N_2O_6$ requires C, 62.7; H, 6.5; N, 7.0.

τ ($CDCl_3$), −1.08 (2H, s, N*H*); 0.47 (2H, s, 2 × CO*H*); 6.08 (2H, s, 2′-CH_2-2); 6.38 (6H, s, 2 × OCH_3); 7.00 (4H, t, CH_2CH_2CO); 7.48 (4H, t, CH_2CH_2CO); 7.98 (6H, s, 2 × CH_3).

MS *m/e* (%); FD, M^+ 402 (100).

Dibenzyl - 3,3′ - di - (2 - methoxycarbonylethyl) - 4,4′ - di - (methoxycarbonylmethyl)pyrromethane-5,5′-dicarboxylate (**29a**). Benzyl-5-acetoxymethyl-4-(2′methoxycarbonylethyl)-3-methoxycarbonylmethyl pyrrole-2-carboxylate (1.84 g, 4.28 mmol) was dissolved in dry methanol (25 ml) and concentrated hydrochloric acid (1.5 ml) and refluxed for 5 hr under nitrogen. The reaction mixture was poured into ice water (500 ml) and extracted with dichloromethane (3 × 50 ml). The combined extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$). Removal of the solvent gave the required *pyrromethane* (0.950 g, 1.35 mol, 63%) that was recrystallised from aqueous methanol, mp 131–134°C.

Found: C, 64.0; H, 5.6; N, 4.0. $C_{39}H_{42}N_2O_{12}$ requires C, 64.1; H, 5.8; N, 3.8.

τ($CDCl_3$), 0.50 (2H, s, 2 N*H*); 2.65 (10H, s, 2 × P*h*CH_2O); 4.77 (4H, s, 2 × PhCH_2O); 6.00 (2H, s, 2′-CH_2-2); 6.18 (4H, s, 2 × CH_2CO); 6.42 (12H, s, 4 × OCH_3); 7.23 (4H, t, 2 × CH_2CH_2CO); 7.50 (4H, t, 2 × CH_2CH_2CO).

MS *m/e* (%); FD M^+ 730 (100).

3,3′-Di-(2-methoxycarbonylethyl)-4,4′-dimethoxycarbonylmethyl pyrromethane-5-5′-dicarboxylic acid (**29b**). Dibenzyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethoxycarbonylmethyl pyrromethane-5-5′-dicarboxylate (1.0 g, 1.4 mmol) was dissolved in tetrahydrofuran (150 ml) containing triethylamine (five drops). The solution was hydrogenolysed over 10% palladium on charcoal (0.2 g) as usual at room temperature and atmospheric pressure. The mixture was filtered through Celite and evaporated to dryness under reduced pressure. The product was dried under reduced pressure (0.1 mm Hg) at room temperature overnight and used without further purification (0.73 g, 133 mmol, 98%).

Dibenzyl - 3,3′ - dimethoxycarbonylmethyl - 4,4′ - di - (2 - methoxy - carbonylethyl)pyrromethane-5,5′dicarboxylate (**28a**). Benzyl-5-acetoxymethyl-4-methoxycarbonylmethyl-3-(2′-methoxycarbonylethyl) pyrrole-2-carboxylate (1.65 g, 3.86 mmol) was dissolved in dry methanol (15 ml) and concentrated hydrochloric acid (0.9 ml) and refluxed for 6 hr. The reaction mixture was left overnight in a refrigerator and the white precipitate filtered off and washed

with cold methanol. It was recrystallised from methylene chloride–petrol (40–60°C) giving the desired *pyrromethane* (0.96 g, 1.31 mmol, 68%), mp 142–144°C (lit. (*53*) mp, 145–146°C).

Found: C, 63.9; H, 5.7; N, 3.8. $C_{39}H_{42}N_2O_{12}$ requires C, 64.1; H, 5.8; N, 3.8.

τ ($CDCl_3$), −0.3 (2H, s, 2 × N*H*); 2.62 (5H, s, *Ph*CH_2O); 2.67 (5H, s, *Ph*CH_2O); 4.75 (4H, s, 2 × PhCH_2O); 6.15 (2H, s, 2-CH_2-2); 6.40 (12H, s, 4 × OCH_3); 6.43 (4H, s, 2 × CH_2CO); 6.97 (4H, t, 2 × CH_2CH_2CO); 7.50 (4H, s, 2 × CH_2CH_2CO).

MS *m/e* (%); FD M^+ 730 (100).

3,3' - Di - (methoxycarbonylmethyl) - 4,4' - di - (2 - methoxycarbonyl - ethyl)pyrromethane-5,5'-dicarboxylic acid (**28b**). Dibenzyl-3,3'-dimethoxycarbonylmethyl-4,4'-(2-methoxycarbonylethyl)pyrromethane-5,5'-dicarboxylate (3.5 g, 4.8 mmol) was dissolved in tetrahydrofuran (150 ml) containing triethylamine (five drops). The solution was hydrogenolysed over 10% palladium on charcoal (0.2 g) at room temperature and atmospheric pressure until uptake of hydrogen ceased. The mixture was filtered through Celite. The filtrate was evaporated to dryness in a rotary evaporator and the residue was mixed together with the solid on the Celite and 0.1 *M* aqueous sodium hydroxide (500 ml) was added to dissolve the acid and stirred for 30 min. The suspension was filtered through Celite to remove the catalyst and the filtrate was cooled and adjusted to pH 7 with concentrated hydrochloric acid and then to pH 4 with acetic acid and left in the refrigerator. After 4 hr the required *pyrromethenone* carboxylic acid was filtered and dried *in vacuo* and used without any further purification (2.3 g, 4.1 mmol, 85%), mp 150–153°C.

τ ($CDCl_3$-DMSO d6), −1.07 (2H, s, 2 × N*H*); 3.20 (2H, br, 2 × CO_2H); 6.15 (2H, s, 2'-CH_2-2); 6.35 (6H, s, 2 × OCH_3); 6.40 (6H, s, 2 × OCH_3); 6.50 (4H, s, 2 × CH_2CO); 7.05 (4H, t, 2 × CH_2CH_2CO); 7.43 (4H, t, 2 × CH_2CH_2CO).

5,5' - Diformyl - 4,4' - di - (2 - methoxycarbonylethyl) - 3,3 - dimethoxycarbonylmethyl pyrromethane (**28e**). 3,3'-Dimethoxycarbonylmethyl-4,4'-di-(2-methoxycarbonylethyl)pyrromethane-5,5'-dicarboxylic acid (1 g, 1.82 mmol) in dimethylformamide (7.7 ml, 7.3 g, 100 mmol) was refluxed under nitrogen for 150 min. The resulting solution was filtered, cooled, and maintained at 0°C while benzoyl chloride (6 ml, 7.27 g, 51.7 mmol) was added dropwise with stirring. After 30 min benzene (15 ml) was added and the mixture allowed to return to room temperature. After 2 hr the imine salt was filtered and washed with dried benzene. A mixture of methanol (15 ml), water (100 ml), and sodium carbonate (1.5 g) was stirred for 20 min at room temperature with the imine salt and then water was added to dissolve the residual sodium carbonate. The mixture was left in the refrigerator overnight. The product was filtered off and recrystallised from methylene chloride–petrol (40–60°C) giving the desired 5,5'-diformyl pyrromethane (0.358 g, 0.7 mmol, 38%), mp 203–205°C (lit. (*24*) mp 207–208°C).

τ ($CDCl_3$), −0.95 (1H, s, N*H*); −0.75 (1H, s, N*H*); 0.47 (2H, s, CHO); 6.10 (2H, s, 2-CH_2-2'); 6.37 (6H, s, OCH_3); 6.40 (6H, s, OCH_3); 6.55 (4H, s, −CH_2CO); 7.05 (4H, m, $CH_2 \cdot CH_2$CO), 7.43 (4H, m, $CH_2 \cdot CH_2$CO).

MS *m/e* (%); FD M^+ 518 (100).

Dibenzyl-3,4'-di-(2-methoxycarbonylethyl)-3',4-dimethyl pyrromethane-5,5'-dicarboxylate (**37a**). A mixture of benzyl-5-acetoxymethyl-4-methyl-3-(2'-

methoxyethyl)pyrrole (1.0 g, 2.68 mmol) and benzyl-4-(2′methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (0.807 g, 2.68 mmol) was dissolved in glacial acetic acid (15 ml) and heated at 90°C for 2 hr under nitrogen. Then the solution was poured into ice water (200 ml) and kept overnight at 0°C. The precipitate was filtered and dissolved in methylene chloride and decolourised (charcoal), filtered through Celite, and the solvent evaporated under reduced pressure. The residue was chromatographed on alumina (Merck Grade III) eluting with chloroform–light petroleum (bp 40–60°C) (1 : 5, v/v) giving the required *pyrromethane* which was recrystallised from diethylether–petroleum (bp 60–80°C) (1.2 g, 1.94 mmol, 72.5%), mp 88–89°C.

Found: C, 68.7; H, 5.9; N, 4.5. $C_{35}H_{38}N_2O_8$ requires C, 68.4; H, 6.2; N, 4.6.

τ ($CDCl_3$), 0.67 (1H, s, N*H*); 1.18 (1H, s, N*H*); 2.68 (10H, s, 2 × *Ph*CH_2O); 4.75 (4H, s, 2 × Ph*CH*$_2$O); 6.12 (2H, s, 2′-*CH*$_2$-2); 6.39 (3H, s, O*CH*$_3$); 6.43 (3H, s, O*CH*$_3$); 6.86–7.64 (8H, m, 2 × *CH*$_2$*CH*$_2$CO); 7.75 (3H, s, *CH*$_3$); 8.00 (3H, s, *CH*$_3$).

MS *m/e* (%); FD M^+ 61 (100).

3,4′-Di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane-5,5′-dicarboxylic acid (**37b**). Dibenzyl-3,4′-di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane-5,5′-dicarboxylate (1.0 g, 1.6 mmol) was dissolved in tetrahydrofuran (200 ml) containing triethylamine (five drops). This solution was hydrogenolysed over 10% palladium on charcoal (0.2 g) at room temperature and atmospheric pressure. When the hydrogen uptake ceased the mixture was filtered through Celite and evaporated to dryness in a rotary evaporator to give the desired *pyrromethane-5,5′-dicarboxylic acid* (0.65 g, 1.5 mmol, 95%) which was used without further purification, mp 103–107°C.

τ ($CDCl_3$) ($DMSOd_6$), −0.97 (2H, s, 2 × N*H*); 4.20 (2H, br, 2 × CO_2*H*); 6.23 (2H, s, 2′-*CH*$_2$-2); 6.39 (3H, s, O*CH*$_3$); 6.41 (3H, s, O*CH*$_3$); 6.92–7.85 (8H, m, 2 × *CH*$_2$*CH*$_2$CO); 7.83 (3H, s, -*CH*$_3$); 8.04 (3H, s, *CH*$_3$).

5,5′-Diformyl-3,4′-di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane (**37e**). 3,4-Di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane-5,5′-dicarboxylic acid (0.44 g, 0.95 mmol), finely ground, was added in small portions to trifluoroacetic acid (4 ml) and the mixture stirred for 5 min at room temperature. The dark solution was cooled to 0°C and triethylorthoformate (1.2 ml) was added. The mixture was kept at 0°C for 10 min and poured into ice water (80 ml). The precipitate was filtered off and then added to a mixture of ethanol (10 ml) and aqueous 1 *M* ammonium hydroxide (20 ml), the product was filtered off after stirring for 10 min and recrystallised from chloroform–petroleum (40–60°C) giving the desired *diformyl pyrromethane* (0.180 g, 0.45 mmol, 47%), mp. 175°.

τ ($CDCl_3$), −0.70 (1H, s, N*H*); −0.52 (1H, s, N*H*); 0.48 (2H, s, 2 × CO*H*); 6.03 (2H, s, 2′-CH_2-2); 6.34 (3H, s, O*CH*$_3$); 6.37 (3H, s, O*CH*$_3$); 6.90–7.68 (8H, m, 2 × *CH*$_2$*CH*$_2$CO); 7.75 (3H, s, *CH*$_3$); 7.97 (3H, s, *CH*$_3$).

MS *m/e* (%); FD 402 (100).

Dibenzyl 3,4′-di-(2-methoxycarbonylethyl)-4-methoxycarbonyl methyl-3′-methyl pyrromethane · 5,5′-dicarboxylate (**31a**). Benzyl-5-acetoxymethyl-3-methoxycarbonylmethyl-4-(2′ methoxycarbonylethyl)pyrrole-2-carboxylate (1.73 g, 4.0 mmol) and benzyl-4-methyl-3-(2′-methoxycarbonylethyl)pyrrole-2-carboxylate (1.22 g, 4.1 mol) were dissolved in dry methanol (10 ml) and toluene-

p-sulphonic acid monohydrate (30 mg) was added and the mixture heated at 40°C for 18 hr under dry nitrogen. The mixture was then poured into ice water (250 ml) and extracted with methylene chloride (3 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (20 ml), water (2 × 20 ml), dried ($MgSO_4$), and filtered. Removal of the solvent gave an oil which was chromatographed on alumina (Merck Grade III), eluting with chloroform–light petroleum (bp 40–60°C) (1:9, v/v) giving the required *pyrromethane* (1.70 g, 2.52 mmol, 63%) as a pink oil which did not crystallise.

Found: C, 66.3, H, 5.8; N, 4.4. $C_{37}H_{40}N_2O_{10}$ requires C, 66.1; H, 6.0; N, 4.2.

MS *m/e* (%); FD, M^+ 672 (100), 673 (41).

τ ($CDCl_3$), 1.25 (1H, s, N*H*); −1.05 (1H, s, N*H*); 2.63 (10H, s, 2 × *Ph*CH_2O); 4.70 (2H, s, PhCH_2O); 6.14 (2H, s, 2′-CH_2-2); 6.25 (2H, s, CH_2CO), 6.35 (3H, s, OCH_3); 6.40 (3H, s, OCH_3); 6.45 (3H, s, OCH_3), 6.85–7.90 (8H, m, 2 × CH_2CH_2CO); 8.00 (3H, s, 3′-CH_3).

3,4-Di-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-3′-methyl pyrromethane-5,5′-dicarboxylic acid (**31b**). Dibenzyl-3,4′-di-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-3′-methyl pyrromethane-5,5′-dicarboxylate (0.8 g, 1.1 mmol) was dissolved in tetrahydrofuran (200 ml) containing triethylamine (five drops). The solution was hydrogenolyzed over 10% palladium on charcoal (0.1 g) at room temperature and atmospheric pressure. The mixture was filtered through Celite and evaporated to dryness under reduced pressure to yield the required pyrromethane-5-5′-dicarboxylic acid which was used without further purification (0.50 g, 1.0 mol, 92%).

Dibenzyl-3,4′-di-(2-methoxycarbonylethyl)-4,3′-dimethoxycarbonylmethyl pyrromethane-5,5′-dicarboxylate (**38a**). Benzyl-5-acetoxymethyl-4-(2′-methoxycarbonylethyl)-3-methoxycarbonylmethyl pyrrole-2-carboxylate (0.517 g, 1.2 mol) and benzyl-4-methoxycarbonylmethyl-3-(2′-methoxycarbonylethyl)pyrrole-2-carboxylate (0.413 g, 1.2 mmol) were dissolved in dry methanol (7.5 ml) and toluene-*p*-sulphonic acid monohydrate (20 mg) was added and heated at 38°C for 24 hr under nitrogen. The mixture was diluted with water (5 ml) and an oil separated which was extracted with methylene chloride (3 × 25 ml). The combined extracts were washed with 10% aqueous bicarbonate (20 ml), water (2 × 20 ml), dried ($MgSO_4$), and filtered. Removal of the solvent, after decolourising with charcoal, gave an orange oil, which was chromatographed on alumina (Merck Grade III) eluting with chloroform–light petroleum (bp 40–60°C) (1:9 v/v) giving the required *pyrromethane* which was crystallised from aqueous methanol and recrystallised from methylene chloride–petroleum (40–60°C) (0.596 g, 0.82 mmol, 68%), mp 114–117°C (lit. (*53*) mp 118–119°C).

Found: C, 64.0; H, 5.7; N, 4.0. $C_{39}H_{42}N_2O_{12}$ requires C, 64.1; H, 5.8; N, 3.8.

τ($CDCl_3$), −0.1 (1H, s, N*H*); 0.1 (1H, s, N*H*); 2.70 (10H, s, 2 × *Ph*CH_2O); 4.75 (2H, s, PhCH_2O); 4.78 (2H, s, PhCH_2O); 6.00 (2H, s, pyr-CH_2-pyr); 6.20 (2H, s, CH_2CO); 6.40 (3H, s, OCH_3), 6.42 (6H, s, 2 × OCH_3); 6.45 (2H, s, CH_2CO); 6.48 (2H, s, OCH_3); 6.85–7.60 (pH, m, 2 × CH_2CH_2CO).

MS *m/e* (%); FD M^+ 730 (100).

3,4′-Di-(2-methoxycarbonylethyl)-4,3-′di-(methoxycarbonylmethyl)pyrromethane-5,5′-dicarboxylic acid (**38b**). Dibenzyl-3,4-di-(2-methoxycarbonylethyl)-4,3′-dimethoxycarbonylmethyl pyrromethane-5,5′-dicarboxylate (1.5 g, 2.06 mmol)

was dissolved in tetrahydrofuran (200 ml) and triethylamine (five drops). The solution was hydrogenolysed over 10% palladium on charcoal (200 mg) at room temperature and atmospheric pressure. The mixture was filtered through Celite and evaporated to dryness in a rotary evaporator. The product was dried under reduced pressure at room temperature, overnight, and used without further purification (1.04 g, 1.89 mmol, 92%).

Dibenzyl-3-methoxycarbonylmethyl-3',4-di-(2-methoxycarbonylethyl)-4'-methyl pyrromethane-5,5'-dicarboxylate (**30a**). A mixture of benzyl-5-acetoxymethyl-4-methoxycarbonylmethyl-3-(2'-methoxycarbonylethyl)pyrrole-2-carboxylate (1.72; 4 mmol), benzyl-4-(2'-methoxycarbonylethyl)-3-methylpyrrole-2-carboxylate (1.22 g, 4 mmol), and toluene-*p*-sulphonic acid monohydrate (30 mg) in dry methanol (20 ml) was heated at 38°C for 24 hr under nitrogen. The reaction mixture was diluted with water (250 ml) and extracted with methylene chloride (4 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (50 ml), water (2 × 50 ml), and dried ($MgSO_4$). Removal of the solvent gave an oil which was crystallised from ethanol and recrystallised from methylene chloride–petrol (40–60°C) to yield the desired *pyrromethane* (1.04 g, 3.0 mmol, 75.8%), mp 94–96°C (lit. (*54*) mp 98.5–102.5°C).

Found: C, 66.1; H, 5.8; N, 4.1. $C_{37}H_{40}N_2O_{10}$ requires C, 66.1; H, 6.0; N, 4.2.

τ ($CDCl_3$), 0.1 (2H, s, 2 × N*H*); 2.62 (10H, s, 2 × *Ph*CH_2O); 4.72 (4H, s, 2 × PhCH_2O); 6.05 (2H, s, 2'-CH_2-2); 6.35 (3H, s, OCH_3); 6.38 (3H, s, OCH_3); 6.45 (5H, s, OCH_3 and CH_2CO); 6.84–7.60 (8H, m, 2 × CH_2CH_2CO); 7.70 (3H, s, 4'-CH_3).

MS *m/e* (%); FD M^+ 672 (100).

3'-Methoxycarbonylmethyl-3,4'-di-(2-methoxycarbonylethyl)-4-methyl pyrromethane-5,5'-dicarboxylic acid (**30b**). Dibenzyl-3'-methoxycarbonylmethyl-3-4'-di-(2-methoxycarbonylethyl)-4-methyl pyrromethane-5,5'-dicarboxylate (3.2 g, 4.8 mmol) was dissolved in tetrahydrofuran (200 ml) and triethylamine (five drops). The solution was hydrogenolysed over 10% palladium charcoal (0.2 g) at room temperature and atmospheric pressure. When the hydrogen uptake ceased the mixture was filtered through Celite and evaporated to dryness under reduced pressure to yield the required *pyrromethane*-5-5'-dicarboxylic acid which was used without further purification (2.3 g, 4.7 mmol, 98%).

τ ($CDCl_3$/$DMSOd_6$), −0.98 (1H, s, N*H*); −0.68 (1H, s, N*H*); 2.90 (2H, br, 2 × CO_2H); 6.10 (2H, s, 2'-CH_2-2); 6.32 (6H, s, 2 × OCH_3); 6.37 (3H, s, OCH_3); 6.48 (2H, s, CH_2CO); 6.90–7.70 (8H, m, 2 × CH_2CH_2CO); 7.85 (3H, s, 4-CH_3).

5,5'-Diformyl-3-methoxycarbonylmethyl-3',4-di-(2-methoxycarbonylethyl)-4'-methyl pyrromethane (**30c**). Finely ground 3-methoxycarbonylmethyl-3',4-di-(2-methoxycarbonylethyl)-4-methyl pyrromethane-5,5'-dicarboxylic acid (1 g, 2.03 mmol) was added in small portions to trifluoroacetic acid (5 ml) and the mixture stirred for 5 min at 40°C. The solution was then cooled to 0°C and triethylorthoformate (1.4 ml) was added. The mixture was filtered off and then added to a mixture of ethanol (5 ml) and aqueous 1 *M* ammonium hydroxide (25 ml), the product was filtered off after stirring for 10 min and recrystallised from methylene chloride–petrol (40–60°C) giving the required *5,5'-diformyl pyrromethane* (0.5 g, 1.08 mmol, 53%) mp 162–164°C (lit. (*54*) mp 157–163°C).

Found: C, 60.0, H, 6.3, N, 5.9. $C_{23}H_{28}N_2O_8$ requires C, 60.0; H, 6.1; N, 6.10.

τ($CDCl_3$), −0.60 (1H, s, N*H*); −0.45 (1H, s, N*H*); 0.45 (1H, s, CO*H*); 0.55 (1H, s, CO*H*); 6.00 (2H, s, pyr-CH_2 pyr); 6.25 (3H, s, OCH_3); 6.30 (3H, s, OCH_3); 6.35 (3H, s, OCH_3); 6.45 (2H, s, CH_2CO); 6.83–7.55 (8H, m, 2 × CH_2CH_2CO); 7.72 (3H, s, CH_3).

MS *m/e* (%); FD M^+ 460 (100).

t-Butyl-3,3'-di-(2-methoxycarbonylethyl)-4-methyl-4'-methoxycarbonylmethyl-5'-benzyloxycarbonyl pyrromethane-5-carboxylate (**33a**). (i). A mixture of t-butyl-4-(2-methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (0.315 g, 1.2 mmol), benzyl-5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-carboxylate (0.502 g, 1.2 mmol) and toluene-*p*-sulphonic acid monohydrate (20 mg) in dry methanol (15 ml) was heated at 47°C for 40 hr under nitrogen. The reaction mixture was then cooled and diluted with water (100 ml) and extracted with methylene chloride (4 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (50 ml), water (2 × 50 ml), and dried ($MgSO_4$). Removal of the solvent gave a brown oil which was chromatographed on alumina (Merck Grade III) eluting with chloroform–petrol (40–60°C) (1:9, v/v), giving the required pyrromethane (0.418 g, 0.655 mmol 54.6%) as a colourless oil which could not be crystallised.

τ($CDCl_3$), 0.66 (1H, s, N*H*); 1.13 (1H, s, N*H*); 2.65 (5H, s, *Ph*CH_2O); 4.75 (2H, s, Ph.CH_2O); 6.03 (2H, s, 2-CH_2-2'); 6.17 (CH_2CO); 6.32 (3H, s, OCH_3); 6.42 (6H, s, 2 × OCH_3); 7.27 (4H, t, 2 × CH_2CH_2CO); 7.52 (4H, t, CH_2CH_2CO); 7.75 (3H, s, 4-CH_3); 8.47 (9H, s, OC (CH_3)$_3$).

MS *m/e* (%); FD M^+ 638 (100).

(ii) Benzyl-5-acetoxymethyl-4-(2'-methoxycarbonylethyl)-3-methoxycarbonylmethyl pyrrole-2-carboxylate (1.455 g, 3.4 mmol) and t-butyl-4-(2'-methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (0.860 mg, 3.4 mmol) were dissolved in glacial acetic acid (10 ml). Toluene-*p*-sulphuric acid (20 mg) was added and the mixture heated at 45°C for 3 hr under dry nitrogen. The mixture was poured into ice water (600 ml) and extracted with methylene chloride (3 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (50 ml), water (2 × 50 ml), and dried ($MgSO_4$). The solvent was removed in a rotary evaporator and the residual oil was chromatographed on alumina (Merck Grade III) eluting with chloroform–petrol (40–60°C; 1:9, v/v) giving the required *pyrromethane* (1.34 g, 2.1 mmol, 61.8%) as colourless oil which could not be crystallised; the nmr spectrum was identical with that of the material prepared by method (i) above.

Benzyl-3,3'-di-(2-methoxycarbonylethyl)-4'-methyl-4-methoxycarbonylmethyl pyrromethane-5-carboxylate (**33b**). The foregoing pyrromethane t-butyl ester (303 mg, 0.47 mmol) was dissolved in dry trifluoroacetic acid (5 ml) under nitrogen and stirred at room temperature for 2 hr. The reaction mixture was poured into ice water (200 ml) and extracted with methylene chloride (4 × 50 ml) and the combined extracts were washed with 10% aqueous sodium carbonate (2 × 20 ml), water (3 × 20 ml), and dried ($MgSO_4$). Removal of the solvent gave the required α-free pyrromethane (226 mg, 0.42 mmol, 90%) as a colourless oil.

τ($CDCl_3$), 0.85 (1H, s, N*H*); 1.93 (1H, s, N*H*); 2.67 (5H, s, *Ph*CH_2); 3.60 (1H, s, 5'-H); 4.79 (2H, s, PhCH_2O); 6.10 (2H, s, 2'-CH_2-2); 6.21 (2H, s, CH_2CO);

6.40 (3H, s, OCH_3); 6.45 (3H, s, OCH_3); 6.47 (3H, s, OCH_3); 7.27 (4H, t, 2 × CH_2CH_2CO); 7.52 (4H, t, 2 × CH_2CH_2CO); 8.02 (3H, s, 4'-CH_3).

MS *m/e* (%); FD M^+ 538 (100).

t - Butyl - 3,4' - di - (2 - methoxycarbonylethyl) - 3',4 - dimethyl - 5' - benzyloxycarbonyl pyrromethane-5-carboxylate (**50a**). (i). A mixture of t-butyl-5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (3.97 g, 0.012 mmol), benzyl-3-methyl-2-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (3.55 g, 0.012 mmol), and toluene-*p*-sulphonic acid monohydrate (179 mg) in dry methanol (30 ml) was heated at 43°C for 18 hr under nitrogen. The reaction mixture was diluted to 100 ml with water and extracted with methylene chloride (4 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (50 ml), water (2 × 50 ml), and dried ($MgSO_4$). Removal of the solvent gave an oil which was chromatographed on alumina (Merck Grade III) eluting with chloroform–petrol (40–60°C) (1 : 19, v/v) giving the required *pyrromethane* (3.55 g, 6.1 mmol, 55%) which was crystallised from diethyl ether, mp 156–158°C.

Found: C, 66.2; H, 7.1; N, 4.5. $C_{32}H_{40}O_8N_2$ requires C, 66.2; H, 6.9; N, 4.8.

τ($CDCl_3$), 0.77 (1H, s, N*H*); 1.50 (1H, s, N*H*); 2.71 (5H, s, *Ph*CH_2O); 4.79 (2H, s, PhCH_2O); 6.13 (2H, s, 2'-CH_2-2); 6.40 (3H, s, OCH_3); 6.45 (3H, s, OCH_3); 6.9–7.6 (8H, m, 2 × CH_2CH_2CO); 7.8 (3H, s, CH_3); 8.00 (3H, s, CH_3); 8.50 (9H, s, OC(CH_3)$_3$.

MS *m/e* (%); FD M^+ 580 (100).

(ii) t-Butyl-4-(2-methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (2 g, 7.4 mmol) and benzyl-5-acetoxymethyl-4-methyl-2-(2-methoxycarbonylethyl) pyrrole-2-carboxylate (2.76 g, 7.4 mmol) were dissolved in glacial acetic acid (30 ml) and heated at 90°C for 2 hr under nitrogen. Then the solution was poured into ice water (300 ml) and left overnight at 0°C. The precipitate was filtered off and dissolved in chloroform decolourised (charcoal), filtered through Celite, and the solvent evaporated off under reduced pressure. The residue was chromatographed on alumina (Merck Grade III) eluting with chloroform–petrol (40–60°C) (1 : 19; v/v) giving the required pyrromethane which was recrystallised from diethylether (0.768 g, 1.33 mmol, 48%).

Benzyl-3,4'-di-(2-methoxycarbonylethyl)-3',4-dimethyl pyrromethane-5'-carboxylate (**50b**). t-Butyl-3,4'-di-(2-methoxycarbonylethyl)-3',4-dimethyl-5'-benzyloxycarbonyl pyrromethane-5-carboxylate (0.605 g, 1.16 mmol) was dissolved in dry trifluoroacetic acid (5 ml) and stirred at room temperature for 1 hr. To the reaction mixture was added methylene chloride (20 ml) and it was then washed with 10% aqueous sodium bicarbonate (2 × 10 ml), water (2 × 20 ml), dried ($MgSO_4$), and the solvent removed under reduced pressure at 20°C giving the required α-free *pyrromethane* as a colourless oil (520 mg, 1.08 mmol, 93%), which was used without any further purification.

τ ($CDCl_3$), 0.66 (1H, s, N*H*); 1.00 (1H, s, N*H*); 2.70 (5H, s, P*h*CH_2O); 3.65 (1H, d, 5'-H); 4.78 (2H, s, PhCH_2O); 6.15 (2H, s, 2'-CH_2-2); 6.40 (3H, s, OCH_3); 6.45 (3H, s, OCH_3); 6.90–7.55 (8H, m, 2 × CH_2CH_2CO); 8.02 (6H, s, 2 × CH_3).

MS *m/e* (%); FD M^+ 480 (100).

t-Butyl-3,4'-di-(2-methoxycarbonylethyl)-4-methyl-3'-methoxycarbonylmethyl-5'-benzyloxycarbonyl pyrromethane-5-carboxylate (**41a**). A mixture of t-butyl-4-

(2-methoxycarbonylethyl)-3-methyl pyrrole-2-carboxylate (0.54 g, 2.2 mmol), benzyl - 5 - acetoxymethyl - 4 - methoxycarbonylmethyl - 3 - (2 - methoxycarbonylethyl)pyrrole-2-carboxylate (0.95 g, 2.2 mmol), and toluene-*p*-sulphonic acid monohydrate (30 mg) in dry methanol (13 ml) was heated at 47°C for 55 hr under nitrogen. The reaction mixture was cooled and diluted to 100 ml with water and partitioned with methylene chloride (4 × 50 ml). The combined extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$). Removal of the solvent gave an oil which was chromatographed on alumina (Merck Grade III) eluting with chloroform–light petroleum (bp 40–60°C) (1 : 4, v/v) giving the required *pyrromethane* (0.73 g, 1.14 mmol, 52%) as a colourless oil which was induced to crystallise from benzene–petrol (40–60°C), mp 40–45°C.

Found: C, 64.1; H, 6.6; N, 4.5. $C_{34}H_{42}O_{10}N_2$ requires C, 64.0; H, 6.6; N, 4.4.

τ ($CDCl_3$), 0.25 (1H, s, N*H*); 0.40 (1H, s, N*H*); 2.70 (5H, s, P*h*CH_2O); 4.77 (2H, s, PhCH_2O); 6.10 (2H, s, 2'-CH_2-2); 6.25 (2H, s, -CH_2CO); 6.40 (3H, s, OCH_3); 6.45 (3H, s, OCH_3); 6.48 (3H, s, OCH_3); 6.9–7.5 (8H, m, 2 × CH_2CH_2CO); 7.75 (3H, s, CH_3); 8.48 (9H, s, OC(CH_3)$_3$).

MS *m/e* (%); FD M^+ 638 (100).

Benzyl-3-methoxycarbonylmethyl-3',4-di-(2-methoxycarbonylethyl)-4'-methyl pyrromethane-5-carboxylate (**41b**). t-Butyl-3,4'-di-(2-methoxycarbonylethyl)-4-methyl-3'-methoxycarbonylmethyl-5'-benzyloxycarbonyl pyrromethane (538 mg, 0.84 mmol) was dissolved in dry trifluoroacetic acid (5 ml) and stirred at room temperature for 1 hr. To the reaction mixture was added methylene chloride (20 ml) and it was then washed with 10% aqueous sodium carbonate (2 × 10 ml), water (2 × 20 ml), dried ($MgSO_4$), and the solvent removed in a rotary evaporator at room temperature, giving the required α-free *pyrromethane* (0.386 mg, 0.72 mmol, 85%).

τ ($CDCl_3$), 0.28 (1H, s, N*H*); 1.05 (1H, s, N*H*); 2.69 (5H, s, *Ph*CH_2O); 3.60 (1H, d, 5'-H); 4.75 (2H, s, PhCH_2O); 6.13 (2H, s, 2'-CH_2 · 2); 6.28 (3H, s, OCH_3); 6.40 (3H, s, OCH_3); 6.45 (2H, s, CH_2CO); 6.48 (3H, s, OCH_3); 6.9–7.5 (8H, m, 2 × CH_2CH_2CO); 8.00 (3H, s, 4-CH_3).

MS *m/e* (%); FD M^+ 538 (100).

Benzyl - 5' - dimethylcarbamoyl - 3,4' - dimethoxycarbonylmethyl - 4,3' - di - (2 - methoxycarbonylethyl)pyrromethane-5-carboxylate (**32**). A mixture of 4-(2'-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-*N*,*N*-dimethylamido pyrrole (0.59 g, 1.99 mmol), benzyl-5-acetoxymethyl-4-methoxycarbonylmethyl-3-(2-methoxycarbonylethyl)pyrrole-2-carboxylate (0.86 g, 1.99 mmol), and toluene-*p*-sulphonic acid monohydrate (30 mg) was stirred at 42°C for 48 hr under nitrogen. The reaction mixture was stirred onto ice water (300 ml) and extracted with chloroform (4 × 50 ml). The combined extracts were washed with 10% aqueous sodium bicarbonate (50 ml), water (2 × 50 ml), and dried ($MgSO_4$). Removal of the solvent gave an oil which was chromatographed on alumina (Merck Grade III) eluting with chloroform–petrol (40–60°C) (1 : 9 to 3 : 7, v/v) giving the required *pyrromethane* as a colourless oil, which was crystallised from aqueous methanol (0.92 g, 1.36 mmol, 68.5%), mp 138–142°C.

Found: C, 61.5; H, 6.2; N, 6.5. $C_{34}H_{41}O_{11}N_3$ requires C, 61.2; H, 6.2; N, 6.3.

τ ($CDCl_3$), 0.08 (1H, s, N*H*); 0.28 (1H, s, N*H*); 2.68 (5H, s, *Ph*CH_2)); 4.77 (2H,

s, PhCH_2O); 6.13 (2H, s, 2'-CH_2-2); 6.30 (3H, s, OCH_3); 6.36 (3H, s, OCH_3); 6.38 (2H, s, CH_2CO); 6.40 (2H, s, CH_2CO); 6.42 (3H, s, OCH_3); 6.48 (3H, s, OCH_3); 6.90–7.58 (8H, m, 2 × CH_2CH_2CO); 7.06 (6H, s, CON(CH_3)$_2$).

MS *m/e* (%); FD M$^+$ 667 (100).

Benzyl-5'-dimethylcarbamoyl-3,3'-di-(2-methoxycarbonylethyl)-4-methyl-4'-methoxycarbonylmethyl pyrromethane-5-carboxylate (**42**). A mixture of benzyl-5-acetoxymethyl-4-(2-methoxycarbonylethyl)-3-methyl-2-carboxylate (794 mg, 2.13 mmol), 4-(2-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-*N,N*-dimethylamido pyrrole (630 mg, 2.13 mmol), and toluene-*p*-sulphonic acid monohydrate (30 mg) in dry methanol (15 ml) was heated at 47°C for 52 hr under nitrogen. The reaction mixture was stirred into water (200 ml) and extracted with methylene chloride (4 50 ml). The extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue chromatographed on alumina (Merck Grade III) eluting with chloroform–petroleum (bp 40–60°C) (3:7, v/v) giving the required *pyrromethane* (808 mg, 1.33 mmol, 62.3%) as an oil which could not be induced to crystallise.

Found: C, 63.7; H, 6.7; N, 7.4. $C_{32}H_{39}N_3O_9$ requires, C, 63.1; H, 6.4; N, 6.9.

τ(CCl_3), 0.15 (1H, s, N*H*); 1.20 (1H, s, N*H*); 2.60 (5H, s, P*h*CH_2O); 4.66 (2H, s, PhCH_2O); 6.03 (2H, s, 2'-CH_2-2); 6.25 (3H, s, OCH_3); 6.28 (3H, s, OCH_3); 6.30 (2H, s, 4'-CH_2CO); 6.32 (3H, s, OCH_3); 6.94 (6H, s, N (CH_3)$_2$); 7.08–7.52 (8H, m, 2 × CH_2CH_2CO); 7.65 (3H, s, 4-CH_3).

MS *m/e* (%); FD 609 (100).

Benzyl-5'-dimethylcarbamoyl-4,3'-di-(2-methoxycarbonylethyl)-3-methyl-4'-methoxycarbonylmethyl pyrromethane-5-carboxylate (**46**). A mixture of 4-(2'-methoxycarbonylethyl)-3-methoxycarbonylmethyl-2-*N,N*-dimethylamido pyrrole (0.74 g, 2.51 mmol), benzyl-5-acetoxymethyl-4-methyl-3-(2-methoxycarbonylethyl)-2-carboxylate (0.93 g, 2.5 mmol), and toluene-*p*-sulphonic acid monohydrate (25 mg) in dry methanol (10 ml) was heated at 45°C for 40 hr under nitrogen. (After 24 hr a white precipitate appeared.) The reaction mixture was cooled and left in the refrigerator overnight and filtered, washed with methanol (15 ml) at −20°C, and recrystallised first from methanol, then from methylene chloride–petroleum (40–60°C) giving the desired *5-dimethylamido pyrromethane* (1.088 g, 1.79 mmol, 71.2%), mp 154–155°C.

Found: C, 63.4; H, 6.4; N, 7.1. $C_{32}H_{39}O_9N_3$ requires C, 63.1; H, 6.4; N, 6.9.

τ(CCl_3), 0.45 (1H, s, N*H*); 0.72 (1H, s, N*H*); 2.67 (5H, s, P*h*CH_2O); 4.76 (2H, s, PhCH_2O); 6.22 (2H, s, 2'-CH_2-2); 6.38 (3H, s, OCH_3); 6.40 (3H, s, OCH_3); 6.42 (3H, s, OCH_3); 6.47 (2H, s, CH_2CO); 6.82–7.66 (8H, m, 2 × CH_2CH_2CO); 7.06 (6H, s, CON(CH_3)$_2$); 8.06 (3H, s, 3-CH_3).

MS *m/e* (%); FD M$^+$ 609 (100).

Oxobilanes

Dibenzyl - 1,3,6,7 - tetra - (2 - methoxycarbonylethyl) - 2,4,8 - trimethoxycarbamoylmethyl-5-methyl-b-oxobilane-1',8'-dicarboxylate (**34b**). Benzyl-5'-dimethylcarbonyl - 3,4 - di - (methoxycarbonylmethyl) - 4,3' - di - (2 - methoxycarbonylethyl)pyrromethane-5-carboxylate (254 mg, 0.38 mmol) was dissolved in

freshly distilled phosphoryl chloride (5 ml) and stirred at 50°C for 45 min under nitrogen. (The new band formed in the uv at 378 nm had then reached a maximum intensity.) Excess phosphoryl chloride was removed under vacuum, the last traces being "chased out" with 1,2-dibromoethane (2 × 10 ml).

A solution of the resulting brown oil (λ_{max} nm (log ϵ_{max}) 273 (4.40); 378 (4.25)) in dry methylene chloride (10 ml) was treated under nitrogen with a solution of benzyl-3,3′-di-(2-methoxycarbonylethyl)-4′-methyl-4-methoxycarbonylmethyl pyrromethane-5-carboxylate (205 mg, 0.38 mmol) in dry methylene chloride (10 ml). The mixture was heated under reflux in the dark and under nitrogen (a bathochromic shift occurring) until the new band at λ_{max} 407 nm had reached its maximum (48 h). Methylene chloride (100 ml) was added and the solution washed with water (2 × 50 ml) and dried ($MgSO_4$). Removal of the solvent gave a brown oil which was chromatographed on alumina (Merck, Grade III) eluting with light petroleum (bp 40–60°C), gradually enriching with ethyl acetate, up to 100% ethyl acetate. The column was stripped with methanol to elute the bilane imino salt. The methanol eluate was evaporated under vacuum and the desired imino salt was obtained as a light brown oil (265 mg, 0.22 mmol; 57%) λ_{max} nm (log ϵ_{max}) in CH_2Cl_2 278.5 (4.45); 3.67 shoulder (4.15); 407 (4.34).

The imino salt (225 mg, 0.18 mmol) was dissolved in methylene chloride (25 ml) and hydrolysed by stirring under reflux with 10% aqueous sodium carbonate (20 ml) until the new band in the uv at 356 nm reached its maximum (12 hr). The organic layer was separated, washed with water (2 × 20 ml), and dried ($MgSO_4$). The solvent was evaporated under vacuum and the oily residue chromatographed on alumina (Merck Grade III) eluting with light petroleum (bp 40–60°C) gradually enriching with ethyl acetate, finally ethyl acetate containing a small amount of methanol was used and the required *b-oxobilane* was obtained as a light brown oil which could not be crystallized (163 mg, 0.14 mmol, 76%).

λ_{max} nm (log ϵ_{max}) EtOH, 277 (4.63); 356 (4.37); EtOH/C · HCl bathochromic shift to 450 (4.38).

τ ($CDCl_3$), 0.40 (2H, br, 2 × N*H*); 0.50 (2H, br, 2 × N*H*); 2.68 (10H, s, 2 × PhCH_2O); 4.78 (4H, s, 2 × PhCH_2O); 5.95 (2H, s, pyr · CH_2 · pyr); 5.98 (pyr · CH_2 · pyr); 6.25 (2H, s, CH_2CO); 6.37 (3H, s, OCH_3); 6.42 (6H, s, 2 × OCH_3); 6.44 (3H, s, 2 × OCH_3); 6.46 (6H, s, 2 × OCH_3); 6.51 (3H, s, OCH_3); 6.60 (2H, s, CO_2CO); 6.70 (2H, s, CH_2CO); 7.00–7.75 (16H, m, 4 × CH_2CH_2CO); 7.08 (3H, s; 5-CH_3).

Dibenzyl - 1,3,6,7 - tetra - (2 - methoxycarbonylethyl) - 2,5 - dimethoxycarbonylmethyl-4,8-dimethyl-b-oxobilane-1′,8′-dicarboxylate (**43b**). Benzyl-5′-dimethylcarbamoyl - 3,3′ - di - (2 - methoxycarbonylethyl) - 4 - methoxycarbonylmethyl 4-methyl pyrromethane-5-carboxylate (597 mg, 0.98 mmol) was dissolved in freshly distilled phosphoryl chloride (10 ml) and stirred at 70°C for 60 min under nitrogen. (A new band in the uv at 385 nm had reached a maximum intensity.) The excess of phosphoryl chloride was removed under vacuum, the last traces being chased out with 1,2-dibromoethane (2 × 10 ml).

A solution of the resulting brown oil (λ_{max} nm 385 and 278) in dry methylene chloride (10 ml) was treated under nitrogen with a solution of benzyl-3-methoxycarbonylmethyl-3′,4-di-(2-methoxycarbonylethyl)-4′-methyl pyrromethane-5-car-

boxylate (530 mg, 0.99 mmol). The mixture was heated under reflux in the dark and under nitrogen (a bathochromic shift occurring) until the new band at 408 nm had reached its maximum (52 hr). Methylene chloride (100 ml) was added and the solution washed with water (2 × 50 ml) and dried ($MgSO_4$). Removal of the solvent gave an oil which was chromatographed on alumina (Merck Grade III) eluting with petrol (40–60°C) gradually enriching with ethyl acetate, until finally just ethyl acetate. The column was stripped with methanol where the bilane imino salt was eluted. Methanol was evaporated off under vacuum and the desired imino salt was obtained as a light brown oil (750 mg, 0.64 mol, 65.4%) λ_{max} nm (in CH_2Cl_2) 408.

The imino salt (710 mg, 0.61 mmol) was dissolved in methylene chloride (25 ml) and hydrolysed by stirring under reflux with 10% aqueous sodium carbonate (30 ml) until the new band in the uv at 356 nm reached its maximum (8 hr). The organic layer was separated, washed with water (2 × 20 ml), and dried ($MgSO_4$). The solvent was evaporated off under vacuum and the oily residue chromatographed on alumina (Merck Grade III) eluting with petrol (40–60°C), gradually enriching with ethyl acetate until finally just ethyl acetate and methanol. The required *b*-oxobilane was obtained as a light brown oil which was not possible to induce to crystallise (528 mg, 0.48 mmol; 78%).

λ_{max} nm in ethanol 362; in ethanol + concd HCl bathochromic shift to 451.

τ($CDCl_3$), −0.05 (1H, s, N*H*); −0.02 (1H, s, N*H*); 0.10 (1H, s, N*H*); 0.12 (1H, s, NH); 2.68 (10H, s, 2 × P*h*CH_2O); 4.80 (4H, s, 2 × PhCH_2O); 6.16 (2H, s, pyr · CH_2 pyr); 6.20 (2H, s, pyr · CH_2 pyr); 6.40 (9H, s, 3 × OCH_3); 6.45 (6H, s, 2 × OCH_3); 6.48 (3H, s, OCH_3); 6.50 (4H, s, CH_2CO); 6.83–7.50 (16H, m, 4 × CH_2CH_2CO); 8.08 (6H, s, 2 × CH_3).

Dibenzyl - 1,3,6,7 - tetra - (2 - methoxycarbonylethyl) - 2,5 - dimethyl - 4,8 - dimethoxycarbonylmethyl-b-oxobilane-1',8'-dicarboxylate (**47b**) was prepared by the procedure described above from benzyl-5'-dimethylcarbamoyl-4,3'-di-(2-methoxycarbonylethyl)-3-methyl-4'-methoxycarbonylmethyl pyrromethane-5-carboxylate (874 mg); 1.44 mmol) (phosphoryl chloride complex λ_{max} nm (in CH_2Cl_2) 384) and benzyl-3,3'-di-(2-methoxycarbonylethyl)-4'-methyl-4-methoxycarbonylmethyl pyrromethane-5-carboxylate (849 mg; 1.58 mmol). The required imino salt was obtained as an oil (438.5 mg, 0.373 mmol, 26%); λ_{max} nm (in EtOH) 409.

The imino salt (412 mg, 0.350 mmol) was hydrolysed and purified as previously described and the desired *b-oxobilane* was obtained as an oil (275 mg, 0.250 mmol, 71%).

λ_{max} nm (in methanol) 361, (in methanol + concd HCl) bathochromic shift to 455.

τ($CDCl_3$), −0.08 (1H, s, N*H*); −0.03 (1H, s, N*H*); 0.015 (2H, s, 2 × N*H*); 2.77 (10H, s, 2 × P*h*CH_2O); 4.83 (2H, s, PhCH_2O); 4.85 (2H, s, PhCH_2O); 6.13 (2H, s, pyr CH_2 pyr); 6.23 (2H, s, pyr-CH_2 pyr); 6.44 (12H, s, 4 × OCH_3); 6.50 (6H, s, 2 × OCH_3); 6.54 (4H, s, 2 × -CH_2CO); 6.93–7.80 (16H, m, 4 (CH_2CH_2CO); 8.08 (6H, s, 2 × CH_3).

Dibenzyl - 1,3,6,7 - tetra - (2 - methoxycarbonylethyl) - 2,4,8 - trimethyl - 5 -methoxycarbonylmethyl-b-oxobilane-1',8'-dicarboxylate (**51b**). This compound was

synthesised by the procedure described above from benzyl-5′-dimethylcarbamoyl 3,3′-di-(2-methoxycarbonylethyl)-4-methyl-4′-methoxycarbonylmethyl pyrromethane-5-carboxylate (415 mg, 0.681 mmol) and benzyl-3′-4-di-(2-methoxycarbonylethyl)-3,4′-dimethyl pyrromethane 5-carboxylate (343 mg, 0.715 mmol). (Amido pyrromethane-phosphoryl chloride complex λ_{max} nm 278; 385). The desired imino salt was obtained as a light brown oil (444 mg, 0.397 mmol, 58.3%); λ_{max} nm (in CH_2Cl_2) 406.

The imino salt (425.5 mg, 0.381 mmol) was hydrolysed and purified as previously described and the required *b*-oxobilane was obtained as an oil (293 mg, 0.280 mmol, 73.5%).

λ_{max} nm (in methanol) 362, (in methanol + concd HCl) bathochromic shift to 448.

τ($CDCl_3$), −0.10 (1H, s, N*H*); −0.05 (1H, s, N*H*); 0.08 (1H, s, N*H*); 0.12 (1H, s, N*H*); 2.67 (10 × H, s, 2 × P*h*CH_2O); 4.76 (4H, s, 2 × PhCH_2O); 6.13 (2H, s, pyr · CH_2 · pyr); 6.17 (2H, s, pyr · CH_2 pyr); 6.35 (6H, s, 2 × OCH_3); 6.38 (3H, s, OCH_3); 6.42 (3H, s, OCH_3); 6.44 (3H, s, OCH_3); 6.50 (2H, s, CH_2CO); 6.78–7.68 (16H, m, 4 × CH_2CH_2CO); 7.98 (3H, s, CH_3); 8.08 (6H, s, 2 × CH_3).

Porphyrins

1 - Methyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 3,5,8 - tri-(methoxycarbonylmethyl) porphyrin (**2b**). 5,5′-Diformyl-3-methoxycarbonylmethyl-3′,4-di-(2-methoxycarbonylethyl)-4-methyl pyrromethane (0.100 g, 0.22 mmol) was dissolved in a solution of 3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethoxycarbonylmethyl pyrromethane-5,5′-dicarboxylic acid (157 mg, 0.29 mmol) in methylene chloride (200 ml) and methanol (5 ml), with strict exclusion of light, and toluene-*p*-sulphonic acid monohydrate (0.95 g) in methanol (20 ml) was added. The mixture was stirred for 24 hr in the dark at 20°C and then a saturated solution of zinc acetate in methanol (20 ml) was added. Stirring in the dark at 20°C was continued until the Soret band had reched a maximum (46 hr), then the mixture was washed with 10% aqueous sodium bicarbonate (2 × 50 ml), water (3 × 100 ml), dried ($MgSO_4$), and the solvent evaporated under reduced pressure. The residue was dissolved in 5% (v/v) sulphuric acid in methanol (100 ml) and stirred overnight in the dark, and then poured into methylene chloride (300 ml). The solution was washed with water (150 ml), 10% aqueous sodium bicarbonate (2 × 100 ml), water (2 × 100 ml), 7% aqueous sodium chloride (100 ml), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue chromatographed twice on alumina (Merck Grade III) eluting first with methylene chloride to obtain the porphyrin fraction, and secondly with chloroform–toluene (1 : 1, v/v) giving the desired porphyrin *heptamethyl ester* which crystallised from chloroform–methanol (87.5 mg, 0.10 mmol, 45%), mp 214–215°C (lit. (*55*) mp 213–216°C, (*39*) 217–219°C.

Found: C, 62.3; H, 5.8; N, 6.4. $C_{46}H_{52}O_{14}N_4$ requires C, 62.4; H, 5.9; N, 6.3.

λ_{max} (log ϵ) in $CHCl_3$, 404 (5.33); 501 (4.18); 536 (3.95); 571 (3.84); 622 (3.56).

τ($CDCl_3$) (0.055 *M*), 0 (2H, s, 2 *meso-H*); 0.09 (2H, s, 2 × *meso-H*); 4.92 (2H, s, CH_2CO); 4.97 (4H, s, 2 × CH_2CO); 5.51–5.70 (8H, m, 4 × CH_2CH_2CO); 6.22

(9H, s, 3 × OCH_3); 6.30 (3H, s, OCH_3); 6.32 (9H, s, 3 × OCH_3); 6.40 (3H, s, 1-CH_3); 6.50–6.72 (8H, m, 4 × CH_2CH_2CO); 14.02 (2H, s, N*H*).

MS *m/e* (%); FD M^+ 884 (100).

1,5,8-Tri(methoxycarbonylmethyl)-3-methyl-2,4,6,7-tetra-(2-methoxycarbonylethyl)porphyri (**3b**) was synthesised by the procedure described above from 5,5′-diformyl-3-methoxycarbonylmethyl-3′,4-di-(2-methoxycarbonylethyl)-4-methyl pyrromethane (0.1 g, 0.22 mmol) and 3,3′-dimethoxycarbonylmethyl-4,4′-di-(2-methoxycarbonylethyl)pyrromethane 5,5′-dicarboxylic acid (157 mg, 0.29 mmol). After chromatographing twice on alumina (Merck Grade III) eluting first with methylene chloride and then with chloroform–toluene (1 : 1, v/v) the *porphyrin heptacarboxylic heptamethyl ester* was recrystallised twice from chloroform–methanol (82 mg, 0.092 mmol, 42%), mp 224–226°C (lit. mp 227–228°C (*53*), 229–230°C (*39*).

Found: C, 62.7; H, 6.2; N, 6.1. $C_{46}H_{52}O_{14}N_4$ requires C, 62.4; H, 5.9; N, 6.3).

λ_{max} (log ϵ) in $CHCl_3$, 404 (5.27); 501 (4.13); 536 (3.95); 571 (3.81); 624 (3.42).

τ ($CDCl_3$) (0.056 *M*), −0.06 (2H, s, 2 × *meso-H*); 0.01 (1H, s, *meso-H*); 0.09 (1H, s, *meso-H*); 4.85 (2H, s, CH_2CO); 4.92 (4H, s, 2 × CH_2CO); 5.43–5.71 (8H, m, 4 × CH_2CH_2CO); 6.20 (9H, s, 3 × OCH_3); 6.30 (6H, s, 2 × OCH_3); 6.33 (6H, s, 2 × OCH_3); 6.43 (3H, s, 3-CH_3); 6.47–6.75 (8H, m, 4 × CH_2CH_2CO); 14.05 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 884 (100).

1,3,8-Trimethoxycarbonylmethyl-2,4,6,7-tetra(2-methoxycarbonylethyl)-5-methylporphyrin (**4b**) was synthesised by the procedure described above from 5,5′-diformyl-4,4′-di-(2-methoxycarbonylethyl)-3,3′-dimethoxycarbonylmethyl pyrromethane (67 mg, 0.13 mmol) and 3,4′-di-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-3′-methyl pyrromethane-5,5′-dicarboxylic acid (83 mg, 0.17 mmol). After the Soret band of the porphyrin had reached a maximum (60 hr) the solution was worked up and purified as described for the preceding porphyrins yielding the *heptacarboxylic porphyrin heptamethylester* as red needles (42 mg, 0.048 mmol, 36.5%), mp 239–241°C (lit. (*53, 57*) mp. 237–240°C, (*39*) 243–244°C).

Found: C, 62.5; H, 6.1; N, 6.0. $C_{46}H_{52}O_{14}N_4$ requires C, 62.4; H, 5.9; N, 6.3.

λ_{max} (log ϵ) in $CHCl_3$, 404 (5.28); 501 (4.14); 535 (3.96); 569 (3.80); 624 (3.37).

τ ($CDCl_3$) (0.056 *M*), −0.14 (1H, s, *meso-H*); −0.07 (2H, s, 2 × *meso* H); 0.02 (1H, s, *meso* H); 4.90 (2H, s, CH_2CO); 4.95 (2H, s, CH_2CO); 5.05 (2H, s, CH_2CO); 5.50–5.80 (8H, m, 4 × CH_2CH_2CO); 6.22 (6H, s, 2 × OCH_3); 6.25 (3H, s, OCH_3); 6.33 (9H, s, 3 × OCH_3); 6.39 (3H, s, OCH_3); 6.43 (3H, s, 5-CH_3); 6.57–6.80 (8H, m, 4 × CH_2CH_2CO); 13.98 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 884 (100).

1,3,5-Trimethoxycarbonylmethyl-2,4,6,7-tetra-(2-methoxycarbonylethyl)-8-methyl-δ-acetoxyporphyrin (**36**). Dibenzyl-1,3,6,7-tetra-(2-methoxycarbonylethyl)-2,4,8-trimethoxycarbonylmethyl-5-methyl-*b*-oxobilane-1′8′-dicarboxylate (150 mg, 0.129 mmol) was dissolved in dry tetrahydrofuran (50 ml) and triethylamine (five drops) and hydrogenolysed on 10% palladium on charcoal (0.1 g) at room temperature and atmospheric pressure. When the hydrogen uptake finished (and tlc showed the product remained on the baseline) the suspension was filtered through Celite and the solvent evaporated under reduced pressure at

20°C to give the desired *b-oxobilane-1',8'-dicarboxylic acid* (124 mg, 0.126 mmol, 98%), λ_{max} nm (ethanol) 272 and 346, (ethanol + concd HCl) bathochromic shift to 449. The *b*-oxobilane-1',8'-dicarboxylic acid was dissolved in 1 *M* trichloroacetic acid in methylene chloride (20 ml). Methylene chloride (100 ml) was added followed by methylorthoformate (1 ml). The solution was stirred for 3 hr at 20°C in the dark and in the presence of air; then pyridine (2.5 ml) was added and the solution stirred for further 24 hr. The green solution was evaporated to dryness under reduced pressure. The residual oxophlorin was dissolved in pyridine (15 ml) and acetic anhydride (5 ml). The solution was left stirring overnight in the dark with a constant stream of air bubbling through it. Then the resulting red solution was evaporated under reduced pressure (0.1 mm Hg) and the residue was dissolved in methylene chloride (50 ml) and washed with water, then dried ($MgSO_4$). The solution was evaporated under reduced pressure and the residue was chromatographed twice on alumina (Merck Grade III), first eluting with methylene chloride, then chloroform–toluene (1 : 1, v/v). After removal of the solvents the *acetoxy porphyrin* crystallised from methylene chloride–methanol as dark red needles (31 mg, 0.033 mmol, 26%), mp 230–232°C.

Found: C, 61.2; H, 5.8; N, 6.0. $C_{48}H_{54}O_{16}N_4$ requires C, 61.2; H, 5.7; N, 5.9.

Ultraviolet λ_{max} nm (log ϵ) in $CHCl_3$, 406 (5.18), 504 (4.03); 536 (3.58); 577 (3.58); 603 (2.89).

τ ($CDCl_3$), −0.22 (2H, s, 2 *meso*-H); −0.08 (1H, s, *meso*-H), 4.87 (4H, s, 2 × CH_2CO); 5.00 (2H, q (J : 19Hz) 1-CH_2CO); 5.40–5.68 (8H, m, 4 × CH_2CH_2CO); 6.14 (6H, s, 2 × OCH_3); 6.18 (3H, s, OCH_3), 6.20 (3H, s, OCH_3); 6.25 (6H, s, 2 × OCH_3); 6.27 (6H, s, 2 × OCH_3); 6.43 (3H, s, 8-CH_3); 6.48–6.72 (8H, m, 4 × CH_2CH_2CO); 7.00 (3H, s, O_2CCH_3); 13.80 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 942 (100).

1,3,5-Tri-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2-methoxycarbonylethyl)-8-methyl porphyrin. 1,3,5-Tri-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2'-methoxycarbonylethyl)-8-methyl-δ-acetoxyporphyrin (19.5 mg, 0.021 mmol) was dissolved in tetrahydrofuran (100 ml) and triethylamine (three drops) and hydrogenolysed over 10% palladium on charcoal (50 mg). When the hydrogen uptake ceased the solution was filtered through Celite. This solution was treated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (10 mg) in dry benzene (1 ml). The red solution was evaporated under reduced pressure and then chromatographed twice on alumina (Merck Grade III), eluting first with methylene chloride then chloroform–toluene (1 : 1, v/v). The required *porphyrin* wsa recrystallised twice from chloroform–methanol (13 mg, 0.015 mmol, 71%), mp 224–226°C (lit. (*39*) mp 225–226°C, (*53*) 223–225°C).

Found: C, 62.66; H, 5.67; N, 6.53, $C_{46}H_{52}O_{14}N_4$ requires C, 62.44; H, 5.88; N, 6.34.

τ ($CDCl_3$) (0.056 *M*), −0.05 (2H, s, 2 × *meso-H*); −0.10 (2H, s, 2 × *meso-H*); 4.95 (2H, s, CH_2CO); 5.00 (4H, s, 2 × CH_2CO); 5.48–5.80 (8H, m, 4 × CH_2CH_2CO); 6.23 (9H, s, 3 × OCH_3); 6.31 (9H, s, 3 × OCH_3); 6.40 (3H, s, OCH_3); 6.43 (3H, s, 8-CH_3); 14.00 (2H, s, 2 × N*H*).

λ_{max} (log ϵ) in $CHCl_3$, 404 (5.26); 500 (4.08); 535 (3.92); 569 (3.75); 623 (3.31).

MS *m/e* (%); FD M^+ 884 (100).

1,3-Dimethyl-2,4,6,7-tetra-(2-methoxycarbonylethyl)-5,8-di-(methoxycarbonylmethyl)porphyrin (**6b**) was synthesised by the procedures described above from 5,5′-diformyl-3,4-di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane (64 mg, 0.16 mmol) and 3,3′-di-(2-methoxycarbonylethyl)-4,4′-di-(methoxycarbonylmethyl) pyrromethane-5,5′-dicarboxylic acid (92 mg, 0.17 mmol).

After chromatographing twice on alumina (Merck Grade III) eluting first with methylene chloride and then with chloroform–toluene (1 : 1, v/v), the *porphyrin hexacarboxylic hexamethyl ester* was recrystallised twice from chloroform–methanol (53 mg, 0.064 mmol, 39%), mp 169–171°C.

Found: C, 63.78; H, 6.05; N, 6.84. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$, 403 (5.25); 501 (4.17); 536 (3.98); 568 (3.86); 623 (3.71).

τ ($CDCl_3$) (0.056 *M*), −0.10 (1H, s, *meso-H*); −0.02 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 4.98 (2H, s, CH_2CO); 5.02 (2H, s, CH_2CO); 5.53–5.82 (8H, m, 4 × CH_2CH_2CO); 6.23 (6H, s, 2 × OCH_3); 6.33 (9H, s, 3 × OCH_3); 6.37 (3H, s, OCH_3); 6.48 (6H, s, 2 × OCH_3); 6.60–6.87 (8H, m, 4 × CH_2CH_2CO); 14.00 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 826 (100).

1,8-Di-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2-methoxycarbonylethyl)-3,5-dimethyl porphyrin (**7b**) was synthesised by the procedure described above from 5,5′-diformyl-3,4′-di-(2-methoxycarbonylethyl)-3′,4-dimethyl pyrromethane (109 mg, 0.271 mmol) and 3,3′-dimethoxycarbonylmethyl-4,4′-di-(2-methoxycarbonylethyl)-5,5′-dicarboxylic acid (156 mg, 0.285 mmol). After the Soret band of the porphyrin had reached a maximum (72 hr) the solution was worked up and purified as described for the preceding porphyrins yielding the desired *hexacarboxylic porphyrin hexamethyl ester* (78.3 mg, 0.095 mmol; 35%), mp 196–197°C.

Found: C, 63.89; H, 5.96; N, 6.95. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$ 403 (5.26); 501 (4.16); 536 (3.96); 570 (3.82); 623 (3.64).

τ ($CDCl_3$) (0.056 *M*), −0.12 (1H, s, *meso-H*); −0.05 (1H, s, *meso-H*); 0.03 (1H, s, *meso-H*); 0.07 (1H, s, *meso-H*); 4.93 (2H, s, CH_2CO); 4.96 (2H, s, CH_2CO); 5.50–5.80 (8H, m, 4 × CH_2CH_2CO); 6.24 (6H, s, 2 × OCH_3); 6.33 (3H, s, OCH_3); 6.35 (3H, s, OCH_3); 6.36 (3H, s, OCH_3); 6.38 (3H, s, OCH_3); 6.45 (3H, s, CH_3); 6.48 (3H, s, CH_3); 6.60–6.90 (8H, m, 4 × CH_2CH_2CO); 13.93 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 826 (100).

1,3-Di-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2-methoxycarbonylethyl)-5,8-dimethyl porphyrin (**8b**). This porphyrin was prepared from the pyrromethane 5,5′-diformyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethyl pyrromethane (48.5 mg, 0.121 mmol) and 3′,4-dimethoxycarbonylmethyl-3,4′-di-(2-methoxycarbonylethyl)pyrromethane-5,5′-dicarboxylic acid (70 mg, 0.127 mmol) and purified by the procedure described above (43.8 mg, 0.053 mmol, 49%), mp 187–189°C.

Found: C, 63.90; H, 6.04; N, 6.81. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$, 403 (5.23); 501 (4.21); 536 (4.05); 569 (3.94); 623 (3.78).

τ ($CDCl_3$) (0.056 *M*), −0.07 (1H, s, *meso-H*); −0.05 (1H, s, *meso-H*); 0.00 (2H, s, 2 × *meso-H*); 5.00 (2H, s, CH_2CO); 5.02 (2H, s, CH_2CO); 5.64–5.80 (8H, m, 4 ×

CH_2CH_2CO); 6.28 (6H, s, 2 × OCH_3); 6.36 (3H, s, OCH_3); 6.38 (3H, s, OCH_3); 6.41 (6H, s, 2 × OCH_3); 6.48 (6H, s, 2 × CH_3); 6.62–6.90 (8H, m, 4 × CH_2CH_2CO); 13.82 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 826 (100).

1,8 - Dimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 3,5 - di - (methoxycarbonylmethyl) porphyrin (**9b**). This porphyrin was prepared from 5,5′-diformyl-4,4′-di-(2-methoxycarbonylethyl)-3,3′-dimethyl pyrromethane (96.5 mg, 0.24 mmol) and 3,4′-di-(2-methoxycarbonylethyl)-3′,4-dimethoxycarbonylmethyl pyrromethane-5,5′dicarboxylic acid (170.5 mg, 0.31 mmol) following the procedure described above. After being recrystallised twice from chloroform–methanol the *porphyrin hexacarboxylic hexamethylester* was obtained as red needles (103 mg, 0.125 mmol, 52%), mp 194–195°C.

Found: C, 64.4; H, 5.9; N, 6.8. $C_{44}H_{50}O_{12}N_4$ requires C, 63.9; H, 6.0; N, 6.8.

λ_{max} (log ϵ) in $CHCl_3$, 403 (5.25); 501 (4.17); 536 (3.97); 569 (3.82); 623 (3.49).

τ ($CDCl_3$) (0.056 *M*), −0.12 (1H, s, *meso-H*); −0.04 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 0.09 (1H, s, *meso-H*); 4.96 (4H, s, 2 × CH_2CO); 5.66 (8H, q, 4 × CH_2CH_2); 6.24 (6H, s, 2 × OCH_3); 6.31 (3H, s, OCH_3); 6.33 (3H, s, OCH_3); 6.37 (3H, s, OCH_3); 6.39 (3H, s, OCH_3); 6.51 (6H, s, 2 × CH_3); 6.77 (8H, q, 4 × CH_2CH_2CO); 13.98 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 826 (100).

1,5 - Dimethyl - 2,4,6,7 - tetra - (2′ - methoxycarbonylethyl) - 3,8 - di - (methoxycarbonylmethyl) - δ-acetoxyporphyrin (**45**). Dibenzyl-1,3,6,7-tetra-(2-methoxycarbonylethyl)-2,5-di(methoxycarbonylmethyl)-4,8-dimethyl-*b*-oxobilane-1′,8′-dicrboxylate (486 mg, 0.44 mmol) was dissolved in dry tetrahydrofuran (100 ml) and triethylamine (five drops) and hydrogenolysed on 10% palladium on charcoal (0.1 g) at 20°C and 760 mm. When the hydrogen uptake finished (tlc showed the diacid compound) the suspension was filtered through Celite and the solvent evaporated under reduced pressure at room temperature giving the desired *b*-oxobilane-1′,8′-dicarboxylic acid (389 mg, 0.42 mmol, 95%) (λ_{max} nm (ethanol) 285; 360 (ethanol + concd HCl) bathochromic shift to 425).

The *b*-oxobilane-1′,8′-dicarboxylic acid was dissolved in 1 *M* trichloroacetic acid in methylene chloride (30 ml). Methylene chloride (100 ml) was added followed by methylorthoformate (2.5 ml). The solution was stirred for 3 hr at room temperature in the dark and in presence of air, the pyridine (5 ml) was added and the solution was stirred for a further 24 hr. The green solution was evaporated under reduced pressure. The oxophlorin was dissolved in pyridine (15 ml) and acetic anhydride (5 ml). The solution was left stirring overnight in the dark with a constant stream of air bubbling through it. Then the resulting red solution was evaporated under reduced pressure (0.1 mm Hg) and the residue was dissolved in methylene chloride (50 ml) and washed with water and dried ($MgSO_4$). The solution was evaporated under reduced pressure and the residue was chromatographed twice on alumina (Merck Grade III), first eluting with methylene chloride, then chloroform–toluene (1 : 1, v/v). The *acetoxyporphyrin* was recrystallised from chloroform–methanol (130 mg, 0.147 mmol, 35%), mp 252–255°C.

Found: C, 62.40; H, 5.88; N, 6.34. $C_{46}H_{52}O_{14}N_4$ requires C, 62.4; H_1 5.9; N_1 6.3.

Ultraviolet λ_{max} nm (log ϵ) in $CHCl_3$, 407 (5.35); 503 (4.23); 537 (3.80); 574 (3.81); 630 (3.20).

τ ($CDCl_3$), −0.16 (1H, s, *meso-H*); −0.09 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 4.97 (2H, s, CH_2CO); 5.11 (2H, q, CH_2CO); 5.53–5.78 (8H, m, 4 × CH_2CH_2CO); 6.23 (6H, s, 2 × OCH_3); 6.30 (3H, s, OCH_3); 6.33 (3H, s, OCH_3); 6.35 (3H, s, OCH_3); 6.36 (3H, s, OCH_3); 6.40 (3H, s, CH_3); 6.50 (3H, s, CH_3); 6.62–6.83 (8H, m, 4 × CH_2CH_2CO); 7.09 (3H, s, CH_3CO_2); 13.55 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 884 (100).

1,5-Dimethyl-2,4,6,7-tetra(2-methoxycarbonylethyl)-3,8-di-(methoxycarbonylmethyl)porphyrin (**10b**). 1,5-Dimethyl-2,4,6,7-tetra-(2-methoxycarbonylethyl)-3,8-dimethoxycarbonylmethyl-δ-acetoxyporphyrin (170 mg, 0.192 mmol) was dissolved in tetrahydrofuran (150 ml) and triethylamine (five drops) and hydrogenolysed over 10% palladium on charcoal (50 mg). When the hydrogen uptake ceased the solution was filtered through Celite. The colourless solution was treated with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (20 mg) in dry benzene (1 ml). The red solution was evaporated under reduced pressure and then chromatographed twice in alumina (Merck Grade III), eluting first with methylene chloride then chloroform–toluene (1 : 1, v/v). The required *porphyrin* was recrystallised twice from chloroform–methanol (103 mg, 0.125 mmol, 65%), mp 246–247°C.

Found: C, 63.62; H, 5.95; N, 6.72. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$, 404 (5.33); 501 (4.18), 536 (4.14); 569 (3.94); 623 (3.58).

τ ($CDCl_3$) (0.056 *M*), −0.07 (2H, s, 2 × *meso-H*); −0.03 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 5.01 (2H, s, CH_2CO); 5.03 (2H, s, CH_2CO); 5.50–5.80 (8H, m, 4 × CH_2CH_2CO); 6.23 (6H, s, 2 × OCH_3); 6.30 (3H, s, OCH_3); 6.32 (3H, s, OCH_3); 6.37 (6H, s, 2 × OCH_3); 6.39 (6H, s, 2 × CH_3); 6.55–6.87 (8H, m, 4 × Ch_2CH_2CO); 14.01 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 826 (100).

1,5-Di-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2-methoxycarbonylethyl)-3,8-dimethyl-δ-acetoxyporphyrin (**49**) was obtained by the procedure described above from dibenzyl-1,3,6,7-tetra-(2-methoxycarbonylethyl)-2,5-dimethyl-4,8-dimethoxycarbonylmethyl-*b*-oxobilane-1′,8′-dicarboxylate (149 mg, 0.134 mmol) giving after hydrogenolysis the required *b*-oxobilane-1′,8′-dicarboxylic acid (115.6 mg, 0.125 mmol, 93%) (λ_{max} nm (in CH_2Cl_2), 286; 362; in (CH_2Cl_2 + TCA), 425 after 1.5 hr A_{286} disappeared).

This compound was then used as previously described to get the δ-acetoxyporphyrin (35 mg, 0.040 mmol; 32%), mp 175–176°C.

Found: C, 62.20; H, 6.00; N, 6.47. $C_{46}H_{52}N_{14}O_4$ (requires C, 62.44; H, 5.88; N, 6.34.

Ultraviolet λ_{max} nm (log ϵ) in $CHCl_3$, 4.07 (5.35); 503 (4.24); 538 (3.78); 575 (3.80); 630 (3.20).

τ ($CDCl_3$), −0.14 (1H, s, *meso-H*); 0.06 (1H, s, *meso-H*); 0.02 (1H, s, *meso-H*); 5.00 (2H, s, CH_2CO); 5.15 (2H, q, J : 12H_z CH_2CO); 5.48–5.82 (8H, m, 4 × CH_2CH_2CO); 6.25; 6.34; 6.36; 6.38; 6.50 (24H, s, 6 × OCH_3; 2 × CH_3); 6.5–6.80 (8H, s, 4 × CH_2CH_2CO); 7.10 (3H, s, CH_3CO_2); 13.50 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 884 (100).

1,5-Di-(methoxycarbonylmethyl)-2,4,6,7-tetra-(2′-methoxcarbonylethyl)-3,8-dimethyl porphyrin (**11b**) was obtained as previously described from 1,5-dimethoxycarbonylmethyl-2,4,6,7-tetra-(2-methoxycarbonylethyl)-3,8-dimethyl-δ-

acetoxy porphyrin (28.7 mg, 0.033 mmol) as red needles (15.3 mg, 0.019 mmol, 57%), mp 228–230°C.

Found: C, 63.96; H, 6.32; N, 6.74. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$, 403 (5.27); 501 (4.18); 536 (4.01); 568 (3.90); 623 (3.61).

τ ($CDCl_3$) (0.056 *M*), −0.18 (3H, s, *meso-H*); −0.10 (1H, s, *meso-H*); 4.93 (2H, s, CH_2CO); 4.95 (2H, s, CH_2CO); 5.48–5.60 (8H, m, 4 × CH_2CH_2CO); 6.25 (6H, s, 2 × OCH_3); 6.33 (9H, s, 3 × OCH_3); 6.37 (6H, s, OCH_3 and pyr-CH_3); 6.40 (3H, s, pyr-CH_3); 6.57–6.88 (8H, m, 4 × CH_2CH_2CO); 13.7 (2H, s, 2 × N*H*).

1,3,5 - Trimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 8 - methoxycarbonylmethyl-δ-acetoxyporphyrin (**53**) was synthesised by the procedure described above from dibenzyl-1,3,6,7-tetra-(2-methoxycarbonylethyl)-2,4,8-trimethyl-5-methoxycarbonylmethyl-*b*-oxobilane-1′,8′-dicarboxylate (268 mg, 0.256 mmol) giving as intermediate the *b*-oxobilane-1′,8′-di-carboxylic acid (215 mg, 0.248 mmol, 97%). The desired *δ-acetoxyorphyrin* (78 mg, 0.094 mmol, 38%) was obtained as red needles, mp 232–234°C.

Found: C, 63.93; H, 5.90; N, 6.92. $C_{44}H_{50}O_{12}N_4$ requires C, 63.92; H, 6.05; N, 6.78.

λ_{max} nm (log ϵ) in $CHCl_3$, 405 (5.33); 502 (4.20); 535 (3.80); 572 (3.82); 628 (3.22).

τ ($CDCl_3$) (0.056 *M*), −0.01 (1H, s, *meso-H*); 0.14 (1H, s, *meso-H*); 0.36 (1H, s, *meso-H*); 5.07 (2H, q, J: 19Hz, 8-CH_2CO); 5.53–6.01 (8H, m, 4 × CH_2CH_2CO); 6.34 (3H, s, OCH_3); 6.36 (3H, s, OCH_3); 6.38 (6H, s, 2 × OCH_3); 6.40 (3H, s, CH_3); 6.55 (3H, s, CH_3); 6.60 (3H, s, CH_3); 6.64 (3H, s, CH_3); 6.68–6.98 (8H, m, 4 × CH_2CH_2CO); 7.10 (3H, s, H_3CCOO); 13.73 (2H, s, (3H, s, H_3CCOO); 13.73 (2H, s, 2 × N*H*).

MS m/e (%); FD M^+ 826 100.

1,3,5 - Trimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 8 - methoxycarbonylmethyl porphyrin (**12b**) was prepared as described above from 1,3,5-trimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 8 - methoxycarbonylmethyl-δ-acetoxyporphyrin (53 mg, 0.065 mmol), after recrystallising twice from chloroform–methanol (33 mg, 0.043 mmol, 66%), mp 211–212°C (lit. (*39*) mp 218–219°C).

Found: C, 64.95; H, 6.22; N, 7.33. $C_{42}H_{48}N_4O_{10}$ requires C, 65.63; H, 6.25; N, 7.29.

λ_{max} nm (log ϵ) in $CHCl_3$, 402 (5.19); 500 (4.11); 536 (3.98); 568 (3.83); 622 (3.66).

τ ($CDCl_3$) (0.056 *M*), −0.05 (2H, s, 2 × *meso-H*); 0.05 (1H, s, *meso-H*); 0.08 (1H, s, *meso-H*); 5.00 (2H, s, CH_2CO); 5.53–5.82 (8H, m, 4 × CH_2CH_2CO); 6.25 (3H, s, OCH_3); 6.33 (6H, s, 2 × OCH_3); 6.37 (6H, s, 2 × OCH_3); 6.42 (3H, s, CH_3); 6.44 (3H, s, CH_3); 6.50 (3H, s, CH_3); 6.62–6.90 (8H, m, 4 × CH_2CH_2CO); 14 (2H, s, 2 × N*H*).

MS *m/e* (%); FD M^+ 768 (100).

1 - Methoxycarbonylmethyl - 2,4,6,7 - tetra-(2-methoxycarbonylethyl)-3,5,8-trimethyl porphyrin (**13G**). This porphyrin was prepared from 5,5′-diformyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethyl pyrromethane (84 mg, 0.21 mmol) and 3,4′-di-(2-methoxycarbonylethyl)-4-methoxycarbonylmethyl-3′-methyl pyrrome-

thane 5,5′-dicarboxylic acid (108.5 mg, 0.22 mmol) following the procedure described above (60 mg, 0.078 mmol, 37.2%), mp 154–156°C (lit (*39*) mp 154–155°C).

Found: C, 65.70; H, 6.20; N, 7.40. $C_{42}H_{48}N_4O_{10}$ requires C, 65.63; H, 6.25; N, 7.29.

λ_{max} nm (log ϵ) in $CHCl_3$, 402 (5.28); 500 (4.15); 536 (3.97); 568 (3.82), 622 (3.62).

τ ($CDCl_3$) (0.056 *M*), −0.05 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 0.05 (2H, s, 2 × *meso-H*); 5.05 (2H, s, CH_2CO); 5.55–5.83 (8H, m, 4 × CH_2CH_2CO); 6.26 (3H, s, OCH_3); 6.33 (3H, s, OCH_3); 6.36 (6H, s, 2 × OCH_3); 6.38 (3H, s, OCH_3); 6.42 (3H, s, CH_3); 6.48 (6H, s, 2 × CH_3); 6.65–6.92 (8H, m, 4 × CH_2CH_2CO); 14.00 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 768 (100).

1,5,8 - Trimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 3 - methoxycarbonylmethyl porphyrin (**14b**). This porphyrin was prepared from 5,5′-diformyl-3,3′-di-(2-methoxycarbonylethyl)-4,4′-dimethyl pyrromethane (108.5 mg, 0.27 mmol) and 3-methoxycarbonylmethyl-3′,4-di-(2-methoxycarbonylethyl)-4′-methyl pyrromethane-5,5′-dicarboxylic acid (174 mg, 0.35 mmol) and purified by the procedure described above. After two recrystallisations from chloroform–methanol the desired *porphyrin pentamethyl ester* was obtained (98 mg, 0.125 mmole, 46%), mp 219–220°C (lit. (*39*) mp 218–219°C).

Found: C, 64.9; H, 6.0; N, 7.4. $C_{42}H_{48}N_4O_{10}$ requires C, 65.6; H, 6.2; N, 7.3.

λ_{max} (log ϵ) in $CHCl_3$, 402 (5.20); 500 (4.11); 536 (3.98); 568 (3.84); 622 (3.64).

τ ($CDCl_3$) (0.056 *M*), −0.03 (2H, s, 2 × *meso-H*); 0.00 (1H, s, *meso-H*); 0.06 (1H, s, *meso-H*); 4.98 (2H, s, CH_2CO); 5.60–5.88 (8H, m, 4 × CH_2CH_2CO); 6.25 (3H, s, OCH_3); 6.31 (3H, s, OCH_3); 6.38 (12H, s, 3 × OCH_3 and 1 × CH_3); 6.44 (3H, s, CH_3); 6.48 (3H, s, CH_3); 6.58–6.87 (8H, m, 4 × CH_2CH_2CO); 13.90 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 768 (100).

1,3,8 - Trimethyl - 2,4,6,7 - tetra - (2 - methoxycarbonylethyl) - 5 - methoxycarbonylmethyl porphyrin (**15b**) was synthesised by the procedure described above from 5,5′-diformyl-3,3′-dimethyl-4,4′-di-(2-methoxycarbonylethyl)pyrromethane (96.5 mg, 0.24 mmol) and 3-methoxycarbonylmethyl-3′,4-di-(2-methoxycarbonylethyl)-4′-methyl pyrromethane-5,5′-dicarboxylic acid (156 mg, 0.32 mmol). After being chromatographed twice on alumina (Merck Grade III) eluting first with methylene chloride and second with chloroform–toluene (1 : 1, v/v), the *porphyrin pentacarboxylic pentamethylester* formed deep red needles after recrystallising twice from chloroform–methanol (78.5 mg, 0.102 mmol, 41.8%), mp 205–206°C (lit. (*39*) mp 210–211°C).

Found: C, 65.1; H, 6.0; N, 7.4. $C_{42}H_{48}N_4O_{10}$ requires C, 65.6; H, 6.2; N, 7.3.

λ_{max} (log ϵ) in $CHCl_3$, 402 (5.24); 500 (4.13); 5.36 (4.00); 568 (3.84); 622 (3.66).

τ ($CDCl_3$) (0.056 *M*), −0.03 (1H, s, *meso-H*); 0.00 (1H, s, *meso-H*); 0.16 (2H, s, 2 × *meso-H*); 5.00 (2H, s, CH_2CO); 5.55–5.93 (8H, m, 4 × CH_2CH_2CO); 6.27 (3H, s, OCH_3); 6.34 (3H, s, OCH_3); 6.39 (6H, s, 2 × OCH_3); 6.42 (3H, s, OCH_3); 6.46 (3H, s, CH_3); 6.52 (3H, s, CH_3); 6.58 (3H, s, CH_3); 6.58–6.97 (8H, m, 4 × CH_2CH_2CO); 14.00 (2H, s, 2 × NH).

MS *m/e* (%); FD M^+ 768 (100).

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