Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 2.[1,2] Syntheses of *C*-Methylated Chlorins *Via* Lactams

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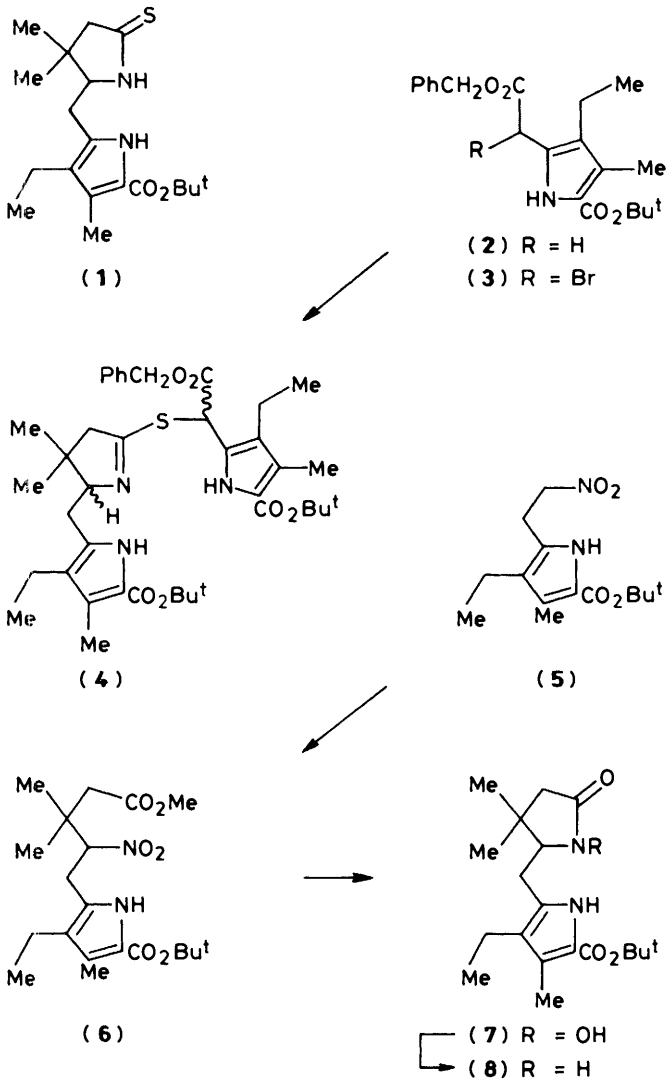
C-Methylated chlorins have been synthesised by two approaches. For one, ring-B and ring-C of the final chlorin were built sequentially onto a thiolactam system which acted as the A-D component. The preferred alternative method involved joining together a lactam (a dihydropyrromethenone) as A-D precursor with a pyrromethane as the B-C component, the final ring-closure to the chlorin being carried out on a Cu^{II} template.

The preceding paper[1] gave details of two routes to *C*-methylated chlorins which made use of Δ^1-pyrrolines (3,4-dihydropyrroles) as precursors of the reduced ring (ring A). Here we describe researches on alternative methods based on a lactam or a thiolactam as the building block for ring A.

The Approach Using Sulphur Contraction.—This route involved the joining of an A-D fragment (**1**) to a ring B precursor (**3**) to generate the sulphide (**4**) ready for an Eschenmoser sulphur-extrusion step.[3] The thiolactam (**1**) was prepared from the nitroethylpyrrole (**5**), the first step being Michael addition of the pyrrole (**5**) as in the preceding paper[1] to methyl 3,3-dimethylacrylate (Scheme 1). This Michael acceptor is known to be unreactive and all attempts to achieve the addition using various amines as catalysts failed. However, fluoride ion[4] was a very effective catalyst, the nitro ester (**6**) being obtained in 65% yield.

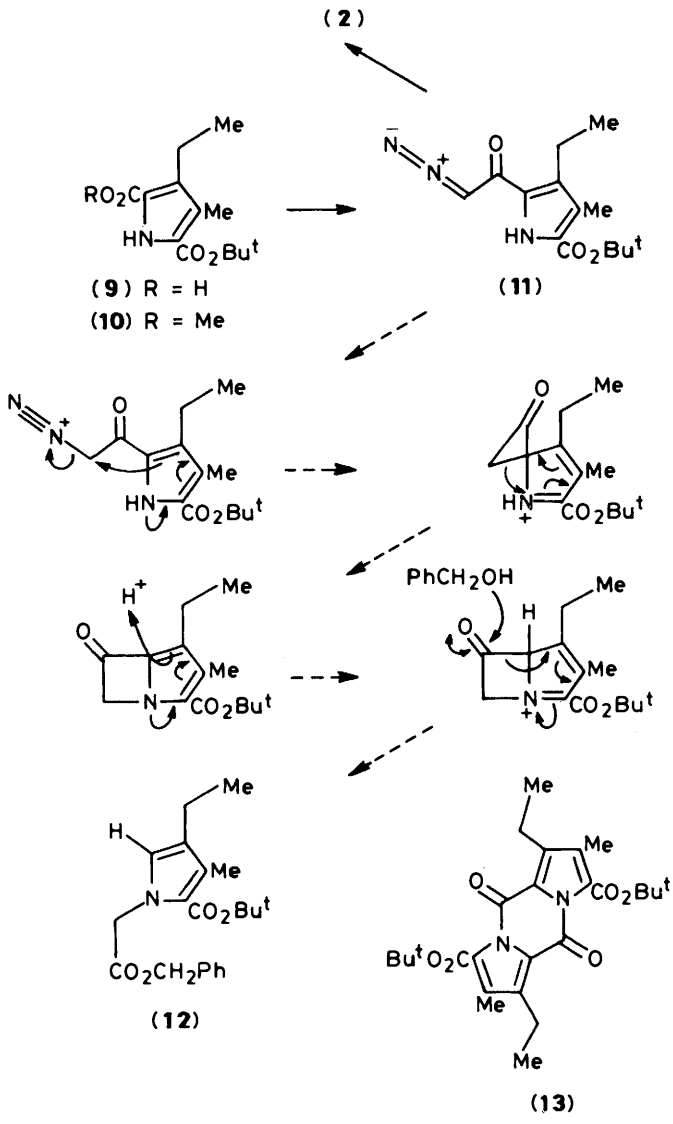
Reductive cyclisation of ester (**6**) with zinc in acetic acid gave the desired lactam (**8**) together with the hydroxamic acid (**7**). Since the conversion of a nitrone into an imine had been smoothly achieved using titanium(III) chloride,[1] the nitro ester (**6**) was reduced as before followed by addition of titanium(III). This resulted in reduction of the hydroxamic acid (**7**) to the lactam (**8**), which was then obtained in 94% yield. At the time, this was a novel conversion of an hydroxamic acid into an amide though later, the formation of β-lactams from 1-hydroxyazetidinones was reported.[5] Phosphorus pentasulphide then smoothly converted the lactam (**8**) into the corresponding thiolactam (**1**).

The pyrrolylacetic ester (**2**) was chosen for the ring-B fragment because an electron withdrawing group on the bridging carbon atom was known to be necessary in similar cases.[6] The route to the ester (**2**) involved Arndt-Eistert homologation of the known acid[7] (**9**) by treatment of its acid chloride with 2.2 equivalents of diazomethane. Rearrangement of the resulting diazoketone (**11**) using silver benzoate in warm benzyl alcohol gave the desired product (**2**) in 20% overall yield [the by-product was the methyl ester (**10**)]. Though the yield is moderate, it is comparable with that from the only alternative approach of treating an α-free pyrrole with diazoacetic esters.[8] Interestingly, when the diazoketone (**11**) was prepared using only 1 equivalent of diazomethane with 1 equivalent of triethylamine to scavenge the hydrogen chloride, and then subjected to the rearrangement, a different mixture of products was obtained. The major one was isomeric with ester (**2**) and it showed a 1H-singlet at δ 6.48, typical of an α-free pyrrole, but no NH-proton so indicating structure (**12**). The n.m.r. signal from the CH_2CO methylene protons of this product appeared at δ 4.96, as estimated,[9] compared with δ 3.58 for the corresponding methylene group of the ester (**2**). The methyl ester (**10**) and the pyrrocol (**13**) were also formed together with a trace of the desired product (**2**). It is not certain how the *N*-alkylated product (**12**) is formed but a plausible mechanism involves protonation of the diazoketone followed by the steps in Scheme 2.

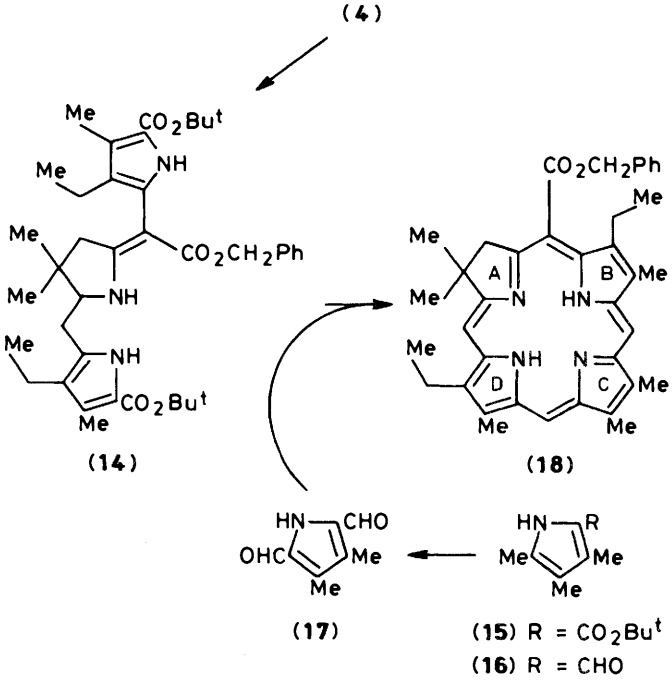


Scheme 1.

Bromination of the ester (**2**) gave the bromo ester (**3**) quantitatively which reacted with the thiolactam (**1**) in the presence of potassium t-butoxide to yield the sulphide (**4**) as a mixture of diastereoisomers. A standard sulphur-contraction step then gave the tricyclic system (**14**) as a single geometric



Scheme 2.



isomer in 93% yield from the thiolactam (**1**). The *Z*-stereochemistry is illustrated because this was the stereochemical outcome for related systems.[3] Clearly, this is not the correct arrangement for ring-closure to the final chlorin macrocycle but the system (**14**) was expected to undergo isomerisation under the acidic conditions of the final ring-closure step (see later).

The symmetrical diformylpyrrole (**17**) was the selected building block for ring-C of the chlorin. This was prepared by converting the pyrrole (**15**) into (**16**) by Clezy's method[10] followed by oxidation of the 5-methyl group. The t-butyloxycarbonyl residues were removed from the tricyclic system (**14**) with the trifluoroacetic acid and the product was condensed with the dialdehyde (**17**). After oxidation of the intermediate(s) with dichlorodicyanoquinone, the chlorin (**18**) was isolated in *ca.* 2% yield.

This sequence could be developed into a regio-controlled synthesis of chlorins but the low yield and parallel developments caused us to concentrate our effort on the approach now to be described.

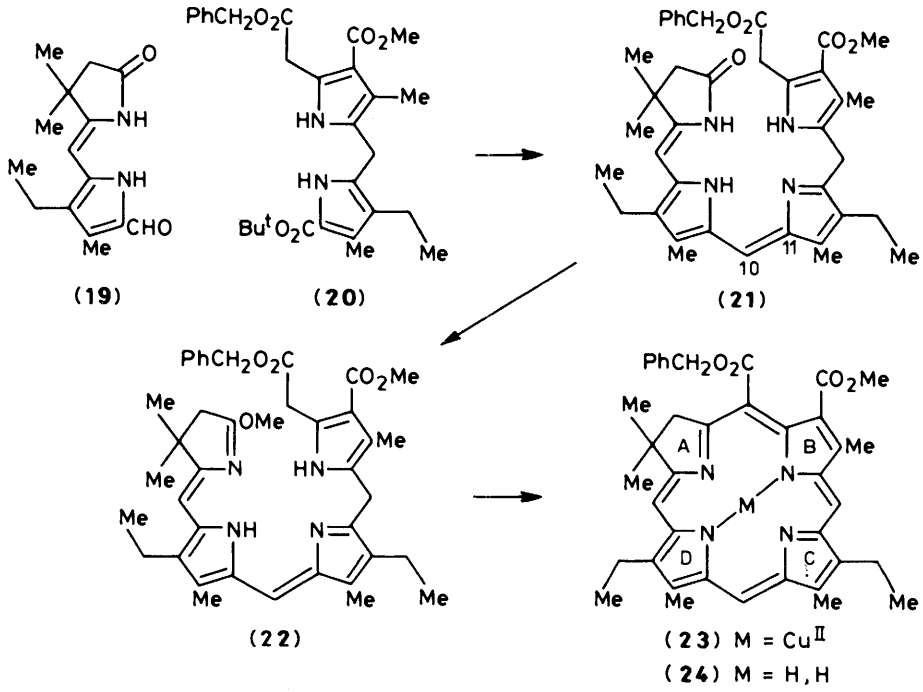
The Approach Via an Imino Ether.—A convergent route was planned in which an A-D unit (**19**) was to be joined to a B-C component (**20**) and later generation of an imino ether was envisaged as an electrophilic precursor of the reduced ring A of the final chlorin as shown in Scheme 3. The corresponding nucleophile was to be the anion formed at the benzyloxycarbonylmethyl group of the intermediate (**22**). In contrast to the foregoing synthesis and to those in the preceding paper,[1] the present route aimed to have the substrate for the final cyclisation step close to the desired oxidation level.

The necessary unsaturated lactam (**19**) was produced in two ways (Scheme 4). The first involved treatment of the nitro ester (**6**) with potassium t-butoxide and aqueous titanium(III) chloride[11] followed by re-esterification to give the keto ester (**25**) in 45% yield. Cyclisation of this using ammonium acetate led to extensive decomposition though the desired lactam (**26**) was isolated in 26% yield. The alternative route started with the lactam (**8**) which was chlorinated with t-butyl hypochlorite to yield the lactam (**27**). This underwent hydrolysis during work up to the alcohol (**28**) which yielded the unsaturated lactam (**26**) in 67% overall yield by acid-catalysed dehydration.

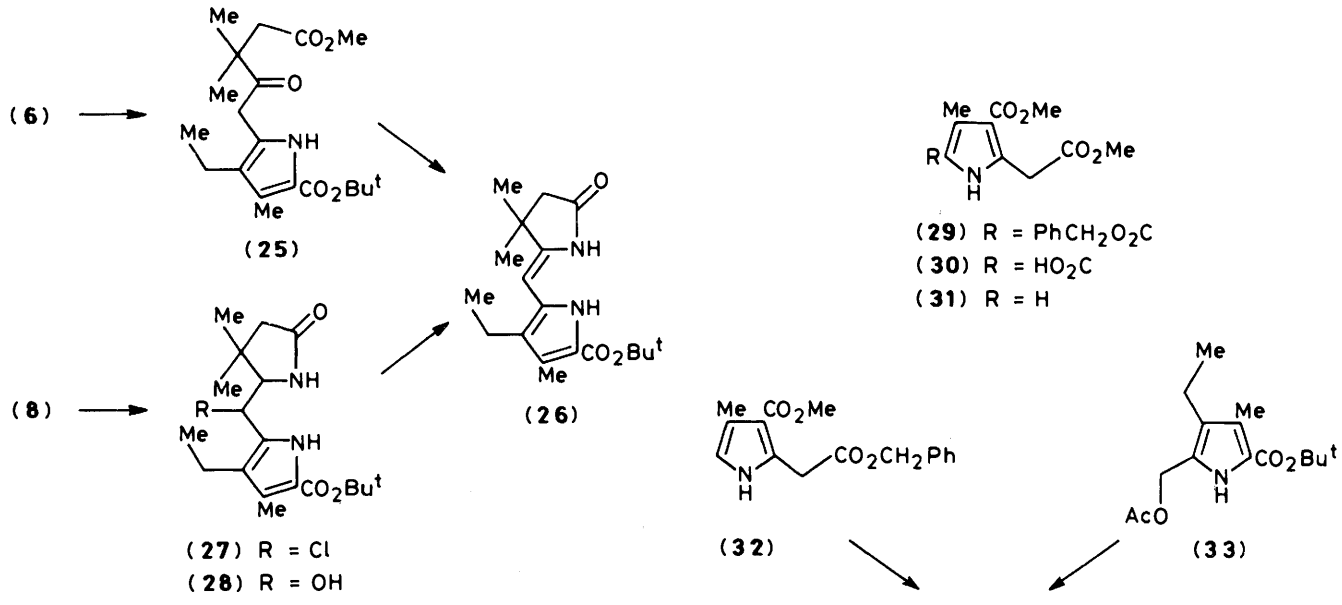
One stereoisomer of the unsaturated lactam (**26**) was obtained and evidence that it had the desired *Z*-configuration came from a 22% n.O.e. enhancement of the signal from the vinylic proton at δ 5.28 on irradiation at δ 1.36 where the protons of the gem-dimethyl group resonate. This assignment was confirmed by *X*-ray analysis[12] which revealed the almost planar structure shown in the Figure. The final step of replacement of the t-butyloxycarbonyl group of lactam (**26**) by a formyl group proceeded smoothly (86%).

The B-C component (**20**) for the synthesis was prepared as follows. A Knorr reaction involving benzyl acetoacetate and dimethyl acetonedicarboxylate[13] gave the pyrrole (**29**) which was converted into the α-free pyrrole (**31**) *via* the acid (**30**) by standard methods. Selective acid-catalysed transesterification using benzyl alcohol then afforded the ester (**32**) which was alkylated using the acetoxymethylpyrrole (**33**) in the presence of toluene-*p*-sulphonic acid to give the B-C component (**20**) (67%). Small amounts of the two symmetrical pyrromethanes (**34**) and (**35**) were also isolated.

With the building blocks (**19**) and (**20**) available, studies were made of the generation of the system (**21**) and of its conversion into the chlorin macrocycle. Deprotection of (**20**) with tri-



Scheme 3.



Scheme 4.

fluoroacetic acid and condensation of the product with the aldehyde (**19**) generated the required material (**21**) (76%). This is illustrated as the *Z*-isomer about the C-10/C-11 double bond because this is known to be the preferred configuration of the related bile pigments.[8b] On treatment of the lactam (**21**) with trimethyloxonium tetrafluoroborate, the imidate (**22**) was formed which was sufficiently stable to be isolated chromatographically in 77% yield, based on unrecovered starting material. However, the imidate (**22**) decomposed on keeping so it was cyclised without delay.

As earlier,[1] copper ions served as the template for the cyclisation. On treating the imidate (**22**) with copper acetate, there was a rapid colour change indicating the formation of a

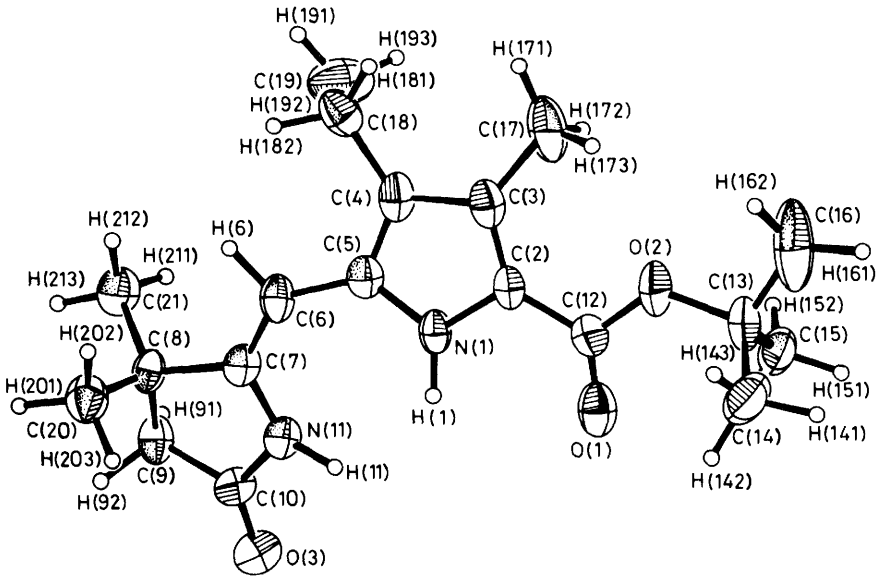


Figure. Structure of compound (**26**)

copper complex. Diazabicycloundecene was then added and the visible absorption spectrum of the heated solution changed to that of a chlorin copper complex. Thus (**23**) was isolated and demetallated as described earlier[1,14] to yield the chlorin (**24**) in 7.4% yield over the three steps from precursor (**21**).

The work in this paper and the preceding one has provided rational synthetic routes to *C*-methylated chlorins, the simplest approach[1] being useful when small amounts of a chlorin are desired by a short synthesis. In addition, these studies laid the foundations for the development of a high-yielding and mild synthesis of chlorins which has been briefly described.[15,16]

Experimental

For general directions, see ref. 1.

t-Butyl 5-(4-*Methoxycarbonyl*-3,3-*dimethyl*-2-*nitrobutyl*)-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate* (**6**).—A solution of tetrabutylammonium fluoride (4.71 g, 14.9 mmol) in DMF (40 ml) containing Type 3A molecular sieve (5 g), was stirred for 30 min. The nitroethylpyrrole (**5**) (4.20 g, 14.9 mmol) and methyl 3-methylbut-2-enoate (6.78 g, 60 mmol) were added rapidly and the solution was heated to 50 °C for 4 h. The mixture was diluted with ether, filtered, and washed with hydrochloric acid (2M; 2 × 100 ml) and the residue from the ether was chromatographed with dichloromethane–light petroleum (1:1), increasing to neat dichloromethane as eluant. Crystallisation of the product from methanol–water gave the *nitro ester* (3.83 g, 65%), m.p. 92—95 °C (Found: C, 60.6; H, 7.9; N, 7.0%; M^+, 396.2264. $C_{20}H_{32}N_2O_6$ requires: C, 60.6; H, 8.1; N, 7.1%; M^+, 396.2260); $\lambda_{max.}$ 275 nm; $\nu_{max.}$ 3 440, 1 735s, 1 680s, 1 550, and 1 370 cm^{-1}; *m/z* 396 (35%, M^+), 323 [18, $M-(CH_3)_3CO$], and 293 (100); δ 1.05 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.18 and 1.24 [each 3 H, s, $C(CH_3)_2$], 1.56 [9 H, s, $C(CH_3)_3$], 2.22 (3 H, s, $ArCH_3$), 2.36 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.44 (2 H, s, $CH_2CO_2CH_3$), 3.02 (1 H, dd, *J* 3, 15 Hz, CH_2CHNO_2), 3.32 (1 H, dd, *J* 11, 15 Hz, CH_2CHNO_2), 3.72 (3 H, s, CO_2CH_3), 4.95 (1 H, dd, *J* 3, 11 Hz, $CHNO_2$), and 8.66 (1 H, br, NH).

5-(3-*Ethyl*-4-*methyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-4,4-*dimethylpyrrolidin*-2-*one* (**8**).—A stirred solution of the foregoing nitro ester (**6**) (792 mg, 2 mmol) in glacial acetic acid (20 ml) was treated with zinc dust (3 g). The temperature rose spontaneously to 45 °C. After 15 min, the mixture was heated to 70 °C for 30 min. Ammonium acetate (0.4 g, 5.2 mmol) was added to the cooled solution followed by titanium(III) chloride solution (15%, 0.5 ml, 0.5 mmol). After 20 min of vigorous stirring, the mixture was filtered through Celite, the pad washed well with acetic acid, and the filtrate evaporated (45 °C/1 mmHg). The residue was partitioned between ether (80 ml) and saturated sodium hydrogen carbonate solution (50 ml), the aqueous layer was filtered and extracted with more ether (2 × 60 ml). The residue from the combined ethereal solutions was crystallised from ether–hexane to give the *lactam* (625 mg, 93.6%), m.p. 176—178.5 °C (Found: C, 68.5; H, 9.0; N, 8.3%; M^+, 334.2259. $C_{19}H_{30}N_2O_3$ requires C, 68.2; H, 9.0; N, 8.4%; M^+, 334.2256); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 3 620w, 3 440br, and 1 690s cm^{-1}; *m/z* 334 (13%, M^+), 261 [26, $M-(CH_3)_3CO$], and 223 (100); δ 1.08 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.19 and 1.23 [each 3 H, s, $C(CH_3)_2$], 1.50 [9 H, s, $C(CH_3)_3$], 2.05 (1 H, d, *J* 16 Hz, CH_2CONH), 2.20 (3 H, s, $ArCH_3$), 2.25—2.35 (3 H, m, CH_2CONH and CH_2CH_3), 2.62—2.75 (2 H, m, CH_2CHNH), 3.34 (1 H, dd, *J* 5, 10 Hz, $CHNHCO$), 6.66 (1 H, br, lactam NH), and 9.92 (1 H, br, pyrrole NH).

5-(3-*Ethyl*-4-*methyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-1-*hydroxy*-4,4-*dimethylpyrrolidin*-2-*one* (**7**).—Reduction of the nitro ester (**6**) (100 mg, 0.252 mmol) was carried out as above, the mixture being stirred at room temperature for 90 min. The filtered solution was evaporated and the residue partitioned between dichloromethane (20 ml) and saturated aqueous sodium hydrogen carbonate (15 ml). The residue from the dichloromethane layer was purified by p.l.c., with dichloromethane–methanol (19:1) as eluant. The higher R_F band yielded the foregoing lactam (**8**) (58 mg, 69%), whilst the lower band gave the *hydroxamic acid* as a gum (15 mg, 17%); $\lambda_{max.}$ 281 nm; $\nu_{max.}$ 3 450—3 200vbr, 1 680s, and 1 650s cm^{-1}; *m/z* 350 (57%, M^+ for $C_{19}H_{30}N_2O_4$), 334 (30), 294 [100, $M-(CH_3)_2C{=}CH_2$], 277 (70), and 261 (35); δ 1.05—1.20 [9 H, m, CH_2CH_3 and $C(CH_3)_2$], 1.54 [9 H, s, $C(CH_3)_3$], 2.25 (3 H, s, $ArCH_3$), 2.20—2.45 (4 H, m, CH_2CH_3 and CH_2CONOH), 2.90 (3 H, br, CH_2CHNOH), 3.70 (1 H, m, $CHNOH$), and 9.42 (1 H, br, NH).

5-(3-*Ethyl*-4-*methyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-4,4-*dimethylpyrrolidine*-2-*thione* (**1**).—A solution of the fore-

going lactam (**8**) (200 mg, 0.6 mmol) in acetonitrile (20 ml) containing powdered phosphorus pentasulphide (385 mg) was stirred vigorously under nitrogen for 15 min, then pyridine (0.4 ml) was added. After 62 h at 20 °C, the mixture was filtered, the solids were washed thoroughly with dichloromethane, and the filtrate was evaporated. Chromatography of the residue on silica H (4 g), with dichloromethane gave the *thiolactam* (159 mg, 76%), m.p. 89—92 °C from ether–hexane (113 mg, 54%) (Found: C, 65.0; H, 8.7; N, 8.1; S, 9.2%; M^+, 350.2017. $C_{19}H_{30}N_2O_2S$ requires C, 65.1; H, 8.6; N, 8.0%; S, 9.25%; M^+, 350.2028); $\lambda_{max.}$ 275 nm; $\nu_{max.}$ 3 440, 3 380, 3 230br, 1 665s, 1 485, and 1 440 cm^{-1}; *m/z* 350 (58%, M^+), 277 [23, $M - (CH_3)_3CO$], and 223 (100); δ 1.06 (3 H, t, *J* 7 Hz, CH_2CH_3); 1.14 and 1.18 [each 3 H, s, $C(CH_3)_2$], 1.49 [9 H, s, $C(CH_3)_3$], 2.20 (3 H, s, $ArCH_3$), 2.37 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.50—3.00 (4 H, m, CH_2CHNH and CH_2CSNH), 3.56 (1 H, dd, *J* 6, 9 Hz, CHNH), 8.88 (1 H, br, lactam NH), and 9.84 (1 H, br, pyrrole NH).

t-Butyl 5-Benzyloxycarbonylmethyl-4-ethyl-3-methylpyrrole-2-carboxylate (**2**).—To a solution of 5-t-butoxycarbonyl-3-ethyl-4-methylpyrrole-2-carboxylic acid (**9**) (0.5 g, 1.97 mmol), prepared by Kenner's method (iii),[7] in dichloromethane (30 ml) was added thionyl chloride (0.28 g, 2.36 mmol) and DMF (3 drops), and the solution was heated under reflux. After 30 min, more thionyl chloride (0.02 g, 0.16 mmol) was added, and heating continued for 20 min. The evaporated solution gave the acid chloride which was dissolved in dry ether (15 ml), and the solution added dropwise to a stirred solution of diazomethane in ether (0.3M; 19.7 ml, 5.91 mmol), under nitrogen, at 0 °C. Stirring was continued at 0 °C for 3 h and at 20 °C for 16 h, after which the solvent was evaporated. The residue in benzyl alcohol (15 ml) under nitrogen was stirred and heated to 80 °C. A solution of silver benzoate (0.25 g) in triethylamine (2.5 ml) was added in 0.2 ml aliquots until further addition caused no more gas to be evolved (6 additions over 45 min). Heating was continued for 1.5 h, after which charcoal was added and stirring continued for 5 min. The cooled solution was diluted with ether (40 ml) and filtered through Celite, the latter then being washed with ether. The ether was evaporated and the benzyl alcohol removed by short-path distillation (80 °C/0.1 mmHg). The residue was partitioned between ether (50 ml) and nitric acid (2M; 40 ml), and the ether layer washed with aqueous sodium carbonate (10%; 2 × 30 ml) and brine, and then evaporated. Column chromatography on silica H (28 g), with dichloromethane–light petroleum (1:1) as eluant gave the desired *benzyloxycarbonylmethylpyrrole* as the second eluted compound, which was crystallised from methanol (140 mg, 19.8%), m.p. 93.5—95 °C (Found: C, 70.5; H, 7.8; N, 3.8. $C_{21}H_{27}NO_4$ requires C, 70.6; H, 7.6; N, 3.9%); $\lambda_{max.}$ (MeOH) 206 and 278 nm; $\nu_{max.}$ 3 450, 1 735s, 1 690s, 1 680s, and 1 580w cm^{-1}; *m/z* 357 (71%, M^+), 301 [100, $M - (CH_3)_2C{=}CH_2$], and 284 (23); δ 0.97 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.52 [9 H, s, $C(CH_3)_3$], 2.21 (3 H, s, $ArCH_3$), 2.33 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.58 (2 H, s, $CH_2CO_2CH_2Ph$), 5.10 (2 H, s, CH_2Ph), 7.28 (5 H, s, C_6H_5), and 8.98 (1 H, br, NH).

The compound eluted first was *2-t-butyl 5-methyl 4-ethyl-3-methylpyrrole-2,5-dicarboxylate* (**10**) (40 mg, 7.6%). This compound was identical with a sample prepared by treating the starting acid (**9**) with diazomethane; δ 1.06 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.54 [9 H, s, $C(CH_3)_3$], 2.22 (3 H, s, $ArCH_3$), 2.72 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.83 (3 H, s, CO_2CH_3), and 9.30 (1 H, br, NH).

t-Butyl 1-Benzyloxycarbonylmethyl-4-ethyl-3-methylpyrrole-2-carboxylate (**12**).—The pyrrolecarboxylic acid (**9**) (1 g, 3.94 mmol) was treated as above, except that a solution of diazomethane (4.36 mmol) in ether (25 ml) containing triethylamine (394 mg, 3.94 mmol) was used to form the diazoketone, and the resultant solution was filtered before evaporation. Chromatography of the product on silica H (26 g) with dichloromethane–light petroleum (1:1) as eluant gave as the first compound eluted, the *1-benzyloxycarbonylmethylpyrrole* (274 mg, 19.5%) (Found M^+, 357.1931. $C_{21}H_{27}NO_4$ requires M^+, 357.1940); $\lambda_{max.}$ 270 nm; $\nu_{max.}$ 1 755s and 1 685s cm^{-1}; *m/z* 357 (45%, M^+), 301 [100, $M - (CH_3)_2C{=}CH_2$], and 225 (8); δ 1.15 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 1.51 [9 H, s, $C(CH_3)_3$], 2.24 (3 H, s, $ArCH_3$), 2.41 (2 H, q, *J* 7.5 Hz, CH_2CH_3), 4.96 (2 H, s, NCH_2CO), 5.19 (2 H, s, CH_2Ph), 6.48 (1 H, s, ArH), and 7.32 (5 H, s, C_6H_5). The next component to be eluted was the methyl ester (**10**) (152 mg, 14.4%). The third component was *1,6-diethyl-2,7-dimethyl-3,8-di-t-butoxycarbonyl-5H,10H-dipyrrolo[1,2-a:1′,2′-d]pyrazine-5,10-dione* (**13**) (156 mg), m.p. 166—174 °C from aqueous methanol; δ 1.17 (6 H, t, *J* 7 Hz, 2 × CH_2CH_3), 1.62 [18 H, s, 2 × $C(CH_3)_3$], 2.09 (6 H, s, 2 × $ArCH_3$), and 2.90 (4 H, q, *J* 7 Hz, 2 × CH_2CH_3). Finally p.l.c. of the mother liquors from (**13**), using benzene–ether (9:1) as eluant, yielded the 5-benzyloxycarbonylmethylpyrrole (**2**) (24 mg, 1.7%).

t-Butyl 5-(Benzyloxycarbonyl)bromomethyl-4-ethyl-3-methylpyrrole-2-carboxylate (**3**).—A solution of the foregoing 5-benzyloxycarbonylmethylpyrrole (**2**) (100 mg, 0.28 mmol) in carbon tetrachloride (3 ml), containing *N*-bromosuccinimide (55.5 mg, 0.31 mmol), was heated under reflux and irradiated with a 250 W sunlamp.[6] After 15 min, the n.m.r. spectrum of the filtered solution showed greater than 95% conversion into the *bromomethylpyrrole*, which was used in the next reaction without purification; δ 0.97 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.47 [9 H, s, $C(CH_3)_3$], 2.08 (3 H, s, $ArCH_3$), 2.30 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.12 (2 H, s, CH_2Ph), 5.33 [1 H, s, $CH(Br)CO_2$], 7.22 (5 H, s, C_6H_5), and 9.50 (1 H, br, NH).

2-[Benzyloxycarbonyl-(3-ethyl-4-methyl-5-t-butoxycarbonylpyrrol-2-ylmethylthio)]-5-(3-ethyl-4-methyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-4,4-dimethylpyrrole (**4**).—The thiolactam (**1**) (98 mg, 0.28 mmol) and a solution of potassium t-butoxide in t-butyl alcohol (89.5 mM; 3.2 ml, 0.28 mmol) were stirred under argon for 30 min. The carbon tetrachloride solution of the foregoing bromomethylpyrrole (**3**) was concentrated (to 2.5 ml) and added as rapidly as possible to the thiolactam solution, being washed in with more carbon tetrachloride (1 ml). After being stirred for 1 h, the solution was partitioned between dichloromethane (30 ml) and water (15 ml), and the organic layer was evaporated. The residue was purified by column chromatography, with dichloromethane as eluant, to give the *tricyclic thioimidate* as a gum (192 mg, 97%). N.m.r. spectroscopy showed that it was a mixture of diastereoisomers; $\lambda_{max.}$ (MeOH) 204 and 281 nm; $\nu_{max.}$ 3 440br, 1 730m, 1 685s,br, and 1 600m cm^{-1}; *m/z* (F.D.) 705 (100%, M^+ for $C_{40}H_{55}N_3O_6S$); δ 0.87—1.10 (6 H, m, 2 × CH_2CH_3), 1.38—1.54 [24 H, m, 2 × $C(CH_3)_3$ and $C(CH_3)_2$], 2.20 and 2.26 (each *ca.* 3 H, s, $ArCH_3$), 2.35—2.55 [8 H, m, 2 × CH_2CH_3, CH_2CHN and $CH_2C(S){=}N$], 3.47 (1 H, br d, *J* 12 Hz, CH_2CHN), 5.04 (1.1 H, s, CH_2Ph of isomer A), 5.15 (0.9 H, s, CH_2Ph of isomer B), 5.57 (0.45 H, s, $SCHCO_2$ of isomer B), 5.67 (0.55 H, s, $SCHCO_2$ of isomer A), 7.15—7.30 (5 H, m, C_6H_5), and 9.18 and 9.60 (each 1 H, br, 2 × NH).

Di-t-butyl 5-Benzyloxycarbonyl-3,12-diethyl-2,8,8,13-tetramethyl-7,8,9,10,16,17-hexahydrotripyrrin-1,14-dicarboxylate (**14**).—A stirred solution of the foregoing thioimidate (**4**) (192 mg, 0.272 mmol) in dry benzene (5 ml) containing *N,N*-diisopropylethylamine (0.2 ml) and trimethyl phosphite (0.4 ml) was heated to 60 °C under argon. After 44 h, the mixture was evaporated at 0.1 mmHg, the residue being chromatographed on silica H (4 g), with dichloromethane to give the *hexa-*

hydrotripyrrin (176 mg, 93% from the thiolactam); $\lambda_{max.}$ 286 nm; $\nu_{max.}$ 3 460, 1 670br,s, 1 585, and 1 570 cm^{-1}; *m/z* (F.D.) 673 (100%, M^+ for $C_{40}H_{55}N_3O_6$); δ 1.01 and 1.04 (each 3 H, t, *J* 6 Hz, 2 × CH_2CH_3), 1.55 and 1.56 [each 9 H, s, 2 × $C(CH_3)_3$], 1.62 [6 H, s, $C(CH_3)_2$], 2.25 and 2.27 (each 3 H, s, 2 × $ArCH_3$), 2.25—2.60 (6 H, m, 2 × CH_2CH_3 and CH_2CHNH), 3.47 (1 H, dd, *J* 6, 9 Hz, CHNH), 5.02 (2 H, ABq, *J* 11 Hz, $CH_2C(NH)=C$), 5.27 (2 H, s, CH_2Ph), 7.10—7.30 (5 H, m, C_6H_5), and 8.20—8.40 (3 H, br, 3 × NH).

2-*Formyl*-3,4,5-*trimethylpyrrole* (**16**).—A solution of t-butyl 3,4,5-trimethylpyrrole-2-carboxylate[17] (**15**) (2 g, 9.6 mmol) in TFA (20 ml) was stirred at 20 °C for 10 min and then cooled to 0 °C. Trimethyl orthoformate (5 ml) was added rapidly, and after 1 min, the solution was allowed to warm up over 15 min; it was then cooled again to 0 °C and water was added until the solution just became turbid. After 30 min, the solution was partitioned between ether (120 ml) and water (50 ml), the organic layer being washed with aqueous ammonia (3M; 3 × 60 ml) and brine, and then evaporated. The residue was crystallised twice from hexane to give the formylpyrrole (0.62 g, 47.3%), m.p. 146—149.5 °C (lit.,[18] 147 °C); δ 1.97 (3 H, s, 4-CH_3), 2.33 (6 H, s, 3-CH_3, 5-CH_3), 9.53 (1 H, s, CHO), and 10.10 (1 H, br, NH).

2,5-*Diformyl*-3,4-*dimethylpyrrole* (**17**).—Freshly distilled sulphuryl chloride (0.65 g, 4.82 mmol) in ether (2 ml) was added dropwise during 15 min to a vigorously stirred solution of the foregoing pyrrole (0.3 g, 2.19 mmol) in dry ether (20 ml), containing powdered anhydrous potassium carbonate (3 g) at 0 °C. Stirring at 0 °C was continued for 1 h, after which the mixture was allowed to warm to 20 °C over 4 h before being filtered and evaporated. The residue in acetone (12 ml) was added slowly to a solution of sodium acetate (1.4 g) in water (10 ml) and acetone (16 ml) at 60 °C. Heating was continued for 30 min, and most of the acetone was boiled off. The cooled solution was diluted with dichloromethane (50 ml) and the aqueous layer basified with saturated aqueous sodium carbonate solution. The residue from the organic layer was chromatographed on silica H (3 g), with dichloromethane and the product crystallised from dichloromethane–hexane to give the diformylpyrrole (64 mg, 23.5%), m.p. 155—158.5 °C (lit.,[19] m.p. 158 °C); δ 2.31 (6 H, s, 2 × CH_3), 9.90 (2 H, s, 2 × CHO), and 10.19 (1 H, br, NH).

5-*Benzyloxycarbonyl*-7,18-*diethyl*-2,2,8,12,13,17-*hexamethylchlorin* (**18**).—A solution of the hexahydrotripyrrin (**14**) (176 mg, 0.262 mmol) in TFA (2.5 ml) was stirred for 15 min under argon, after which a solution of the foregoing diformylpyrrole (**17**) (39.6 mg, 0.262 mmol) in methanol (30 ml) was added rapidly. The resulting red solution ($\lambda_{max.}$ 483 nm) was stirred for 24 h in the dark, and then evaporated; the residue was then partitioned between dichloromethane (100 ml) and aqueous sodium hydrogen carbonate (5%; 50 ml). The dried dichloromethane solution was stirred with dichlorodicyanoquinone (82 mg, 0.33 mmol) for 1 h, and then filtered through a silica column (4 × 2 cm). The latter was eluted with dichloromethane–ether (9:1) until no more material with a chlorin-like visible spectrum was obtained. The eluted material was purified by repeated p.l.c. first with dichloromethane–ether (3:1), then with chloroform, and finally on a Merck plate with dichloromethane–ether (19:1) as eluant. This yielded the *chlorin* as a bright green solid (2.8 mg, 1.8%) (Found: M^+, 586.3319. $C_{38}H_{42}N_4O_2$ requires M^+, 586.3307); $\lambda_{max.}$ (rel.int.) 391 (100), 486 (7.7), 492 (8.1), 588 (3.6), and 642 nm (25.4); (in CH_2Cl_2 + 5% TFA) 403 (77.5), 521 (3.1), and 644 nm (14.9); *m/z* 586 (100%, M^+), 571 (23, $M - CH_3$), 495 (42, $M - C_7H_7$), and 451 (19); δ 1.65 [3 H, s, $C(CH_3)_2$], 1.77 (6 H, t, *J* 7.5 Hz, 2 × CH_2CH_3), 2.27 [3 H, s, $C(CH_3)_2$], 3.38, 3.39, 3.51, and 3.55 (each 3 H, s, 4 × ring CH_3), 3.70 and 3.91 (each 2 H, q, *J* 7.5 Hz, 2 × CH_2CH_3), 5.67—6.10 (2 H, ABq, *J* 12 Hz, CH_2Ph), 5.68—6.00 (2 H, ABq, *J* 12 Hz, 3-H_2), 7.40—7.75 (5 H, m, C_6H_5), 8.88 (1 H, s, 20-H), and 9.65 and 9.85 (each 1 H, s, 10-H, 15-H).

t-Butyl 4-*Ethyl*-5-(4-*methoxycarbonyl*-3,3-*dimethyl*-2-*oxobutyl*)-3-*methylpyrrole*-2-*carboxylate* (**25**).—The nitro ester (**6**) (600 mg, 1.52 mmol) and a solution of potassium t-butoxide in t-butyl alcohol (0.087M; 35 ml, 3.05 mmol) were stirred vigorously for 30 min under argon and then diluted with THF (20 ml). Buffered titanium(III) chloride solution (19 ml; *ca.* 7.5 mmol) was added as rapidly as possible, with a further portion (5 ml) added after 2 h. After a further 3 h, the mixture was diluted with ether (150 ml) and filtered through Celite, the pad being worked with ether (50 ml) and water (150 ml). The aqueous layer was acidified to pH 1 with hydrochloric acid (10M), and extracted with more ether (2 × 100 ml). The combined ethereal solutions were concentrated (to 70 ml), and an ethereal solution of diazomethane was added portionwise until effervescence ceased. The solution was washed with water (60 ml) and evaporated. Column chromatography of the residue on silica H, with dichloromethane–light petroleum (7:3) afforded the *keto ester*, as a gum (250 mg, 45.2%) (Found: M^+, 365.2202. $C_{20}H_{31}NO_5$ requires M^+, 365.2202); $\lambda_{max.}$ 277 nm; $\nu_{max.}$ 3 440 and 1 720—1 680s,br cm^{-1}; *m/z* 365 (100%, M^+), 309 [26, $M - (CH_3)_2C=CH_2$], 292 (24), and 277 (26); δ 1.04 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.27 [6 H, s, $C(CH_3)_2$], 1.55 [9 H, s, $C(CH_3)_3$], 2.26 (3 H, s, $ArCH_3$), 2.36 (2 H, q, *J* 7 Hz, CH_2CH_3), 2.64 (2 H, s, $CH_2CO_2CH_3$), 3.62 (3 H, s, CO_2CH_3), 3.80 (2 H, s, $ArCH_2CO$), and 9.12 (1 H, br, NH).

5-(3-*Ethyl*-4-*methyl*-5-*t-butoxycarbonylpyrrol*-2-*ylmethylidene*)-4,4-*dimethylpyrrolidin*-2-*one* (**26**).—*Method A*. A solution of the foregoing keto ester (**25**) (149 mg, 0.41 mmol) in glacial acetic acid (8 ml) containing ammonium acetate (300 mg, 4.1 mmol) was heated to 75 °C. After 24 h, more ammonium acetate (600 mg) was added, and heating continued for a total of 72 h. The solution was diluted with ether (60 ml), washed with saturated aqueous sodium hydrogen carbonate (3 × 30 ml) and brine (30 ml), and evaporated. The residue was purified by p.l.c. with ether as eluant, and the major band further purified by p.l.c. with dichloromethane–ether (4:1) as eluant, to give the *pyrrolylmethylidenepyrrolidinone* (35 mg, 25.8%), which crystallised from methanol, m.p. 154—155.5 °C (Found: C, 68.4; H, 8.2; N, 8.4%; M^+, 332.2107. $C_{19}H_{28}N_2O_3$ requires C, 68.6; H, 8.5; N, 8.4%; M^+, 332.2100); $\lambda_{max.}$ 304 nm; $\nu_{max.}$ 3 440m, 3 410m, 1 720s, and 1 675s cm^{-1}; *m/z* 332 (22%, M^+), 276 [100, $M - (CH_3)_2C=CH_2$], and 258 (14); δ 1.05 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 1.36 [6 H, s, $C(CH_3)_2$], 1.56 [9 H, s, $C(CH_3)_3$], 2.24 (3 H, s, $ArCH_3$), 2.39 (2 H, q, *J* 7.5 Hz, CH_2CH_3), 2.41 (2 H, s, CH_2CONH), 5.28 (1 H, s, NC=CH), 8.29 (1 H, br, lactam NH), and 8.80 (1 H, br, pyrrole NH).

Method B. To a vigorously stirred solution of the lactam (**8**) (143 mg, 1.2 mmol) in carbon tetrachloride (36 ml) containing anhydrous potassium carbonate (1.2 g), at 5 °C, was added a solution of t-butyl hypochlorite (143 mg, 1.32 mmol) in the same solvent (2.5 ml) during 5 min. A further portion of t-butyl hypochlorite (14 mg) was added after 3 h at 5 °C and the solution allowed to warm to 20 °C during 1 h. It was filtered through Celite, diluted with dichloromethane (100 ml), washed with hydrochloric acid (2M; 100 ml), and evaporated. The residue in carbon tetrachloride (80 ml) was heated under reflux in a flask fitted with a pressure-equalising dropping funnel containing Type 3A molecular sieve (0.5 g), so that the condensed solvent passed through the sieve. After 16 h, the solution was evaporated and the residue purified by column chromatography on silica H with dichloromethane, and then with dichloromethane–ether (3%). The major product was the

pyrrolylmethylidenepyrrolidinone (266 mg, 66.9%), which was recrystallised from methanol (231 mg, 58%) and was identical with that obtained by Method A.

5-(3-*Ethyl*-5-*formyl*-4-*methylpyrrole*-2-*ylmethylidene*)-4,4-*dimethylpyrrolidin*-2-*one* (**19**).—A solution of the foregoing lactam (**26**) (370 mg, 1.11 mmol) in TFA (10 ml) was stirred under nitrogen for 5 min and then cooled to 15 °C; trimethyl orthoformate (5 ml) was then added rapidly. After 20 min, water was added until the solution just became turbid (*ca.* 10 ml), and stirring was continued for a further 30 min before dilution with dichloromethane (50 ml) and washing with aqueous ammonia (1M; 2 × 20 ml). The residue from the organic layer was purified by p.l.c. on a Merck Type 5717 2 mm plate using dichloromethane–methanol (19:1) as eluant and a continuous elution technique. The major band crystallised from dichloromethane–hexane to give the yellow *product* (248 mg, 85.6%), m.p. 188—190 °C (Found: C, 69.0; H, 7.6; N, 10.8%; M^+, 260.1523. $C_{15}H_{20}N_2O_2$ requires C, 69.2; H, 7.7; N, 10.8%; M^+, 260.1524); $\lambda_{max.}$ (rel.int.) 243 (100) and 355 nm (78); $\nu_{max.}$ 3 620m,br, 1 720s, 1 665s, and 1 600s cm^{-1}; *m/z* 260 (100%, M^+), 245 (77, $M - CH_3$), and 217 (28); δ 1.09 (3 H, t, *J* 7.5 Hz, CH_2CH_3), 1.37 [6 H, s, $C(CH_3)_2$], 2.30 (3 H, s, $ArCH_3$), 2.42 (2 H, s, CH_2CONH), 2.48 (2 H, q, *J* 7.5 Hz, CH_2CH_3), 5.31 (1 H, s, HNC=C*H*), 9.52 (1 H, s, CHO), and 10.83 (2 H, br, 2 × NH).

t-Butyl 5-*Acetoxymethyl*-4-*ethyl*-3-*methylpyrrole*-2-*carboxylate* (**33**).—To a stirred solution of t-butyl 3,5-dimethyl-4-ethylpyrrole-2-carboxylate[20] (5.58 g, 25 mmol) in glacial acetic acid (50 ml) was added lead tetra-acetate (12.18 g, 27.5 mmol) portionwise during 10 min. After 2.5 h, ice (50 g) and water (150 ml) were added. The precipitate was collected, washed with water, and partitioned between dichloromethane (150 ml) and aqueous sodium hydrogen carbonate (5%; 50 ml). The organic solution was passed through a silica column (4 × 2 cm), eluting with more dichloromethane. The residue from the eluate crystallised from dichloromethane–hexane to give the *acetoxymethylpyrrole* (5.97 g, 85%), m.p. 114—116 °C (Found: C, 64.0; H, 8.3; N, 4.8%; M^+, 281.1623. $C_{15}H_{23}NO_4$ requires C, 64.0; H, 8.2; N, 5.0%; M^+, 281.1627); $\lambda_{max.}$ 272 nm; $\nu_{max.}$ 3 450, 1 730s, 1 680s, 1 600w, and 1 580w cm^{-1}; *m/z* 281 (47%, M^+), 225 [53, $M - (CH_3)_2C{=}CH_2$], 222 (16, $M - CH_3CO_2$), and 166 [100, $M - (CH_3)_2C{=}CH_2$ and CH_3CO_2]; δ 1.14 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.62 [9 H, s, $C(CH_3)_3$], 2.09 (3 H, s, CH_3CO_2), 2.30 (3 H, s, $ArCH_3$), 2.51 (2 H, q, *J* 7 Hz, CH_2CH_3), 5.06 (2 H, s, $ArCH_2O$), and 9.05 (1 H, br, NH).

2-*Benzyl* 4-*Methyl* 5-*Methoxycarbonylmethyl*-3-*methylpyrrole*-2,4-*dicarboxylate* (**29**).—A solution of sodium nitrite (13.8 g, 0.2 mol) in water (25 ml) was added during 10 min to a stirred solution of benzyl acetoacetate (38.4 g, 0.2 mol) in glacial acetic acid at 0 °C and the resulting mixture was kept overnight at 20 °C. This solution was then added dropwise to a mechanically stirred solution of dimethyl acetonedicarboxylate (34.8 g, 0.2 mol) in glacial acetic acid (80 ml) in a 1-l conical flask, at the same time as an intimate mixture of zinc dust (35 g) and sodium acetate (35 g) was added portionwise. The additions were regulated such that the zinc was always in excess and the temperature remained at 70—80 °C. When the additions were complete and the reaction subsided, the mixture was heated on a water-bath to 70—80 °C for 1 h; it was then cooled on ice with stirring for 15 min and the solid collected, washed with water, dissolved in dichloromethane (600 ml), and the solution filtered. The filtrate was washed with water (200 ml), saturated aqueous sodium hydrogen carbonate (200 ml), and brine (200 ml); the aqueous layers were back-washed with dichloromethane (50 ml). The residue from the combined dichloromethane solutions crystallised from aqueous methanol to give the *pyrrole* (24.2 g, 35%), m.p. 121—126 °C (Found: C, 62.9; H, 5.55; N, 3.9. $C_{18}H_{19}NO_6$ requires C, 62.6; H, 5.55; N, 4.1%); $\lambda_{max.}$ (MeOH) 270 nm; $\nu_{max.}$ 3 690w, 3 610w, 3 440br, 1 740sh, and 1 690s cm^{-1}; *m/z* 345 (100%, M^+), 313 (91, $M - CH_3OH$), 254 (82, $M - C_7H_7$), 178 (44), and 91 (99, $C_7H_7^+$); δ 2.53 (3 H, s, $ArCH_3$), 3.65 and 3.74 (each 3 H, s, 2 × CO_2CH_3), 3.97 (2 H, s, $ArCH_2CO_2$), 5.25 (2 H, s, CH_2Ph), 7.31 (5 H, s, C_6H_5), and 10.27 (1 H, br, NH).

4-*Methoxycarbonyl*-5-*methoxycarbonylmethyl*-3-*methylpyrrole*-2-*carboxylic Acid* (**30**).—A solution of the foregoing pyrrole triester (17.25 g, 50 mmol) in methanol (350 ml) and THF (200 ml) containing palladium on charcoal (10%, 0.7 g) was stirred under hydrogen until uptake ceased (5 h). The solution was filtered through Celite and the solvent removed to give the *pyrrole*-2-*carboxylic acid* (12 g, 94%), which was used in the next step without purification. An analytical sample was recrystallised from methanol, m.p. 212—215 °C (sublimes) (Found: C, 51.6; H, 5.2; N, 5.5. $C_{11}H_{13}NO_6$ requires C, 51.8; H, 5.1; N, 5.5%); $\lambda_{max.}$ (MeOH) 255 and 265 nm; $\nu_{max.}$ (Nujol) 3 340s, 3 300—2 500vbr, 1 735s, 1 690sh, and 1 665s cm^{-1}; *m/z* 255 (30%, M^+), 223 (100, $M - CH_3OH$), 205 (54), 178 (77), and 148 (54); δ 2.57 (3 H, s, $ArCH_3$), 3.74 and 3.80 (each 3 H, s, 2 × CO_2CH_3), 4.06 (2 H, s, $ArCH_2CO_2$), and 9.96 (1 H, br, NH).

Methyl 2-*Methoxycarbonylmethyl*-4-*methylpyrrole*-3-*carboxylate* (**31**).—To a vigorously stirred suspension of the foregoing acid (6.8 g, 26.7 mmol) in boiling, ethanol-free chloroform (220 ml) was added hot (60 °C) aqueous sodium hydrogen carbonate (8.08 g, 94 mmol in 150 ml). Heating under reflux was continued until all the solid had dissolved (*ca.* 5 min), when immediately a solution of iodine (9.12 g, 35.9 mmol) and potassium iodide (10.8 g, 65 mmol) in water (55 ml) was added rapidly, down the condenser. Heating was continued for 10 min after which the flask was cooled on ice and solid sodium metabisulphite added until colour change ceased. The aqueous layer was separated and washed with dichloromethane (2 × 50 ml). The residue from the combined organic layers was chromatographed on silica (4.5 × 6 cm) with dichloromethane followed by dichloromethane–ether (49:1) as eluant to yield methyl 5-iodo-2-methoxycarbonylmethyl-4-methylpyrrole-3-carboxylate (7.96 g, 88%), δ 2.17 (3 H, s, $ArCH_3$), 3.62 and 3.70 (each 3 H, s, 2 × CO_2CH_3), 3.91 (2 H, s, $ArCH_2CO_2$), and 9.50 (1 H, br, NH). This was used in the next step without delay. A solution of the iodopyrrole in methanol (140 ml) containing sodium acetate (7 g) and palladium on charcoal (10%, 1 g) was stirred under hydrogen until uptake ceased (6 h). The solution was then filtered through Celite and the filtrate concentrated (to 30 ml) and partitioned between dichloromethane (150 ml) and saturated aqueous sodium hydrogen carbonate (100 ml); the aqueous layer was extracted with more dichloromethane (2 × 50 ml). The residue from the combined organic layers was chromatographed on silica (4 × 5 cm), using dichloromethane followed by dichloromethane–ether (49:1) as eluant. Crystallisation from dichloromethane–hexane gave the α-*free pyrrole* (3.62 g, 64.3% from the carboxylic acid), m.p. 91—93 °C (Found: C, 56.8; H, 6.45; N, 6.7. $C_{10}H_{13}NO_4$ requires C, 56.9; H, 6.2; N, 6.6%); $\lambda_{max.}$ (MeOH) 243 and 259 nm; $\nu_{max.}$ 3 690w, 3 610w, 3 460, 3 420, 1 730s, and 1 690s cm^{-1}; *m/z* 211 (24%, M^+), 179 (100, $M - CH_3OH$), 152 (35, $M - CO_2CH_3$), and 120 (23); δ 2.22 (3 H, s, $ArCH_3$), 3.70 and 3.77 (each 3 H, s, 2 × CO_2CH_3), 4.03 (2 H, s, $ArCH_2CO_2$), 6.41 (1 H, br, ArH), and 9.27 (1 H, br, NH).

Methyl 2-*Benzyloxycarbonylmethyl*-4-*methylpyrrole*-3-*carboxylate* (**32**).—Sulphuric acid (18M; 2 ml) was added dropwise to a stirred solution of the foregoing α-free pyrrole (**31**) (2 g, 9.47 mmol) in THF (20 ml) and benzyl alcohol (20 ml) at 15 °C.

A precipitate formed which redissolved after 30 min. After being stirred for 24 h at 20 °C, the solution was partitioned between dichloromethane (500 ml) and saturated aqueous sodium hydrogen carbonate (450 ml). The aqueous layer was washed with dichloromethane (100 ml), and the combined organic layers were washed with brine (300 ml). The solvent was evaporated at 45 °C (0.1 mm) and the residue by flash chromatography using dichloromethane–ether (49:1) gave the *benzyloxycarbonylmethylpyrrole* (2.22 g, 81.6%) which was recrystallised from dichloromethane–hexane (1.86 g, 68.4%), m.p. 69—71.5 °C (Found: C, 66.9; H, 6.0; N, 4.9. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%); $\lambda_{max.}$ (MeOH) 234 and 260 nm; $\nu_{max.}$ 3 690w, 3 600w, 3 460, 3 420, 1 720s, 1 690s, and 1 600 cm^{-1}; *m/z* 287 (26%, M^+), 196 (23, $M - C_7H_7$), 179 (18, M – $PhCH_2OH$), 152 (60), and 91 (100, $C_7H_7^+$); δ 2.25 (3 H, s, $ArCH_3$), 3.77 (3 H, s, CO_2CH_3), 4.12 (2 H, s, $ArCH_2CO_2$), 5.18 (2 H, s, CH_2Ph), 6.45 (1 H, br, ArH), 7.35 (5 H, s, C_6H_5), and 9.56 (1 H, br, NH).

5-t-Butyl 4'-Methyl 5'-Benzyloxycarbonylmethyl-4,3'-dimethyl-3-ethyl-2,2'-pyrromethane-5,4'-dicarboxylate (**20**).—Toluene-*p*-sulphonic acid (80 mg, 0.47 mmol) was added to a stirred solution of the foregoing α-free pyrrole (**32**) (1.8 g, 6.27 mmol) and the acetoxymethylpyrrole (**33**) (1.79 g, 6.28 mmol) in dichloromethane (50 ml) under nitrogen. After 10 min, the solution was washed with saturated aqueous sodium hydrogen carbonate (30 ml) and evaporated. The residue by flash chromatography using ethyl acetate–light petroleum (1:4) gave three components, the second to be eluted being the desired *pyrromethane* which was recrystallised from ethyl acetate–hexane (2.15 g, 67.4%), m.p. 126—128 °C (Found: C, 68.8; H, 7.05; N, 5.5. $C_{29}H_{36}N_2O_6$ requires C, 68.5; H, 7.1; N, 5.5%); $\lambda_{max.}$ (MeOH) 232 and 281 nm; $\nu_{max.}$ 3 690w, 3 610w, 3 440, 1 730sh, 1 690s, and 1 600 cm^{-1}; *m/z* 508 (100%, M^+), 452 (21), 436 (12), 362 (58), and 318 (31); δ 1.01 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.52 [9 H, s, $C(CH_3)_3$], 2.20 and 2.23 (each 3 H, s, 2 × $ArCH_3$), 2.37 (2 H, q, *J* 7 Hz, CH_2CH_3), 3.72 (5 H, s, CO_2CH_3, $ArCH_2Ar$), 3.98 (2 H, s, $ArCH_2CO_2$), 5.09 (2 H, s, CH_2Ph), 7.28 (5 H, s, C_6H_5), and 8.44 and 8.87 (each 1 H, br, 2 × NH).

The least polar component (0.35 g) was crystallised from dichloromethane–hexane to give *di-t-butyl 3,3'-diethyl-4,4'-dimethyl-2,2'-pyrromethane-5,5'-dicarboxylate* (**34**), m.p. 158—164 °C, $\lambda_{max.}$ 273 and 284 nm; $\nu_{max.}$ 3 690w, 3 530w, 3 440, 1 670s, and 1 600 cm^{-1}; *m/z* 430 (56%, M^+), 374 [14, M – $(CH_3)_2C{=}CH_2$], 357 [13, $M - (CH_3)_3CO$], and 318 [100, $M - 2 \times (CH_3)_2C{=}CH_2$]; δ 1.03 (6 H, t, *J* 7.5 Hz, 2 × CH_2CH_3), 1.52 [18 H, s, 2 × $C(CH_3)_3$], 2.23 (6 H, s, 2 × $ArCH_3$), 2.38 (4 H, q, *J* 7.5 Hz, 2 × CH_2CH_3), 3.80 (2 H, s, $ArCH_2Ar$), and 8.70 (2 H, br, 2 × NH). The most polar component (260 mg) was crystallised from dichloromethane-hexane to afford *dimethyl 5,5'-bisbenzyloxycarbonylmethyl-3,3'-dimethyl-2,2'-pyrromethane-4,4'-dicarboxylate* (**35**), m.p. 158—161 °C (Found: C, 67.4; H, 5.85; N, 4.7. $C_{33}H_{34}N_2O_8$ requires C, 67.6; H, 5.8; N, 4.8%); $\lambda_{max.}$ (MeOH) 232 and 268 nm; $\nu_{max.}$ 3 690w, 3 610w, 3 430br, 1 730s, 1 690s, and 1 600 cm^{-1}; *m/z* 586 (100%, M^+) and 300 (39, M – pyrrole ring); δ 2.18 (6 H, s, 2 × $ArCH_3$), 3.70 (8 H, s, 2 × CO_2CH_3, $ArCH_2Ar$), 3.96 (4 H, s, 2 × $ArCH_2CO_2$), 5.08 (4 H, s, 2 × CH_2Ph), 7.27 (10 H, s, 2 × C_6H_5), and 9.05 (2 H, br, 2 × NH).

19-Benzyloxycarbonylmethyl-7,13-diethyl-18-methoxycarbonyl-3,3,8,12,17-pentamethyl-1,2,3,9,15,22,24-hexahydro-(21H)bilin-1-one (**21**).—A solution of the foregoing pyrromethane (**20**) (39.1 mg, 76.8 μmol) in TFA (2 ml) was stirred for 10 min under argon. A solution of the aldehyde (**19**) (20 mg, 76.8 μmol) in methanol (2 ml) and TFA (1 ml) was added, the whole being washed in with methanol (2 ml). After 45 min in the dark, the solvent was evaporated and the violet residue partitioned between dichloromethane (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml). The organic layer was filtered through sodium sulphate and the solvent removed. Purification of the residue by p.l.c., using dichloromethane–ether (4:1) yielded the bright red *hexahydrobilinone* (38 mg, 76%); $\lambda_{max.}$ (rel.int.) 296 (47.9) and 502 nm (50.5); (in CH_2Cl_2 + 1 drop TFA) 304 (48.5), 394 (28.3), and 550 nm (100); $\nu_{max.}$ 3 700w, 3 420, 3 360br, 1 730sh, 1 695s, 1 640s, 1 610s, and 1 550m cm^{-1}; *m/z* 650 (100%, M^+ for $C_{39}H_{46}N_4O_5$); δ 1.06 (6 H, t, *J* 7.5 Hz, 2 × CH_2CH_3), 1.36 [6 H, s, $C(CH_3)_2$], 2.10, 2.13, and 2.15 (each 3 H, s, 3 × ring CH_3), 2.42 (2 H, s, CH_2CONH), 2.43 (4 H, m, 2 × CH_2CH_3), 3.62 (5 H, s, CO_2CH_3, 15-H_2), 3.92 (2 H, s, $ArCH_2CO_2$), 5.03 (2 H, s, CH_2Ph), 5.40 (1 H, s, 5-H), 6.57 (1 H, s, 10-H), 7.19 (5 H, s, C_6H_5), and 11.50 (3 H, br, 3 × NH).

19-Benzyloxycarbonylmethyl-7,13-diethyl-1-methoxy-18-methoxycarbonyl-3,3,8,12,17-pentamethyl-2,3,15,24-tetrahydro-(22H)bilin (**22**).—Trimethyloxonium tetrafluoroborate (90 mg, 0.6 mmol) was added to a stirred solution of the foregoing bilinone (**21**) (39 mg, 59.9 μmol) in dichloromethane, under argon. After 1 h, the violet solution was partitioned between dichloromethane (20 ml) and ice-cold aqueous sodium hydrogen carbonate (2%, 15 ml). The organic layer was rapidly filtered through sodium sulphate, and the solvent removed. P.l.c. of the residue using dichloromethane–ether (7:3) as eluant gave recovered starting bilinone (20.9 mg) and a broad violet band near the baseline which yielded the *l-methoxybilin* (14.2 mg, 76.7% based on unrecovered starting material); $\lambda_{max.}$ (rel.int.) 298 (76.5) and 530 nm (69.9); (in CH_2Cl_2 + 5% TFA) 305 (61.0), 387 (69.1), 548sh (78.7), and 576 nm (100); $\nu_{max.}$ 3 700, 1 730sh, 1 700s, and 1 600s cm^{-1}; *m/z* 664 (32%, M^+ for $C_{40}H_{48}N_4O_5$) and 650 (100).

5-Benzyloxycarbonyl-12,18-diethyl-7-methoxycarbonyl-2,2,8,13,17-pentamethylchlorin (**24**).—Hydrated copper(II) acetate (93 mg, 0.4 mmol) was added to a stirred solution of the foregoing methoxybilin (14.2 mg, 21.3 μmol) in acetonitrile, under argon. After 10 min, DBU (33 mg, 200 μmol) was added, and the green solution was heated under reflux in the dark for 4 h. The cooled mixture was diluted with dichloromethane (30 ml) and filtered through Celite. The filtrate was washed with water (2 × 40 ml) and saturated aqueous sodium hydrogen carbonate (40 ml), and the solvent then removed. The residue was purified by p.l.c., using dichloromethane–ether (9:1) to give the chlorin copper complex; $\lambda_{max.}$ (rel.int.) 385sh (69), 404 (100), 490 (6), and 628 (33) nm. This was dissolved in TFA, and the solution saturated with hydrogen sulphide gas. After the mixture had been stirred in the dark for 22 h, the solution was filtered through Celite and the solvent removed. The residue in dichloromethane (30 ml) was washed with water (2 × 20 ml) and aqueous ammonia (2M; 20 ml), and evaporated. P.l.c. of the residue using dichloromethane gave the bright green *chlorin* (1 mg, 7.4%); $\lambda_{max.}$ (rel.int) 398 (100), 494 (7.8), 524 (3.6), 604 (3.8, and 656 nm (28.2); (in CH_2Cl_2 + 5% TFA) 404 (71.3), 520 (2.4), 568 (3.8), and 660 nm (19.4); $\nu_{max.}$ 3 690, 3 610, 1 720s, and 1 605s cm^{-1}; *m/z* 630 (100%, M^+ for $C_{39}H_{42}N_4O_4$); δ 1.70 (6 H, t, 2 × CH_2CH_3), 1.91 [6 H, s, $C(CH_3)_2$], 3.25 and 3.36 (each 3 H, s, 13-CH_3, 17-CH_3), 3.64 (3 H, s, 8-CH_3), 3.74 (4 H, m, 2 × CH_2CH_3), 4.17 (3 H, s, CO_2CH_3), 4.53 (2 H, s, 3-H_2), 5.64 (2 H, s, CH_2Ph), 7.35 (5 H, m, C_6H_5), 8.50 (1 H, s, 20-H), and 9.30 and 9.66 (each 1 H, s, 10-H, 15-H).

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