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Synthetic Studies Relevant to Biosynthetic Research on Vitamin B_{12}. Part 3.[1] An Approach to Isobacteriochlorins *via* Nitrones

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2,2,8,8,12,13,17,18-Octamethylisobacteriochlorin has been synthesised in modest yield by a route which makes use of the chemistry of nitrones to build a linear system which is cyclised using copper(II) acetate.

Vitamin B_{12} (**5**) is biosynthesised by a complex sequence of reactions, the early stages being the same as those which Nature uses for the synthesis of haem and chlorophyll.[2] These early steps produce uroporphyrinogen-III (**1**) (uro'gen-III), which is the last intermediate common to all three pigments of life mentioned above. At this point on the pathway, the route to vitamin B_{12} branches away as a result of *C*-methylation of uro'gen-III (**1**) first at C-2[3] to give an intermediate [(**2**) or tautomer] which will not be our concern here. The second *C*-methylation occurs at C-7 and the third at C-20 (Scheme 1). It has been shown[4] that the intermediate formed by di-*C*-methylation of uro'gen-III (**1**) is the dihydroisobacteriochlorin (**3**). Unless special precautions are taken, this intermediate undergoes aerial oxidation and is isolated[5] as the ester (**7**) of the aromatised isobacteriochlorin (**6**). This structure was first deduced in 1977[5a] and was confirmed by two independent approaches.[6] There is considerable evolutionary interest in the fact that this same substance (**6**), named sirohydrochlorin, had been isolated earlier[7] as the metal-free prosthetic group from sulphite and nitrite reductase enzymes, though at that time, its complete structure was unknown. Two years later, the surprising constitution (**8**) was derived[8] for the aromatised tri-*C*-methylated macrocycle, also isolated[9] as its ester (**9**); here too, it is highly probable that the true biosynthetic intermediate is the dihydro-system (**4**).

The isolation of these dimethylated and trimethylated pigments (**6**) and (**8**) together with the elucidation of their structures totally changed the course of research into the biosynthesis of vitamin B_{12}. These pigments are unquestionably of great importance for future biosynthetic work in this area but these efforts are hamstrung by the scarcity of the natural materials. A major biological effort is required to produce some tens of milligrams of sirohydrochlorin (**6**) or a few milligrams of the rare 20-methylsirohydrochlorin (**8**). Accordingly, work was initiated in 1979 with the initial aim of developing practical synthetic routes capable of yielding hundreds of milligrams of isobacteriochlorins related to structures (**6**) and (**8**) but having symmetry and being achiral. A second long-term objective, recognised to be a highly demanding one, was the synthetic production in workable amounts of the natural pigments themselves, *viz.* sirohydrochlorin (**6**) and its 20-methyl derivative (**8**). The present series of papers will describe our progress towards both objectives.

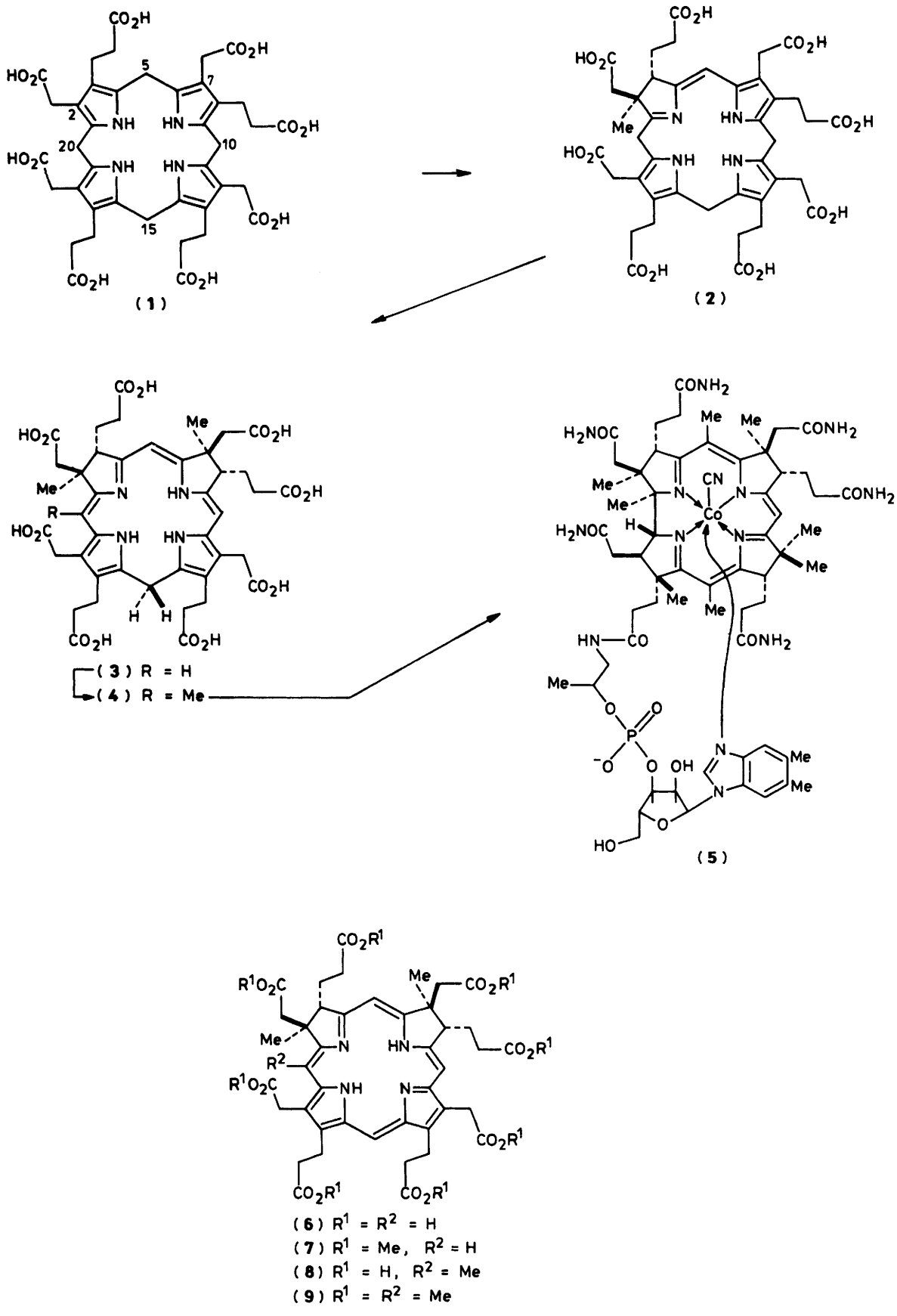
One rational synthesis of the isobacteriochlorin macrocycle, resulting from a collaborative effort between Zürich and Cambridge,[10] had just been described at the outset of our work. The route involved construction of the macrocycle by joining a northern portion (A-B) to a southern portion (C-D) [retro-cleavage E, structure (**10**)] and it successfully yielded the octamethylisobacteriochlorin (**11a**). However, the strongly basic conditions necessary to form the macrocycle caused difficulties when acetic and propionic acid side-chains (as their methyl esters) were present. Accordingly, it was decided to explore alternatives based on the union of western (A-D) and eastern (B-C) parts [retro-cleavage F, structure (**10**)].

A key problem in such a plan is how to join the reduced rings A and B [see (**10**)]. A promising approach seemed to be offered by the chemistry of nitrones, extensively studied by Todd *et al.*[11] who found that two reduced rings could be coupled as in Scheme 2. Since our first synthetic target was the symmetrical octamethylisobacteriochlorin (**11b**), the two nitrones (**12**) and (**13**) were required to allow study of their conversion into the seco-system (**14**). The introduction of a one-carbon unit late in the synthesis to close the macrocycle between the pyrrolic rings of product (**14**) was not expected to be a difficult step.

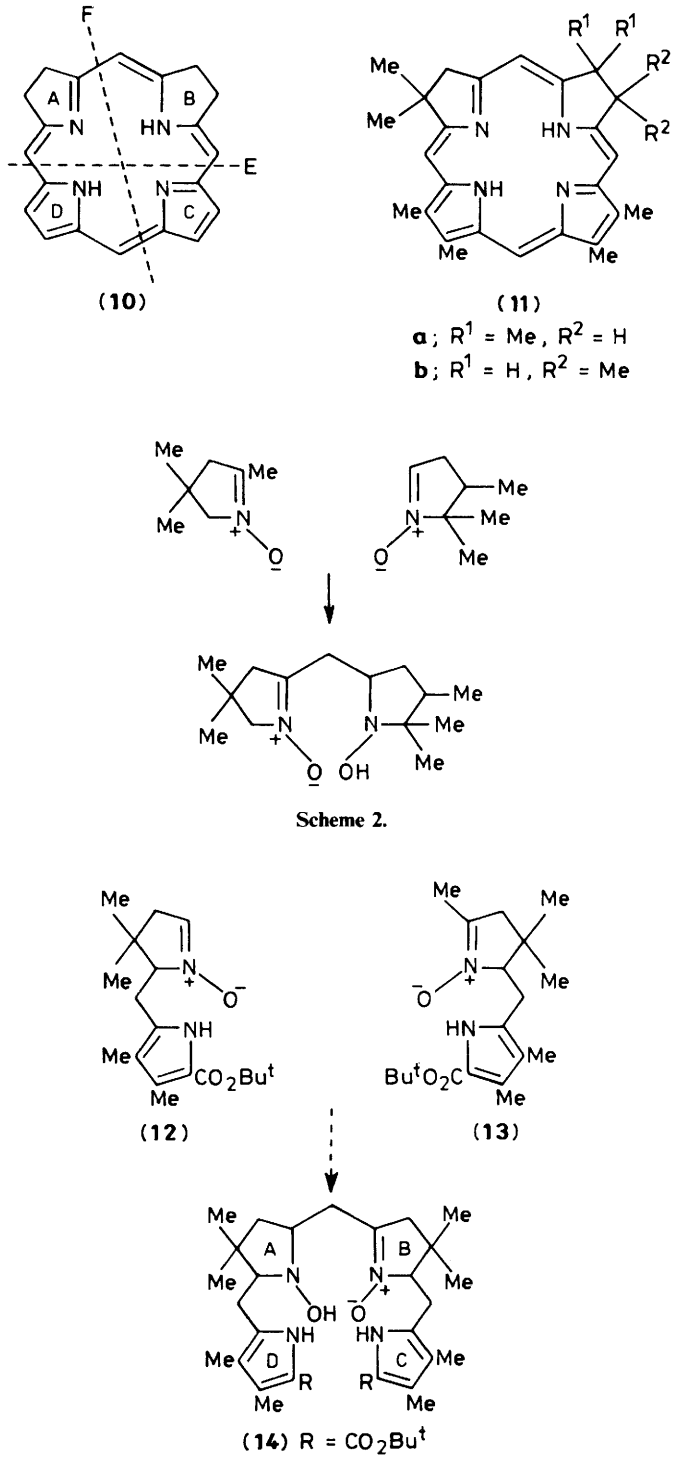
The nitrones (**12**) and (**13**) were synthesised using chemistry related to that described in earlier papers.[1,12] Thus, t-butyl 5-formyl-3,4-dimethylpyrrole-2-carboxylate (**15**)[13] was condensed with nitromethane to give the expected nitro-olefin (see Scheme 3) which was cleanly reduced to the nitroethyl derivative (**16**) with sodium borohydride. This product underwent Michael addition to mesityl oxide and the resulting adduct was cyclised by reduction of the nitro group with zinc. The yield of nitrone (**13**) from the pyrrole aldehyde (**15**) was 28% overall. In an effort to make the synthesis of nitrone (**13**) more convergent, we attempted to react the pyrrole aldehyde (**15**) with nitroalkane (**17**),[14] but no reaction occurred presumably owing to steric problems.

The synthesis of the nitrone (**12**) required the formal addition of nitroethylpyrrole (**16**) to 3-methylcrotonaldehyde. Since a direct condensation of these two compounds was unlikely to occur in the desired sense, the nitroethylpyrrole (**16**) was combined with methyl 3-methylcrotonate and the ester group in the resulting Michael adduct was reduced with di-isobutylaluminium hydride to the desired aldehyde (**18**). Cyclisation of the nitro aldehyde (**18**) with zinc was a more complex reaction than for cyclisation of the nitrone (**13**) and, as a result, only a moderate yield of the nitrone (**12**) [13% overall from (**15**)] was obtained. Literature precedent[15,16] suggested that the conversion of nitro aldehydes into cyclic nitrones may best be accomplished by first converting the aldehyde into the corresponding acetal, then reducing the nitro group to the hydroxylamine, and finally effecting cyclisation by unmasking the aldehyde. In the present case, however, such a sequence did not prove advantageous.

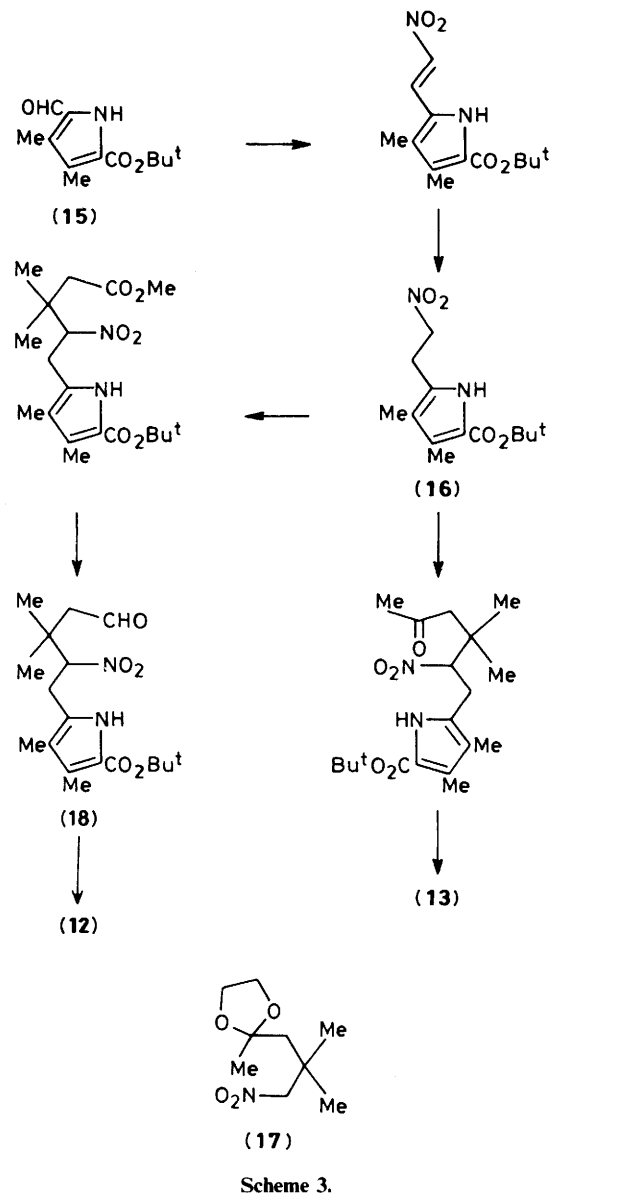
Treatment of an equimolar mixture of the nitrones (**12**) and (**13**) with sodium hydride in tetrahydrofuran led to a clean coupling reaction and the resulting product (**14**) had the expected mass and u.v. spectra. Its ^1H n.m.r. spectrum was complex, not surprisingly because a mixture of diastereoisomers will be formed in the coupling step. This success left three manipulations to be effected: removal of the oxygen atoms from the nitrone and hydroxylamine moieties in structure (**14**), cyclisation of the macrocycle by joining rings C and D and adjustment of the oxidation state of the macrocycle. Space-filling models showed that the two oxygen atoms on nitrogen



Scheme 1.



Scheme 2.

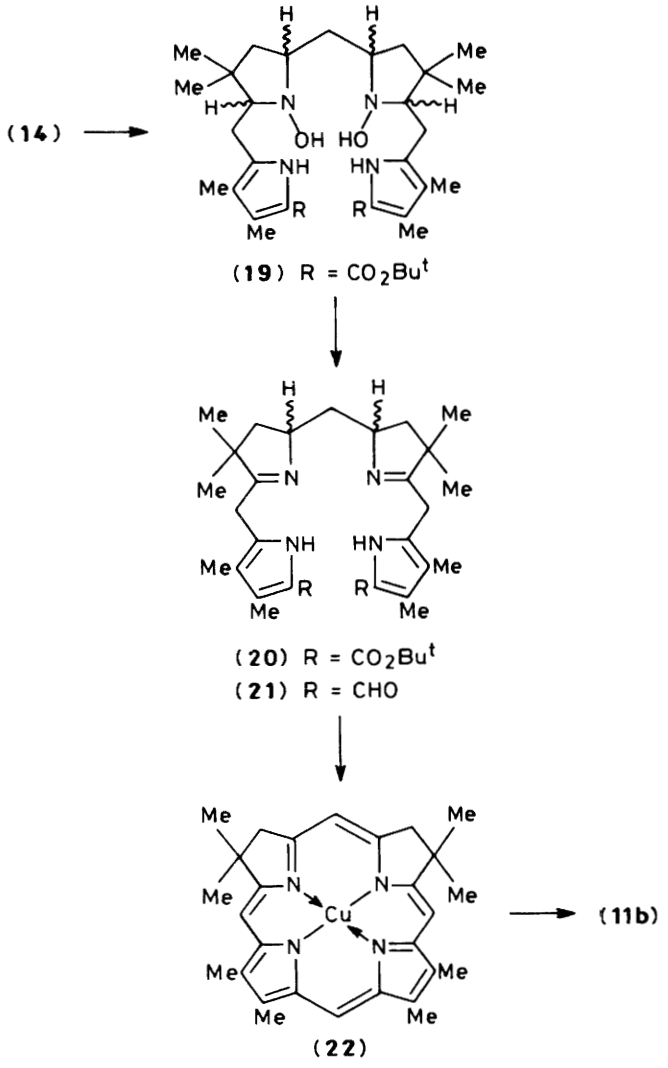


Scheme 3.

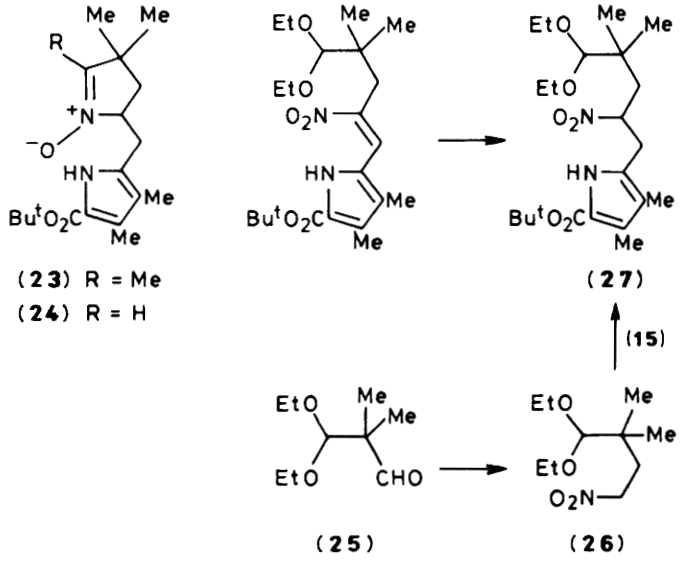
severely crowd the cavity of the seco-macrocycle (**14**); their removal was therefore a first priority. Following earlier experience with a simpler nitrone-hydroxylamine system,[11,17] the seco-system (**14**) was reduced to the bis-hydroxylamine (**19**) with sodium borohydride or, more effectively, with sodium cyanoborohydride. The product (**19**) was then treated with phosphoryl chloride and triethylamine in benzene[11] to yield the desired dehydration product [(**20**) or tautomers] now lacking the crowding oxygen atoms.

To effect cyclisation between rings C and D of product (**20**), the first step was to remove the two t-butyl groups with neat trifluoroacetic acid which also caused decarboxylation. Addition of trimethyl orthoformate then gave the bis-aldehyde (**21**). Attempted direct cyclisation of the bis-aldehyde (**21**) was unsuccessful, presumably owing, in part, to the entropic problem of achieving close proximity of the two ends of this mobile molecule; also, the deactivated state of rings C and D is unhelpful. A study of metal ions to act as templates led to treatment of bis-aldehyde (**21**) with copper(II) acetate which has been used in syntheses of porphyrins.[18] It was also hoped that Cu^{II} would oxidatively aromatise the initially formed macrocycle. In the event, the Cu^{II}-isobacteriochlorin (**22**) was formed [16% over the four steps from (**20**)] and it was demetallated with acidified ethanedithiol[19] to yield the octamethylisobacteriochlorin (**11b**) which was our synthetic target.

Preliminary studies have also been made of the potential of this approach for the synthesis of the unsymmetrical isobacteriochlorin (**11a**) which has a substitution pattern corresponding to sirohydrochlorin (**6**). This work is briefly outlined and experimental details are provided for the intermediates prepared. The macrocycle (**11a**) is, in principle, derivable by (**12**) + (**23**) or (**13**) + (**24**). A possible route to the nitrone (**24**) involves condensation of the nitroethylpyrrole (**16**)



with the known mono-diethyl acetal of dimethylmalonaldehyde[20] (**25**) but this reaction could not be achieved. To reduce steric congestion at the reaction centre, the aldehyde (**25**) was converted, by condensation with nitromethane followed by reduction, into the nitroalkane (**26**). This did react with the



pyrrole aldehyde (**15**) but despite much experimentation the yield of product, isolated as the acetal (**27**) after reduction, was very low. This study has not been carried further.

The work reported here shows that the isobacteriochlorin macrocycle can be synthesised by a sequence based on the chemistry of nitrones but our experience clearly indicated that a preparatively valuable method would need to be based on a different approach. The successful development of such a method, based on a photochemical ring-closure, has been briefly described.[21]

Experimental

General Directions.—Melting points were determined in a Buchi 510 melting point apparatus and are uncorrected. Solutions were dried over magnesium sulphate and all evaporations were under reduced pressure at <40 °C. ^1H N.m.r. spectra were recorded on Varian EM-360 or HA-100 spectrometers. I.r. and u.v. spectra were recorded on Perkin-Elmer 157G and Pye Unicam SP 8-100 spectrophotometers respectively. Analytical thin layer chromatography was performed with Merck analytical plates.

2-t-Butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (**15**).—This compound was prepared according to ref. 13 with modification as below.

2-t-Butoxycarbonyl-3,4,5-trimethylpyrrole (20.9 g, 0.1 mol) in acetic acid (100 ml) was treated portionwise with lead tetra-acetate (100 g, 0.22 mol) over 20 min, during which the temperature rose to *ca.* 65 °C. After the mixture had been warmed to 70 °C for 20 min and then cooled to 20 °C, the excess of oxidant was destroyed with ethylene glycol (2 ml). The mixture was diluted with water (600 ml) and extracted with methylene chloride (3 × 100 ml), the combined extracts being washed with water (100 ml), filtered, and evaporated. The residue was then heated under reflux in tetrahydrofuran–water (1 : 1, 300 ml) for 1 h, cooled, diluted with ether (150 ml), washed with 5% aqueous $NaHCO_3$ (3 × 100 ml) and then with brine (100 ml), and finally dried. The filtered solution was evaporated and the residue crystallised from hexane (100 ml) to give the aldehyde (14.5 g, 65%), m.p. 90—91 °C (hexane) [lit.,[13] 100—101 °C (CH_2Cl_2–hexane)]; $\lambda_{max.}$ 305 nm.

(E)-2-t-Butoxycarbonyl-3,4-dimethyl-5-(2-nitrovinyl)-pyrrole.—2-t-Butoxycarbonyl-5-formyl-3,4-dimethylpyrrole (8.92 g, 40 mmol), nitromethane (4.90 g, 80 mmol), potassium acetate (4.32 g, 44 mmol), and methylamine hydrochloride (2.70 g, 40 mmol) were stirred together in dry methanol (60 ml) for 3 h. The mixture was then diluted with water (300 ml) and extracted with methylene chloride (100 ml, 4 × 50 ml). The combined extracts were washed with water (100 ml) and the residue from evaporation crystallised from methanol (50 ml) to give the *nitro-olefin* (7.22 g, 68%), m.p. 159—160 °C (Found: C, 58.4; H, 6.8; N, 10.6. $C_{13}H_{18}N_2O_4$ requires C, 58.6; H, 6.8; N, 10.5%); $\nu_{max.}$ 3 450, 1 690, and 1 625 cm^{-1}; $\lambda_{max.}$ 264 and 395 nm; δ 1.61 [9 H, s, $C(CH_3)_3$], 2.19 (3 H, s, CH_3), 2.29 (3 H, s, CH_3), 7.50 (1 H, d, *J* 13 Hz, *H*C=CHNO$_2$), 8.06 (1 H, d, *J* 13 Hz, –CH=C*H*NO$_2$), and 9.83 (1 H, br s, NH).

2-t-Butoxycarbonyl-3,4-dimethyl-5-(2-nitroethyl)pyrrole (**16**).—A slurry of 2-t-butoxycarbonyl-3,4-dimethyl-5-(2-nitrovinyl)pyrrole (7.53 g, 28.3 mmol) in absolute ethanol (285 ml) was treated with sodium borohydride (2.14 g, 56.6 mmol). After 30 min, the colourless mixture was evaporated, the residue taken up in water (100 ml), and the solution acidified with acetic acid. The precipitate was collected, washed with water, and recrystallised from methanol (75 ml) to give the *nitroethylpyrrole* (5.29 g, 70%). A second crop was obtained from the mother

liquors (1.03 g, 13%), m.p. 155—156 °C (Found: C, 58.2; H, 7.3; N, 10.3. $C_{13}H_{20}N_2O_4$ requires C, 58.2; H, 7.5; N, 10.4%) $\nu_{max.}$ 3 450 and 1 685 cm^{-1}; $\lambda_{max.}$ 278 nm; δ 1.59 [9 H, s, $C(CH_3)_3$], 1.96 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 3.31 (2 H, t, *J* 7 Hz, $CH_2CH_2NO_2$), 4.53 (2 H, t, *J* 7 Hz, CH_2NO_2), and 9.47 (1 H, br s, NH).

4,4-*Dimethyl*-6-(5-*t*-*butoxycarbonyl*-3,4-*dimethylpyrrol*-2-*yl*)-5-*nitrohexan*-2-*one*.—3,4-Dimethyl-5-(2-nitroethyl)-2-t-butoxycarbonylpyrrole (4.02 g, 15 mmol), mesityl oxide (6.36 g, 65 mmol), and tetra-n-butylammonium fluoride (4.72 g, 15 mmol) were stirred together in dry DMF (150 ml) with 4 Å molecular sieves (7.5 g) for 2 h. The mixture was then diluted with water (450 ml), extracted with ether (6 × 100 ml), and the combined extracts then washed with 1M-HCl (100 ml), 5% aqueous $NaHCO_3$ (100 ml), and brine (100 ml), and finally dried. The filtered extracts were evaporated and the residue crystallised from hexane–ethyl acetate to give the *nitro ketone* (3.53 g, 64%), m.p. 122—123 °C (Found: C, 62.3; H, 8.2; N, 7.5. $C_{19}H_{30}N_2O_5$ requires C, 62.3; H, 8.2; N, 7.6%); $\nu_{max.}$ 3 450, 1 720, and 1 685 cm^{-1}; $\lambda_{max.}$ 277 nm; δ 1.12 (3 H, s, CCH_3), 1.24 (3 H, s, CCH_3), 1.54 [9H, s, $C(CH_3)_3$], 1.90, 2.13, and 2.17 (each 3 H, s, 3 × CH_3), 2.42 (1 H, d, *J* 17 Hz, CHCO), 2.58 (1 H, d, *J* 17 Hz, CHCO), 2.96 (1 H, dd, *J* 3 and 15 Hz, $CHCNO_2$), 3.28 (1 H, dd, *J* 11 and 15 Hz, $CHCNO_2$), 5.10 (1 H, dd, *J* 3 and 11 Hz, $CHNO_2$), and 8.74 (1 H, br s, NH).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-3,4-*dihydro*-2,4,4-*trimethylpyrrole* 1-*Oxide* (**13**).—6-(3,4-Dimethyl-5-t-butoxycarbonylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (1.83 g, 5 mmol) in absolute ethanol–acetic acid (1:1; 100 ml) was cooled to 0 °C and treated portionwise with zinc (10 g) [pre-washed with 1M-HCl (× 1), water (× 2) and absolute ethanol (× 2)] such that the temperature did not rise above 10 °C. After 45 min, the excess of zinc was filtered off through Celite and washed thoroughly with ethanol. The filtrate was evaporated and the residue was dissolved in 1M-HCl (200 ml) and extracted with chloroform (4 × 25 ml). The combined organic extracts were washed with 5% aqueous $NaHCO_3$ (100 ml) and dried, filtered and evaporated. The residue crystallised from hexane–ethyl acetate to give the *nitrone* (1.28 g, 77%), m.p. 142—143 °C (Found: C, 68.0; H, 9.2; N, 8.6. $C_{19}H_{13}N_2O_3$ requires C, 68.2; H, 9.0; N, 8.4%); $\nu_{max.}$ 3 250, 1 690, and 1 605 cm^{-1}; $\lambda_{max.}$ 237 and 280 nm; δ 1.09 (3 H, s, CCH_3), 1.21 (3 H, s, CCH_3), 1.59 [9 H, s, $C(CH_3)_3$], 1.95 (3 H, s, CH_3), 2.09 (3 H, m, $ON{=}CCH_3$), 2.26 (3 H, s, CH_3), 2.38 (2 H, m, $ON{=}CCH_2$), 2.96 (2 H, m, pyrrole-CH_2), and 10.70 (1 H, br s, N*H*).

Methyl 5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-3,3-*dimethyl*-4-*nitropentanoate*.—3,4-Dimethyl-2-(2-nitroethyl)-5-t-butoxycarbonylpyrrole (1.34 g, 5 mmol), methyl 3,3-dimethylacrylate (2.85 g, 25 mmol), tetra-n-butylammonium fluoride trihydrate (1.58 g, 5 mmol) and 4 Å molecular sieves (2 g) in dry DMF (50 ml) were stirred at 50 °C for 4 h under nitrogen. The cooled mixture was diluted with water (200 ml) and extracted with ether (4 × 50 ml). The ether extracts were washed with 1M-HCl (50 ml), 5% aqueous $NaHCO_3$ (50 ml), and brine (50 ml) and dried. The residue from filtration and evaporation of the extracts crystallised from light petroleum (10 ml) and then from hexane (20 ml) to give the *nitro ester* (860 mg, 45%), m.p. 104—105 °C (Found: C, 59.6; H, 7.8; N, 7.4. $C_{19}H_{30}N_2O_6$ requires C, 59.7; H, 7.9; N, 7.3%); $\nu_{max.}$ 3 450, 1 740, and 1 685 cm^{-1}; $\lambda_{max.}$ 277 nm; δ 1.18 (3 H, s, CH_3), 1.24 (3 H, s, CH_3), 1.58 [9 H, s, $C(CH_3)_3$], 1.92 (3 H, s, CH_3), 2.20 (3 H, s, CH_3), 2.44 (2 H, s, CH_2CO), 3.06 (1 H, dd, *J* 3 and 16 Hz, $CHCNO_2$), 3.30 (1 H, dd, *J* 11 and 16 Hz, $CHCNO_2$), 3.73 (3 H, s, CO_2CH_3), 4.94 (1 H, dd, *J* 3 and 11 Hz, $CHNO_2$), and 8.60 (1 H, br s, NH).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-3,3-*dimethyl*-4-*nitropentanal* (**18**).—The foregoing nitro ester (4.26 g, 11.1 mmol) in dry toluene (110 ml) at −75 °C under argon was treated with di-isobutylaluminium hydride (13.9 ml, 22 mmol), the reaction temperature being kept below −65 °C. After the mixture had been stirred at −75 °C for 90 min, it was treated with 1M-HCl (30 ml) and then allowed to warm to 20 °C. After a further dilution with 1M-HCl (120 ml), the toluene layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). The combined organic fractions were washed with 1M-HCl (3 × 50 ml), 5% aqueous $NaHCO_3$ (50 ml), and brine (2 × 50 ml) and dried. Filtration and evaporation gave an oil which crystallised from hexane–ethyl acetate to give the *aldehyde* (3 g, 77%). A second crop was obtained from the mother liquors (0.45 g, 12%), m.p. 119—121 °C (Found: C, 61.3; H, 8.0; N, 7.9. $C_{18}H_{28}N_2O_5$ requires C, 61.3; H, 8.0; N, 8.0%); $\nu_{max.}$ 3 450, 1 730, and 1 685 cm^{-1}; $\lambda_{max.}$ 272 nm; δ 1.24 (3 H, s, CH_3), 1.30 (3 H, s, CH_3), 1.57 [9 H, s, $C(CH_3)_3$], 1.92 (3 H, s, CH_3), 2.20 (3 H, s, CH_3), 2.46 (1 H, dd, *J* 2 and 16 Hz, C*H*CHO), 2.64 (1 H, dd, *J* 2 and 16 Hz, C*H*CHO), 3.02 (1 H, dd, *J* 3 and 15 Hz, $CHCHNO_2$), 3.30 (1 H, dd, *J* 11 and 15 Hz, $CHCHNO_2$), 4.82 (1 H, dd, *J* 3, and 11 Hz, $CHNO_2$), 8.53 (1 H, br s, N*H*), and 9.76 (1 H, t, *J* 2 Hz, CHO).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-3,3-*dimethyl*-4-*nitropentanal Dimethyl Acetal*.—The foregoing aldehyde (1.76 g, 5 mmol), toluene-*p*-sulphonic acid (190 mg, 1 mmol), and trimethyl orthoformate (5.5 ml, 50 mmol) were stirred together at 20 °C in dry methanol (50 ml). After 30 min, the mixture was concentrated and the residue in ether (100 ml) was washed with 5% aqueous $NaHCO_3$ (2 × 25 ml) and brine (25 ml) and dried. Filtration and evaporation gave an oil which crystallised from pentane (10 ml) to give the *acetal* (1.70 g, 89%), m.p. 94—95 °C (Found: C, 60.4; H, 8.5; N, 7.0. $C_{20}H_{34}N_2O_6$ requires C, 60.3; H, 8.6; N, 7.0%); $\nu_{max.}$ 3 450 and 1 675 cm^{-1}; $\lambda_{max.}$ 278 nm; δ 1.12 (3 H, s, CH_3), 1.15 (3 H, s, CH_3), 1.57 [9 H, s, $C(CH_3)_3$], 1.70 [1 H, dd, *J* 3 and 14 Hz, $CHCH(OCH_3)_2$], 1.89 (3 H, s, CH_3), 1.92 [1 H, dd, *J* 7 and 14 Hz, $CHCH(OCH_3)_2$], 2.19 (3 H, s, CH_3), 3.00 (1 H, dd, *J* 3 and 15 Hz, $CHCHNO_2$), 3.30 (1 H, dd, *J* 11 and 15 Hz, $CHCHNO_2$), 3.34 (3 H, s, OCH_3), 3.47 (3 H, s, OCH_3), 4.57 [1 H, dd, *J* 3 and 7 Hz, $CH(OCH_3)_2$], 4.76 (1 H, dd, *J* 3 and 11 Hz, $CHNO_2$), and 8.49 (1 H, br s, NH).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*ylmethyl*)-3,4-*dihydro*-4,4-*dimethylpyrrole* 1-*Oxide* (**12**).—5-(3,4-Dimethyl-(5-t-butoxycarbonylpyrrol-2-yl)-3,3-dimethyl-4-nitropentanal (1.05 g, 3 mmol) and ammonium chloride (320 mg, 6 mmol) in water–THF (1:3) (40 ml) at 0 °C were treated with zinc (1.96 g, 30 mmol) in one portion and stirred. After 30 min, the zinc was filtered off through Celite and washed with ethyl acetate (50 ml). The filtrate was washed with saturated aqueous NH_4Cl (2 × 10 ml), dried, filtered, and evaporated. The residue was flash chromatographed using acetone and the *nitrone* crystallised from hexane (10 ml) (568 mg, 59%), m.p. 134—135 °C (Found: C, 67.1; H, 8.7; N, 8.7. $C_{18}H_{28}N_2O_3$ requires C, 67.5; H, 8.8; N, 8.7%); $\nu_{max.}$ 3 280, 1 695, and 1 580 cm^{-1}; $\lambda_{max.}$ 239 and 279 nm; δ 1.14 (3 H, s, CH_3), 1.25 (3 H, s, CH_3), 1.61 [9 H, s, $C(CH_3)_3$], 1.98 (3 H, s, CH_3), 2.29 (3 H, s, CH_3), 2.45 (2 H, m, $CH_2CH{=}N$), 2.94 (1 H, d, *J* 2 Hz, C*H*CHN), 2.98 (1 H, s, C*H*CHN), 3.88 (1 H, m, CH–N), 6.97 [1 H, q, *J* 2 Hz, CH=N], and 10.71 (1 H, br s, NH).

2,2,8,8,12,13,17,18-*Octamethylisobacteriochlorin* (**11b**).—5-(3,4-Dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-4,4-dimethylpyrrole 1-oxide (64 mg, 0.2 mmol) and 5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-2,4,4-trimethylpyrrole 1-oxide (67 mg, 0.2 mmol) were heated at reflux under nitrogen in dry THF (10 ml) with 50% sodium hydride dispersion (50 mg) for 2 h. The cooled mixture was then quenched with saturated aqueous NH_4Cl (10 ml) and diluted with ether (25 ml). The separated organic phase was

washed with saturated aqueous NH_4Cl (10 ml), dried, filtered, and evaporated. The residue was chromatographed on thick layer plates (8% methanol in chloroform) and the product was eluted with methyl acetate to give 5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-2-[5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl-1-hydroxy-4,4-dimethylpyrrolidin-2-ylmethyl]-3,4-dihydro-4,4-dimethylpyrrole 1-oxide as an oil (115 mg, 88%); *m/z* 654; (M^+), 636 (M − 18), and 620 (M − 34); $\lambda_{max.}$ 241 and 282 nm.

The foregoing product (94 mg) in methanol (10 ml) and 1M-HCl (0.5 ml) was treated with sodium cyanoborohydride (40 mg) for 1 h. The mixture was then diluted with ether (25 ml), washed with water (3 × 10 ml) and brine (10 ml), dried, filtered, and evaporated. Purification of the residue by p.l.c. (8% methanol in chloroform) and elution of the product with methyl acetate gave bis-[5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-1-hydroxy-4,4-dimethylpyrrolidin-2-yl]methane (**19**) as an oil (86 mg, 91%); *m/z* 656 (M^+), 638 (M − 18), and 620 (M − 36); $\lambda_{max.}$ 285 nm.

Bis[5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-yl)methyl-1-hydroxy-4,4-dimethylpyrrolidin-2-yl]methane (102 mg, 0.155 mmol) in dry toluene (10 ml) at 0 °C was treated successively with $POCl_3$ (75 mg, 0.5 mmol) and triethylamine (200 mg, 2 mmol). After the mixture had been stirred at 20 °C for 1.5 h, it was diluted with ether (25 ml), washed with 1M-HCl (2 × 10 ml), 5% aqueous $NaHCO_3$ (2 × 10 ml), and brine (2 × 10 ml), dried, filtered, and evaporated. The residue was chromatographed on thick-layer plates (8% methanol in chloroform). The main fraction, of just lower R_F than the broad yellow band, was eluted with ethyl acetate to give bis[2-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-3,3-dimethylpyrrol-5-yl]methane (**20**) (32 mg, 33%); *m/z* 620 (M^+); $\lambda_{max.}$ 280 nm.

The yellow band yielded an oil (11 mg) which was apparently a mixture of oxo and dioxo derivatives of the desired product; *m/z* 648 (M^+, dioxo) and 634 (M^+, oxo).

Bis[2-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-ylmethyl)-3,4-dihydro-3,3-dimethylpyrrol-5-yl]methane (32 mg, 0.051 mmol) was treated in a glove-box with neat TFA (2 ml) for 10 min. The mixture was then diluted with chloroform (10 ml) and trimethyl orthoformate (150 mg) added. After 15 min, the mixture was washed with water (25 ml) and the residue from the chloroform ($\lambda_{max.}$ 312 nm) was dissolved in methanol (15 ml) and treated with acetic acid (2 ml) and cupric acetate hydrate (410 mg) at reflux for 1 h. The solution was then diluted with water (25 ml) and extracted with chloroform (3 × 10 ml); the residue left after evaporation of the chloroform was chromatographed on a thick-layer plate (10% methanol in chloroform). The high R_F purple band was eluted with ethyl acetate to give 2,2,8,8,12,13,17,18-octamethylisobacteriochlorin copper complex (**22**) (4 mg, 16%); $\lambda_{max.}$ 387, 545, and 589 nm. (Relative ratios: 1.0, 0.15, and 0.64.)

The above copper complex (4 mg) was treated in a glove box with TFA (5 ml), concentrated sulphuric acid (10 drops), and ethanedithiol[19] (20 drops) for 1 h at room temperature. The mixture was then diluted with chloroform (25 ml), filtered through Celite, and washed with water (2 × 25 ml) and saturated aqueous $NaHCO_3$ (25 ml). The residue from the chloroform layer was chromatographed on a thick-layer plate, (50% ethyl acetate in chloroform), the pink band being eluted with ethyl acetate cleanly to give 2,2,8,8,12,13,17,18-*octamethylisobacteriochlorin* (**11b**) as an amorphous solid (Found: M^+, 426.2786. $C_{28}H_{34}N_4$ requires M^+, 426.2784); $\lambda_{max.}$ 364, 504, 541, 582, and 630 nm (relative ratios; 1.0, 0.07, 0.13, 0.22, and 0.05); δ(CD_2Cl_2) 1.72 (12 H, s, 4 × CH_3), 2.82 (6 H, s, $ArCH_3$), 2.94 (6 H, s, $ArCH_3$), 3.79 (4 H, s, 2 × CH_2), 6.97 (1 H, br s, 5-H), 7.36 (2 H, s, 10-H and 20-H), and 8.48 (1 H, s, 15-H).

(E)-2,2-*Dimethyl*-4-*nitrobut*-3-*enal Diethyl Acetal*.—2,2-Dimethylmalonaldehyde diethyl acetal[20] (9.45 g, 54.3 mmol), potassium acetate (1.61 g, 16.4 mmol), and methylamine hydrochloride (7.35 mg, 10.9 mmol) were heated under reflux together in nitromethane (55 ml) for 2 h. The cooled mixture was diluted with ether (250 ml) and washed with water (3 × 100 ml), 5% aqueous $NaHCO_3$ (100 ml), and brine (100 ml), and then dried. The residue from evaporation was distilled under reduced pressure to give the *nitro olefin* (8.88 g, 75%), b.p. 76 °C at 0.5 Torr (Found: C, 55.6; H, 8.7; N, 6.6. $C_{10}H_{19}NO_4$ requires C, 55.3; H, 8.8; N, 6.4%); $\nu_{max.}$ 1 645, 1 530, and 1 350 cm^{-1}; δ 1.15 [6 H, s, $C(CH_3)_2$], 1.22 (6 H, t, *J* 7 Hz, 2 × OCH_2CH_3), 3.67 (4 H, m, OCH_2CH_3), 4.15 [1 H, s, $CH(OEt)_2$], 6.98 (1 H, d, *J* 15 Hz, CH=$CHNO_2$), and 7.40 (1 H, d, *J* 14 Hz, CH=$CHNO_2$).

2,2-*Dimethyl*-4-*nitrobutanal Diethyl Acetal* (**26**).—A solution of the foregoing product (10.7 g, 49.3 mmol) in absolute ethanol (98 ml) was treated with sodium borohydride (2.8 g, 74 mmol) in one portion; the reaction warmed considerably. After 30 min, excess of sodium borohydride was destroyed with acetic acid (5 ml) and the mixture was diluted with ether (300 ml) and washed with water (2 × 100 ml), 5% aqueous $NaHCO_3$ (100 ml), and brine (100 ml), dried, and evaporated. The residual oil was distilled to give the nitroalkane (9.67 g, 90%), b.p. 66—70 °C at 0.3 Torr (Found: C, 55.3; H, 9.4; N, 6.4. $C_{10}H_{21}NO_4$ requires C, 54.8; H, 9.6; N, 6.4%); $\nu_{max.}$ 1 550 and 1 380 cm^{-1}; δ 0.97 [6 H, s, $C(CH_3)_2$], 1.20 (6 H, t, *J* 7 Hz, 2 × OCH_2CH_3), 2.05 (2 H, m, $CH_2CH_2NO_2$), 3.65 (4 H, m, 2 × OCH_2CH_3), 4.00 [1 H, s, $CH(OEt)_2$], and 4.50 (2 H, m, CH_2NO_2).

5-(3,4-*Dimethyl*-5-*t*-*butoxycarbonylpyrrol*-2-*yl*)-2,2-*dimethyl*-4-*nitropentanal Diethyl Acetal* (**27**).—2-Formyl-3,4-dimethyl-5-t-butoxycarbonylpyrrole (669 mg, 3 mmol), 2,2-dimethyl-4-nitrobutanal diethyl acetal (548 mg, 2.5 mmol), and piperidine (212 mg, 2.5 mmol) were heated under nitrogen at 100 °C for 96 h. The resulting mixture was chromatographed on thick-layer plates (5% ethyl acetate in chloroform) and the product from the yellow, high R_F fraction was 5-(3,4-dimethyl-5-t-butoxycarbonylpyrrol-2-yl)-2,2-dimethyl-4-nitropent-4-enal diethyl acetal; $\lambda_{max.}$ 272 and 395 nm; δ 1.03 [6 H, s, $C(CH_3)_2$], 1.08 (6 H, t, *J* 7 Hz, 2 × OCH_2CH_3), 1.60 [9 H, s, $C(CH_3)_3$], 2.08 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 3.04 [2 H, s, $CH_2C(CH_3)_2$], 3.65 (4 H, m, 2 × OCH_2CH_3), 4.07 [1 H, s, $CH(OEt)_2$], 7.87 (1 H, s, CH=CNO_2), and 10.48 (1 H, br s, NH).

All of this nitro-olefin in absolute ethanol (10 ml) was treated with sodium borohydride (80 mg, 2 mmol). After 30 min, the mixture was acidified with acetic acid and diluted with ether (50 ml), the ether layer being washed with water (25 ml) and 5% aqueous $NaHCO_3$ (25 ml) and dried. The product from the ether was chromatographed on thick-layer plates (5% ethyl acetate in chloroform). The main band gave material which crystallised from hexane (2 ml) to yield the *nitroalkane* (90 mg, 8%), m.p. 100—101 °C (Found: C, 61.7; H, 8.9; N, 6.7. $C_{22}H_{38}N_2O_6$ requires C, 61.9; H, 9.0; N, 6.6%); $\nu_{max.}$ 3 450 and 1 675 cm^{-1}; $\lambda_{max.}$ 278 nm; δ 0.89 [3 H, s, $C(CH_3)CH_3$], 0.93 [3 H, s, $C(CH_3)CH_3$], 1.20 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.24 (3 H, t, *J* 7 Hz, OCH_2CH_3), 1.58 [9 H, s, $C(CH_3)_3$], 1.92 (3 H, s, CH_3), 1.96 [1 H, dd, *J* 3 and 15 Hz, $CHC(CH_3)_2$], 2.14 [1 H, dd, *J* 8 and 15 Hz, $CHC(CH_3)_2$], 2.21 (3 H, s, CH_3), 3.00 (1 H, dd, *J* 6 and 15 Hz, $CHCHNO_2$), 3.18 (1 H, dd, *J* 7 and 15 Hz, $CHCHNO_2$), 3.52 (2 H, m, OCH_2CH_3), 3.76 (2 H, m, OCH_2CH_3), 3.98 (1 H, s, $CH(OEt)_2$), 5.02 (1 H, m, $CHNO_2$), and 8.54 (1 H, br s, NH).

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