Synthesis of *N*-Substituted Prodigiosenes

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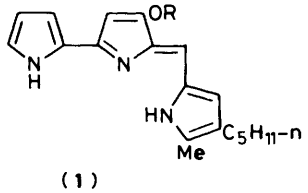
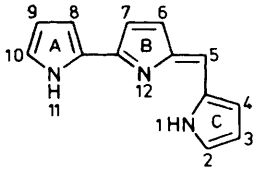
Prodigiosenes bearing *N*-methyl or *N*-benzyl groups in each of the three pyrrole rings have been prepared by coupling either a bipyrrole with a pyrrolecarbaldehyde or a bipyrrolecarbaldehyde with an α-free pyrrole. Synthesis *via* the bipyrrole route can lead to fragmentation of the products through further attack by the bipyrrole. In contrast to the demethyl series, the salts of 11-methylprodigiosenes exist as *E*/*Z* mixtures. In the base form only *Z* isomers were detected. A number of novel pyrroles (**30b**, **c**, **d**) are accessible by a regioselective Grignard reaction on 3-bromo-2-bromomethylpyrroles.

Since the determination[1] of the structure of 'Prodigiosin' (**1a**) a dozen or more related compounds containing the prodigiosene‡ nucleus (**2**) have been isolated from natural sources, particularly from a restricted group of eubacteria and actinomycetes.[2] With the exception of the 6-hydroxy derivative[3]—'norprodigiosin' (**1b**)—all the natural products[4] bear a 6-methoxy substituent, and differ in alkyl substitution in the terminal pyrrole ring. In a few natural prodigiosenes[5] an alkyl or substituted alkyl group links the α-positions of rings A and C [positions 2 and 10 in (**2**)].



(**1**)

a; R = Me
b; R = H



(**2**)

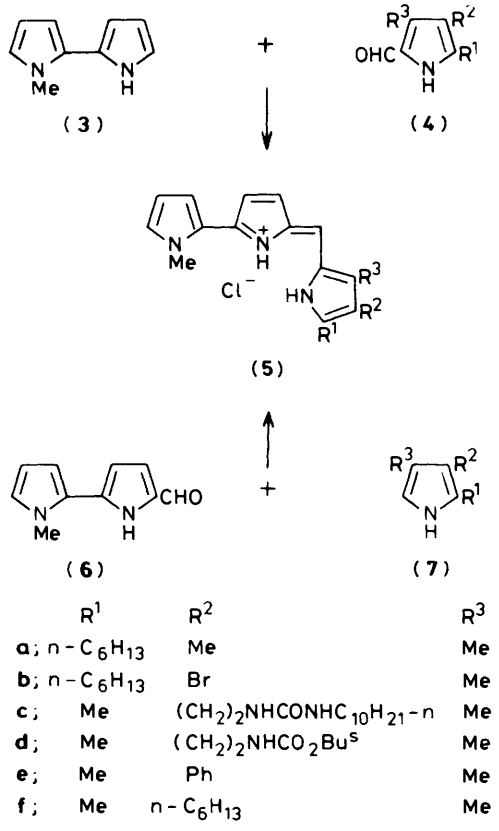
Prodigiosin (**1a**) has considerable antibacterial and antifungal activity,[6] but its high toxicity has precluded its use as a therapeutic agent. We have prepared a selection of the 20 or so synthetic prodigiosenes reported in the chemical literature[7] and observed similar cytotoxicity in these synthetic analogues.[8]

We report here the synthesis of members of three novel series of *N*-substituted prodigiosenes, some members of which have interesting pharmacological actions, but are devoid of the cytotoxic properties of the natural series.[8]

Results and Discussion

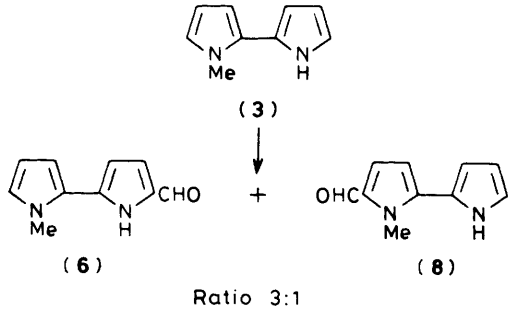
(A) *Preparation of* 11-*Substituted Prodigiosenes.*—The majority of prodigiosenes reported in the chemical literature have been prepared by an acid-catalysed condensation of either a 5,5′-bipyrrole, *e.g.* (**3**) (Scheme 1) with a pyrrole-2-carbaldehyde (**4**), or a 2,2′-bipyrrole-5-carbaldehyde, *e.g.* (**6**) with an α-free pyrrole (**7**). In the former reaction both α-positions of the bipyrrole are strongly nucleophilic and a mixture of products is obtained unless one of these positions is blocked by substitution. Consequently, the synthesis of our target 11-methylprodigiosenes (**5**) was more conveniently approached by coupling an *N*-methylbipyrrolecarbaldehyde such as (**6**) with an α-free pyrrole.

The aldehyde (**6**) was prepared by Vilsmeier formylation of the *N*-methylbipyrrole (**3**). The reaction (Scheme 2) gave a 3:1



	R^1	R^2	R^3
a;	n-C_6H_{13}	Me	Me
b;	n-C_6H_{13}	Br	Me
c;	Me	$(CH_2)_2NHCONHC_{10}H_{21}$-n	Me
d;	Me	$(CH_2)_2NHCO_2Bu^s$	Me
e;	Me	Ph	Me
f;	Me	n-C_6H_{13}	Me

Scheme 1. Two major routes to prodigiosenes. *Reagents:* HCl in ethanol.



Scheme 2. Preparation of *N*-methylbipyrrolecarbaldehydes by a Vilsmeier procedure. *Reagents:* PhCOCl, DMF, Et_2O.

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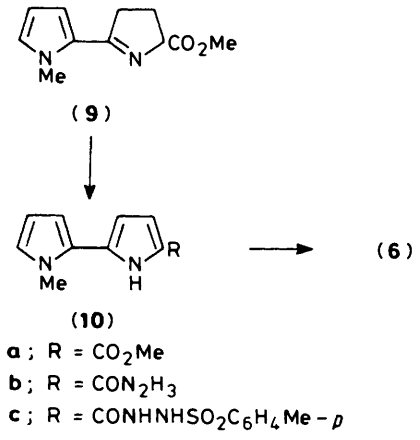
‡ The nomenclature proposed by Hearn *et al.*[7a] is adopted here.

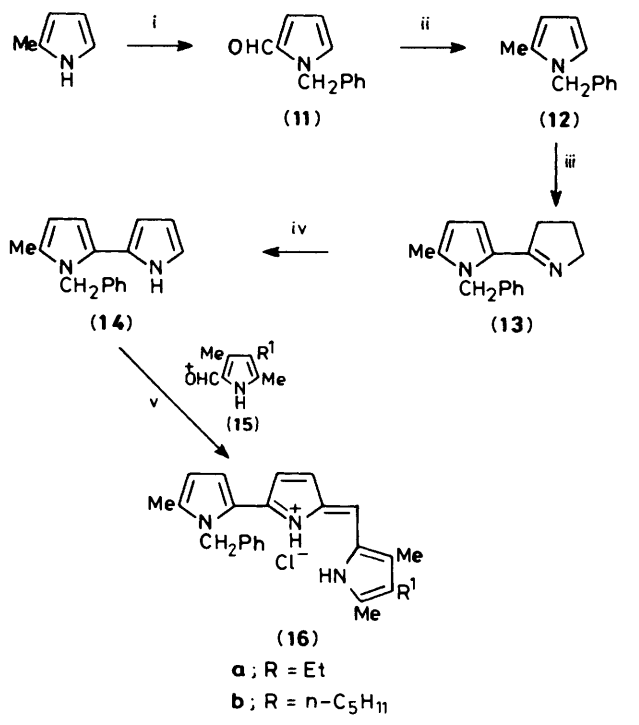


Scheme 3. Unambiguous synthesis of the *N*-methylbipyrrolecarbaldehyde (**6**). *Reagents:* (**10a**), 30% Pd/C in xylene; (**10b**), $N_2H_4H_2O$; (**10c**) TsCl, C_5H_5N; (**6**) Na_2CO_3, digol, 170 °C.

mixture of the α-substituted regioisomers. These were readily separated by fractional crystallisation from ethyl acetate–light petroleum (1:1), and exhibited discrete ^1H n.m.r. spectra [($CDCl_3$) N–CH_3 3.72 and 4.02]. To establish beyond question the structural assignment of the two isomers, compound (**6**) was synthesized by an unambiguous route (Scheme 3). Condensation of *N*-methylpyrrole and methyl pyroglutamate under Vilsmeier conditions gave the dihydropyrrolylpyrrole (**9**) which was dehydrogenated with 30% Pd-on-charcoal catalyst to the *N*-methylbipyrrolecarboxylic ester (**10a**). Since pyrrolecarboxylic esters are generally inert to hydride donor reagents,[1] (**10a**) was converted into the aldehyde (**6**) by the method of MacFadyen and Stevens.[9] Thus the ester (**10a**) was converted into the hydrazide (**10b**); and the tosylate of the hydrazide (**10c**) was decomposed under mildly basic conditions to give the aldehyde (**6**) which was identical (by m.p., mixed m.p., t.l.c., and ^1H n.m.r.) with the major product from the Vilsmeier formylation of *N*-methylbipyrrole.

In ethanolic HCl the aldehyde (**6**) was condensed with a selection of α-free pyrroles to give a series of 11-*N*-methylprodigiosenes (**5a**—**f**) containing alkyl, phenyl, halogeno, alkylureido, and alkyurethane substituents in ring C.

The ^1H n.m.r. spectra of the *N*-methylprodigiosene salts contain several minor peaks which do not occur in the spectra of the corresponding 11-NH series.[8] For instance, in the spectrum of (**5a**) the sharp peak at δ 3.86 (*N*-methyl) is accompanied by a further small peak of variable intensity at δ 3.74. Two unexpected peaks are also present in the alkyl region. The ^{13}C n.m.r. spectrum of (**5a**) in $CDCl_3$ indicates the presence of an excess of 9 aromatic-type carbons and 1 aliphatic type carbon in *ca.* 20% abundance in samples of the hydrochloride salt, but not in samples of the free base. Since the salt can be converted into the free base (with CH_2Cl_2–aqueous NH_3), and then reconverted into the hydrochloride in 95% overall yield, with disappearence of the extraneous peaks in the free base* and reappearance in the hydrochloride, the extra peaks are evidently not due to impurity. The evidence favours a 4:1 mixture of *Z* and *E* isomers of the *N*-methylprodigiosene hydrochloride. The free base apparently exists totally in the *Z* form. The appearance of the *E* isomer in hydrochlorides of the 11-methyl series may be due to steric crowding between the proton and the *N*-methyl group. Indeed, silica-gel column chromatography of salts of 11-



Scheme 4. Synthesis of 10-methyl-11-benzylprodigiosenes. *Reagents:* $C_6H_5CH_2Br$ $(C_4H_9)_4N^+$ Br^-, CH_2Cl_2; ii, $N_2H_4H_2O$, KOH, digol; iii, pyrrolidin-2-one, $POCl_3$, ether; iv, 30% Pd/C, xylene; v, Et_2O/HCl.

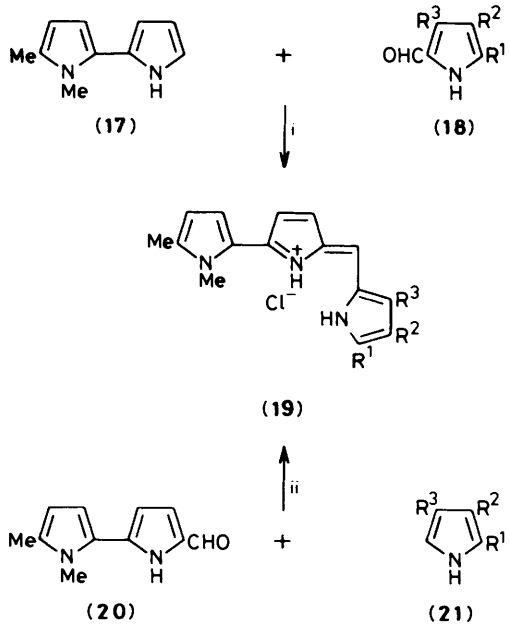
methylprodigiosenes resulted in elution of the free bases, whereas salts of 11-NH-prodigiosenes were eluted unchanged.

The alternative coupling of a bipyrrole with a pyrrolecarbaldehyde was used to prepare 10-methyl-11-benzylprodigiosenes (**16**) (Scheme 4), since the blocking of one α-position gives unambiguous coupling. The required 1-benzyl-2-methylbipyrrole (**14**) was prepared by a Vilsmeier condensation of 1-benzyl-2-methylpyrrole (**12**) with pyrrolidin-2-one, with subsequent dehydrogenation with 30% Pd-on-charcoal catalyst; partial debenzylation occurred. 1-Benzyl-2-methylpyrrole (**12**) was conveniently prepared by Wolff-Kishner reduction of 1-benzylpyrrole-2-carbaldehyde (**11**), which was itself obtained by phase-transfer catalysed benzylation of pyrrole-2-carbaldehyde. [Jones[10] has previously obtained (**11**), contaminated with 18% of the β-carbaldehyde, *via* formylation of *N*-benzylpyrrole.]

In general, the synthesis of prodigiosenes *via* a bipyrrolecarbaldehyde intermediate proved to be higher yielding than coupling a bipyrrole with a pyrrolecarbaldehyde, even if the competing α′-position of the bipyrrole is blocked by substitution. Thus the reaction (Scheme 5) of 1,2-dimethylbipyrrole (**17**) with pyrrolecarbaldehydes (**18a,b**) gave low yields of prodigiosenes (**19a,b**); whereas the alternative coupling of the derived bipyrrole-carbaldehyde (**20**) with α-free pyrroles (**21**) gave substantially higher yields of prodigiosenes (**19d,e**). The products are rapidly formed in both reactions, but apparently the nucleophilic bipyrrole reagent can readily attack the protonated prodigiosene product at the methene function (**22**) (Scheme 6) causing fragmentation to an α-free pyrrole (**21**) and a dipyrryldipyrromethene (**23**). The released pyrrole (**21**) can then condense with the pyrrolecarbaldehyde reagent (**18**) to give symmetrically substituted dipyrrylmethenes (**24**). By-products of type (**23**) and (**24**) were commonly produced† during

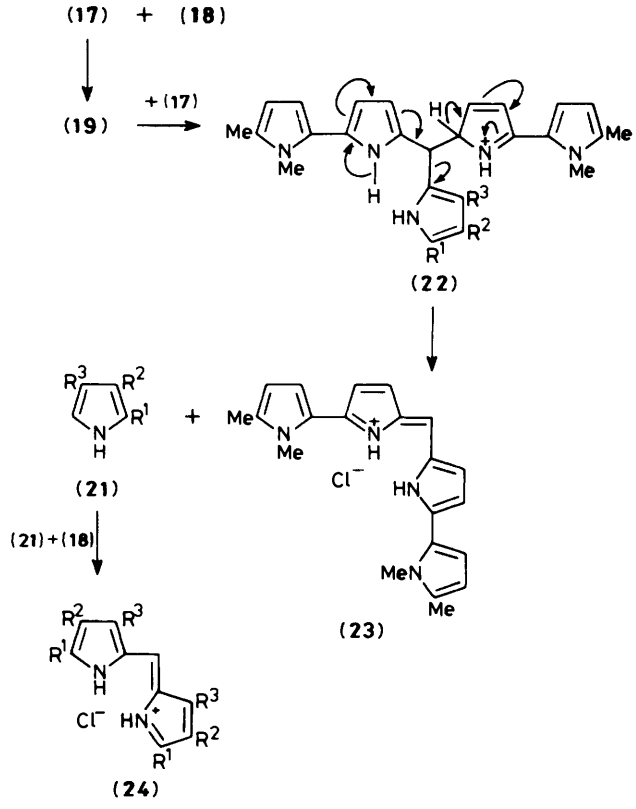
* Splitting of the ^{13}C peaks is also observed with (**5b**) hydrochloride. In this case the ratio is approximately 2:1.

† Detected as blue and orange spots, respectively, on t.l.c.; and by the appearance of their mass ions on mass spectroscopy.



	R^1	R^2	R^3	Route	Yield (%)
a;	Me	$(CH_2)_2CO_2Me$	Me	i	14.5
b;	Me	Ph	Me	i	14.0
c;	Me	CO_2Et	Pr	i	43.0
d;	C_6H_{13}-n	Me	Me	ii	54.0
e;	Me	C_6H_{13}-n	Me	ii	65.0

Scheme 5. Comparison of yields from two routes to 10, 11-dimethylprodigiosenes.



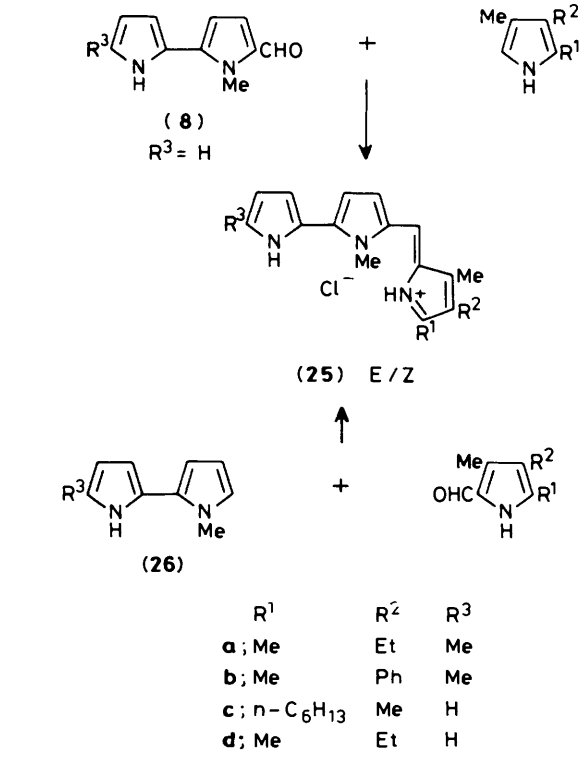
Scheme 6. Attack of bipyrroles on prodigiosenes causing fragmentation to dipyrrylmethenes (**24**) and dipyrryldipyrromethenes (**23**)

coupling of bipyrroles with pyrrolecarbaldehydes with concomitant purification problems and losses in yield. The susceptibility of the prodigiosene methene function to nucleophilic attack probably accounts for the gross instability that we encountered in prodigiosenes lacking a substituent at either the 4 or 6 position—such substituents must offer significant steric hindrance to an incoming nucleophile.

Side reactions of the type depicted in Scheme 6 become less significant however, if the low solubility of the prodigiosene (together with the use of minimal solvent volumes) causes its rapid precipitation from the reaction medium. This is reflected in the higher yield of (**19c**), even though it was prepared from the bipyrrole. Indeed we found the bipyrrole route (Scheme 5, path i) to be the method of choice for prodigiosene-3-carboxylic esters, because in the alternative coupling the weak nucleophilic character of pyrrolecarboxylic esters leads to slower reaction rates and concomitant partial decomposition and coupling of the bipyrrolecarbaldehyde.

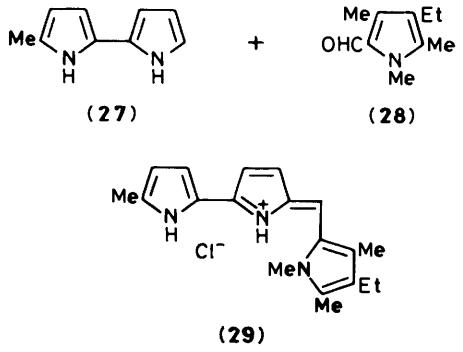
(B) 12-*Methylprodigiosenes* (**25**).—Both modes of coupling were used to prepare 12-methylprodigiosenes (**25a—d**) (Scheme 7). The very low solubility of these products resulted in their rapid precipitation from the reaction mixture in relatively high yield and purity. The characteristic strong intramolecular hydrogen bond between rings B and C is absent in these 12-methyl derivatives, and the presence of *E* and *Z* isomers is signified by the appearance of two close-running purple spots on t.l.c.

(C) 1-*Methylprodigiosenes* (**29**).—One ring-C *N*-methylated derivative (Scheme 8) was prepared by coupling the 2-



	R^1	R^2	R^3
a;	Me	Et	Me
b;	Me	Ph	Me
c;	n-C_6H_{13}	Me	H
d;	Me	Et	H

Scheme 7. Synthesis of 12-methylprodigiosenes.

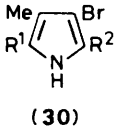


Scheme 8. Synthesis of 1-*N*-methylprodigiosene

methylbipyrrole (**27**) with 4-ethyl-1,3,5-trimethylpyrrole-2-carbaldehyde (**28**). The latter compound was conveniently prepared by a phase-transfer catalysed methylation of cryptopyrrole-2-carbaldehyde.

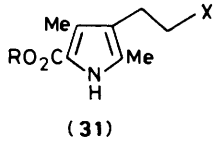
(D) *Pyrrole Intermediates.*—Access to the 2,4-dialkyl-3-bromoprodigiosene (**5b**) required 4-bromo-5-hexyl-3-methylpyrrole-2-carboxylic acid (**30c**). This was obtained *via* a regioselective Grignard alkylation of the bromo(bromomethyl)-pyrrole (**30a**) followed by de-esterification to the acid (**30c**).

Alkylurea and alkylcarbamate substituted pyrroles (**31d,e**) were accessible from the isocyanate (**31c**), which was itself obtained by thermal rearrangement of the azide (**31b**).



(**30**)

	R^1	R^2
a	CO_2Et	CH_2Br
b	CO_2Et	$n\text{-}C_6H_{13}$
c	CO_2H	$n\text{-}C_6H_{13}$
d	H	$n\text{-}C_6H_{13}$



(**31**)

	X	R
a	CON_2H_3	CH_2Ph
b	CON_3	CH_2Ph
c	NCO	CH_2Ph
d	$NHCO_2Bu^s$	CH_2Ph
e	$NHCONHC_{10}H_{21}\text{-}n$	CH_2Ph
f	$NHCO_2Bu^s$	H
g	$NHCONHC_{10}H_{21}\text{-}n$	H

Experimental

Thin-layer chromatography (t.l.c.) was run on Merck aluminium-backed silica gel G F_{254} (0.25 mm) plates. Column chromatography was performed using Merck silica gel (Kieselgel 60) unless otherwise stated. M.p.s are uncorrected. Light petroleum refers to the fraction boiling in the range 60—80 °C. 'Ethanolic HCl' means 25% (w/v) anhydrous hydrogen chloride in absolute ethanol.

^1H N.m.r. spectra were recorded at 90 MHz and 25 °C with a Bruker HX90 or a Varian EM 390 spectrometer using tetramethylsilane as internal standard.

^{13}C N.m.r. spectra were recorded on a Jeol FX90Q spectrometer. Mass spectra were recorded on a VG-1212 Quadrupole spectrometer.

1-*Methyl-2-pyrrol-2-ylpyrrole* (**3**).—Phosphorus oxychloride (110 ml, 1.2 mol) was added dropwise over 1 h to a stirred solution of pyrrolidin-2-one (85 g, 1 mol) and *N*-methylpyrrole (81 g, 1 mol) in diethyl ether (500 ml) maintained at 0 °C. After the addition was complete the mixture was stirred for a further 2.5 h with the temperature slowly rising to 20 °C, and then poured into an ice-cold solution of sodium acetate (450 g) in water (1 500 ml). This mixture was cautiously adjusted to pH 9 with 10M-aqueous sodium hydroxide, whilst being cooled to 0—5 °C. Sufficient water was added to dissolve the inorganic salts. The ethereal phase was separated and the aqueous phase was extracted with ether (3 × 1 000 ml). The combined ether extracts were washed with water (1 000 ml) dried ($MgSO_4$), and evaporated. The residual oil was distilled to give 1-*methyl*-2-(4,5-*dihydropyrrol*-2-*yl*)*pyrrole* (50.9 g, 34.4%) as an oil, b.p. 68—76 °C/0.6 mmHg (Found: C, 73.0; H, 8.2; N, 18.9. $C_9H_{12}N_2$ requires C, 73.0; H, 8.1; N, 18.9%); δ($CDCl_3$) 1.8 (2 H, q, $CH_2CH_2CH_2$), 2.8 (2 H, t, CH_2), 3.85 (3 H, s, NCH_3), 3.9 (2 H, t, NCH_2), 6.05 (1 H, m, CH), 6.35 (1 H, m, CH), and 6.6 (1 H, m, CH); *m/z* 148 (M^+), 147, 120, and 106.

This dihydropyrrolylpyrrole (50.5 g) was heated under reflux in an argon atmosphere for 5 h in xylene (500 ml) containing palladium-on-charcoal catalyst (30 g; 30% w/w). The hot mixture was separated by filtration and the residue was washed with hot chloroform (3 × 250 ml). The combined filtrate and washes were cooled, washed with aqueous acetic acid (3 × 100 ml; 25% v/v), water (200 ml), and aqueous sodium hydrogen carbonate (200 ml), and then dried ($MgSO_4$) and evaporated. The residual oil was distilled to give (**3**) (24.3 g, 48.8%) as an oil, b.p. 95—103 °C/0.6 mmHg (Found: C, 74.2; H, 6.8; N, 19.0. $C_9H_{10}N_2$ requires C, 74.0; H, 6.85; N, 19.2%); δ($CDCl_3$) 3.55 (3 H, s, NCH_3), 6.15 (4 H, m, 4 × CH), and 6.6 (2 H, m, 2 × CH); *m/z inter alia* 146 (M^+) and 131.

5-(1-*Methylpyrrol*-2-*yl*)*pyrrole*-2-*carbaldehyde* (**6**).—*Method A.* Benzoyl chloride (41 ml, 335 mmol) was added dropwise over 15 min to a stirred solution of the *N*-methylbipyrrole (**3**) (48.9 g, 0.335 mmol) in dimethylformamide (DMF, 84 ml) and dry ether (230 ml) maintained at 0—5 °C. A yellow precipitate formed. The mixture was stirred at 20 °C for 6 h, after which the precipitate was filtered off and washed with dry ether (100 ml). The crystalline material was added to a solution of sodium carbonate [42 g in water (420 ml) and ethanol (250 ml)] and stirred for 1 h. Water (420 ml) was added and the mixture was extracted with ether (3 × 500 ml). The combined ether extracts were washed with water (3 × 200 ml), dried ($MgSO_4$), and evaporated. The residual oil was dissolved in ethyl acetate (60 ml) and light petroleum (60 ml) was added; the solution was then cooled to 4 °C for 2 h. The supernatant liquid was decanted off and the residual crystalline mass was washed with solvent mixture and filtered to give (**6**) (13.2 g, 22.7%) m.p. 96—98 °C (Found: C, 68.8; H, 5.7; N, 16.2. $C_{10}H_{10}N_2O$ requires C, 68.9; H, 5.7; N, 16.1%); δ($CDCl_3$) 3.72 (3 H, s, NCH_3) 6.15 (1 H, m, CH), 6.45 (1 H, m, CH), 6.7 (1 H, m, CH) 6.95 (1 H, m, CH), 9.45 (1 H, s, CHO), and 9.8 (1 H, br, NH).

The supernatant liquid was evaporated and the residual solid was recrystallised from ethyl acetate–light petroleum (1:1) to give 1-*methyl*-5-*pyrrol*-2-*ylpyrrole*-2-*carbaldehyde* (**8**) (3.6 g, 6.2%), m.p. 90—92 °C (Found: C, 68.6; H, 5.7; N, 15.9. $C_{10}H_{10}N_2O$ requires C, 68.9; H, 5.7; N, 16.1%); δ($CDCl_3$) 4.02 (3 H, s, NCH_3), 6.3 (3 H, m, 3 × CH), 6.9 (2 H, m, 2 × CH), 8.99 (1 H, br, NH), and 9.45 (1 H, s, CHO).

Method B. Phosphorus oxychloride (10.9 ml) was added dropwise to a stirred solution of *N*-methylpyrrole (8.1 g) and methyl pyroglutamate (14.3 g) in dry ether (50 ml) maintained at 0—5 °C. After the addition was complete, the mixture was stirred at 0—5 °C for 30 min and then at 20 °C for 2 h; it was then poured into an ice-cold solution of sodium acetate [45 g in water (150 ml)]. This mixture was cautiously adjusted to pH 10 with 10M-aqueous sodium hydroxide, whilst being cooled at 0—5 °C. The ethereal phase was separated, and the aqueous phase

was extracted with ether (2 × 100 ml). The combined ether layers were washed with water (2 × 50 ml), dried ($MgSO_4$), and evaporated. The residual oil was distilled to give 1-*methyl*-2-(5-*methoxycarbonyl*-4,5-*dihydropyrrol*-2-*yl*)*pyrrole* (**9**) (6.8 g, 33%), b.p. 120—124 °C/0.5 mmHg, m.p. 50—51 °C (Found: C, 63.9; H, 7.2; N, 13.3. $C_{11}H_{14}N_2O_2$ requires C, 64.1: H, 6.8; N, 13.6%); δ($CDCl_3$) 2.2 (2 H, m), 3.0 (2 H, m), 3.8 (3 H, s), 4.05 (3 H, s), 4.85 (1 H, m), 6.13 (1 H, m), 6.55 (1 H, m), and 6.75 (1 H, m).

The dihydropyrrolylpyrrole (**9**) (5.5 g) was heated under reflux for 4 h in xylene (125 ml) containing palladium-on-charcoal catalyst (30% w/w; 4.0 g) in a nitrogen atmosphere. The hot mixture was separated by filtration and the residue washed with hot chloroform (4 × 25 ml). The filtrate and washings were evaporated and the resulting residue (5.5 g) was recrystallised from cyclohexane containing a few drops of ether. The product was separated by filtration and triturated with cyclohexane to give *methyl* 5-(1-*methylpyrrol*-2-*yl*)*pyrrole*-2-*carboxylate* (**10a**) (3.65 g, 67%), m.p. 95—97 °C (Found: C, 64.7; H, 6.0; N, 13.4. $C_{11}H_{12}N_2O_2$ requires C, 64.7; H, 5.9; N, 13.7%); δ($CDCl_3$) 3.55 (3 H, s, NCH_3), 6.15 (4 H, m, 4 × CH), and 6.7 (2 H, m, 2 × CH).

The bipyrrolecarboxylic ester (**10a**) (3.6 g) was heated under reflux for 2 h in hydrazine hydrate (20 ml) under a nitrogen atmosphere. The mixture was cooled, and the resulting precipitate filtered off and washed with water to give 5-(1-*methylpyrrol*-2-*yl*)*pyrrole*-2-*carbohydrazide* (**10b**) (3.0 g, 83%), m.p. 198—200 °C (Found: C, 58.8; H, 5.7; N, 26.9. $C_{10}H_{12}N_4O$ requires C, 58.8; H, 5.9; N, 27.4%). The hydrazide (**10b**) (2.95 g, 14.5 mmol) in dry pyridine (30 ml) was treated dropwise with a solution of toluene-*p*-sulphonyl chloride (3.33 g, 17.5 mmol) in dry pyridine (6 ml). The solution was stirred for 15 min, and then poured onto ice–water (200 g), and extracted with ether (3 × 30 ml). Evaporation of the ether extracts to *ca.* 1/3 volume gave a precipitate of 5-(1-methylpyrrol-2-yl)-*N'*-toluene-*p*-sulphonylpyrrole-2-carbohydrazide (**10c**) (4.3 g, 91%), m.p. 213 °C (Found: C, 56.7; H, 5.1; N, 15.8. $C_{17}H_{18}N_4O_3S$ requires C, 57.0; H, 5.0; N, 15.6%).

The tosylhydrazide (**10c**) (1 g) was added to a stirred suspension of anhydrous sodium carbonate (1.5 g) in dry diethyleneglycol (5 ml) at 170—180 °C. The mixture was stirred until effervescence ceased and then poured onto ice–water (20 ml). The resulting tarry suspension was extracted with ether (2 × 25 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated. The waxy solid obtained was purified by column chromatography on silica (20 g) using 8% (v/v) ethyl acetate–hexane as eluant, to give (**6**) (0.136 g, 28%), m.p. 98 °C (Found: C, 68.8; H, 5.9; N, 16.0. $C_{10}H_{10}N_2O$ requires C, 68.9; H, 5.7; N, 16.1%); n.m.r. identical with sample from method A.

General Method for Preparation of 11-*Methylprodigiosenes* (**5**).—5-(1-Methylpyrrol-2-yl)pyrrole-2-carbaldehyde (**6**) (1.04 g, 6.0 mmol) and either a pyrrole of formula (**7**) (6.0 mmol) or its corresponding α-carboxylic acid were dissolved in ethanol (9 ml) at 30 °C and HCl (3 ml; 25% w/v) was added dropwise with stirring. The deep blue mixture was stirred for 20 min, after which the solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (100 ml) and water (50 ml). The organic phase was separated, dried ($MgSO_4$), and concentrated to *ca.* 10 ml. Addition of light petroleum (*ca.* 10 ml) gave the prodigiosene as its crystalline hydrochloride which was filtered off. 2-Hexyl-3,4-dimethylpyrrole gave 2-*hexyl*-3,4,11-*trimethylprodigiosene hydrochloride* (**5a**) (81%), m.p. 167 °C (Found: C, 71.1; H, 8.4; N, 11.3. $C_{22}H_{30}Cl_1N_3$ requires C, 71.1; H, 8.1; N, 11.3%); δ($CDCl_3$) 0.85 (3 H, t, CH_2CH_3), 1.2—1.9 [8 H, br, $(CH_2)_4$], 2.0 (3 H, s, CH_3), 2.2 (3 H, s, CH_3), 2.98 [2 H, t, C(2)CH_2CH_2], 3.86 + shoulder at 3.74 (3 H, s, N-CH_3), 6.25 (1 H, m, CH), 6.55 (1 H, m, CH), 6.77 (1 H, m, CH), 6.95 (1 H, s, 5-H), 7.12 (1 H, m, CH), 7.72 (1 H, m, CH), 13.2 (1 H, H^+), and 14.3 (1 H, NH); δ_C($CDCl_3$) 8.6, 9.9 (split), 13.6, 22.1, 26.7, 28.6, 28.8, 31.1, 36.3, 109.4, 113.3, 117.1, 121.8, 123.6, 124.3, 127.6, 128.5, 128.8, 135.1, 142.6, 144.5, and 160.1, with splitting of most aromatic peaks; δ_C($CDCl_3$) (free base), 9.1, 9.4, 13.9, 22.5, 28.2 (2 carbons), 29.1, 31.6, 36.7, 108.3, 111.7, 117.2, 118.2, 122.8, 126.1, 128.3, 133.4, 136.1, 141.8, 148.7, and 153.1, with no splitting of aromatic peaks; *m/z* 335 (M^+), 320, 264, 249, 228, 179, 146, 133, and 108.

2-*Hexyl*-3,4-*dimethylpyrrole* (**7a**). This was prepared in 23% yield from 3,4-dimethylpyrrole using the procedure of Wasserman *et al.*[4e] except that 1-bromohexane was used in place of 1-bromodecane. The compound was purified by distillation (b.p. 90 °C/0.8 mmHg).

3-*Bromo*-2-*hexyl*-4,11-*dimethylprodigiosene hydrochloride* (**5b**). 4-Bromo-5-hexyl-3-methylpyrrole-2-carboxylic acid (**30c**) (6.2 mmol) was stirred in trifluoroacetic acid (24 ml) under an argon atmosphere for 20 min. Dichloromethane (300 ml) was added and the solution was washed with water (3 × 150 ml), dried ($MgSO_4$), and the solvent removed. The resulting α-free pyrrole (**7b**) was condensed with the *N*-methylbipyrrole-carbaldehyde (**6**) to give the *hydrochloride* (**5b**) (69%), m.p. 148—150 °C (Found: C, 58.0; H, 6.6; N, 9.3. $C_{21}H_{27}BrClN_3$ requires C, 57.7; H, 6.2; N, 9.6%); δ($CDCl_3$) 0.88 (3 H, t, CH_2CH_3), 1.35—1.85 [8 H, br $(CH_2)_4$], 2.24 (3 H, s, CH_3), 3.0 (2 H, t, CH_2), 3.9 + sharp shoulder at 3.8 (3 H, s, NCH_3), 6.3 (1 H, m, CH), 6.7 (1 H, m, CH), 6.87 (1 H, m, CH), 7.04 (1 H, s, 5-H), 7.22 (1 H, m, CH), 7.9 (1 H, m, CH), 9.5 (1 H, br, NH), and 10.4 (1 H, br, NH); (**5b**) (free base) δ($CDCl_3$) 0.88 (3 H, t, CH_2CH_3), 1.2—1.8 [8 H, br, $(CH_2)_4$], 2.18 (3 H, s, CH_3), 2.65 (2 H, t, CH_2), 4.0 (3 H, s, NCH_3—no shoulder), 6.21 (1 H, m, 9-H), 6.62 (2 H, m, 2 × CH), 6.65 (1 H, s, CH), 6.7 (1 H, m, CH), 6.88 (1 H, d, 6-H), and 9.65 (1 H, br, NH); δ_C($CDCl_3$) 11.3, 13.7, 22.2, 27.0, 28.5, 28.8, 31.1, 36.8, 106.2, 110.4, 115.0, 119.7, 121.9, 123.3, 126.1, 129.7, 130.9, 137.9, 141.3, 147.4, and 154.9, with splitting of most aromatic peaks; δ_C($CDCl_3$) (free base), 10.7, 13.9, 22.5, 27.8, 28.8, 28.9, 31.6, 36.6, 107.6, 108.6, 111.9, 116.5, 118.7, 135.2, 128.0, 137.3, 139.9, 146.7, and 154.0, with no splitting of aromatic peaks.

3-(2-*Decylureidoethyl*)-2,4,11-*trimethylprodigiosene dihydrobromide* (**5c**). The pyrrolecarboxylic acid (**31g**) (0.24 g, 0.66 mmol) and the carbaldehyde (**6**) (0.116 g, 0.66 mmol) in ethanol (3 ml) were treated with aqueous HBr (48% w/v; 0.5 ml) and stirred for 35 min. The mixture was filtered and the crystalline product was washed with diethyl ether to give (**5c**) (0.18 g, 42.5%), m.p. 142—144 °C (Found: C, 54.9; H, 7.1; N, 11.0. $C_{29}H_{45}Br_2N_5O$ requires C, 54.5; H, 7.0; N, 10.95%); *m/z* 477 (M^+).

3(2-*s*-*Butoxycarbamoylethyl*)-2,4,11-*trimethylprodigiosene hydrochloride* (**5d**). The pyrrolecarboxylic acid (**31f**) (0.35 g, 1.1 mmol) and the aldehyde (**6**) (0.19 g, 1.1 mmol) in ethanol (6 ml) were treated with aqueous HBr (48%; 4 ml) and stirred for 1 h. The solution was taken into dichloromethane (50 ml) and washed with saturated aqueous sodium hydrogen carbonate and then with water, and then dried ($MgSO_4$). The solvent was removed and the residual red-brown oil was 'flash' chromatographed using 5% methanol–dichloromethane as eluant. The fractions containing the prodigiosene were treated with ethereal HCl and the solvent was removed. The residual glassy solid was treated with ether and filtered to give the *hydrochloride* (**5d**) (0.3 g, 63.8%), m.p. 126—128 °C (Found: C, 62.8; H, 7.1; N, 12.5. $C_{23}H_{31}Cl_1N_4O_2 \cdot 0.5H_2O$ requires C, 62.8; H, 7.3; N, 12.7%); δ (CD_3CO_2D) 0.85 (3 H, t, CH_2CH_3), 1.1 [3 H, d, $CH(C_2H_5)CH_3$], 1.5 (2 H, q, CH_2CH_3), 2.3—2.5 (6 H, 2 × s, 2 × CH_3), 2.6 (2 H, m, CH_2), 3.2 (2 H, m, CH_2NH), 3.9 (3 H, s, NCH_3), 4.6 [1 H, m, $CH(CH_3)C_2H_5$], 6.2 (1 H, t, CH), 7.0 (3 H, m, 3 × CH), 7.5 (1 H, s, CH), and 7.8 (1 H, br, NH); *m/z* 394 (M^+), 264, 250, 238, 121, and 108.

3-*Phenyl*-2,4,11-*trimethylprodigiosene hydrochloride* (**5e**). 2,4-Dimethyl-3-phenylpyrrole[11] gave (**5e**) (53.6%), m.p. 134 °C (Found: C, 72.8; H, 6.0; N, 11.5. $C_{22}H_{22}ClN_3$ requires C, 72.6; H, 6.1; N, 11.6%); δ($CDCl_3$) 2.3 (3 H, s, CH_3), 2.69 (3 H, s, CH_3), 3.93 (3 H, s, NCH_3), 6.3 (1 H, m, CH), 6.66 (1 H, m, CH), 6.83 (1 H, s, 5-H), 7.06—7.45 (2 H, m, 2 × CH), and 7.78 (1 H, m, CH).

3-*Hexyl*-2,4,11-*trimethylprodigiosene hydrochloride* (**5f**). 2,4-Dimethyl-3-hexylpyrrole (**7f**) gave (**5f**) (27.9%), m.p. 134—138 °C (Found: C, 71.0; H, 8.5; N, 11.3. $C_{22}H_{30}ClN_3$ requires C, 71.1; H, 8.1; N, 11.3%); δ($CDCl_3$) 0.9 (3 H, t, CH_2CH_3) 1.25—1.45 [8 H, br, $(CH_2)_4$], 2.22 (3 H, s, CH_3), 2.35 (2 H, t, $CH_2CH_2CH_3$), 2.65 (3 H, s, CH_3), 2.85 (3 H, s, NCH_3), 6.24 (1 H, m, CH), 6.6 (1 H, m, CH), 6.8 (1 H, m, CH), 6.95 (1 H, s, 5-H), 7.1 (1 H, m, CH), and 7.65, (1 H, m, CH); *m/z* 335 (M^+), 264 ($M - C_5H_{11}$), 179, 146, and 108.

2,4-*Dimethyl*-3-*hexylpyrrole* (**7f**). Ethyl 4-hexyl-3,5-dimethylpyrrole-2-carboxylate was obtained in 78% yield as a solid (m.p. 62—63 °C) using a procedure analogous to that described by Wang and Chang[12] but starting from nonan-2-one.

The ester (5.5 g) in warm cellosolve (20 ml) was treated with aqueous potassium hydroxide (20% w/v; 20 ml). The mixture was refluxed for 3 h, and then cooled to 10 °C whilst aqueous acetic acid (50% v/v; 18 ml) was added slowly. Filtration gave 4-*hexyl*-3,5-*dimethylpyrrole*-2-*carboxylic acid* (4.3 g, 88%), m.p. 252 °C (decomp.).

The pyrrolecarboxylic acid (4.3 g) was refluxed in 2-aminoethanol (10 ml) for 1 h. The solution was cooled and poured into water (250 ml) and the resulting mixture was extracted with dichloromethane (2 × 300 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed. Distillation of the residue gave (**7f**) (2.45 g, 63% overall yield from the ester), b.p. 83 °C/0.3 mmHg.

1-*Benzylpyrrole*-2-*carbaldehyde* (**11**). Pyrrole-2-carbaldehyde (6.2 g, 65 mmol), benzyl bromide (7.75 ml, 72 mmol), and tetrabutylammonium bromide (2.1 g, 6.5 mmol) were stirred in dichloromethane (65 ml) at 5 °C whilst aqueous sodium hydroxide [17.5 g in water (35 ml)] was added dropwise during 0.5 h. The mixture was stirred and refluxed for 6 h, then cooled, and water (50 ml) and dichloromethane (100 ml) were added. The organic phase was separated and washed with 2M-HCl (50 ml) and water (50 ml), and then dried ($MgSO_4$) and evaporated to dryness. The residual oil was distilled to give (**11**) (11 g, 92%), b.p. 96—98 °C/0.1 mmHg (lit.,[10] b.p. 106 °C/0.4 mmHg); δ($CDCl_3$) 5.5 (2 H, s, CH_2), 6.2 (1 H, t, 4-H), 6.8 (2 H, d, 3-H and 5-H), 7.2 (5 H, m, C_6H_5), and 9.5 (1 H, s, CHO).

1-*Benzyl*-2-*methylpyrrole* (**12**). The aldehyde (**11**) (11 g) was refluxed for 2 h in digol (90 ml) with hydrazine hydrate (9.3 ml) and potassium hydroxide (13.4 g), after which the distillate was collected until the internal temperature of the vessel reached 225 °C. The distillate was extracted with diethyl ether (200 ml), and the ether extract was washed with water, dried ($MgSO_4$), and evaporated to dryness. The residual oil was distilled to give (**12**) (8.7 g, 86%), b.p. 108 °C/2 mmHg (Found: C, 83.8; H, 7.6; N, 8.2. $C_{12}H_{13}N$ requires C, 84.2; H, 7.6; N, 8.2%); δ($CDCl_3$) 2.05 (3 H, s, CH_3), 4.9 (2 H, s, CH_2), 6.0 (1 H, t, 4-H), 6.5 (1 H, t, 3-H), 6.8 (1 H, m, 5-H), and 7.2 (5 H, m, C_6H_5).

1-*Benzyl*-2-*methyl*-5-(4,5-*dihydropyrrol*-2-*yl*)*pyrrole* (**13**). 1-Benzyl-2-methylpyrrole (**12**) (8.7 g, 0.051 mol) and pyrrolidin-2-one (3.9 ml, 51 mmol) in diethyl ether (80 ml) were cooled to 5 °C and stirred whilst phosphorus oxychloride (5.4 ml, 0.05 mol) was added dropwise over 0.5 h. The mixture was allowed to warm to ambient temperature and then stirred for a further 2 h; after this it was poured into an ice-cold solution of sodium acetate (20 g) in water (75 ml). The pH was adjusted to 11 with 2M-KOH, and the organic phase was separated. The aqueous phase was extracted with ether (2 × 100 ml) and the combined ether extracts were dried ($MgSO_4$) and evaporated to dryness. The residual oil was eluted from a silica column with toluene → 10% ethyl acetate–toluene, to give an oil which solidified with time. Recrystallisation from aqueous ethanol gave (**13**) (2.5 g, 21%), m.p. 64—65 °C, R_F 0.15 [toluene–ethyl acetate (4:1)] (Found: C, 80.7; H, 7.9; N, 11.7. $C_{16}H_{18}N_2$ requires C, 80.7; H, 7.6; N, 11.8%); δ($CDCl_3$) 1.8 (2 H, m, 3′-CH_2), 2.0 (3 H, s, CH_3), 2.8 (2 H, t, 4′-CH_2), 3.8 (2 H, t, 2′-CH_2), 5.8 (2 H, s, NCH_2), 6.4 (1 H, d, 3-H), and 6.8—7.2 (6 H, m, C_6H_5 and 4-H).

1-*Benzyl*-2-*methyl*-5-*pyrrol*-2-*ylpyrrole* (**14**). The dihydropyrrolylpyrrole (**13**) (4.2 g, 17 mmol) and palladium-on-charcoal catalyst (30% w/w; 3 g) were refluxed in xylene for 2 h. The mixture was filtered, and the filtrate evaporated to dryness. The crude green oil was eluted from a silica column (dichloromethane), to give an oily solid (3.2 g, 79%) (Found: C, 81.2; H, 6.7; N, 11.7. $C_{16}H_{16}N_2$ requires C, 81.4; H, 6.8; N, 11.9%); δ($CDCl_3$) 2.0 (3 H, s, CH_3), 5.0 (2 H, s, $CH_2C_6H_5$), 5.8—6.0 (4 H, m, 3′-H, 3-H, 4′-H, 4-H), 6.5 (1 H, m, 2′-H), and 6.8—7.2 (5 H, m, C_6H_5).

General Method for Preparation of 11-*Benzyl*-10-*methylprodigiosenes* (**16**).—The bipyrrole (**14**) (0.01 mol) and the pyrrolecarbaldehyde (**15**) (0.01 mol) were dissolved in ethanol (15 ml) and stirred whilst ethereal HCl (2 ml) was added in one batch. The mixture was stirred for 0.5 h and the product was collected by filtration and washed with ether (2 × 50 ml).

11-*Benzyl*-3-*ethyl*-2,4,10-*trimethylprodigiosene hydrochloride* (**16a**). 3-Ethyl-2,4-dimethylpyrrolecarbaldehyde[13] gave (**16a**) (24%), m.p. 196—198 °C; R_F 0.65 (1:9 $CH_3OH:CH_2Cl_2$) (Found: C, 74.0; H, 6.9; N, 10.2. $C_{25}H_{22}ClN_3$ requires C, 74.0; H, 6.9; N, 10.35%); δ($CDCl_3$) 1.05 (3 H, t, CH_2CH_3), 2.3 (6 H, s × 2, 4-CH_3), 2.5 (2 H, m, CH_2CH_3), 2.7 (3 H, s, 2-CH_3), 5.35 (2 H, s, $CH_2C_6H_5$), 6.2 (2 H, d, 7-H, 8-H), 6.9 (1 H, s, 9-H), 7.0—7.25 (5 H, m, C_6H_5), and 7.7 (1 H, d, 6-H); *m/z inter alia* 369 (M^+).

11-*Benzyl*-3-*pentyl*-2,4,10-*trimethylprodigiosene hydrochloride* (**16b**). 3,5-Dimethyl-4-pentylpyrrole-2-carbaldehyde (**15b**) gave the title prodigiosene (10%), m.p. 177—178 °C; R_F 0.7 (1:9 CH_3OH—CH_2Cl_2) (Found: C, 75.5; H, 7.9; N, 9.0. $C_{28}H_{34}ClN_3$ requires C, 75.1; H, 7.6; N, 9.4%); δ($CDCl_3$) 0.9 [3 H, m, $(CH_2)_4CH_3$], 1.4 [6 H, m, $(CH_2)_3$], 2.2 (6 H, s × 2, 2-CH_3, 4-CH_3), 2.35 (2H, m, CH_2), 2.6 (3H, s, 10-CH_3), 5.3 (2 H, s, $CH_2C_6H_5$), 6.2 (2 H, m, 8-H, 9-H), 6.8 (1 H, s, =CH–), 6.9—7.3 (6 H, m, 7-H and C_6H_5), 7.7 (1 H, d, 6-H), 13.0 (1 H), and 14.3 (1 H); *m/z* 411 (M^+), 334, 236, 165, 145, 108, 91, and 77.

3,5-*Dimethyl*-4-*pentylpyrrole*-2-*carbaldehyde* (**15b**) (71%), m.p. 49—51 °C was prepared from 2,4-dimethyl-3-pentylpyrrole by Vilsmeier formylation using a method analogous to that used to prepare (**6**) (method A).

2,4-*Dimethyl*-3-*pentylpyrrole*, b.p. 85 °C/0.6 mmHg was prepared analogously to its 3-hexyl homologue (**7f**) (Found: C, 80.3; H, 11.6; N, 8.3. $C_{11}H_{19}N$ requires C, 80.0; H, 11.5; N, 8.5%).

Intermediates in its synthesis were:

Ethyl 3,5-*dimethyl*-4-*pentylpyrrole*-2-*carboxylate* (25%) m.p. 72—74 °C (Found: C, 70.5; H, 10.0; N, 5.9. $C_{14}H_{23}NO_2$ requires C, 70.9; H, 9.7; N, 5.9%); *m/z* 237 (M^+), 192 ($M - OC_2H_5$), 180 ($M - C_4H_9$), 134 (180 − C_2H_5OH), and 106 (134 − CO).

3,5-*Dimethyl*-4-*pentylpyrrole*-2-*carboxylic acid* (29%), m.p. 66 °C (Found: C, 68.6; H, 9.1; N, 6.5. $C_{12}H_{19}NO_2$ requires C, 68.9; H, 9.1; N, 6.7%); *m/z inter alia* 209 (M^+).

1,2-*Dimethyl*-5-*pyrrol*-2-*ylpyrrole* (**17**). Phosphorus oxychloride (33 ml) was added dropwise to a stirred solution of 1,2-dimethylpyrrole (28.5 g, 0.3 mol) and pyrrolidin-2-one (25.5 g, 0.36 mol) in dichloromethane (80 ml) at 0—5 °C. The mixture was stirred at 10 °C for 1 h and at room temperature for a further 1 hour and then poured slowly into a stirred solution of sodium acetate (150 g) in water (1 500 ml). After 15 minutes, 10M-aqueous potassium hydroxide was added with ice-cooling until the pH was stabilised at pH 10. The mixture was then stirred for 3 h, cooled to 4 °C for 72 h, and the resulting granular

precipitate filtered off to give 1,2-*dimethyl*-5-(4,5-*dihydropyrrol*-2-*yl*)*pyrrole* (30.9 g, 64%), m.p. 55—59 °C (Found: C, 74.1; H, 8.5; N, 17.2. $C_{10}H_{14}N_2$ requires C, 74.07; H, 8.64; N, 17.28%); t.l.c. (CH_2Cl_2) R_F 0.15.

This compound (30 g) was heated under reflux for 1.75 h in xylene (300 ml) containing palladium-on-charcoal catalyst (30% w/w, 24 g) in an argon atmosphere. The hot mixture was separated by filtration and the residue washed with hot chloroform (4 × 25 ml). The filtrate and washings were evaporated under reduced pressure and the resulting oil dissolved in warm hexane. On cooling the solution there was obtained 1,2-dimethyl-5-pyrrol-2-ylpyrrole (**17**) (8.7 g, 30%), m.p. 64—66 °C (Found: C, 74.8; H, 7.4; N, 17.6. $C_{10}H_{12}N_2$ requires C, 75.0; H, 7.5; N, 17.5%); δ($CDCl_3$) 2.24 (3 H, s, CH_3), 3.54 (3 H, s, NCH_3), 6.92 (1 H, m, CH), 7.04 (1 H, m, CH), 7.2 (2 H, m, 2 × CH), 7.75 (1 H, m, CH), and 8.1 (1 H, br, NH); t.l.c. (CH_2Cl_2) R_F 0.80.

2,4-*Dimethyl*-3-*phenylpyrrole*-5-*carbaldehyde* (**18b**). Benzoyl chloride (13.5 ml, 115 mmol) was added dropwise over 20 min to a solution of 2,4-dimethyl-3-phenylpyrrole[11] (18.1 g, 106 mmol) in DMF (25 ml) and diethyl ether (35 ml) at 0 °C. The suspension was stirred at room temperature for 1.5 h, and then ether (85 ml) was added. The precipitate was collected by filtration and added to a solution of sodium acetate [14 g in water (85 ml) and ethanol (30 ml)] over 15 min. The mixture was stirred for 1.5 h, and then water (85 ml) was added. Filtration followed by washing with water gave the product (**18b**) (18.6 g, 88.3%), m.p. 150—152 °C (Found: C, 77.9; H, 6.5; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.5; N, 7.0%).

Ethyl 5-*formyl*-2-*methyl*-4-*propylpyrrole*-3-*carboxylate* (**18c**). To a stirred mixture of ethyl acetoacetate (17.33 g, 133 mmol) and 2-bromopentan-1-al (22.0 g, 133 mmol) was added (in one batch) water (76 ml) and ammonium hydroxide solution (28% w/v; 76 ml). The mixture was stirred at room temperature for 18 h, and then extracted with ether (2 × 300 ml). The combined ether extracts were washed sequentially with 2M-NaOH, water, 2M-HCl, and water, and dried ($MgSO_4$). Removal of solvent gave ethyl 2-methyl-4-propylpyrrole-3-carboxylate (10.2 g) as a crude oil which was used without further purification.

The crude oil (10.2 g) was formylated under the modified Vilsmeier conditions used for (**18b**) to give (**18c**) (10.0 g, 84.7% based on the crude pyrrole), m.p. 104—105 °C (Found: C, 65.0; H, 7.4; N, 6.2. $C_{12}H_{17}NO_3$ requires C, 64.57; H, 7.62; N, 6.28%).

General Method for Preparation of 10,11-*Dimethylprodigiosenes* (**19a,b**) *from the Bipyrrole* (**17**).—The bipyrrole (**17**) (2 mmol) and the pyrrolecarbaldehyde (**18**) (2 mmol) were dissolved in ethanol (3 ml) and treated with ethanolic HCl (1 ml). The mixture was stirred in an argon atmosphere for 20 min, and then dichloromethane (250 ml) was added and the solution was washed with water (2 × 150 ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated to leave a blue-black solid which contained (t.l.c., Al_2O_3–CH_2Cl_2) both the orange dipyrrylmethene (**24**) and the blue-black dipyrrolyldipyrromethene (**23**) as impurities. The mixture was dissolved in methylene chloride and shaken with 1M-aqueous ammonia. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The pure product was obtained by elution (hexane ⟶ 5% CH_2Cl_2–hexane) from an alumina column (Woelm neutral Grade IV). The prodigiosene base was converted into its hydrochloride salt by dissolution in CH_2Cl_2 and shaking with 2M-HCl.

Methyl (2,4,10,11-*tetramethyl*)*prodigiosene*-3-*propionate hydrochloride* (**19a**). Methyl-(5-formyl-2,4-dimethyl)pyrrole-3-propionate (**18a**) gave (**19a**) (14.5%), m.p. 164—165 °C (Found: C, 65.3; H, 6.7; N, 10.5. $C_{21}H_{28}ClN_3O_2$ requires C, 65.0; H, 6.7; N, 10.8%); δ($CDCl_3$) 2.25 (3 H, s, CH_3), 2.28 (3 H, s, CH_3), 2.3—2.8 (4 H, m, CH_2CH_2), 2.65 (3 H, s, CH_3), 3.6 (3 H, s, NCH_3), 3.7 (3 H, s, OCH_3), 6.1 (1 H, d, 9-H), 6.6 (1 H, m, CH), 6.9 (1 H, s, 5-H), 7.1 (1 H, m, CH), and 7.5 (1 H, m, 6-H).

2,4,10,11-*Tetramethyl*-3-*phenylprodigiosene hydrochloride* (**19b**). 3,5-Dimethyl-4-phenylpyrrole-2-carbaldehyde (**18b**) gave (**19b**) (14%), m.p. 194 °C (decomp.) (Found: C, 72.9; H, 6.1; N, 11.0. $C_{23}H_{24}ClN_3$ requires C, 73.1; H, 6.4; N, 11.1%); ($CDCl_3$) 2.25 (3 H, s, CH_3), 2.4 (3 H, s, CH_3), 2.6 (3 H, s, CH_3), 3.72 (3 H, s, NCH_3), 6.05 (1 H, d, 9-H), 6.6 (1 H, m, CH), 6.95 (1 H, s, 5-H), 7.04—7.4 (6 H, m, CH and C_6H_5), and 7.57 (1 H, d, 6-H); *m*/*z* 341 (M^+), 326, 310, 220, and 170.

Ethyl 2,10,11-*trimethyl*-4-*propylprodigiosene*-3-*carboxylate hydrochloride* (**19c**). The bipyrrole (**17**) (161 mg, 1 mmol) and ethyl 5-formyl-2-methyl-4-propylpyrrole-3-carboxylate (**18c**) (223 mg, 1 mmol) were dissolved in ethanol (1 ml) and treated with ethanolic HCl (0.5 ml). The mixture was stirred for 20 min at 5 °C, and the product was filtered off and washed with a small volume of cold ethanol and diethyl ether to give (**19c**) (175 mg, 43.6%) as a blue-black powder, m.p. 154—155 °C (Found: C, 65.4; H, 7.0; N, 10.3. $C_{22}H_{28}ClN_3O_2$ requires C, 65.8; H, 7.0; N, 10.5%); δ($CDCl_3$) 1.35 (3 H, t, CH_2CH_3), 1.4 (6 H, t, 2 × CH_3), 1.7 [1 H, m, $CH(CH_3)_2$], 2.4 (3 H, s, CH_3), 2.55 (3 H, s, CH_3), 4.1 (3 H, s, NCH_3), 4.3 (2 H, q, CH_2CH_3), 6.02 (1 H, d, 9-H), 6.7 (1 H, d, CH), 6.83 (1 H, d, CH), 6.87 (1 H, s, 5-H), 7.05 (1 H, d, CH), and 7.25 (1 H, d, CH).

General Procedure for the Preparation of 10,11-*Dimethylprodigiosenes* (**19d,e**) *from the Bipyrrolecarbaldehyde* (**20**).—The method used to prepare 11-methylprodigiosenes (**5**) was employed. 2-Hexyl-3,4-dimethylpyrrole gave 2-*hexyl*-3,4,10,11-*tetramethylprodigiosene hydrochloride* (**19d**) (54%), m.p. 153—155 °C (Found: C, 71.9; H, 8.3; N, 10.9. $C_{23}H_{32}ClN_3$ requires C, 71.6; H, 8.3; N, 10.9%); δ($CDCl_3$) 0.8 (3 H, t, CH_2CH_3), 1.15—1.45 [8 H, m, $(CH_2)_4$], 1.9 (3 H, s, CH_3), 2.15 (3 H, s, CH_3), 2.85 (2 H, t, CH_2CH_2), 3.68 (3 H, s, NCH_3), 6.05 (1 H, d, 9-H), 6.5 (1 H, m, CH), 6.85 (1 H, s, 5-H), 7.0 (1 H, m, CH), and 7.5 (1 H, d, 9-H); *m*/*z* 349 (M^+), 278 ($M - C_5H_{11}$), 263, 248, 228, 183, and 140.

3-Hexyl-2,4-dimethylpyrrole gave 3-*hexyl*-2,4,10,11-*tetramethylprodigiosene hydrochloride* (**19e**) (65%), m.p. 92—94 °C (Found: C, 71.2; H, 8.4; N, 10.8. $C_{23}H_{32}ClN_3$ requires C, 71.6; H, 8.3; N, 10.9%); δ($CDCl_3$) 0.85 (3 H, t, CH_2CH_3), 1.25 [8 H, br, $(CH_2)_4$], 2.2 (3 H, s, CH_3), 2.25 (3 H, s, CH_3), 3.6 (3 H, s, CH_3), 3.7 (3 H, s, NCH_3), 6.05 (1 H, d, 9-H), 6.55 (1 H, m, CH), 6.9 (1 H, s, 5-H), 7.05 (1 H, m, CH), and 7.5 (1 H, d, 6-H); *m*/*z* 349 (M^+), 334, 278 ($M - C_5H_{11}$), and 108.

5-(1,2-*Dimethylpyrrol*-5-*yl*)*pyrrole*-2-*carbaldehyde* (**20**). Reaction of the dimethylbipyrrole (**17**) with benzoyl chloride and DMF under the conditions used to prepare (**6**) gave (**20**) (29%), m.p. 157—160 °C, R_F (CH_2Cl_2) 0.15 (Found: C, 70.4; N, 6.6; H, 15.0. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%); δ($CDCl_3$) 2.3 (3 H, s, CH_3), 3.6 (3 H, s, NCH_3), 5.95 (1 H, d, 3-H), 6.3 (2 H, m), 7.0 (1 H, m, 4-H), and 9.45 (1 H, s, CHO); *m*/*z* 188 (M^+) and 159 (M – HCO).

General Procedure for the Preparation of 12-*Methylprodigiosenes* (**25**).—Either the bipyrrolecarbaldehyde (**8**) (2 mmol) and an α-free pyrrole, or the bipyrrole (**26**) (2 mmol) and a pyrrolecarbaldehyde (Scheme 7), were dissolved in ethanol (5 ml) and stirred and cooled to 5 °C whilst ethanolic HCl (0.5 ml) was added. A purple precipitate formed immediately. After 20 min the mixture was filtered and the product was washed with ethanol (10 ml) and then recrystallised from glacial acetic acid.

1-Methyl-2-(5-methylpyrrol-2-yl)pyrrole (**26**) and 3-ethyl-2,4-dimethylpyrrolecarbaldehyde gave 3-*ethyl*-2,4,10,12-*tetramethylprodigiosene hydrochloride* (**25a**) (62%), m.p. 262 °C (decomp.) (Found: C, 68.7; H, 7.6; N, 12.8. $C_{19}H_{24}ClN_3$ requires C, 69.2; H, 7.3; N, 12.7%); δ [$(CD_3)_2SO$] 1.1 (3 H, t, CH_2CH_3), 2.3 (3 H, s, CH_3), 2.35 (3 H, s, CH_3), 2.5 (CH_3 under DMSO),

3.2 (CH_2CH_3 under water), 3.9 (3 H, s, NCH_3), 6.2 (1 H, m, CH), 6.9 (1 H, m, CH), 7.25 (1 H, d, CH), 7.5 (1 H, s, CH), and 8.1 (1 H, d, CH).

The bipyrrole (**26**) and 3,5-dimethyl-3-phenylpyrrole-2-carbaldehyde gave 2,4,10,12-*tetramethyl*-3-*phenylprodigiosene hydrochloride* (**25b**) (61%), m.p. 221 °C (Found: C, 72.0; H, 6.3; N, 11.0. $C_{23}H_{24}ClN_3 + H_2O$ requires C, 72.3; H, 6.2; N, 11.0%); too insoluble in $(CD_3)_2SO$ and in CF_3CO_2D for n.m.r.; free base decomposed in CF_3CO_2D; *m/z* 341 (M^+), 326, 311, 170, and 160.

1-Methyl-5-pyrrol-2-ylpyrrole-2-carbaldehyde (**8**) and 2-hexyl-3,4-dimethylpyrrole gave 2-*hexyl*-3,4,12-*trimethylprodigiosene hydrochloride* (**25c**) (87%), m.p. 202 °C (Found: C, 70.8; H, 8.4; N, 11.3. $C_{22}H_{30}ClN_3$ requires C, 71.1; H, 8.1; N, 11.3%); too insoluble for n.m.r.; *m/z* 335 (M^+), 320 ($M - CH_3$), 278 ($M - C_4H_9$), 265, and 146.

The bipyrrolecarbaldehyde (**8**) and 3-ethyl-2,4-dimethylpyrrole gave 3-*ethyl*-2,4,12-*trimethylprodigiosene hydrochloride* (**25d**) (92%), m.p. 193 °C (Found: C, 68.3; H, 7.1; N, 12.9; $C_{18}H_{22}ClN_3$ requires C, 68.5; H, 7.0; N, 13.3%); too insoluble for n.m.r.; *m/z* 279 (M^+), 264 ($M - CH_3$), 249 (264 − CH_3), 146, and 108.

Preparation of the 1-*methylprodigiosene* (**29**). 2-Methyl-5-pyrrol-2-ylpyrrole (**27**) and 3-ethyl-1,2,4-trimethylpyrrole-5-carbaldehyde (**28**) reacted under the conditions used to prepare the 12-methyl derivatives (**25**) to give 3-*ethyl*-1,2,4,10-*tetramethylprodigiosene hydrochloride* (**29**) (17%), m.p. > 300 °C (Found: C, 69.1; H, 7.4; N, 12.4. $C_{19}H_{24}ClN_3$ requires C, 69.2; H, 7.3; N, 12.7%); too insoluble for n.m.r.; *m/z* 293 (M^+), 278 ($M - CH_3$), 263 (278 − CH_3), 137, and 122.

4-*Ethyl*-1,3,5-*trimethylpyrrole*-2-*carbaldehyde* (**28**). 3-Ethyl-2,4-dimethylpyrrolecarbaldehyde (5.5 g, 36 mmol) was dissolved in dichloromethane (50 ml) and tetrabutylammonium bromide (11.6 g, 0.036 mol) and methyl iodide (2.51 ml, 0.04 mol) were added. The mixture was stirred vigorously as aqueous sodium hydroxide (50% w/v; 35 ml) was added over 2 min. The mixture was stirred and refluxed for 5 h and then cooled and dichloromethane (150 ml) and water (100 ml) were added. The organic fraction was separated and washed with water (100 ml), dried ($MgSO_4$), treated with carbon, and the solvent was removed. The residual oily solid was cooled to 4 °C overnight, and then triturated with ether and filtered to give (**28**) (62%), m.p. 135—138 °C (Found: C, 72.4; H, 9.3; N, 8.2. $C_{10}H_{15}NO$ requires C, 72.7; H, 9.1; N, 8.5%).

Ethyl 4-*bromo*-5-*hexyl*-3-*methylpyrrole*-2-*carboxylate* (**30b**). Magnesium turnings (5.22 g, 0.215 mol) and iodine (20 mg) in dry ether (200 ml) were treated with 1-bromopentane (2 ml) and the mixture was warmed to initiate reaction. The mixture was stirred as dry ether (300 ml) was added, followed by dropwise addition of 1-bromopentane (22.8 ml, to give 0.2 mol total). The mixture was stirred for 1 h and then treated dropwise over 0.5 h with ethyl 4-bromo-5-bromomethyl-3-methylpyrrole-2-carboxylate[15] (**30a**) (32.5 g, 0.1 mol) in dry THF (300 ml). The dark mixture was refluxed for 4 h and then cooled; saturated aqueous ammonium formate (150 ml) was then added to it. The organic layer was separated. The aqueous layer was washed with ether (200 ml) and the combined ether extracts were washed with water (100 ml), dried (Na_2SO_4), and evaporated to dryness. The product was purified by silica-gel chromatography [CH_2Cl_2–light petroleum (1:4—1:1) as eluant to give (**30b**) (7.65 g, 24%) as an off-white solid, m.p. 76—77 °C (Found: C, 53.0; H, 7.0; N, 4.4. $C_{14}H_{22}BrNO_2$ requires C, 53.2; H, 7.0; N, 4.4%); δ($CDCl_3$) 0.85 (3 H, t, CH_2CH_3), 1.2—1.75 [10 H, br, $(CH_2)_5$], 2.28 (3 H, s, CH_3), 2.6 (3 H, t, CH_2CH_3), 4.3 (2 H, q, CH_2CH_3), and 9.25 (1 H, br, NH); *m/z* 315/317 (M^+), 270/272, 244/246, 236, 216/218, 198/200, 166, and 120.

4-*Bromo*-5-*hexyl*-3-*methylpyrrole*-2-*carboxylic acid* (**30c**). A solution of the ester (**30b**) (1.58 g, 5 mmol) in ethanol (12 ml) was refluxed for 2 h with KOH [1.12 g, 20 mmol in water (4.5 ml)]. The mixture was cooled and adjusted to pH 4 with glacial acetic acid. Filtration, followed by drying over P_2O_5 *in vacuo* gave the product (1.39 g, 96%), m.p. 109—110 °C (decomp.) (Found: C, 50.4; H, 6.6; N, 4.6. $C_{12}H_{18}BrNO_2$ requires C, 50.0; H, 6.25; N, 4.9%); *m/z inter alia* 289/287 (M^+), 243/245, 216/218, 208, 198/200, 172/174, 164, and 138 (**31b**). To the hydrazide[16] (**31a**) (4.1 g, 0.013 mol) in glacial acetic acid (41 ml) was added 2M-HCl (14 ml) followed by water (41 ml). The solution was cooled to 0 °C, and treated dropwise with saturated aqueous sodium nitrite until a slight excess was present (starch/I_2 paper). The mixture was stirred at 0—5 °C for 0.5 h after which water (50 ml) was added and stirring continued for a further 1 h. The solid azide (**31b**) was filtered off and dissolved in dichloromethane (25 ml) and the solution was washed with water (15 ml) and dried ($MgSO_4$). The solvent required for further reaction was added and the dichloromethane was removed under reduced pressure.

Compound (**31c**). The crude azide (**31b**) in toluene (25 ml) was refluxed for 5 h, after which time no azide was present (i.r.) and a strong isocyanate peak was evident in the i.r. spectrum ($\nu_{max.}$ 2 250 cm^{-1}). The crude isocyanate was used immediately.

Compound (**31d**). The azide (**31b**) (1.5 g, 4.6 mmol) in s-butyl alcohol (20 ml) was heated on a steam-bath for 18 h. Removal of the solvent gave a solid which was treated with light petroleum and then filtered off to give the carbamate (**31d**) (1.0 g, 58.5%), m.p. 123—125 °C (Found: C, 67.8; H, 7.4; N, 7.5. $C_{21}H_{28}N_2O_4$ requires C, 67.7; H, 7.5; N, 7.5%); δ($CDCl_3$) 1.0 (3 H, m, CH_2CH_3), 1.2 [3 H, d, $CH(CH_3)C_2H_5$], 1.5 (2 H, m, CH_2CH_3), 2.2—2.3 (6 H, 2 × s, 2 × CH_3), 2.6 (2 H, m, CH_2), 3.2 (2 H, m, CH_2NH), 4.7 [2 H, m, NH and $CH(CH_3)C_2H_5$], 5.3 (2 H, s, $C_6H_5CH_2$), 7.4 (5 H, m, C_6H_5), and 8.9 (1 H, br, NH).

Compound (**31e**). The isocyanate (**31c**) (4.47 g, 15 mmol) and n-decylamine (2.9 ml, 15 mmol) in toluene (30 ml) were refluxed for 18 h. On cooling, the urea (**31e**) was obtained as a crystalline solid (3.2 g, 43.4%), m.p. 158—159 °C (Found: C, 71.5; H, 9.4; N, 9.2. $C_{27}H_{41}N_3O_3$ requires C, 71.2; H, 9.0; N, 9.2%); δ [$(CD_3)_2SO$] 0.9 (3 H, m, CH_3), 1.25 (16 H, m, 8 × CH_2), 2.2 (6 H, 2 × s, 2 × CH_3), 2.5 (2 H, m, CH_2), 3.0 (4 H, m, $CH_2NHCONHCH_2$), 5.2 (2 H, s, $C_6H_5CH_2$), 5.6 (2 H, m, NHCONH), 7.4 (5 H, m, C_6H_5), and 10.9 (1 H, m, NH); *m/z* 455 (M^+), 255, 242, 152, 134, 121, 108, 99, and 91.

Compound (**31f**). The benzyl ester (**31d**) (0.5 g, 1.3 mmol) in ethanol (20 ml) was stirred for 0.5 h with palladium-on-charcoal catalyst (10% w/w; 0.25 g) and ammonium formate (0.4 g, 5.2 mmol). The mixture was filtered and the solvent was removed to give an oily solid which was treated with light petroleum and filtered off. The crude product (0.35 g, 92.1%) (R_F 0.2 in 10% methanol–dichloromethane) rapidly darkened and was used immediately.

Compound (**31g**). The benzyl ester (**31e**) (3 g; 6.6 mmol) in ethanol (200 ml) was hydrogenated over palladium-on-carbon catalyst (5% w/w; 0.5 g) at room temperature and 1 atm. When the theoretical volume of hydrogen (148 ml) had been taken up the mixture was filtered and the solvent was removed under reduced pressure to give a pink solid which was treated with light petroleum and filtered to give the pyrrolecarboxylic acid (**31g**) (1.9 g, 79%), m.p. 114 °C (decomp.) (Found: C, 66.0; H, 9.5; N, 11.3. $C_{20}H_{35}N_3O_3$ requires C, 65.75; H, 9.6; N, 11.5%); δ[$(CD_3)_2SO$] 0.9 (3 H, m, CH_2CH_3), 1.2 (16 H, m, 8 × CH_2), 2.1 (6 H, 2 × s, 2 × CH_3), 2.4 (2 H, m, CH_2), 3.0 (4 H, m, 2 × CH_2), 5.8 (2 H, m, NHCONH), and 10.8 (1 H).

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