An Improved Approach to 5'-Unsubstituted 5-Formyldipyrromethanes

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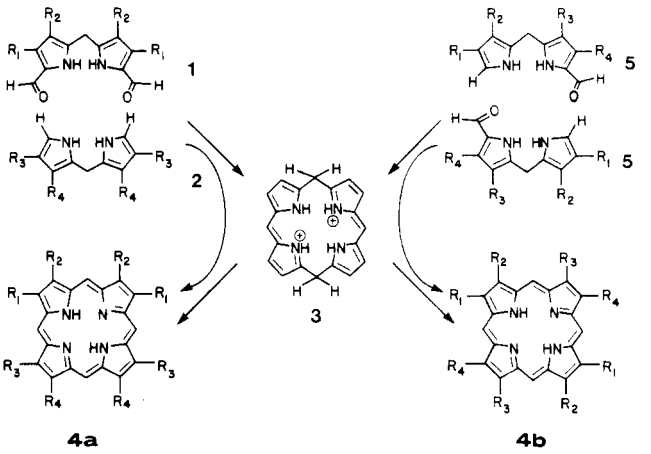
A general synthesis of 5'-unsubstituted 5-formyl-2,2'-dipyrromethanes, precursors to centrosymmetric porphyrins, is described. Cyanovinyl groups are used to protect the aldehydes and stabilize the dipyrromethanes. 5-(Chloromethyl)-2-(2,2-dicyanovinyl)pyrroles were condensed with 5-unsubstituted pyrrole-2-carboxylate ethyl esters in warm glacial acetic acid to give a series of 5'-(ethoxycarbonyl)-5-(2,2-dicyanovinyl)-2,2'-dipyrromethanes in high yield. Aqueous alkali was used to deprotect the dicyanovinyl substituent to regenerate the aldehyde and saponify the ethyl ester in a single step. The acid group was subsequently decarboxylated thermally to give the 5'-unsubstituted 5-formyl-2,2'-dipyrromethane. An alternative route was also designed by substitution of a benzyl for an ethyl ester. Hydrogenolysis released the carboxylic acid without affecting the cyanovinyl group, and the subsequent decarboxylation in neat trifluoroacetic acid occurred without rearrangement. Deprotection using aqueous alkali produced crystalline 5'-unsubstituted 5-formyldipyrromethane. The complete lack of rearrangement during the synthesis and manipulation of the dipyrromethanes was confirmed by ^{13}C NMR spectroscopy.

Among the various syntheses of porphyrins that have been devised since the 1950s, one of the more useful has been that developed independently by Woodward[1] and MacDonald[2] which involves the use of the well-known reaction[3] whereby 2-formylpyrroles condense with acid and 2-unsubstituted pyrroles to afford efficiently the stable 2,2'-dipyrromethenium salts. The extension of this reaction to porphyrin synthesis (Scheme I) entails the coupling of a 5,5'-diformyldipyrromethane (**1**) with a 5,5'-diunsubstituted dipyrromethane (**2**) to produce an intermediary porphodimethene (**3**), which upon air oxidation is converted to the final porphyrin (**4a** or **4b**). The MacDonald synthesis requires that at least *one* of the two components be symmetrical in order to obtain a single product. The MacDonald synthesis has been employed to produce uro-,[2,3] copro-,[4] and aetioporphyrins of symmetry types II, III, and IV.[3]

Somewhat later,[5] it was appreciated that 5'-unsubstituted 5-formyldipyrromethane **5** could also condense and lead to porphyrins via similar porphodimethenes (Scheme I). In order to obtain a single product, such pyrromethanes must be allowed to react only with themselves, to produce porphyrins of twofold axial symmetry (which includes porphyrins of type I or II). Recently, Chakrabarty et al.[6] have employed mixed condensations using *two* such dipyrromethanes. By arranging to have substituents of differing polarity and number on the three possible products, the resulting porphyrins proved separable by HPLC.

It occurred to us, that under conditions of sufficiently high dilution, covalently linked bis(dipyrromethanes) of this type could be made to condense *intramolecularly*, to lead, after oxidation, to porphyrins variously *strapped* at diametrically opposed β-positions. This paper presents the studies that were made to optimize the synthesis of such dipyrromethanes employing the (cyanovinyl)pyrrole aldehyde protecting groups, a strategy that we have found to be extremely efficient and especially suited to extension to dimeric homologues (as briefly reported elsewhere[7]).

Scheme I



(Cyanovinyl)pyrroles[8] have been employed since Hans Fischer's time for the synthesis of dipyrromethanes,[9] but their first deliberate use for synthesis of 5-formyldipyrromethanes was made by Woodward[1] in his classical assault on chlorophyll *a*. Woodward showed that (dicyanovinyl)cryptopyrrole (**17**) could be oxidized with sulfuryl chloride in glacial acetic acid[10] at the 5-methyl substituent without significant destruction of the dicyanovinyl group. The resulting monochloromethylpyrrole **19** was condensed with 3-(ethoxycarbonyl)-4-methylpyrrole in ethanolic hydrochloric acid. This substrate bore *two* unsubstituted α-positions, and although the 3-carbonyl substituent strongly discouraged reaction at the adjacent 2-position, it did not prevent it entirely, with the result that the product required a complex workup (fractional crystallization) to remove the byproduct tripyrrane, ethyl 2,5-bis[(5-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrol-2-yl)methyl]-4-methylpyrrole-3-carboxylate.[11] By use of the appropriate 2:1 stoichiometry, such tripyrranes could be obtained in up to 87% yield.[12]

Subsequently, Davies[13] and Flaugh and Rapoport[14] have made similar use of this synthon. We have earlier[15] re-

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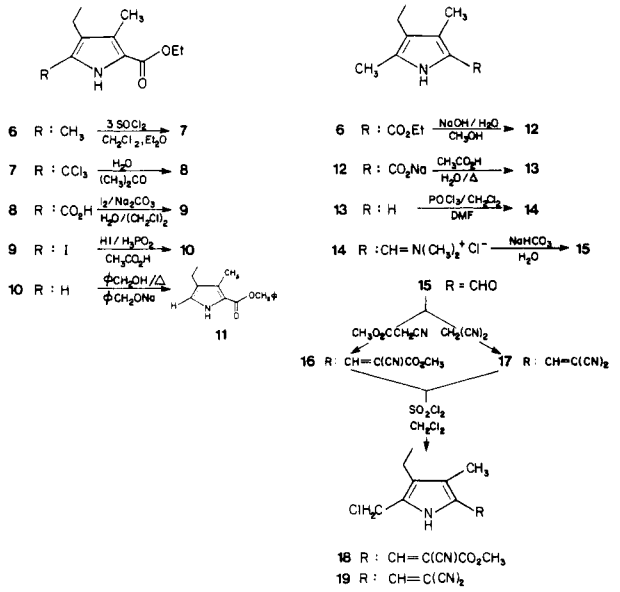
Scheme II



ported the use of these materials in the general synthesis of 5,5′-diformyldipyrromethanes. It was apparent that by condensing **19** with a pyrrole such as **10**, a stable precursor **5** could be obtained unambiguously.

Inasmuch as aqueous alkali is required to deprotect the dicyanovinyl substituent back to aldehyde, it seemed reasonable to combine this step with the saponification of an ester function, and for this purpose, the readily available ethyl esters would serve admirably. The requisite 2-(ethoxycarbonyl)-3,4-dialkylpyrroles **10** are readily available by a standard degradation[16-20] (Scheme II) (see Experimental Section for improved procedures) of the analogous 2-(ethoxycarbonyl)-5-methylpyrrole **6**, a class of compounds available from Knorr-type ring syntheses.[21]

The 5-(chloromethyl)-2-(2,2-dicyanovinyl)pyrrole synthons themselves (**19**) are also available from **6** via the standard steps[15] depicted in Scheme II and whose practical realization are detailed in the Experimental Section.

The initial attempts to condense **10** and **19** involving the use of inert solvents such as refluxing toluene or forcing conditions such as stannic chloride in dichloromethane[15] resulted in incomplete reaction or extensive decomposition, and only a low yield of the desired product **20** was obtained after chromatographic workup. However, when glacial acetic acid was used, the two reagents were found to react smoothly on warming above 60 °C and gave a single product (**20**) in nearly quantitative yield after only a few minutes, isolable analytically pure by simple crystallization. There was no evidence for the formation of any symmetrical dipyrromethane byproduct, which in our system would have been especially easy to detect: dipyrromethane 5,5′-diesters are colorless but redden on exposure to bromine vapor (when on a TLC plate). The desired products are yellow (and yellow fluorescent under long-wave UV) and become maroon-violet with bromine. 5,5--Bis(dicyanovinyldipyrromethanes) are also yellow (and fluorescent), but bromine turns these a dark blue-green. The complete lack of "rearrangement" under the conditions used was not entirely unexpected,[16] since the desired product **20** bears *two* electron-withdrawing groups of widely differing strength.[22] The alternative possible pair of precursors to the 5′-(ethoxycarbonyl)-5-(2,2-dicyanovinyl)-2,2′-dipyrromethanes, namely the 5-(chloromethyl)pyrrole-2-carboxylic esters and the 5-unsubstituted 2-(2,2-dicyanovinyl)pyrroles, were investigated by Badger et al.[23] and found to be unreactive to any significant extent, in part due to the unfortunate choice of an alcoholic solvent, which in this case preempted the pyrrylcarbinyl cation. Badger et al.[22] then quantified the inertness of (cyanovinyl)pyrroles generally and abandoned further investigation in this area. We found[15] that such 5-unsubstituted 2-(2,2-dicyanovinyl)pyrroles require *forcing* conditions (inert aprotic solvent, Friedel–Crafts catalysis) to ensure reaction, and such drastic conditions are known[24] to generate symmetrical dipyrromethane diesters from the more reactive (5-alkoxycarbonylpyrryl)-2-carbinyl cation sources. In addition, if any of the desired product (**20**) could be formed in this alternative system, this material would still be subject to attack by electrophiles at the 2′-position guarded only by the weakly protecting 5′-ester function, *and in this case such attack would lead to symmetrical dipyrromethane byproducts.*

Deprotection of the 5′-(ethoxycarbonyl)-5-(2,2-dicyanovinyl)-2,2′-dipyrromethanes was originally carried out in ethanol, but more recently[7] we have found 1-propanol to be more useful since reaction times and premature decarboxylation or base-induced self-condensation are decreased. The product, collected after careful acidification, was decarboxylated in refluxing DMF until the 280-nm absorption disappeared.

An alternative route designed to yield *pure* 5′-unsubstituted 5-formyl-2,2′-dipyrromethanes was also explored. This entailed the substitution of a benzyl for an ethyl ester in the preceding sequence. Hydrogenolysis should cleave the ester but leave the cyanovinyl group intact.[15] Decarboxylation of the resulting carboxylic acid in neat trifluoroacetic acid could be expected to occur without undue rearrangement.[25] Finally, removal of the protecting cyanovinyl group should give **5**. In the event, all of the above was realized but with a single exception: the 5′-(benzyloxycarbonyl)-5-(2,2-dicyanovinyl)-2,2′-dipyrromethane **23** showed extreme reluctance to undergo hydrogenolysis; partial hydrogen uptake was soon followed by poisoning of the catalyst. Addition of further catalyst was of no avail. When this behavior proved reproducible, the cyanoacrylate analogues **24** were investigated. These proved to hydrogenolyze smoothly and quantitatively. In terms of overall yield the benzyl ester route is entirely comparable to the ethyl ester one and avoids the tedious filtration step following the alkaline hydrolysis in the latter sequence. Slightly lower yields with some of the earlier steps were compensated for by a considerably improved yield of porphyrin from the final cyclization step itself, when high-purity (crystalline) 5-formyl-2,2′-dipyrromethane **27** was used.

In these initial studies we examined the synthesis of etioporphyrin II as outlined in Scheme III. The starting

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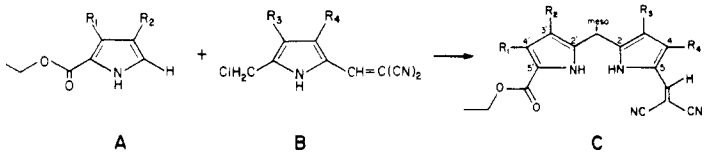
Table I. Preparation of 5′-(Ethoxycarbonyl)-5-(2,2-dicyanovinyl)-2,2′-dipyrromethanes[a]

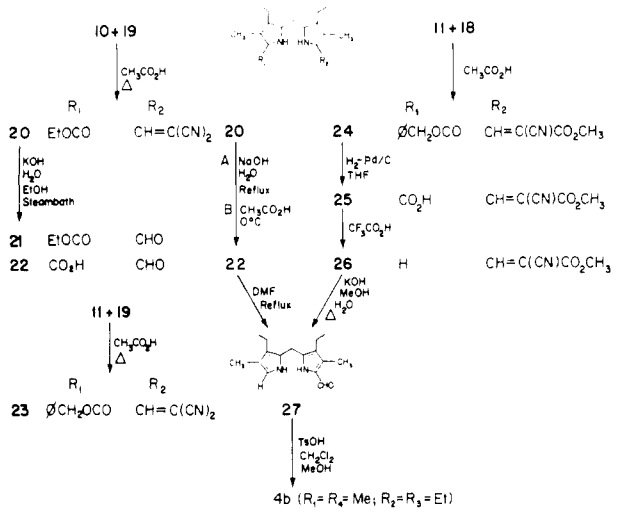


A B C

R_1	R_2	R_3	R_4	A, g (mmol)	B, g (mmol)	acetic acid, mL	product, g (% yield)	mp, °C
Me	Me	Me	Me	1.06 (6.35)	1.24 (5.65)	24	1.84 (93)	222–223.5 dec
Me	Me	Me	Et	1.02 (6.11)	1.24 (5.31)	25	1.78 (92)	207.5–211.5 dec
Me	Me	Et	Me	0.88 (5.27)	1.18 (5.05)	10	1.64 (89)	212–219 dec
Me	Me	Et	Et	1.02 (6.11)	1.38 (5.58)	24	1.93 (92)	202.5–204.5 dec
Me	Et	Me	Me	0.93 (5.14)	1.14 (5.19)	10	1.69 (90)	205–210 dec
Me	Et	Me	Et	1.3 (7.18)	1.74 (7.45)	13	2.26 (83)	193.5–195.5 dec
Me	Et	Et	Me	2.87 (15.8)	3.57 (15.3)	150	5.53 (96)	186–187
Me	Et	Et	Et	0.97 (5.36)	1.26 (5.09)	10	1.66 (83)	180–182.5
Et	Me	Me	Me	1.14 (6.30)	1.25 (5.69)	24.3	1.95 (94)	199–203
Et	Me	Me	Et	1.16 (6.41)	1.34 (5.74)	25	1.96 (90)	205.5–212 dec
Et	Me	Et	Me	0.92 (5.08)	1.21 (5.18)	11	1.63 (85)	204–207.5 dec
Et	Me	Et	Et	1.08 (5.97)	1.33 (5.37)	25	1.80 (86)	196.5–202.5 dec
Et	Et	Me	Me	1.22 (6.26)	1.26 (5.74)	10	2.03 (94)	196.5–199.5 dec
Et	Et	Me	Et	1.24 (6.36)	1.34 (5.74)	10	2.06 (92)	170.5–173.5
Et	Et	Et	Me	1.00 (5.13)	1.20 (5.14)	5	1.59 (79)	185–189
Et	Et	Et	Et	1.25 (6.41)	1.44 (5.82)	10	2.04 (86)	161–164.5

[a] C, H, N values (±0.15%) were determined for all 16 compounds.

Scheme III



material 2-(ethoxycarbonyl)-4-ethyl-3,5-dimethylpyrrole (**6**) is available either from a diborane reduction[26] of ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate[27] or directly from 3-ethyl-2,4-pentanedione with ethyl α-(hydroxyimino)acetoacetate,[28] diethyl (hydroxyimino)malonate,[29] or (best) diethyl aminomalonate.[21] The success of all of the syntheses described above rest on the fact that no rearrangement occurs either during the synthesis and manipulation of the dipyrromethanes or during their coupling to give porphyrins. We find ^{13}C NMR spectroscopy especially useful for detecting rearranged isomers.

In order to assign the ^{13}C NMR spectra of the intermediary 5′-(ethoxycarbonyl)-5-(2,2-dicyanovinyl)-2,2′-dipyrromethanes, we have prepared all fifteen of the possible β-methyl β-ethyl analogues. The preparation and properties of these materials, which all formed in uniformly high yield, are presented in Table I and in the supplementary material.[30]

Examination of etioporphyrin II (**4a**, $R_1 = R_3 = Me$; $R_2 = R_4 = Et$) prepared by both the methods described above showed no detectabe rearrangement to have occurred during either sequence. In addition, both products were identical with material prepared by traditional procedures. The four isomers of etioporphyrin can be distinguished (as their protonated dications) by examination of the meso carbon region of the ^{13}C NMR spectrum. Etioporphyrin II, having D_{2h} symmetry, is the only isomer to show two peaks of equal intensity here.

Experimental Section

NMR spectra were obtained in the indicated solvents, with a Varian HA-100 or XL-100 instruments for ^1H (5-mm tube) or with a Varian CFT-20 or Bruker WH-400 (at 100.6 MHz) instrument for ^{13}C (10-mm tube). Melting points were obtained on a Thomas Hoover Unimelt oil bath/capillary tube or a Thomas Kofler Micro Hot Stage apparatus and are uncorrected. Microanalyses were performed by P. Borda at the University of British Columbia. Reagents were employed as obtained, unless otherwise noted. Where "dry" CH_2Cl_2 or THF are specified these were distilled from CaH_2.

5-Carboxy-2-(ethoxycarbonyl)-4-ethyl-3-methylpyrrole (8). 2-(Ethoxycarbonyl)-4-ethyl-3,5-dimethylpyrrole (**6**) (58.5 g, 0.30 mol) was dissolved in dry dichloromethane (300 mL) in a 5-L round-bottomed flask equipped with magnetic stirring. Anhydrous diethyl ether (500 mL) was added, followed *at once* by a solution of sulfuryl chloride (128.36 g, 0.95 mol) in dichloromethane (200 mL), run in as fast as the effervescence and vigorous boiling permitted. The resulting solution was stirred for an additional 10 min, before being evaporated in vacuo (at 40 °C) to a residual oil.

This was dissolved in reagent acetone (300 mL) and treated with water (200 mL), and after the exothermicity had abated, the mixture was warmed on a steam bath to gentle reflux. Pale yellow crystalline product soon separated and was recovered by filtration (50% aqueous acetone wash) after cooling to 0 °C. The evaporated filtrates afforded a minor second crop. The combined solids were warmed with excess sodium bicarbonate and water until dissolved. The solution was extracted with ethyl acetate, filtered, and finally

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(30) The synthesis of the compounds in Table I and their ^{13}C NMR data are given in the supplementary material.

acidified with hydrochloric acid.

The precipitated product was recovered by filtration, washed thoroughly with water, and dried: yield, 54.1 g (80.2%); mp 210–211 °C (lit.[31] mp 211 °C); ^{1}H NMR (Me_2SO-d_6) δ 1.06 (t, J = 7.5 Hz, 3 H, 4-Et), 1.33 (t, J = 7 Hz, 3 H, ester), 2.24 (s, 3 H, 3-Me), 2.72 (q, J = 7.5 Hz, 2 H, 4-Et), 4.29 (q, J = 7 Hz, 2 H, ester), 11.18 (br s, 1 H, NH), 12.62 (br s, 1 H, CO_2H); MS, m/e 225 (M^+), 210, 196, 180, 178, 164.

2-(Ethoxycarbonyl)-4-ethyl-5-iodo-3-methylpyrrole (9). 5-Carboxy-2-(ethoxycarbonyl)-4-ethyl-3-methylpyrrole (**8**) (120.6 g, 0.54 mol) and potassium bicarbonate (100.42 g, 1.0 mol) were dissolved in water (800 mL) in a 4-L heavy-wall Erlenmeyer flask (steam bath). 1,2-Dichloroethane (500 mL) was added, followed by solid iodine (170.6 g, 0.67 mol), added over 2 min. The mixture was refluxed (hot plate) for an hour.

The remaining excess of iodine was discharged by cautious (effervescence!) addition of aqueous sodium bisulfite. The organic phase (warmed if necessary to redissolve crystallized product) was isolated and evaporated in vacuo, and the chlorocarbon was chased with ethanol (400 mL). The crystalline residue was dissolved in hot ethanol (500 mL). The solution was suction filtered and diluted with water (290 mL) to permanent opalescence. Crystallization was completed at 0 °C. The product was filtered off and washed with 70% aqueous ethanol, 50% ethanol, and finally water.

After drying in air in the dark (the compound darkens rapidly in light), the first crop weighed 137.7 (83.7%): mp 114.0–115.5 °C (lit.[32] mp 114–115 °C); ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.5 Hz, 3 H, 4-Et), 1.33 (t, J = 7 Hz, 3 H, ester), 2.27 (s, 3 H, 3-Me), 2.37 (q, J = 7.5 Hz, 2 H, 4-Et), 4.31 (q, J = 7 Hz, 2 H, ester), 9.02 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.23) δ 161.38 (C=O), 131.88 (4), 126.05 (3), 123.96 (2), 73.42 (5), 60.42 (OCH_2CH_3), 20.00 (4-C-H_3CH_2), 14.81 (4-CH_3CH_2), 14.60 (CH_3CH_2O), 10.98 (3-Me); MS, m/e 307 (M^+), 292, 278, 262, 261, 260, 246.

2-(Ethoxycarbonyl)-4-ethyl-3-methylpyrrole (10). 2-(Ethoxycarbonyl)-4-ethyl-5-iodo-3-methylpyrrole (**9**) (30.7 g, 0.10 mol) was warmed (steam bath) in ethanol (250 mL, 95%) to solution and treated with aqueous (20 mL of H_2O) potassium iodide (26.5 g, 0.16 mol) and then concentrated hydrochloric acid (40 mL). The liberated iodine was discharged by the addition of 50% hypophosphorous acid (2 × 25 mL) and the mixture heated for an additional 15 min. After cooling, the mixture was diluted with dichloromethane (250 mL) followed by water (150 mL). The organic phase was isolated, dried (Na_2SO_4), and evaporated in vacuo to afford a dark red oil.

Filtration through silica gel (Woelm, Activity I, 85 g) with dichloromethane removed all colored impurity. Evaporation of the solvent in vacuo left a pale yellowish oil: 17.2 g (94.9%); mp 22.0–23.0 °C (lit.[33] mp 25 °C); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.5 Hz, 3 H, 4-Et), 1.32 (t, J = 7.2 Hz, 3 H, ester), 2.24 (s, 3 H, 3-Me), 2.40 (q, J = 7.5 Hz, 2 H, 4-Et), 4.27 (q, J = 7.2 Hz, 2 H, ester), 6.61 (d, J = 2.8 Hz, 1 H, 5-H), 8.88 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.50) δ 162.44 (C=O), 127.39 (4), 125.92 (3), 119.82 (5), 119.52 (2), 59.94 (CH_3CH_2O), 18.41 (4-CH_3CH_2), 14.58 (2 C, CH_3CH_2O and 4-CH_3CH_2), 10.34 (3-Me); MS, m/e 181 (M^+), 166, 152, 136, 135, 134, 120.

2-(Benzyloxycarbonyl)-4-ethyl-3-methylpyrrole (11). 2-(Ethoxycarbonyl)-4-ethyl-3-methylpyrrole (**10**) (5.0 g, 0.028 mol) and redistilled (from K_2CO_3) benzyl alcohol (30 mL, 31.2 g, 0.29 mol) were heated to reflux under nitrogen in a 250-mL Erlenmeyer flask (equipped with a Claisen adapter and nitrogen inlet) atop a magnetic-stirring hot plate set at the maximum heating rate. The solvent was boiled to the top of the flask, with the nitrogen stream being permitted to carry off any droplets of water noted condensing therewith.

A freshly prepared solution of sodium in dry benzyl alcohol was added periodically in 1-mL portions until the evolution of ethanol ceased, and the vapor temperature again rose above 200 °C, ensuring the completion of the exchange.

The hot solution was poured into methanol (200 mL) and acetic acid (10 mL). Addition of water (250 mL) precipitated out an oil. This was extracted into petroleum ether–ethyl acetate, and after washing the organic phase with 50% aqueous methanol, the solvent was removed in vacuo. The residue was *twice* chromatographed on silica gel (Woelm, Activity I), the second time after a 10-day hiatus during which the decarboxylated impurities had oxidized to dark material: yield of pale yellow oil, 5.6 g (83.6%); mp 26.5–28.0 °C. A sample was analyzed as such. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.06; H, 7.16, N, 5.63.

^{1}H NMR ($CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3 H, 4-Et), 2.30 (s, 3 H, 3-Me), 2.43 (q, J = 7.5 Hz, 2 H, 4-Et), 5.31 (s, 2 H, ArCH_2O), 6.64 (d, J = 2.8 Hz, 1 H, 5-H), 7.38 (m, 5 H, Ar), 9.00 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.35) δ 161.91 (C=O), 136.80 (Ar-1), 128.54 (2 Ar), 128.04 (3 Ar), 127.46 (4), 126.35 (3), 120.02 (5), 119.09 (2), 65.63 (ArCH_2O), 18.29 (4-CH_3CH_2), 14.62 (4-CH_3CH_2), 10.41 (3-CH_3); MS, m/e 243 (M^+), 228, 152, 136, 108, 107, 92, 91.

3-Ethyl-2,4-dimethylpyrrole (Cryptopyrrole) (13). 2-(Ethoxycarbonyl)-4-ethyl-3,5-dimethylpyrrole (**6**) (195.2 g, 1.00 mol) was warmed to solution in methanol (500 mL) (4-L heavy-wall Erlenmeyer flask) and then treated with a solution of sodium hydroxide (113.23 g, 2.83 mol) in water (250 mL). The mixture was heated (steam bath) for 2 h and then the flask was transferred to a hot plate/magnetic stirrer and equipped with a Claisen adapter, an addition funnel, a distillation adapter, and a condenser. The methanol was distilled off, with the fraction boiling between 90 and 100 °C being collected separately, to facilitate isolation of cryptopyrrole. Water was added as needed, to maintain the volume of the still pot above 700 mL.

When the vapor temperature reached 100 °C, the receiver was replaced by a flask containing some K_2CO_3, and acetic acid (170.0 g, 2.83 mol) (equivalent to the amount of NaOH originally taken) in water (250 mL) was added *cautiously* to the boiling saponification mixture. Care was taken not to stir the mixture too fast as the neutralization proceeded, to allow *local* decarboxylation to occur as much as possible.

Near the end of the addition, decarboxylation became vigorous and was soon complete. The distillation was continued (with further additions of water, as needed) until no further oily phase condensed with water and only minor dark tars remained with the aqueous phase in the distillation flask. The still was flushed of traces of product by cautiously adding dichloromethane to the still pot (these distillates being collected separately).

The organic phase was isolated and employed as such as cryptopyrrole. 20.6 g (17%) of it was diverted elsewhere. The remainder (97 mL), plus the CH_2Cl_2 (2 × 250 mL) extracts of the aqueous phase and 90–100 °C forerun, was employed in the procedure below: ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 3 H, 3-Et), 2.01 (s, 3 H, Me), 2.03 (s, 3 H, Me), 2.37 (q, J = 7.5 Hz, 2 H, 3-Et), 6.22 (br, 1 H, 5-H), 6.99 (v br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.45) δ 123.23 (2), 120.38 (3), 117.44 (4), 113.20 (5), 17.68 (3-CH_3CH_2), 15.74 (3-CH_3CH_2), 11.01 (2-CH_3), 10.34 (4-CH_3).

4-Ethyl-2-formyl-3,5-dimethylpyrrole (15). Phosphorus oxychloride (100 mL, 164.5 g, 1.07 mol) was added over several minutes to a magnetically stirred solution of *N,N*-dimethylformamide (100 mL, 94.4 g, 1.291 mol) in dichloromethane (440 mL). The mixture boiled briefly as the Vilsmeier complex formed. The solution was cooled (ice bath) and then treated, dropwise (magnetic stirring), with a solution of 3-ethyl-2,4-dimethylpyrrole (97 mL) in dichloromethane (500 mL). The CH_2Cl_2 extracts of the aqueous phases above were added afterwards.

The solvent was then removed in vacuo at 40–50 °C. The crystalline residue was treated with ice and water, in part dissolving. Recrystallization occurred due to a change of counter ion. Small portions of sodium bicarbonate were added (warning: effervescence) until the solution was *permanently* neutral. A false end point was achieved early, particularly if the solution remained cool, as the $PO_2Cl_2^-$ anion resists hydrolysis. On warming above 30–40 °C, this hydrolyzed rapidly, with precipitous drop in pH. Ice was added as necessary to keep the temperature below 40 °C until the neutralization was complete, and considerable excess solid $NaHCO_3$ was present in the mixture.

The mixture was warmed (steam bath), and minor tars that separated below 50 °C were removed by decantation (much adhered to the glassware) and then filtration. The filtrates (ca. 2

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(32) Grigg, R.; Johnson, A. W.; Wasley, J. W. F. *J. Chem. Soc.* **1963**, 362.
(33) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Johnson Reprint Corporation: New York, 1968; Vol. I, p 241.

L) were then heated on the steam bath for several hours. Above 65–70 °C, the solution clouded, and the product separated as a floating brown oil. This solidified on cooling to room temperature. It was filtered off and washed with water and dried. The yield of 114.3 g of the formylpyrrole represents a 75.7% conversion of the starting cryptopyrrole ethyl ester (**6**) for a total recovery of greater than 90% of useful products: mp 101.0–102.5 °C (lit.[34] mp 105–106 °C); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3 H, 4-Et), 2.27 (s, 6 H, 3,5-Me), 2.36 (q, J = 7 Hz, 2 H, 4-Et), 9.45 (s, 1 H, CHO), 10.87 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.47) δ 175.44 (CHO), 136.94 (5), 132.59 (3), 128.07 (2), 124.84 (4), 17.03 (4-CH_3CH_2), 15.07 (4-CH_3CH_2), 11.31 (5-CH_3), 8.66 (3-CH_3).

2-(2,2-Dicyanovinyl)-4-ethyl-3,5-dimethylpyrrole (17). 4-Ethyl-2-formyl-3,5-dimethylpyrrole (**15**) (48.84 g, 0.32 mol) and malononitrile (22.56 g, 0.34 mol) were heated in methanol (500 mL) with triethylamine (5 mL) (steam bath) until TLC examination (CH_2Cl_2, silica gel) showed the reaction to be complete. The mixture was cooled to room temperature and filtered. The solids were rinsed with methanol and dried, yield 49.56 g. The filtrates were concentrated in vacuo, to afford 2.72 g more: total, 52.3 g (81.2%); mp 191.0–191.5 °C (lit.[35] mp 191.5 °C); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7 Hz, 3 H, 4-Et), 2.12 (s, 3 H, 3-Me), 2.31 (s, 3 H, 5-Me), 2.39 (q, J = 7 Hz, 2 H, 4-Et), 7.30 (s, 1 H, vinyl), 9.35 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$, at 77.09) δ 141.08 (5), 140.48 (*C*H=C), 136.25 (3), 127.19 (4), 124.14 (2), 117.64 (CN), 116.26 (CN), 62.51 (CH=*C*), 17.14 (4-CH_3*C*H_2), 14.67 (4-*C*H_3CH_2), 12.40 (5-CH_3), 9.45 (3-CH_3).

5-(Chloromethyl)-2-(2,2-dicyanovinyl)-4-ethyl-3-methylpyrrole (19).[1] 2-(2,2-Dicyanovinyl)-4-ethyl-3,5-dimethylpyrrole (**17**) (10.0 g, 50.25 mmol) was dissolved in dichloromethane (200 mL) (in a 500-mL Erlenmeyer flask with magnetic stirring) and treated, under dry nitrogen, at room temperature, dropwise over 15 min, with a solution of sulfuryl chloride (7.12 g, 52.74 mmol) in dichloromethane (70 mL). When the addition was complete, gentle heating was applied, and the solvent was carefully boiled off as anhydrous diethyl ether was added, periodically, to replace it. The product crystallized as lemon yellow needles; when a thick slurry was obtained, it was allowed to cool, and the product was filtered off, washed with ether and then hexane, and dried in the dark, yield 10.54 g (89.8%). The product is unaffected by atmospheric moisture but reddens rapidly on exposure to light. Kept in the dark it is stable indefinitely, mp 176.0–178.0 °C dec. Anal. Calcd for $C_{12}H_{12}ClN_3$: C, 61.67; H, 5.18; N, 17.98; Cl, 15.17. Found: C, 61.38; H, 5.30; N, 17.73; Cl, 15.00. MS, m/e 233 (M^+), 199, 184; ^{1}H NMR ($CDCl_3$) δ 1.13 (t, J = 7.5 Hz, 3 H, 4-Et), 2.18 (s, 3 H, 3-Me), 2.50 (q, J = 7.5 Hz, 2 H, 4-Et), 4.63 (s, 2 H, CH_2Cl), 7.47 (s, 1 H, vinyl), 9.52 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.04 100.6 MHz) δ 141.98 (*C*H=C), 136.36 (5), 135.09 (3), 127.76 (4), 125.06 (2), 116.44 (CN), 114.98 (CN), 68.00 (CH=*C*), 35.81 (CH_2Cl), 17.13 (4-CH_3*C*H_2), 14.87 (4-*C*H_3CH_2), 9.39 (3-CH_3); IR (KBr) ν_{max} 3340 (NH), 2220 (CN), 1595 (C=C) cm^{-1}.

2-[2-Cyano-2-(methoxycarbonyl)vinyl]-4-ethyl-3,5-dimethylpyrrole (16). 4-Ethyl-2-formyl-3,5-dimethylpyrrole (**15**) (30.35 g, 0.20 mol) and methyl cyanoacetate (22.35 g, 0.3 mol) were warmed (steam bath) in toluene (200 mL). Triethylamine (10.7 mL) was added, and the heating was continued until TLC examination (CH_2Cl_2 silica) showed near absence of starting material (20 h). The solution was filtered (with ethyl acetate rinsing), decanted from traces of aqueous phase, and evaporated in vacuo. The product was crystallized from ethanol as bright yellow fibers, in two crops, 30.94 g and then 6.48 g: total recovery, 37.42 g (80.6%); mp 116.0–116.5 °C.

The first crop was analyzed. Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.30; H, 7.00; N, 11.94.

^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.5 Hz, 4-Et), 2.15 (s, 3 H, 3-Me), 2.30 (s, 3 H, 5-Me), 2.38 (q, 2 H, J = 7.5 Hz, 4-Et), 3.80 (s, 3 H, MeO), 7.86 (s, 1 H, vinyl), 9.58 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.56) δ 165.11 (C=O), 139.31 (5), 137.63 (*C*H=C), 135.27 (3), 126.40 (4), 123.46 (2), 119.91 (CN), 84.77 (CH=*C*), 52.28 (*C*H_3O), 17.23 (4-CH_3*C*H_2), 14.86 (4-*C*H_3CH_2), 12.02 (5-CH_3), 9.38 (3-CH_3).

(34) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Johnson Reprint Corporation: New York, 1968; Vol. I, p 157.
(35) Fischer, H.; Orth, H. "Die Chemie des Pyrrols"; Johnson Reprint Corporation: New York, 1968; Vol. I, p 226.

5′-(2,2-Dicyanovinyl)-5-(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane (20). 5-(Chloromethyl)-2-(2,2-dicyanovinyl)-4-ethyl-3-methylpyrrole (**19**) (3.57 g, 15.3 mmol) and 2-(ethoxycarbonyl)-4-ethyl-3-methylpyrrole (**10**) (2.87 g, 15.8 mmol) were suspended in glacial acetic acid (150 mL) under nitrogen and warmed to 70 °C. The chloromethyl component dissolved within 30 min, affording a clear orange solution. Inspection by TLC (silica gel; 2% CH_3OH in CH_2Cl_2) revealed a single-spot product, so the solution was concentrated in vacuo to 20 mL. Methanol (80 mL) was added and the mixture allowed to stand overnight. Filtration and methanol rinse produced a first crop of 5.05 g. Evaporation of the filtrates to small volume led to a second crop of 0.48 g: total, 5.53 g (95.7%); mp 186.0–187.0 °C.

The first crop was analyzed. Anal. Calcd for $C_{22}H_{26}N_4O_2$; C, 69.82; H, 6.92; N, 14.80. Found C, 69.66; H, 6.84; N, 14.80.

^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3 H, J = 7.5 Hz, 3′-Et), 1.08 (t, 3 H, J = 7.5 Hz, 3-Et), 1.35 (t, 3 H, J = 7 Hz, ester), 2.17 (s, 3 H, 4-Me), 2.30 (s, 3 H, 4′-Me), 2.44 (q, 2 H, J = 7.5 Hz, 3′-Et), 2.46 (q, 2 H, J = 7.5 Hz, 3-Et), 3.98 (s, 2 H, meso), 4.30 (q, 2 H, J = 7 Hz, ester), 7.34 (s, 1 H, vinyl), 8.76 (br, 1 H, 1′-NH), 9.20 (br, 1 H, 1-NH); ^{13}C NMR ($CDCl_3$ at 77.10) δ 162.15 (C=O), 140.78 (*C*H=C), 140.44 (2), 136.06 (4), 127.11 (4′), 126.41 (3), 126.21 (2′), 125.15 (3′), 124.16 (5), 118.93 (5′), 116.78 (CN), 115.99 (CN), 64.11 (CH=*C*), 59.96 (CH_3*C*H_2O), 23.75 (meso), 17.34 (3′-CH_3*C*H_2), 17.12 (3-CH_3*C*H_2), 15.36 (3′-*C*H_3CH_2), 14.67 (3-*C*H_3CH_2), 14.48 (*C*H_3CH_2O), 10.52 (4′-CH_3), 9.38 (4-CH_3); IR (KBr) ν_{max} 3400 (NH), 3280 (NH), 2220 (CN), 1665 (C=O), 1585 (C=C) cm^{-1}; MS, m/e 379 (27), 378 (99, M^+), 363 (13), 333 (34), 332 (100), 317 (42), 197 (44).

5′-Carboxy-3,3′-diethyl-5-formyl-4,4′-dimethyl-2,2′-dipyrromethane (22). 5′-(2,2-Dicyanovinyl)-5-(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane (**20**) (500 mg, 1.32 mmol) in boiling ethanol (25 mL) was treated with sodium hydroxide (2.5 g, 62.5 mmol) in water (10 mL). Reflux was maintained under nitrogen. After 30 min, water (50 mL) was added. After 60 min of further reflux, the ethanol was distilled off with periodic addition of water (50 mL in all) to maintain the volume, until the vapor temperature reached 100 °C.

After being cooled to 0 °C, the solution was acidified with acetic acid to pH 5. The gray gelatinous precipitate was filtered, washed with water, and dried over KOH (vacuum desiccator): yield, 380.7 mg (95.3%); mp 188.0–190.0 °C dec.

After drying at 0.2 torr for 18 h at room temperature, the product was analyzed. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.26; H, 7.32; N, 9.35.

^{1}H NMR (Me_2SO-d_6) δ 0.83, 0.85 (2 t, J = 7.5 Hz, 6 H, 3,3′-Et), 2.11 (s, 3 H, 4-Me), 2.15 (s, 3 H, 4′-Me), 2.29, 2.31 (2 q, 3,3′-Et, obscured by Me_2SO), 3.77 (s, 2 H, meso), 9.46 (s, 1 H, CHO), 11.00 (br, 1 H, 1-NH), 11.42 (br, 1 H, 1′-NH) [CO_2H not observed]; MS, m/e 302 (18, M^+), 258 (74, $M^+ - CO_2$), 149 (100), 122 (32), 121 (25), 109 (14), 108 (35); IR (KBr) ν_{max} 3265 (br, NH), 1670 (br, C=O) cm^{-1}.

2-(Ethoxycarbonyl)-3,3′-diethyl-5′-formyl-4,4′-dimethyl-2,2′-dipyrromethane (21). 5′-(2,2-Dicyanovinyl)-5-(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane (**20**) (502 mg, 1.33 mmol) in ethanol (10 mL) and potassium hydroxide (2 g) in water (20 mL) were combined and heated on a steam bath. After an hour, the fluffy yellow starting material had changed into a light tan, powdery solid. Water (50 mL) was added and the product filtered off after cooling on ice. After aqueous rinse and drying, it weighed 275 mg (62.7%). A repetition afforded 305 mg (69.7%), mp 167.5–168.0 °C.

Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.05; H, 7.93; N, 8.48. Found: C, 68.75; H, 8.01; N, 8.42.

^{1}H NMR ($CDCl_3$) δ 1.04, 1.05 (2 t, J = 7.5 Hz, 6 H, 3,3′-Et), 1.25 (t, J = 7 Hz, 3 H, ester), 2.25 (s, 6 H, 4,4′-Me), 2.44 (q, J = 7.5 Hz, 4 H, 3,3′-Et), 3.89 (s, 2 H, meso), 4.19 (q, J = 7 Hz, 2 H, ester), 9.45 (s, 1 H, CHO), 9.97 (br, 1 H, 1-NH), 10.68 (br, 1 H, 1′-NH); MS, m/e 330 (97, M^+), 315 (177), 301 (17), 193 (31), 149 (100); IR (KBr) ν_{max} 3265 (br, NH), 1680 (C=O), 1625 (C=O) cm^{-1}.

5-(Benzyloxycarbonyl)-5′-(2,2-dicyanovinyl)-3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane (23). 5-(Chloromethyl)-2-(2,2-dicyanovinyl)-4-ethyl-3-methylpyrrole (**19**) (1.02 g, 4.37 mmol) and 2-(benzyloxycarbonyl)-4-ethyl-3-methylpyrrole (**11**)

(1.10 g, 4.54 mmol) in glacial acetic acid (70 mL) were treated as above for formation of the corresponding ethyl ester **20**. Yield: first crop, 1.5 g (78%); second crop, 0.2 g (10.3%). An analytical sample was recrystallized from dichloromethane–methanol, mp 192.0–193.0 °C. Anal. Calcd for $C_{27}H_{28}N_4O_2$: C, 73.61; H, 6.41; N, 12.72. Found: C, 73.70; H, 6.37; N, 12.66.

^{1}H NMR ($CDCl_3$) δ 1.02 and 1.04 (2 t, J = 7.5 Hz, 6 H, 3,3'-Et), 2.12 (s, 3 H, 4'-Me), 2.28 (s, 3 H, 4-Me), 2.40 (q, J = 7.5 Hz, 4 H, 3,3'-Et), 3.93 (s, 2 H, meso), 5.21 (s, 2 H, $ArCH_2O$), 7.21 (s, 1 H, vinyl), 7.22–7.37 (m, 5 H, Ar), 9.00 (br, 1 H, 1-NH), 9.17 (br, 1 H, 1'-NH); ^{13}C NMR ($CDCl_3$ at 77.06) δ 161.64 (C=O), 140.87 (*C*H=C), 139.79 (2'), 136.44 (Ar 1), 135.91 (4'), 128.56 (2 Ar), 128.01 (3 Ar), 127.81 (4), 126.32 (2 C, 2,3'), 125.41 (3), 124.24 (5'), 118.62 (5), 116,76 (CN), 115.79 (CN), 65.75 ($ArCH_2O$), 64.68 (CH=*C*), 23.82 (meso), 17.32 (3-CH_3CH_2), 17.13 (3'-CH_3CH_2), 15.33 (3-*C*H_3CH_2), 14.68 (3'-*C*H_3CH_2), 10.60 (4-CH_3), 9.41 (4'-CH_3); MS, m/e 440 (27, M^+), 349 (18), 199 (21), 198 (20), 197 (14), 91 (100); IR (KBr) ν_{max} 3380 (NH), 3320 (NH), 2220 (CN), 1660 (C=O), 1595 (C=C) cm^{-1}.

5-(Chloromethyl)-2-[2-cyano-2-(methoxycarbonyl)-vinyl]-4-ethyl-3-methylpyrrole (18). 2-[2-Cyano-2-(methoxycarbonyl)vinyl]-4-ethyl-3,5-dimethylpyrrole (**16**) (5.0 g, 21.5 mmol) was stirred in dry dichloromethane (70 mL) and treted at 0 °C, dropwise, with a solution of sulfuryl chloride (3.05 g, 22.6 mmol) in dichloromethane (20 mL) over 30 min.

After 30 min. of stirring at room temperature, most of the solvent was removed in vacuo, and the product isolated from ether–hexane. Crops of 2.42 and 2.41 g were obtained (84.2%), mp 157.0–159.0 °C dec.

The first crop was analyzed. Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50; Cl, 13.29. Found: C, 58.64; H, 5.66; N, 10.42; Cl, 13.19.

^{1}H NMR ($CDCl_3$) δ 1.09 (t, J = 7.5 Hz, 3 H, 4-Et), 2.18 (s, 3 H, 3-Me), 2.46 (q, J = 7.5 Hz, 2 H, 4-Et), 3.86 (s, 3 H, OMe), 4.60 (s, 2 H, CH_2Cl), 8.00 (s, 1 H, vinyl), 9.64 (br, 1 H, NH); MS, m/e 266 (M^+), 232, 231, 217, 199, 185; IR (KBr) ν_{max} 3300 (NH), 2220 (CN), 1725 (C=O), 1595 (C=O) cm^{-1}.

5-(Benzyloxycarbonyl)-5'-[2-cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (24). 5-(Chloromethyl)-2-[2-cyano-2-(methoxycarbonyl)vinyl]-4-ethyl-3-methylpyrrole (**18**) (1.19 g, 4.46 mmol) and 2-(benzyloxycarbonyl)-4-ethyl-3-methylpyrrole (**11**) (1.15 g, 4.73 mmol) were treated in the usual manner with glacial acetic acid (80 mL). The volume was reduced to 10 mL in vacuo. Addition of methanol (40 mL) and then water (10 mL) led to finely divided crystalline product: 1.86 g (88.1%) after filtration, methanol rinse, and drying in air. A sample was recrystallized from dichloromethane–methanol for analysis, mp 169.0 °C. Anal. Calcd for $C_{28}H_{31}N_3O_4$: C, 71.02; H, 6.60; N, 8.87. Found: C, 71.09; H, 6.58; N, 8.87.

^{1}H NMR ($CDCl_3$) δ 1.00, 1.02 (2 t, J = 7.5 Hz, 6 H, 3,3'-Et), 2.08 (s, 3 H, 4'-Me), 2.27 (s, 3 H, 4-Me), 2.35, 2.39 (2 q, J = 7.5 Hz, 4 H, 3,3'-Et), 3.77 (s, 3 H, CH_3O), 3.87 (s, 2 H, meso), 5.20 (s, 2 H, $ArCH_2O$), 7.12–7.40 (m, 5 H, Ar), 7.77 (s, 1 H, vinyl), 8.82 (br, 1 H, 1-NH), 9.28 (br, 1 H, 1'-NH); ^{13}C NMR ($CDCl_3$ at 77.17) δ 165.19 (CO_2Me), 161.64 (CO_2Bz), 138.32 (*C*H=C), 137.70 (2'), 136.54 (Ar 1), 135.38 (4'), 128.45 (2 Ar), 127.98 (3 Ar and 2), 127.09 (4), 125.71 (3'), 125.23 (3), 123.65 (5'), 119.42 (CN), 118.43 (5), 86.14 (CH=*C*), 65.57 ($ArCH_2O$), 52.38 (CH_3O), 23.62 (meso), 17.32 (3-CH_3CH_2), 17.13 (3'-CH_3CH_2), 15.35 (3-*C*H_3CH_2), 14.72 (3'-*C*H_3CH_2), 10.57 (4-CH_3), 9.16 (4'-CH_3); MS, m/e 474 (33), 473 (100, M^+), 382 (20), 365 (49), 364 (40), 231 (18), 230 (19), 91 (65); IR (KBr) ν_{max} 3380 (NH), 3310 (br, NH), 2205 (CN), 1685 (br, C=O), 1590 (C=C) cm^{-1}.

5'-Carboxy-5-[2-cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (25). 5-(Benzyloxycarbonyl)-5'-[2-cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (**24**) (1.0 g, 2.12 mmol) and 10% palladized charcoal (101 mg) were stirred in tetrahydrofuran (35 mL) under hydrogen (1 atm, room temperature). Uptake of H_2 was rapid, linear with time, and complete in 25 min. After 10 min of further stirring, the catalyst was filtered off. TLC examination showed complete absence of starting material. The solvent was removed in vacuo and displaced with methanol, causing separation of a lemon yellow microcrystalline solid. After washing with methanol and ether and drying, it weighed 681 mg (84.1%). A repetition with 3.01 g (6.36 mmol) of benzyl ester gave 89.9% in two crops, mp 216.0 °C dec, with darkening above 205 °C. A sample was recrystallized for analysis from tetrahydrofuran–methanol. Anal. Calcd for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.96. Found: C, 65.73; H, 6.46; N, 10.89.

^{1}H NMR (Me_2SO-d_6) δ 0.89 (t, J = 7.5 Hz, 6 H, 3,3'-Me), 2.14 (s, 3 H, 4-Me), 2.20 (s, 3 H, 4'-Me), 2.39 (2 q obscured by Me_2SO 3,3'-Et), 3.80 (s, 3 H, CH_3O), 4.04 (s, 2 H, meso), 7.87 (s, 1 H, vinyl), 10.39 (br, 1 H, 1-NH), 11.05 (br, 1 H, 1'-NH), 11.84 (br, 1 H, CO_2H); MS, m/e 384 (25), 383 (100, M^+), 365 (24), 339 (28), 231 (28), 230 (26); IR (KBr) ν_{max} 3380 (NH), 3265 (br, NH), 2200 (CN), 169 (C=O), 1640 (C=O), 1580 (C=C) cm^{-1}.

5-[2-Cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (26). 5'-Carboxy-5-[2-cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (**25**) (1.01 g, 2.64 mmol) and trifluoracetic acid (8 mL) were stirred under nitrogen for 5 min at room temperature. Examination by TLC (silica gel, dichloromethane) revealed a single yellow spot, colored red by bromine vapor. No spot remained at the origin, indicating the complete disappearance of starting material. Most of the trifluoracetic acid was removed by evaporation under reduced pressure. The residue was taken into dichloromethane (50 mL), washed with saturated aqueous sodium bicarbonate (2 × 20 mL) and then water (20 mL), and dried (Na_2SO_4). Displacement of the solvent by hexane (rotary evaporator) led to an orange microcrystalline solid, 701 mg (78.4%), after filtration, hexane wash, and air-drying. Evaporation of the filtrates afforded an additional 122 mg (13.6%): total yield, 92%; mp 156.0–157.0 °C. Anal. Calcd. for $C_{20}H_{25}N_3O_2$: C, 70.77; H, 7.42; N, 12.38. Found: C, 70.79; H, 7.54; N, 12.36.

^{1}H NMR ($CDCl_3$) δ 1.05 (t, J = 7.5 Hz, 6 H, 3,3'-Et), 2.02 (s, 3 H, 4'-Me), 2.12 (s, 3 H, 4-Me), 2.40 (q, J = 7.5 Hz, 4 H, 3,3'-Et), 3.77 (s, 3 H, OCH_3), 3.87 (s, 2 H, meso), 6.41 (d, J = 2 Hz, 1 H, 5'-H), 7.63 (br, 1 H, 1'-NH), 7.78 (s, 1 H, vinyl), 9.31 (br, 1 H, 1-NH); ^{13}C NMR ($CDCl_3$ at 77.13) δ 165.29 (CO_2CH_3), 140.47 (2), 137.63 (*C*H=C), 135.56 (4), 125.52 (3), 123.54 (5), 122.47 (2'), 120.71 (3'), 119.61 (CN), 118.43 (4'), 115.19 (5'), 85.55 (CH=*C*), 52.37 (OCH_3), 23.68 (meso), 17.62 (3'-CH_3CH_2), 17.12 (3-CH_3CH_2), 15.63 (3'-*C*H_3CH_2), 14.78 (3-*C*H_3CH_2), 10.33 (4'-CH_3), 9.30 (4-CH_3); MS, m/e 340 (23), 339 (100, M^+), 307 (16), 231 (41), 230 (57), 122 (59), 121 (69), 109 (47), 108 (28), 94 (44); IR (KBr) ν_{max} 3410 (NH), 3400 (v weak), 3360 (NH), 2200 (CN), 1690 (C=O), 1590 (C=C) cm^{-1}.

3,3'-Diethyl-5-formyl-4,4'-dimethyl-2,2'-dipyrromethane (27). 5-[2-Cyano-2-(methoxycarbonyl)vinyl]-3,3'-diethyl-4,4'-dimethyl-2,2'-dipyrromethane (**26**) (503 mg, 1.48 mmol) and potassium hydroxide (2 g, ca. 30 mmol) were heated to reflux in methanol (15 mL)–water (20 mL). Within 15 min, the yellow starting material had dissolved, and light tan fluffy needles of product had begun to separate from the solution. Heating was continued for 30 min longer, then water (30 mL) was added, and the cooled mixture was filtered. The solid was rinsed with water and dried. Yield: 380 mg (99.2%). A repetition on 1.43 g of starting material afforded 1.05 g (97.1%) of product, mp 137.0–137.5 °C dec (lit.[36] mp 139–141 °C). The material was analyzed as such. Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.30; H, 8.33; N, 10.72.

^{1}H NMR ($CDCl_3$) δ 1.06, 1.07 (2 t, J = 7.5 Hz, 6 H, 3,3'-Et), 2.02 (s, 3 H, 4'-Me), 2.23 (s, 3 H, 4-Me), 2.43 (q, J = 7.5 Hz, 4 H, 3,3'-Et), 3.83 (s, 2 H, meso), 6.36 (d, J = 2 Hz, 1 H, 5'-H), 8.46 (s, 1 H, CHO), 9.38 (br, 1 H, 1'-NH), 9.99 (br, 1 H, 1-NH); ^{13}C NMR ($CDCl_3$ at 77.12) δ 175.91 (CHO), 138.81 (2), 133.58 (4), 128.43 (5), 124.85 (3), 122.75 (2'), 120.98 (3'), 117.53 (4'), 114.78 (5'), 22.74 (meso CH_2), 17.70 (3'-CH_3CH_2), 17.03 (3-CH_3CH_2), 15.83 (3'-*C*H_3CH_2), 15.21 (3-*C*H_3CH_2), 10.36 (4'-CH_3), 8.76 (4-CH_3); MS, m/e 258 (86, M^+), 243 (13), 229 (22), 149 (100), 122 (33), 121 (28), 109 (17), 108 (37), 94 (13); IR (KBr) ν_{max} 3330 (N–H), 3270 (N–H), 1610 (C=O) cm^{-1}.

3,7,13,17-Tetraethyl-2,8,12,18-tetramethylporphyrin (Etioporphyrin II) (4a, R_1 = R_3 = Me; R_2 = R_4 = Et). Method A. A solution of 5'-carboxy-3,3'-diethyl-5-formyl-4,4'-dimethyl-

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2,2′-dipyrromethane (**22**) (1.013 g, 3.35 mmol) in *N*,*N*-dimethylformamide (100 mL) was refluxed under nitrogen until the UV absorption maximum at 280 nm had vanished, indicating that the decarboxylation had proceeded to completion. (This required 3 h.)

The volume was reduced to 25 mL under reduced pressure (rotary evaporator). Dichloromethane (150 mL) was added, and the solution was extracted with water (2 × 50 mL) to remove most of the remaining DMF.

The dichloromethane solution of 3,3′-diethyl-5-formyl-4,4′-dimethyl-2,2′-dipyrromethane was dried over Na_2SO_4, filtered, and added dropwise to a solution of *p*-toluenesulfonic acid (4.0 g) in methanol (25 mL)–dichloromethane (450 mL) over 2 h. The mixture was stirred in the dark for 16 h and then reduced to a volume of 25 mL in vacuo. Methanol (75 mL) was added, followed by triethylamine (5 mL). After 30 min of refrigeration, the purple solids were filtered off and washed with methanol: yield, 382 mg (47.7%); mp >280 °C; MS, found 478.3093, $^{12}C_{32}{}^{1}H_{38}{}^{14}N_4$ requires 478.3097. Anal. Calcd for $C_{32}H_{38}N_4C$: 80.29, H, 8.00; N, 11.70. Found: C, 80.00; H, 7.93; N, 11.56.

^{1}H NMR ($CDCl_3$) δ 1.89 (t, *J* = 7.5 Hz, 12 H, Et), 3.66 (s, 12 H, Me), 4.12 (q, *J* = 7.5 Hz, 8 H, Et), 10.12 (s, 4 H, methine) [NH not recorded]; ^{13}C NMR (10% w/w CF_3CO_2H–$CDCl_3$, $CDCl_3$ at 77.11) δ 143.54 (3, 7, 13, 17), 142.29 (1, 9, 11, 18), 141.53 (4, 6, 14, 16), 136.92 (2, 8, 12, 18), 98.39 (10, 20), 97.95 (5, 15), 20.11 (C-H_3CH_2), 16.42 (CH_3CH_2), 11.67 (CH_3) [identical with authentic material;[37] CF_3CO_2H at δ 156.77, 113.81].

Method B. Crystalline 3,3′-diethyl-5-formyl-4,4′-dimethyl-2,2′-dipyrromethane (**27**) (706 mg, 2.74 mmol) in dichloromethane (200 mL) was added dropwise to a solution of *p*-toluenesulfonic acid (4.3 g) in methanol (25 mL) and dichloromethane (475 mL) over 2 h. Further procedure as for method A; yield, 447 mg (68.5%) of material identical with that prepared using method A.

Synthesis of Tetraalkyl Derivatives of 5′-(2,2-Dicyanovinyl)-5-(ethoxycarbonyl)-2,2′-dipyrromethane. The complete set of 15 tetraalkyl analogues of **20**, where the β-substituents were variously methyl and/or ethyl, were prepared, as indicated in Table I. The technique differed, from before, in that to facilitate workup and save time, the two reagents were heated rapidly (and briefly) in a small volume of solvent, and the product was isolated directly by crystallization after addition of methanol and/or water, depending on the expected solubility characteristics (increasing solubility in organic solvents expected with increasing ethyl substitution). Typically, approximately 5 mmol of each reagent (α-free ester taken in slight excess) was suspended in ca. 10–20 mL of glacial acetic acid in a 50-mL Erlenmeyer flask and placed atop a preheated hot plate, such that the mixture reached the boiling point within a minute. After 30 s more, the solution was cooled and diluted with solvent.

Only the first crop was isolated, and the yields given are for these. The filtrates were discarded, although further product could have been obtained therefrom if desired. The 5-unsubstituted pyrroles were obtained from the corresponding 5-methyl esters [2-(ethoxycarbonyl)-3,4,5-trimethyl-, -3-ethyl-4,5-dimethyl-, or -3,4-diethyl-5-methylpyrrole] in procedures similar to those starting from 2-(ethoxycarbonyl)-4-ethyl-3,5-dimethylpyrrole. The best procedure for the deiodination step is to employ hydriodic acid with acetic acid and hypophosphorous acids. These same 5-methylpyrrole-2-carboxylic esters were saponified, decarboxylated, formylated, etc. to afford the corresponding 5-(chloromethyl)-2-(2,2-dicyanovinyl)pyrroles in analogous fashion to that described for **19** above.

2-(2,2-Dicyanovinyl)-3-ethyl-4,5-dimethylpyrrole. Prepared from 3-ethyl-2-formyl-4,5-dimethylpyrrole as for its analogue **17**: mp 156.5–158.5 °C. Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.36; H, 6.69; N, 21.20.

^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J* = 7 Hz, 3 H, 3-Et), 1.95 (s, 3 H, 4-Me), 2.30 (s, 3 H, 5-Me), 2.52 (q, *J* = 7.5 Hz, 2 H, 3-Et), 7.27 (s, 1 H, vinyl), 9.42 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.27) δ 143.24 (3), 141.96 (5), 140.29 (*C*H=C), 123.16 (2), 120.00 (4), 117.54 (CN), 116.36 (CN), 62.32 (CH=*C*), 17.91 (3-CH_3CH_2), 15.87 (3-*C*H_3CH_2), 12.40 (5-CH_3), 8.56 (4-CH_3).

5-(Chloromethyl)-2-(2,2-dicyanovinyl)-3-ethyl-4-methylpyrrole. 2-(2,2-Dicyanovinyl)-3-ethyl-4,5-dimethylpyrrole (10.17 g, 51.1 mmol) in CH_2Cl_2 (80 mL) was treated with sulfuryl chloride (7.54 g, 55.85 mmol) in dichloromethane (75 mL) as for its isomer. The usual workup (progressive dilution with ether) gave a first crop of 10.22 g (85.64%) of brilliant lemon-yellow needles, which was analyzed as such. Anal. Calcd for $C_{12}H_{12}ClN_3$ C, 61.67; H, 5.18; N, 17.98; Cl, 15.17. Found: C, 61.70; H, 5.23; N, 18.03; Cl, 15.06.

^{1}H NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.5 Hz, 3 H, Et), 2.07 (s, 3 H, Me), 2.58 (q, *J* = 7.5 Hz, 2 H, Et), 4.63 (s, 2 H, CH_2Cl), 7.47 (s, 1 H, vinyl), 9.56 (br, 1 H, NH); ^{13}C NMR ($CDCl_3$ at 77.03, 100.6 MHz) δ 142.16 (3), 141.83 (*C*H=C), 136.82 (5), 124.05 (2), 120.47 (4), 116.46 (CN), 115.03 (CN), 67.98 (CH=C), 35.94 (CH_2Cl, 17.86 (3-CH_3CH_2), 15.87 (3-*C*H_3CH_2), 8.38 (4-CH_3).

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Registry No. 4a (R_1 = R_3 = Me, R_2 = R_4 = Et), 448-70-4; **6**, 2199-47-5; **7**, 97336-18-0; **8**, 53365-89-2; **9**, 57745-28-5; **10**, 4391-98-4; **11**, 51089-83-9; **13**, 517-22-6; **14**, 97336-19-1; **15**, 6250-80-2; **16**, 97336-20-4; **17**, 37789-73-4; **18**, 97336-23-7; **19**, 37789-74-5; **20**, 97336-21-5; **21**, 53365-90-5; **22**, 4869-79-8; **23**, 97336-22-6; **24**, 97336-24-8; **25**, 97336-25-9; **26**, 97336-26-0; **27**, 36746-28-8; A (R_1 = R_2 = Me), 938-75-0; A (R_1 = Et, R_2 = Me), 4949-58-0; A (R_1 = R2 = Et), 97336-41-9; B (R_3 = Me, R_4 = Et), 97336-28-2; B (R_3 = R_4 = Me), 59435-05-1; B (R_1 = R_4 = Et), 59435-26-6; C (R_1 = R_2 = R_3 = R_4 = Me), 74265-92-2; C (R_1 = R_2 = R_3 = Me, R_4 = Et), 97350-83-9; C (R1 = R_2 = R_4 = Me, R_3 = Et), 97336-29-3; C (R_1 = R_2 = Me, R_3 = R_4 = Et), 97336-30-6; C (R_1 = R_3 = R_4 = Me, R_2 = Et), 97336-31-7; C (R_1 = R_3 = Me, R_2 = R_4 = Et), 97350-84-0; C (R_1 = Me, R_2 = R_3 = R_4 = Et), 97336-32-8; C (R_1 = Et, R_2 = R_3 = Et), 97336-33-9; C (R_1 = R_4 = Et, R_2 = R_3 = Me), 97336-34-0; C (R_1 = R_3 = Et, R_2 = R_4 = Me), 97336-35-1; C (R_1 = R_3 = R_4 = Et, r_2 = Me), 97336-36-2; C (R_1 = R_2 = Et, R_3 = R_4 = Me), 97336-37-3; C (R_1 = R_2 = R_4 = Et, R_3 = Me), 97336-38-4; C (R_1 = R_2 = R_3 = Et, R_4 = Me), 97336-39-5; C (R_1 = R_2 = R_3 = R_4 = Et), 97336-40-8; $PhCH_2OH$, 100-51-6; $Me_2NCHCl^+PO_2Cl_2^-$, 21382-90-1; $CH_2(CN)_2$, 109-77-3; $(CN)CH_2CO_2Me$, 105-34-0; 2-(2,2-dicyanovinyl)-3-ethyl-4,5-dimethylpyrrole, 97336-27-1; 3-ethyl-2-formyl-4,5-dimethylpyrrole, 97336-42-0.

Supplementary Material Available: Complete ^{13}C NMR data on dipyrromethanes (5 pages). Ordering information is given on any current masthead page.