Synthesis of the First α-Linked Quaterpyrrole

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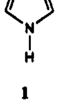
Introduction

Among other reasons, oligopyrroles directly linked at the α-positions are of interest as possible precursors to expanded porphyrins.[1] In principle, such species could allow access to a range of macrocyclic products not obtainable using simpler pyrrolic precursors. For example, 2,2′-bipyrrole (**2**), the "dimer" of pyrrole **1**, has been incorporated into porphycenes,[2] rubyrins,[3] and rosarins,[4] as well as into larger Schiff base-derived macrocyclic systems.[5] Similary, 2,5-bis(4-propyl-2-pyrrolyl)thiophene (**3a**), a heteroatom analogue of terpyrrole **3b**, has been used to construct a large, porphycene-like macrocycle.[6] At present, however, no macrocyclic systems are known which contain a "pure", all-aza terpyrrole such as **3b**, nor are any known which derive from an α-linked quaterpyrrole such as **4**. In fact, the latter class of oligopyrroles, unlike the terpyrroles,[7,8] are completely unknown at present. Therefore, we set out to develop a synthesis of such tetrapyrrolic systems and in this paper wish to report the first successful synthesis of an α-linked quaterpyrrole of generalized structure **4**.



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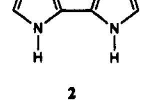

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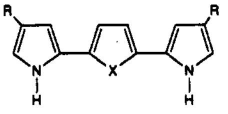
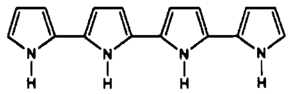


3a. X = S; R = C_3H_7
3b. X = NH; R = H



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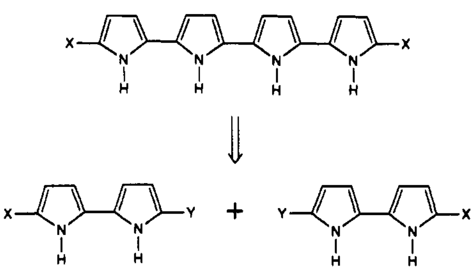
Results and Discussion

α-Linked quaterpyrroles may be considered as being "dimers of 2,2′-bipyrrole." Thus, in a retrosynthetic sense, it was considered likely that if an appropriate unsymmetric 2,2′-bipyrrole could be prepared, it would be possible to couple it using bipyrrole-forming methods to make the desired quaterpyrrole (Scheme I). Thus, the problem was reduced to one of preparing the appropriate bipyrrole starting material and to assessing which, if any, bipyrrole-forming methods might work in the context of a final bond making step. Clearly, this latter assessment of available methodology stood as the critical predicate to the choice of bipyrrolic starting materials. Therefore, it was carried out first.

Scheme I



Methods currently known for the synthesis of 2,2′-bipyrroles include (1) Ullmann coupling of iodopyrroles,[9] (2) Paal–Knorr reaction of diethyl 3-methyl-5-(4-oxopentanoyl)-pyrrole-2,4-dicarboxylate,[10] (3) Vilsmeier–Haack reaction of pyrrolid-2-one with pyrroles followed by oxidative aromatization with Pd/C,[7,11] and (4) oxidative coupling of α-free pyrroles with $Pb(OAc)_4$,[12] polymer supported $Pd(OAc)_2$,[13] or $Na_2Cr_2O_7$ followed by reduction with $NaBH_4$.[14] Several other attractive-looking methods, including (5) Knorr reaction of ethyl 2-amino-3-oxobutylate with ethyl 3-(4-(ethoxycarbonyl)-3,5-dimethylpyrrol-2-yl)-3-oxopropionate and (6) modified Hantzsch synthesis of ethyl 5-(hydroxyacetyl)-2,4-dimethylpyrrole-3-carboxylate with ethyl 3-aminobut-2-enoate have been tried but were reported as being unsuccessful.[9a]

Of the above methods, the Ullman coupling approach (method 1) appears to be the most attractive. This is because method 4 generally gives low yields and because methods 2 and 3, which have actually been used to prepare terpyrroles,[7,8] give only β-free 2,2′-bipyrroles from readily obtainable materials. Thus, what would be needed in accord with the retrosynthetic analysis of Scheme I would be an α-monoiodo-2,2′-bipyrrole. This then could be coupled to provide the desired quaterpyrrole. Such an α-monoiodo-2,2′-bipyrrole could, in principle, be obtained from a range of readily available[9] symmetrical 2,2′-bipyrroles. However, an extrapolation from the chemistry of bi- and terpyrroles led us to predict that (1) quaterpyrroles would be unstable unless most or all of the "free" α and β positions were "protected" by substitution and (2) that those quaterpyrroles bearing esters, or other electron-withdrawing groups, in these positions will be even further stabilized.[2,7,9,11] This then provided us with a severe constraint in terms of possible starting materials and led us, specifically, to choose triethyl 5-iodo-4,4′-dimethyl-2,2′-bipyrrole-3,3′,5′-tricarboxylate (**7**) as the most promising precoupling precursor. The synthesis of this critical

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[1] Sessler, J. L.; Burrell, A. K. *Top. Curr. Chem.* **1991**, *161*, 177–273.

[2] (a) Vogel, E.; Köcher, M.; Schmickler, H.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 257–259. (b) Vogel, E.; Balci, M.; Pramod, K.; Koch, P.; Lex, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *66*, 928–931. (c) Vogel, E. *Pure Appl. Chem.* **1990** *62*, 557–564.

[3] Sessler, J. L.; Morishima, T.; Lynch, V. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 977–980.

[4] Sessler, J. L.; Weghorn, S. J.; Morishima, T.; Rosingana, M.; Lynch, V.; Lee, V. *J. Amer. Chem. Soc.* **1992**, *114*, 8306–8307.

[5] Sessler, J. L.; Mody, T. D.; Lynch, V. *J. Am. Chem. Soc.*, in press.

[6] Johnson, M. R.; Miller, D. C.; Bush, K.; Becker, J. J.; Ibers, J. A. *J. Org. Chem.* **1992**, *57*, 4414–4417.

[7] Rapoport, H.; Castagnoli, N., Jr.; Holden, K. G. *J. Org. Chem.* **1964**, *29*, 883–888.

[8] Merrill, B. A.; LeGoff, E. *J. Org. Chem.* **1990**, *55*, 2904–2908.

[9] (a) Grigg, R.; Johnson, A. W.; Wasley, J. W. F. *J. Chem. Soc.* **1963**, 359–366. (b) Grigg, R.; Johnson, A. W. *J. Chem. Soc.* **1964**, 3315–3322. (c) Sessler, J. L.; Cyr, M.; Burrell, A. K. *Tetrahedron* **1992**, *48*, 9661–9672 and references cited therein.

[10] Hinz, W.; Jones, R. A.; Patel, S. U.; Karatza, M.-H. *Tetrahedron* **1986**, *42*, 3753–3758.

[11] (a) Rapoport, H.; Holden, K. G. *J. Am. Chem. Soc.* **1962**, *84*, 635–642. (b) Rapoport, H.; Castagnoli, N., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 2178–2181. (c) Rapoport, H.; Bordner, J. *J. Org. Chem.* **1964**, *29*, 2727–2731. (d) Bordner, J.; Rapoport, H. *J. Org. Chem.* **1965**, *30*, 3824–3828.

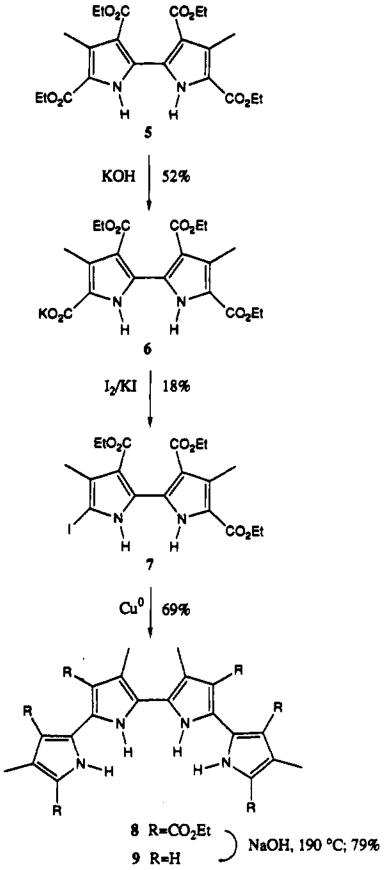
[12] Bauer, H. *Chem. Ber.* **1968**, *101*, 1286–1290.

[13] Boger, D. L.; Patel, M. *J. Org. Chem.* **1988**, *53*, 1405–1415.

[14] Falk, H.; Flödl, H. *Monatsch. Chem.* **1988**, *119*, 247–252.

0022-3263/93/1958-2340$04.00/0

Scheme II



α-monoiodo-2,2'-bipyrrole is shown in Scheme II and is discussed below.

The synthesis of 7 starts with the symmetrical 2,2'-bipyrrole 5. This latter material, in turn, was prepared from 3,5,-dimethylpyrrole-2,4-dicarboxylate[15] via the intermediacy of 3,5-bis(ethoxycarbonyl)-4-methylpyrrole-2-carboxylic acid[16] and diethyl 5-iodo-3-methylpyrrole-2,4-carboxylate,[17] in accord with standard literature methodology.[9a,15-17] Once bipyrrole 5 was in hand, selective hydrolysis[18] of an α-ester group followed by iodination with I_2/KI then gave the α-monoiodobipyrrole 7. Subsequent Ullman coupling then gave the quaterpyrrole 8 in quite good yield (69%). Here, it is of interest to note that it was the iodination step, not the coupling reaction, that proved most problematic. This is consistent with the general impression[2,7,9,11] that electron-withdrawing groups on the β-positions play an important role in stabilizing α-linked polypyrrolic materials. Indeed, attempted iodinations of both ethyl 3,3'-dimethyl-4,4'-diethyl-2,2'-bipyrrole-5-carboxylate[20] and sodium 3,3'-dimethyl-4,4'-diethyl-5'-(ethoxycarbonyl)-2,2'-bipyrrole-5-carboxylate[20] gave only decomposed materials, presumably because of the instability of the putative products.

Compound 8 provides the first reported example of a linear, α-linked quaterpyrrole. It is a pale yellow solid that is quite soluble in usual organic solvents and remarkably stable under normal laboratory conditions. It can, for instance, be easily stored at least for a period of 5 months at 0 °C in the solid state or, when dissolved in chloroform, washed with dilute solutions of aqueous acid without any apparent decomposition. Further, this hexaester material can easily be transformed to the corresponding α- and β-free derivative 9 by the simple action of NaOH in ethylene glycol at 190 °C under N_2. Although this latter material proved far less stable than 8, decomposing in a matter of hours in chloroform solution, the very fact that these harsh saponification–decarboxylation conditions could be employed provides a powerful indication that the basic quaterpyrrolic skeleton present in both 8 and 9 is itself intrinsically stable under at least certain extreme chemical conditions. Thus, the present work stands as important augury indicating that it might be possible to prepare higher purely α-linked oligopyrrolic materials and that such materials, like the present ones, might be sufficiently stable so as to allow their ready incorporation into macrocyclic, expanded porphyrin-type systems. Current work is directed toward exploring these two disparate but interrelated possibilities.

Experimental Section

General Information Melting points were measured on a Mel-Temp apparatus and are uncorrected. Proton and carbon NMR spectra were recorded on a General Electric QE-300 (300 and 75 MHz, respectively) spectrometer. High-resolution mass spectra were obtained using a VG Analytical ZAB E/SE high-resolution mass spectrometer. Fast atom bombardment mass spectra (FAB MS) were determined using a Finningan-MAT TSQ-70 instrument and 3-nitrobenzyl alcohol matrix. Microanalytical data were obtaind from Atlantic Microlab, Inc. Starting material 5 was synthesized according to the literature.[9a,15-17] All other reagents and materials were purchased commercially and used as received unless indicated otherwise. Column chromatography was carried out on Merck type 60 (230–400 mesh) silica gel.

Potassium 3,3',5'-tris(ethoxycarbonyl)-4,4'-dimethyl-2,2'-bipyrrole-5-carboxylate (6). Tetraethyl 4,4'-dimethyl-2,2'-bipyrrole-3,3',5,5'-tetracarboxylate (5, 9.7 g, 22 mmol) was suspended in 450 mL of ethanol held at reflux under N_2. To this was added 5 mL of an aqueous KOH solution (1.51 g/6.2 mL, 22 mmol). Then, the mixture was heated at reflux for 13 h. The reaction mixture was then allowed to cool and the solvent evaporated off. This gave a white solid that was resuspended in 70 mL of water and filtered. The resulting filter cake was then washed with water to remove any traces of the known, water-soluble[9a] bipyrrole diacid that might have been prepared as a reaction by product. The remaining solid was then dried in vacuo, resuspended in 100 mL of boiling chloroform, and then filtered to remove any starting tetraester. The white, monopotassium salt (bipyrrole 6) that resulted (5.2 g, 52%) was found to be insoluble in most common solvents and was, therefore, used directly in the next step without any further purification: ^{1}H NMR (DMSO-d_6) δ 1.27–1.38 (9 H, m, CH_2CH_3), 2.57 (3 H, s, CH_3), 2.62 (3 H, s, CH_3), 4.23–4.40 (6 H, m, OCH_2).

Triethyl 5-Iodo-4,4'-dimethyl-2,2'-bipyrrole-3,3',5'-tricarboxylate (7). The above monopotassium salt (6, 5.1 g, 11 mmol) was suspended in 200 mL of ethanol at 60 °C and $KHCO_3$ (aqueous solution, 2.8 g/50 mL, 28 mmol) added. A solution of I_2 (2.8 g, 11 mmol) and KI (5.5 g, 33 mmol) in 50 mL of water was then added portionwise as fast as possible while still allowing the iodine color to be discharged. The reaction mixture was then stirred at 60 °C for 3.5 h. After the mixture was allowed to cool, an equal volume of water was then added. The resulting solid was filtered, washed with water, and dried in vacuo. The solid so obtained was then resuspended in 20 mL of $CHCl_3$ and filtered. The resulting filtrate was then purified via column chromatography on silica gel ($CHCl_3$ + 20% hexane, eluent) to give 1.0 g (18%)

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[15] Fischer, H. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. 2, pp 202–204.

[16] Corwin, A. H.; Bailey, W. A.; Viohl, P. *J. Am. Chem. Soc.* **1942**, *64*, 1267–1273.

[17] Kleinspehn, G. G.; Corwin, A. H. *J. Am. Chem. Soc.* **1953**, *75*, 5295–5298.

[18] Precedent for the possible success of this partial hydrolysis step came, by analogy, from previous work with bipyrrole 5[9a] and various dipyrromethanes.[19]

[19] Corwin, A. H.; Buc, S. R. *J. Am. Chem. Soc.* **1944**, *66*, 1151–1156.

[20] Ikeda, H.; Sessler, J. L. Unpublished results.

of 7 as a pale yellow solid: mp 172–174 °C; ^{1}H NMR (CDCl$_3$) δ 1.39–1.45 (9 H, m, CH$_2$C*H*$_3$), 2.29 (3 H, s, C*H*$_3$), 2.62 (3 H, s, C*H*$_3$), 4.35–4.44 (6 H, m, OC*H*$_2$), 13.91 (1 H, s, N*H*), 14.20 (1 H, s, N*H*); ^{13}C NMR (CDCl$_3$) δ 12.90, 14.19, 14.32, 16.13 (-*C*H$_3$); 60.32, 61.07, 61.28 (OCH$_2$); 70.64, 112.11, 112.21, 119.08, 128.36, 130.55, 131.68, 132.07 (pyrrole rings); 161.12, 167.09, 168.52 (*C*=O); one methyl carbon not observed.

Hexaethyl 4,4′,3″,4‴-tetramethyl-2,2′:5′,2″:5′,2‴-quaterpyrrole-3,5,3′,4″,3‴,5‴-hexacarboxylate (8). Triethyl 5-iodo-4,4′-dimethyl-2,2′-bipyrrole-3,3′,5′-tricarboxylate (7, 1.7 g, 3.4 mmol), activated copper bronze[21] (1.7 g, 27 mg atom), and 10 mg of iodine were suspended in 10 mL of DMF. The resulting mixture was then heated to and held at 140 °C for 1 h under N$_2$. It was then allowed to cool, and the copper byproducts were removed by filtration through Celite. The Celite was then washed with hot CHCl$_3$ until the washings were colorless. The combined filtrates were then washed with 1 M HCl (1 × 50 mL) and water (2 × 50 mL) and then dried over Na$_2$SO$_4$. Evaporation of the solvent then gave a yellow solid, which was filtered and washed with ethanol. Recrystallization from chloroform–ethanol gave 8 (0.88 g, 69%) as a pale yellow solid: mp 228–230 °C; ^{1}H NMR (CDCl$_3$) δ 1.37–1.47 (18 H, m, CH$_2$C*H*$_3$), 2.34 (6 H, s, C*H*$_3$), 2.64 (6 H, s, C*H*$_3$), 4.32–4.47 (12 H, m, OC*H*$_2$), 13.73 (2 H, s, N*H*), 14.36 (2 H, s, N*H*); ^{13}C NMR (CDCl$_3$) δ 12.92, 13.27, 14.19, 14.31, 14.36 (*C*H$_3$); 60.34, 60.99, 61.08, (O*C*H$_2$); 112.32, 112.65, 119.18, 121.74, 122.87, 128.15, 131.21, 131.59 (pyrrole rings); 161.33, 168.45, 168.51 (*C*=O); HRMS (FAB) calcd for C$_{38}$H$_{46}$N$_4$O$_{12}$ 750.3112, found 750.3110. Anal. Calcd for C$_{38}$H$_{46}$O$_{12}$N$_4$: C, 60.79; H, 6.18; N, 7.46. Found: C, 60.64; H, 6.17; N, 7.36.

4,4′,3″,4‴-Tetramethyl-2,2′:5′,2″:5″,2‴-quaterpyrrole (9). Hexaethyl 4,4′,3″,4‴-tetramethyl-2,2′:5′,2″:5″,2‴-quaterpyrrole-3,5,3′,4″,3‴,5‴-hexacarboxylate (8, 300 mg, 0.40 mmol) and NaOH (0.74 g, 19 mmol) were suspended in 10 mL of ethylene glycol under a gentle stream of N$_2$. The resulting mixture was then heated to and held at 190 °C for 1.2 h. After cooling, the contents of the flask were poured into 10 mL of ice-cold water. The resulting precipitate was filtered off and washed with water. It was then dried in vacuo to give 100 mg (79%) of the title compound 9: ^{1}H NMR (DMSO-d_6) δ 1.97 (12 H, s, C*H*$_3$), 6.09 (4 H, s, C*H*), 6.40 (2 H, s, C*H*), 10.38 (2 H, s, N*H*), 10.44 (2 H, s, N*H*); ^{13}C NMR (DMSO-d_6) δ 12.19 (*C*H$_3$); 104.42, 104.90, 114.84, 116.29, 117.75, 120.49, 125.65, 126.12 (pyrrole rings); one methyl carbon not observed; HRMS (CI) calcd for C$_{20}$H$_{22}$N$_4$ 318.1844, found 318.1836.

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Supplementary Material Available: ^{1}H NMR spectra for compounds 6–9, ^{13}C NMR spectra for compounds 7–9, and mass spectra for compounds 8 and 9 (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(21) Fuson, R. C.; Cleveland, E. A. *Organic Syntheses*; Wiley: New York, 1955; Collect. *Vol.* 3, pp 339–340.