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Synthesis of a Decahydrohexapyrrin: A Novel Oligopyrrole of Biosynthetic Interest

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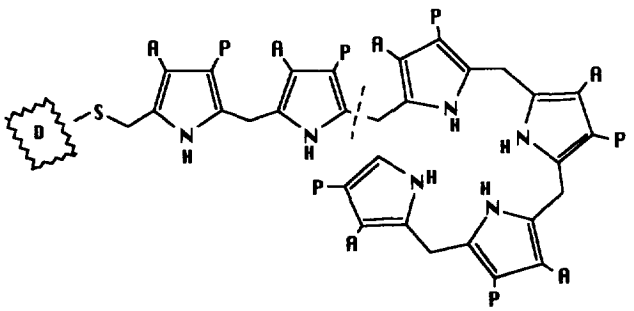
Abstract: A decahydrohexapyrrin substituted with 12 acetic and propionic acid residues was prepared using a (2+2+2) type synthesis. The hexapyrrin mimics the unique intermediate known to be bound to porphobilinogen deaminase.

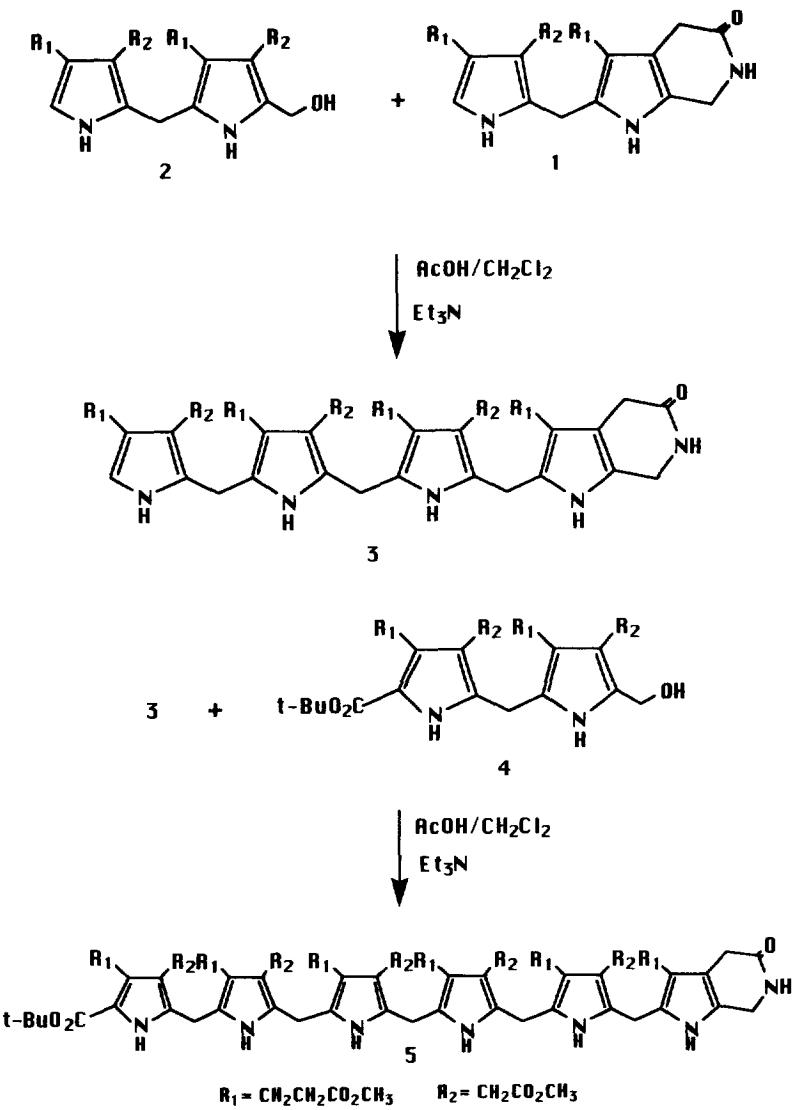
The mechanism of the molecular rearrangement which underlies the biosynthesis of uroporphyrinogen III (the precursor of the natural porphyrins) from porphobilinogen (PBG)[1] is still unresolved, notwithstanding the great advances made in the understanding of this metabolic step.[2,3] It has been convincingly established that a linear hexapyrrylmethane that grows on the condensing enzyme, PBG-deaminase, is enzymatically cleaved to afford a tetrapyrrole segment which rearranges and cyclizes to give uroporphyrinogen III [2,3] (Figure 1).



A= CH_2CO_2H P= $CH_2CH_2CO_2H$

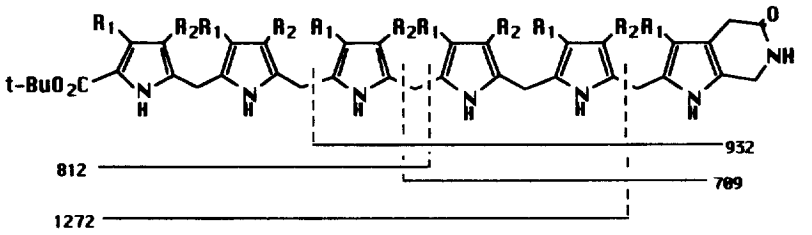
Figure 1

No structural information is available on such oligopyrroles; therefore we undertook the synthesis of a close model (Scheme I) which would mimic the natural intermediate.



Scheme I

The synthetic strategy followed was based on our former work on polypyrroles.[4-8] The dipyrrylmethane-lactame **1**[8] was condensed with the hydroxymethyldipyrrylmethane **2**[9] using a 2:1 ratio of **1** to **2**, to optimize the yield of bilane **3**. The excess of unreacted **1** was removed using TLC on silica gel. Bilane **3** was then brought into reaction with t-butyloxycarbonyl ester **4**, and the hexapyrrin **5** was obtained in good yield (26%). The hexapyrrin **5** was unambiguously identified by FAB-MS; the analysis of the spectrum fitted the expected structure (Scheme II).To the best of our knowledge this is the first reported synthesis of a hexapyrrin substituted with 12 acetic and propionic residues.



Scheme II

Molecular modeling analyses carried out on the hexapyrrin using the PCMODEL FOR WINDOWS program on a PC IBM compatible 486DX2 computer suggest that the oligopyrrole has the structural aspect shown in Figure 2. Hence, its enzymatic and chemical cleavage could be facilitate by the conformational bend at the dipyrrylmethane-bilane junction. The hexapyrrin will serve as a model to understand its chemical breakdown to uroporphyrinogens, and thus shed light on the biological mechanism of uroporphyrinogen III formation.

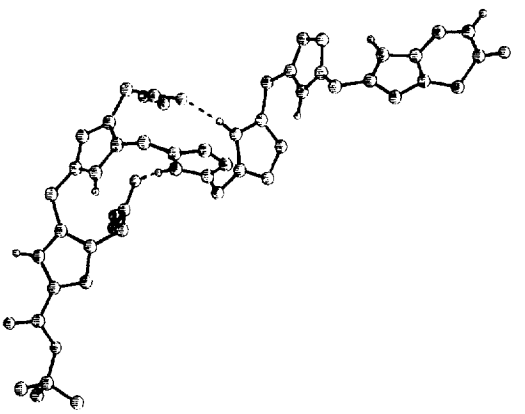


Figure 2: Ball and Stick models of folded intramolecular hydrogen-bonded hexapyrrin **5**, showing only the acetic acid side chains involved in the bonds.

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Synthesis of **3**, **4**, and **5**.

3. A solution of dipyrrylmethane **2** (19.6 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (20 mL) and triethylamine (1mL) was added dropwise at 5 °C to a stirred solution of dipyrrylmethane lactam **1** (36 mg, 008 mmol) in anhydrous CH_2Cl_2 (20 mL) containing acetic acid (2 mL). After 90 min. at 20 °C (protected from light), 40 mL of water was added, the organic phase was separated, washed with 10% $NaHCO_3$ (2x10 mL), dried and evaporated in vacuo at 20 °C. The residue was purified by TLC silica gel using 7% methanol in chloroform as developer. The eluted bilane **3** was then filtered through a small column of TLC silica gel (2x1cm) using the above mentioned solvent as eluant, the product was visualized with bromine vapours (green), or Ehrlich's reagent (purple). Crystallization from methanol afforded 8mg (22%) of pure **3**, mp 156-159 °C. ^1H NMR 300 MHz ($CDCl_3$): 2.26, 2.42, 2.63 (m, each, 16H), 3.30, 3.32, 3.40, 3.42 (s, each, 8H), 3.58, 3.60, 3.61, 3.62, 3.63, 3.66, 3.70 (s, each, 21H), 3.71, 3.73 (s, each, 6H), 4.40 (b, 2H), 6.35 (b, 1H). FAB-MS 933 (M^+, 10), was obtained using m-nitrobenzyl alcohol-glycerol as a matrix.

4. 40 mg of the precursor dipyrrylmethane aldehyde[8] in 4 mL of anhydrous methanol were cooled at 5 °C and 40 mg of $NaBH_4$ were added. After 30 min. at 20 °C, the methanol was removed, the residue was suspended in 20 mL of water, extracted with CH_2Cl_2 (2x10 mL), and the combined organic layers were dried and evaporated. The residue was purified using a TLC silica gel column under a slight pressure with 5% methanol in chloroform as eluant. The oily residue weighed 20 mg, (50%). ^1H NMR, 300 MHz ($CDCl_3$): 1.51 (s, 9H), 2.50-2.62 (m, 4H), 2.75 (m, 2H), 2.95 (m, 2H), 3.50 (s, 2H), 3.55 (s, 2H), 3.68, 3.70, 3.72 (s, each, 12 H), 3.83 (s, 2H), 4.50 (s, 2H). EI-MS (20 ev) 534 (M^+-C_4H_9, 100).

5.A solution of dipyrrylmethane alcohol **4** (6 mg, 0.01 mmol) in CH_2Cl_2 (2.5 mL) and triethylamine (0.1 mL) was added at 0 °C to a stirred solution of bilane **3** (10 mg, 0.01 mmol) in a mixture of CH_2Cl_2 (5mL) and acetic acid (0.25 mL). The reaction mixture was monitored by TLC on silica gel using 7% methanol in chloroform as solvent; the hexamer was visualized with bromine vapours (brown) or with Ehrlich's reagent (red on heating). Once the reaction was completed (40 min, protected from light) 10 mL of water was added, the organic layer was washed with 10% $NaHC0_3$ (2x10mL), dried and evaporated in vacuo at 30°C. The residue was subjected to TLC silica gel purification using 7% methanol in chloroform. The eluted hexapyrrin **5** was filtered through a small column of silica gel (2x1cm) using the above mentioned solvent. The fractions containing the product were evaporated in vacuo and afforded 4 mg (26%) of **5** as a yellowish solid. ^1H NMR, 500 MHz ($CDCl_3$): 1.27 (s, t-Bu), 1.96-2.72 (m, CH_2CH_2), 3.35-3.48 (m, CH_2CO), 3.48-3.80 (b, OCH_3), 4.25 (b, CH_2NH), 8.36, 8.57, 8.81, 8.88, 8.98, 9.12 (s, each, pyrrole-NH). FAB-MS was obtained using m-nitrobenzyl alcohol as a matrix 1507 (M^+, 43), 1641 (M^++Cs, 15), 1272 (10), 932 (7), 812 (14), 709 (21), Scheme II. HRMS calcd. for $C_{76}H_{97}O_{25}N_7$ 1507.6531, found 1507.6520.

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