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## SYNTHESES OF TYPE-I PORPHYRINS VIA MONOPYRROLE TETRAMERIZATION

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Abstract: Treatment of 2-[(N,N-dialkylamino)methyl]pyrrole-5-carboxylic acids (e.g. 10,12 or 11,13) in methanol with  $K_3Fe(CN)_6$  gives type-I porphyrins (etioporphyrin-I 7, coproporphyrin-I tetramethyl ester 16, respectively); with pyrroles 10,12 the product 7 is contaminated with about 8% of other type-isomer(s). Copyright © 1996 Elsevier Science Ltd

We recently showed<sup>1a</sup> that 2,5-bis-(N,N-dimethylaminomethy)pyrroles (e.g. 1) can be reacted with a 2,5-diunsubstituted pyrrole (e.g. 2) under carefully controlled non-acidic conditions to give pure porphyrin 3. This method has since been extended<sup>1b</sup> to afford more unsymmetrical porphyrins (e.g. 4) by condensation of a tripyrrane with a 2,5bis-(N,N-dimethylaminomethy)pyrrole (such as 1). Boudif and Momenteau,<sup>2</sup> Lin and Lash,<sup>3</sup> and Sessler et al.<sup>4</sup> have recently accomplished similar "3+1" syntheses using 2,5-diformylpyrroles (e.g. 5) as the monopyrrole ("1") unit.



Monopyrrole tetramerization has been shown to be a very effective method for synthesis of porphyrins when the 2-position of the pyrrole (e.g. 6) is substituted with a carbon bearing a good leaving group, and the 3- and 4-substituents are identical. It should be possible, in principle, to obtain a "type-I" porphyrin<sup>5</sup> 7 by self-condensation of a pyrrole such as 8, in which the 3- and 4-substituents are different;<sup>6</sup> but such is not the case,<sup>7</sup> presumably due to the fact that these reactions are usually acid catalyzed and the intermediate porphyrinogen 9 (or other non-cyclic polypyrrin precursors)

suffer acid catalyzed "scrambling" of the pyrrole subunits;<sup>8,9</sup> the product is invariably a mixture of all four porphyrin type isomers.<sup>9</sup> However, Chang's group has shown<sup>10</sup> that careful use of steric encumbrance can promote formation of centrosymmetric type-I porphyrins from monopyrrole tetramerizations.

Jeandon and Callot recently showed<sup>11</sup> that even the monopyrrole starting materials used in certain purported etioporphyrin-I syntheses were mis-identified; they further showed that use of controlled conditions can minimize pyrrole redistribution reactions and that as much as 90% of the product can be the type-I isomer. It was stated that "the specific obtention of type-I etioporphyrin is not out of reach."<sup>11</sup> In our hands, a recently published procedure<sup>12</sup> for synthesis of etioporphyrin-I or coproporphyrin-I tetramethyl ester using cyclization of appropriately substituted 2-[(N,Ndiethylamino)methyl]pyrrole-5-carboxylic acid in oxygenated acetic acid failed to give isomerically pure type-I porphyrin (300/500 MHz <sup>1</sup>H-NMR). In the present paper we show that in the coproporphyrin series, monopyrrole tetramerization using a 2-(N,N-dimethylaminomethyl)pyrrole<sup>13</sup> can indeed be used to *uniquely* obtain coproporphyrin-I (*analysis*: mp, <sup>1</sup>H-NMR); however, in the etioporphyrin series, the supposed type-I products is contaminated with about 8% of isomer(s).



The 2-(dialkylaminomethyl)pyrroles 10-13 were prepared as shown in Schemes I and II, either from 2unsubstituted pyrroles 14 or from 2-methylpyrroles 15.<sup>12</sup> When any of the pyrroles 10-13 was first heated in acetic acid at reflux in presence of oxygen, a mixture of all four etio- (31-40%) or coproporphyrin tetramethyl ester (18-26%) type-isomers was obtained, depending upon the identity of R (coproporphyrins: <sup>1</sup>H-NMR - Figure 1A); this outcome is presumably a result of acid catalyzed scrambling of the initially formed porphyrinogen or other methane-type intermediates, prior to aerobic oxidation to porphyrin. However, reaction of (for example) pyrrole 12 (or 13) in methanol/1% NEt<sub>3</sub> in the presence of K<sub>3</sub>Fe(CN)<sub>6</sub> gave<sup>14</sup> a 36% (25%) yield of etioporphyrin-I 7 (or coproporphyrin-I tetramethyl ester 16 {<sup>1</sup>H-NMR - Figure 1B}).



Figure 1: <sup>1</sup>H-NMR spectra (meso-proton region, 300 MHz, in CDCl<sub>3</sub>) of A, coproporphyrin tetramethyl ester mixture; B, pure coproporphyrin-I tetramethyl ester prepared herein.



Figure 2: <sup>1</sup>H-NMR spectra (meso-proton region, 300 MHz, of the mercury(II) double-sandwich complexes from: A, etioporphyrin mixture; B, etioporphyrin-I prepared herein.

The <sup>1</sup>H-NMR spectrum (300 MHz) of the etioporphyrin product showed a single meso-proton at 10.10 ppm, but since it is very difficult to accurately estimate the isomeric purity of the etioporphyrins (they do not melt!), the etioporphyrin product was subjected to further scrutiny. <sup>1</sup>H-NMR spectra of double sandwich mercury(II) complexes have earlier been shown to provide definitive proof of isomeric identity in the etioporphyrin-I series.<sup>6b,16</sup> Figure 2A shows the meso-proton region in the proton NMR spectrum of a mixture of etioporphyrin-I series.<sup>6b,16</sup> Figure 2A shows the meso-proton region in the proton NMR spectrum of a mixture of etioporphyrin-I mercury sandwich complex obtained using the methodology described above); the meso-proton region in the etioporphyrin-I mercury sandwich complex obtained using the methodology we report herein is presented in Figure 2B. Clearly, the etioporphyrin-I is contaminated with about 8% of another isomer (or isomers); the amount of impurity was calculated by integration, and making an assumption that only one half of the dimeric sandwich complex will contain a etioporphyrin isomer other than type-I. Presumably, the difference between the product isomeric purity in the etioporphyrin and coproporphyrin syntheses reported above relate to

the more favorable steric situation in the formation of the coproporphyrin-I isomer, with the propionic ester group being more sterically demanding than ethyl, and thereby tipping the balance to unique formation of the type-I isomer 16, as shown by Chang and Bag<sup>10</sup> in other type-I porphyrin syntheses.

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14. Typical procedure for synthesis of 16: Pyrrole 13 (2.5 g; 8.4 mmol) was dissolved in a mixture of MeOH (200 mL) and NEt<sub>3</sub> (2.0 mL), and then heated at reflux for 10 min before addition of K<sub>3</sub>Fe<sub>1</sub>(CN)<sub>6</sub> (4.4 g; 13.4 mmol) in one portion. The resulting mixture was heated under reflux for an additional 10 h. The solvent was removed and the residue was redissolved in CHCl<sub>3</sub>. Some black/brown insoluble material was filtered off and the red solution was passed through a short plug of silica gel (elution with CHCl<sub>3</sub>). The solvent was evaporated and the residual porphyrin was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/MeOH to afford coproporphyrin-I tetramethyl ester (340 mg; 25% yield), mp 252-254°C (lit.<sup>15</sup> mp 248-252°C).  $\lambda_{max}$  (CH<sub>2</sub>Cl<sub>2</sub>) 399 nm ( $\varepsilon$  156,000), 496 (13,200), 532 (8800), 568 (6100), 620 (4100); <sup>1</sup>H-NMR (CDCl<sub>3</sub>),  $\delta$  -3.78 (br s, 2H, NH), 3.28, 4.41 (each t, 8 H, CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Me), 3.67, 3.69 (each s, 12 H, Me and OMe), 10.08 (s, 4 H, meso-H).

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