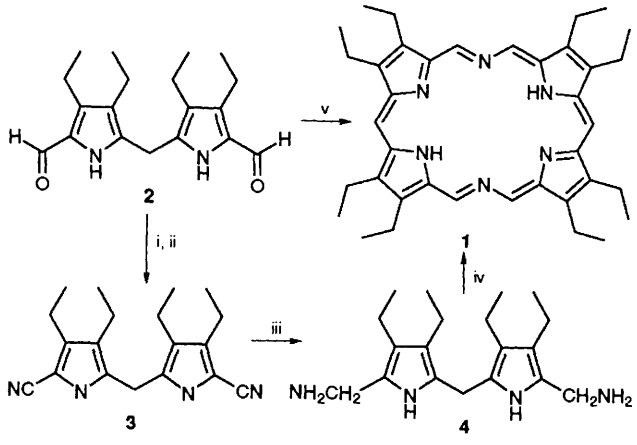
A New Approach to the Aromatic Macrocycle Porphocyanine

Lily Y. Xie and David Dolphin*

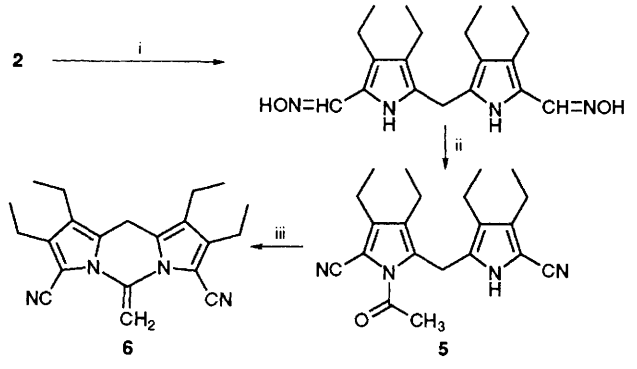
Department of Chemistry, University of British Columbia, Vancouver, BC, Canada V6T 1Z1

Treatment of 3,3′,4,4′-tetraalkyl-5,5′-bisformyldipyrromethanes with ammonia leads directly to the formation of an expanded tetrapyrrolic aromatic macrocyclic compound, porphocyanine.

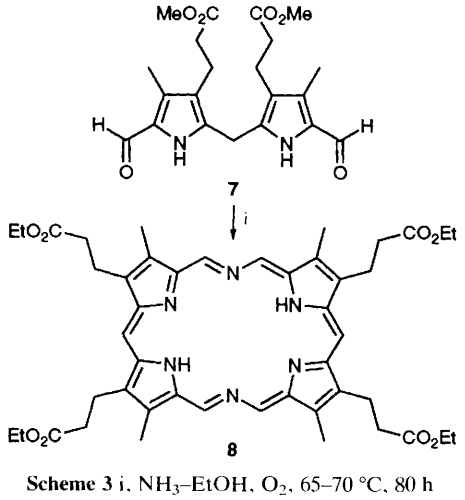
Photodynamic therapy (PDT) for the treatment of malignant tissue and pathogens has stimulated significant interest in search of new photosensitizers in recent years.[1] Stable chlorin[2–4] and bacteriochlorin-like[5] systems as well as the 'expanded porphyrins'[6,7] absorb strongly at longer wavelengths than blood and other tissues thereby conferring a therapeutic advantage due to greater tissue penetration by light. We have recently reported the synthesis and structural characterization of a novel expanded tetrapyrrolic macrocycle, porphocyanine **1**.[7] Unlike other 'expanded porphyrins' containing imine linkages,[8] porphocyanine is fully conjugated in its free base form. We now report a new route to this macrocycle.



Scheme 1 i, NH_2OH·HCl–EtOH; ii, $(MeCO)_2O$; iii, $LiAlH_4$–THF, 0 °C; iv, MeOH–THF, reflux, O_2; v, NH_3–EtOH, O_2, 65–70 °C 80 h



Scheme 2 i, NH_2OH·HCl–EtOH; ii, $(MeCO)_2O$, 100 °C; iii, $-H_2O$



Scheme 3 i, NH_3–EtOH, O_2, 65–70 °C, 80 h

The previously reported synthetic route (i–iv, Scheme 1) utilizes the known 5,5′-bisformyldipyrromethane **2**,[9] which was converted in two steps to the 5,5′-biscyanodipyrromethane **3**, which was then reduced to 5,5′-bis(aminomethyl)-dipyrromethane **4**, a key species which gives porphocyanine by self condensation.[7] Low yields can result from side reactions occurring during the formation of the biscyanodipyrromethanes **3**. Formation of compound **5** and **6**† (Scheme 2) not only lowers the yield of the corresponding 5,5′-dicyanodipyrromethanes but also presents difficulty in their purification

It is known that under appropriate conditions hydrobenzamide $ArCH(-N{=}CHAr)_2$ can be formed from an aromatic aldehyde and ammonia *via* the aromatic imine (ArCH=NH)[11] suggesting that the porphocyanine linkage (=C–N=C–) might be generated from a formyldipyrromethane and ammonia. 5,5′-Bisformyldipyrromethane **2** was suspended in rigorously dried ethanol in a pressure vessel sealed with a Suba-seal septum at 0 °C. Anhydrous ammonia gas was bubbled through the suspension in a steady stream *via* an inserted needle for 30 min, during which time **2** dissolved completely. The needle was then removed and the container was placed in an oil bath and heated at 65–70 °C for 80 h. The colour of the solution gradually turned to dark green. Upon removal of the solvent, the residue was chromatographed on Alumina (4% H_2O added) to give **1** as a green solid in 26% yield. Porphocyanine **1** prepared by this method is identical to that reported previously.[7]

An obvious advantage of this method over the aminomethyl route, apart from great simplification in synthesis, is that no reduction is involved in the later stage of synthesis. Therefore, porphocyanines with reduction-sensitive functional groups can be prepared by this method. This was demonstrated by the successful preparation of **8**‡ using 3,3′-methyl-4,4′-methoxypropylate-5,5′-formyldipyrromethane **7**. Porphocyanine **8**, with four ester side chains, which cannot be obtained *via* the aminomethyl route can be prepared through the route reported here (Scheme 3) in satisfactory yield.§

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Footnotes

† *Spectroscopic data*: **5**: ^{1}H NMR ($CDCl_3$), δ 1.05 (2t, 6H), 1.20 (2t, 6H), 2.45 (2q, 4H), 2.53 (q, 2H), 2.62 (q, 2H), 2.82 (s, 3H), 4.06 (s, 2H), 8.63 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ, 14.6, 15.0, 15.3, 15.7, 17.0, 17.1, 18.4, 18.5, 18.5, 23.5, 26.3, 96.9, 101.0, 114.0, 115.1, 121.8, 128.7, 130.4, 133.4, 137.0, 144.4, 169.8; high-resolution MS (EI) for $C_{21}H_{26}N_4O$ (M^+) calc. 350.2107, found 350.2111. **6**: ^{1}H NMR ($CDCl_3$), δ 1.10 (t, 6H), 1.20 (t, 6H), 2.42 (q, 4H), 2.61 (q, 4H), 3.88 (s, 2H), 5.54 (s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) 15.1, 15.8, 18.4, 20.4, 24.8, 90.2, 98.3, 119.4, 127.0, 132.2, 141.3; high-resolution MS (EI) for $C_{21}H_{24}N_4$ (M^+) calc. 332.2001, found 332.1999; IR ($CDCl_3$) ν_{CN} 2212.5, $\nu_{C=CH_2}$ 1665 cm^{-1}.

‡ *Spectroscopic data* for **8**: ^{1}H NMR (1% TFA in $CDCl_3$), δ −5.80 (br, 4H), 1.05 (t, 12H), 3.60 (t, 8H), 4.03 (q, 8H), 4.22 (s, 12H), 5.06 (t,

8H), 12.28 (s, 2H), 13.67 (s, 4H); high-resolution MS (EI) for $C_{46}H_{56}N_6O_8$ (M^+) calc. 820.4159, found 820.4153.

§ Transesterification occurred to give the tetraethyl ester in 7% yield. Only trace amounts of amide derivatives were formed, they were insoluble and readily removed.

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