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EFFICIENT NEW SYNTHESES OF BENZOCHLORINS, BENZOISOBACTERIOCHLORINS, AND BENZOBACTERIOCHLORINS

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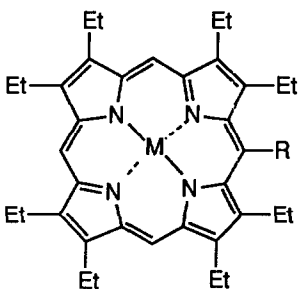
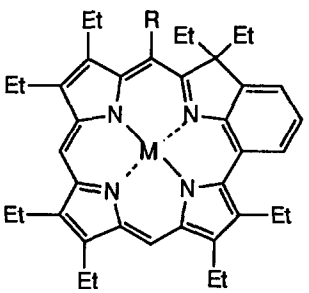
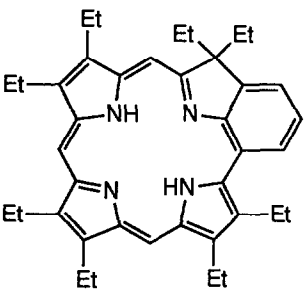
Abstract: *Reaction of nickel(II) or copper(II) porphyrins with 3-dimethylamino-acrolein/$POCl_3$ gives meso-(2-formylvinyl)-porphyrins, which after strong acid treatment give the corresponding benzochlorins. Use of nickel(II) or copper(II) chlorins gives benzoisobacteriochlorins; a modification also gives benzobacteriochlorins. Reductive coupling of (2-formylvinyl) derivatives gives carbon-carbon linked dimers.*

PHOTOFRIN-II® is the only drug currently being evaluated in phase III clinical trials for treatment of various tumors using photodynamic therapy (PDT). It is a purified form of "hematoporphyrin derivative" prepared from hematoporphyrin IX dihydrochloride in two steps by modifications of Lipson's procedure.[1] Photofrin-II® is a complex mixture of porphyrins, believed to be porphyrin dimers and higher oligomers joined by ether, ester, and/or carbon-carbon linkages, and chemical syntheses of all of these types of linked dimers and oligomers have recently been reported.[2-7] Amongst numerous other sensitizers for PDT,[8-10] purpurins[9] and benzochlorins[10] have shown promise. We now outline a new route to benzochlorins using procedures applicable also to purpurin synthesis, and show that intermediates in these approaches can be used to furnish carbon-carbon linked porphyrin dimers related to one of the active principles[7] in Photofrin-II®.







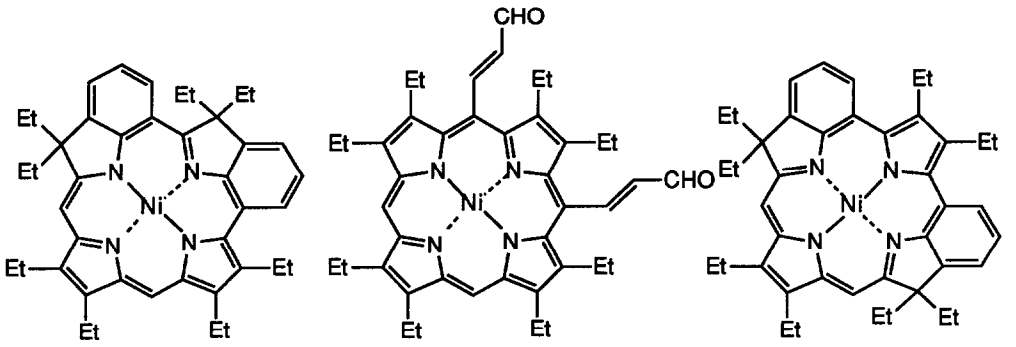
(1) R = H; M = Ni
(2) R = H; M = Cu
(3) R = CH=CH-CHO; M = Ni
(4) R = CH=CH-CHO; M = Cu

(5) R = H; M = Ni
(6) R = H; M = Cu
(8) R = CH=CH-CHO; M = Ni

(7)

Both nickel(II) octaethylporphyrin (**1**; NiOEP) and CuOEP (**2**) reacted with 3-dimethylamino-acrolein (3-DMA) in the presence of phosphoryl chloride[11] to give 85% yield of Ni meso-(2-formylvinyl)-OEP (**3**)[12a] and 57% of Cu meso-(2-formylvinyl)-OEP (**4**), respectively. When treated with strong acids (trifluoroacetic and sulfuric) the acrolein group at the meso positions cyclized onto the pyrrole subunit β-position with concomitant alkyl migration, to give Ni octaethylbenzochlorin (**5**)[12b] and Cu octaethylbenzochlorin (**6**) in 50% and 80% yields, respectively.[13] The free-base

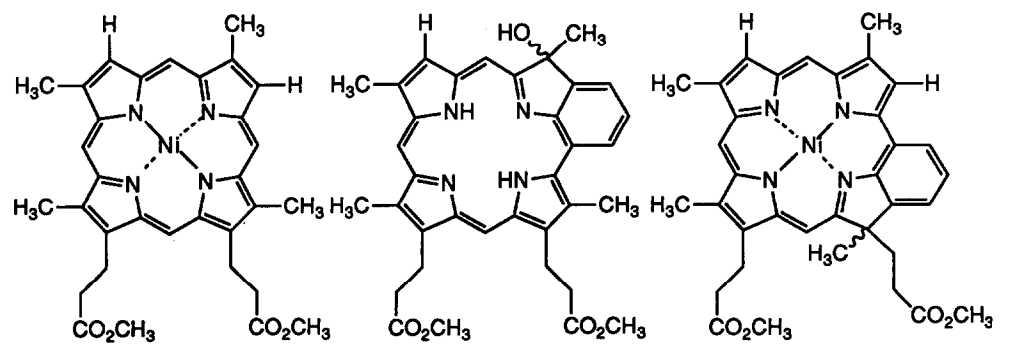
octaethylbenzochlorin (7)[12c] was prepared in 80% yield from sulfuric acid treatment of (6) [or in 10% yield from (5) with trifluoroacetic acid and 1,3-propanedithiol].[14] Further treatment of the Ni octaethylbenzochlorin (5) with 3-DMA/phosphoryl chloride gave compound (8)[12d] in 85% yield; the benzochlorin reacted faster than (1) and gave (8) as the only regioisomer. With acid, compound (8) gave the benzoisobacteriochlorin (9)[12e].



(9) (10) (11)

When exposed to a large excess of the Vilsmeier complex from 3-DMA and phosphoryl chloride, NiOEP (1) gave the Ni bis(2-formylvinyl)-OEP (10)[12f] in 55% yield. Upon acid treatment, this compound yielded several products, but mainly the benzoisobacteriochlorin (9) and the benzobacteriochlorin (11)[12g].

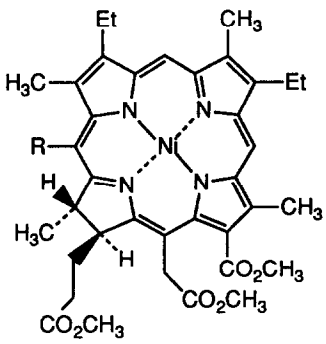
In order to investigate the relative reactivities of meso- versus pyrrolic unsubstituted positions, Ni deuteroporphyrin-IX dimethyl ester (12) was treated with 3-DMA/phosphoryl chloride and gave a mixture of products containing the acrolein group only at the meso positions, and in accord with expectations from previous Vilsmeier formylation studies,[15] mostly at the β-meso-position. Upon acid catalyzed cyclization, the readily separable benzochlorins (13)(metal-free)[12h] and (14)[12i] were produced. A compound similar to (13) has previously been prepared by Clezy et al.[16] from oxidation of rhodins.



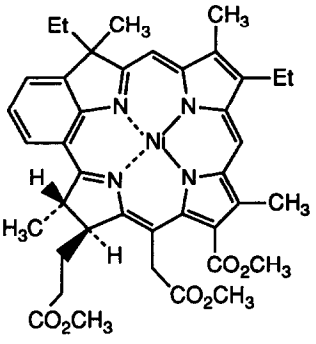
(12) (13) (14)

Using this same chemistry, benzoisobacteriochlorins can be easily formed by the reaction of natural chlorins with 3-DMA/phosphoryl chloride. For example, Ni mesochlorin-e_6 trimethyl ester (15) gave Ni δ-(2-formylvinyl)-mesochlorin-e_6 trimethyl ester (16)[12j] in 89% yield. Under strong acid conditions compound (16) gave the benzoisobacteriochlorin (17)[12k] in 55% yield.

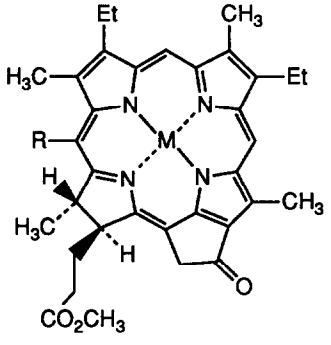
In order for the cyclization step to occur strong acid conditions are required (usually concentrated sulfuric acid from 15 min to 2.5 h), along with a centrally chelated metal to prevent protonation from curtailing the electrophilic cyclization of the meso-substituent to the pyrrolic β-position. If the metal is removed before cyclization occurs then the benzochlorins and benzoisobacteriochlorins cannot be formed. As a demonstration of this chemistry, although methyl Ni meso-(2-formylvinyl)-mesopyropheophorbide-a (**18**)[12l] was easily prepared from methyl Ni-mesopyropheophorbide-a (**19**) in 83% yield, the metal was rapidly extruded during the acidic cyclization step and only methyl meso-(2-formylvinyl)-mesopyropheophorbide-a (**20**)[12m] was obtained instead. Unlike the usual Vilsmeier reagent from DMF/$POCl_3$, the 3-DMA reagent does not react with peripheral vinyl groups in porphyrins and chlorins.[15a]



(**15**) R = H
(**16**) R = CH=CH-CHO

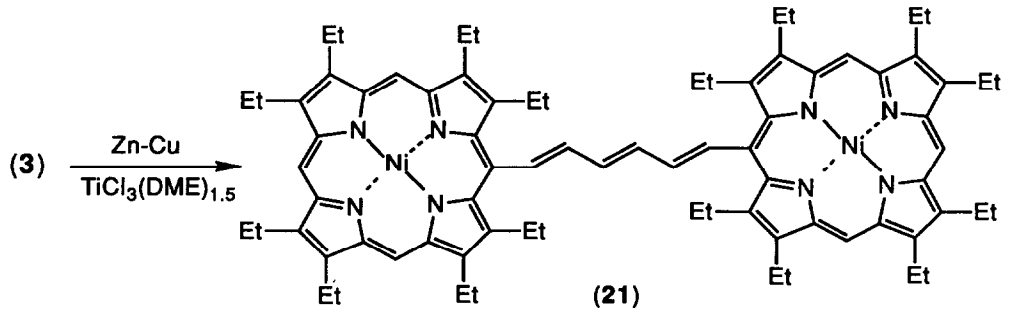


(**17**)



(**18**) M = Ni; R = CH=CH-CHO
(**19**) M = Ni; R = H
(**20**) M = 2H; R = CH=CH-CHO

As mentioned above, carbon-carbon linked dimers of porphyrins are important in photodynamic therapy because of their activity as components in Photofrin-II®. Using the chemistry demonstrated above, chlorins and benzochlorins can be prepared by the reductive coupling of the aldehyde function of the acrolein group, using low-valent titanium.[17] Dimers like compound (**21**)[12n] were prepared by the reaction of Ni (2-formylvinyl)-OEP (**3**) with $TiCl_3(DME)_{1.5}$ in the presence of a zinc-copper couple. Usefulness of such dimers in photodynamic therapy will be reported elsewhere.



(**21**)

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12. Characteristic spectroscopic data: (a) (**3**)Vis: λ_{max} 406 (ε 70 800), 536 (15 900), 564 (17 900), 582 nm (17 200); NMR δ_H 9.84 (d, CHO, J=7.7 Hz), 9.69 (d, C<u>H</u>=CHCHO, J=15.2 Hz), 9.36 (s, 3 meso-H), 5.53 (dd, CH=C<u>H</u>CHO); (b) (**5**)Vis: λ_{max} 373 (ε 14 300), 414 (37 100), 508 (4 600), 564 (4 200), 618 (6 800), 670 nm (20 000); NMR δ_H 8.98 (d, Ar-H), 8.89, 8.54 and 7.83 (s, 3 meso-H), 7.82 (d, Ar-H), 7.79 (t, Ar-H); (c) (**7**)Vis: λ_{max} 392 (ε 87 200), 412 (107 500), 530 (13 750), 564 (15 400), 604 (17 000), 658 nm (35 000); NMR, δ_H 9.23, 8.57, 8.01 (each s, 3 meso-H), 9.54 (d, 1 Ar-H, J=8.1 Hz), 8.12 (t, 1 Ar-H, J=7.8 Hz), 8.04 (d, 1 Ar-H, J=7.6 Hz); (d) (**8**)Vis: λ_{max} 376 (ε 46 700), 444 (70 500), 726 nm (47 900); NMR, δ_H 9.68 (d, CHO, J=7.8 Hz), 8.69 (d, C<u>H</u>=CHCHO, J=15.0 Hz), 8.63 (d, Ar-H, J=8.1 Hz), 8.49, 8.21 (s, 2 meso-H), 7.70 (t, 1 Ar-H), 7.63 (d, 1 Ar-H), 5.72 (dd, CH=C<u>H</u>CHO); (e) (**9**)Vis: λ_{max} 340 (ε 37 000), 444 (45 600), 634 nm (38 600); (f) (**10**)Vis: λ_{max} 338 (ε 58 800), 458 (156 700), 616 nm (29 900); NMR δ_H 9.87 (d, 2 CHO, J=7.8 Hz), 9.56 (d, 2H, C<u>H</u>=CHCHO, J=15.3 Hz), 9.14 (s, 2 meso-H), 5.58 (dd, 2H, CH=C<u>H</u>CHO); (g) (**11**)Vis: λ_{max} 352 (ε 38 200), 384 (41 000), 402 (45 200), 452 (44 000), 644 (18 500), 686 (19 500), 752 nm (41 800); (h) (**13**)Vis: λ_{max} 331 (ε 17 700), 410 (56 200), 538 (7 150), 572 (8 200), 614 (8 100), 670 nm (17 500); NMR δ_H 9.45 (d, 1 Ar-H, J=8.4 Hz), 9.12, 8.63 and 8.27 (s, 3 meso-H), 8.24 (d, 1 Ar-H, J=6.9 Hz), 8.19 (s, 1 β-H), 7.98 (t, 1 Ar-H, J=7.5 Hz); (i) (**14**)Vis: λ_{max} 305 (ε 10 600), 412 (51 000), 508 (4 000) 564 (3 400), 616 (7 250), 668 nm (26 160); NMR δ_H 8.97 (d, 1 Ar-H, J=8.6 Hz), 8.88, 8.57 and 7.94 (s, 3 meso-H), 8.24 and 8.18 (s, 2 β-H), 7.86 (m, 2 Ar-H); (j) (**16**)Vis: λ_{max} 428 (ε 99 800), 574 (15 950), 582 (15 650), 672 nm (42 150); NMR δ_H 9.69 (d, CHO, J=7.8 Hz), 8.72 and 8.62 (s, 2 meso-H), 8.36 (d, C<u>H</u>=CHCHO, J=15.4 Hz), 5.72 (dd, CH=C<u>H</u>CHO); (k) (**17**)Vis: λ_{max} 354 (ε 23 300), 432 (57 000), 602 nm (32 100); NMR δ_H 8.06 (d, Ar-H J=8.4 Hz), 7.98, 6.99 (s, 2 meso-H), 7.58 (d, Ar-H, J=6.6 Hz), 7.44 (t, Ar-H, J=7.5 Hz); (l) (**18**)Vis: λ_{max} 430 (ε 46 850), 682 (26 600), 752 nm (7 800); NMR δ_H 9.79 (d, CHO, J=7.8 Hz), 8.96 and 8.67 (s, 2 meso-H), 8.49 (d, C<u>H</u>=CHCHO, J=15.3 Hz), 5.83 (dd, CH=C<u>H</u>CHO); (m) (**20**) Vis: λ_{max} 414 (ε 118 000), 564 (17 800), 620 (11 000), 680 nm (26 900); NMR δ_H 10.10 (d, CHO, J=7.8 Hz), 9.40, 9.33 (s, 2 meso-H), 9.12 (d, C<u>H</u>=CHCHO, J=15.6 Hz), 6.57 (dd, CH=C<u>H</u>CHO); (n) (**21**) Vis: λ_{max} 404 (ε 101 300), 562 nm (26 800); NMR δ_H 9.37 (s, 6 meso-H), 8.64 (d, 2 vinyl-H), 6.41 (dd, 2 vinyl-H), 5.41 and 5.48 (both dd, 2 vinyl-H).
13. Compound (**5**) has been obtained by a much lengthier approach involving Vilsmeier formylation, Knoevenagel condensation, reduction, oxidation, and cyclization (D.P. Arnold, R. Gaete-Holmes, A.W. Johnson, A.R.P. Smith, and G.A. Williams, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 1660.) Purpurins are also synthesized from cyclization of the corresponding meso-acrylic porphyrins after the Knoevenagel step.[9]
14. An X-ray structure of compound (**7**) has been obtained: K.M. Barkigia, J. Fajer, M.G.H. Vicente, and K.M. Smith, to be published.
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