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SYNTHESIS OF BENZOPURPURINS, ISOBACTERIOBENZOPURPURINS AND BACTERIOBENZOPURPURINS

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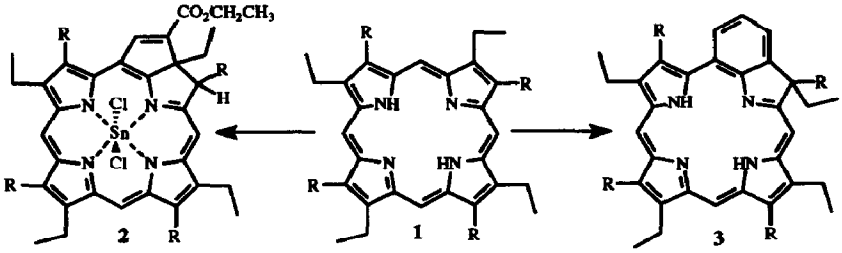
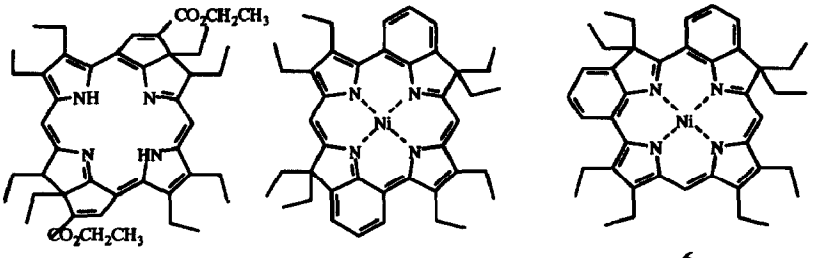
Abstract: *Cyclization of porphyrins substituted at the meso position(s) with acrylate or acrolein groups leads to the formation of benzopurpurin derivatives at the oxidation state of a chlorin, bacteriochlorin or isobacteriochlorin, depending upon reaction conditions.*

The need for compounds which absorb in the far red region of the electromagnetic spectrum for use as photosensitizers in photodynamic therapy, has led to increased interest in the synthesis and spectroscopic characteristics of reduced porphyrin species, particularly chlorins and bacteriochlorins.[1,2] A number of such derivatives have been described in recent years, including the purpurins[3] and the benzochlorins.[4] Purpurins have been reported to show good photodynamic activity and one compound derived from etioporphyrin I (**1**, R=CH_3), tin ethyl etiopurpurin (**2**, R=CH_3) is currently in a combined phase I/II clinical trial for treatment of cutaneous carcinoma. Benzochlorins (e.g. **3**, R=CH_2CH_3) are in pre-clinical trials and have demonstrated good tumoricidal activity, following irradiation with red light, in a number of *in vitro* and *in vivo* model systems.[4c,5]



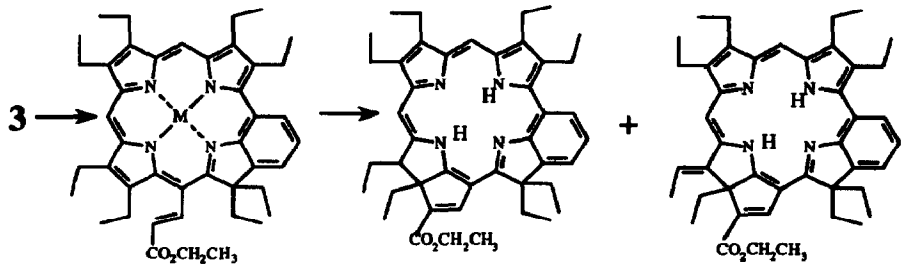
Both purpurins and benzochlorins contain a tetrapyrrolic macrocycle which is formally at the oxidation state of a chlorin and indeed, both classes show spectroscopic properties which are characteristic of chlorins with Q band absorptions in the 660-690nm region. Efforts have been made to produce related analogs with absorptions further into the red, since light of longer wavelengths penetrate deeper into tissue and expand the potential for treating greater depths of neoplastic tissue. Thus for example, the preparation of macrocycles containing two purpurin rings has been reported.[6] Unfortunately, these derivatives (e.g. **4**) proved to be unstable and characterization was achieved using visible spectroscopy where bands at 760nm were attributed to a bacteriochlorin-like chromophore. The

synthesis of porphyrin derivatives bearing two benzochlorin rings has also been reported.[4b] In this case, the nature of the reactant and reaction conditions led to derivatives having either a bacteriochlorin chromophore (bacteriobenzochlorin **5**) or to an isobacteriochlorin chromophore (isobacteriobenzochlorin **6**).



4 **5** **6**

Given the increasing importance of these ring systems, both in terms of synthesis and biological activity, we have investigated the generation of tetrapyrrolic macrocycles in which both a purpurin and benzochlorin moiety are present. Two approaches were taken - one in which each ring was constructed sequentially and one in which both ring systems were introduced at the same time. For the former method, benzochlorin **3** was metallated with nickel acetate and treated with Vilsmeier reagent to introduce a formyl group specifically at the *meso* position adjacent to the reduced pyrrole ring. Subsequent treatment with the Wittig reagent (carbethoxymethylene)triphenyl phosphorane generated the *meso* acrylate substituted benzochlorin **7**. Demetallation (of **7**) with sulfuric acid gave the free base derivative **8** which was then treated with trifluoroacetic acid in order to effect cyclization. Two products



7 M=Ni
8 M=2H **9** **10**

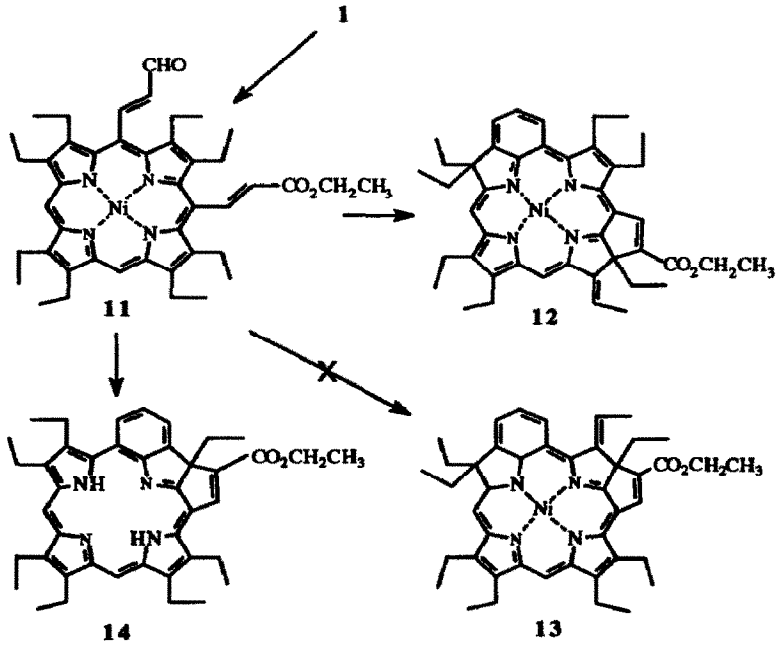
were obtained from the reaction mixture following chromatographic separation on silica gel. The less polar product was shown to be the expected isobacteriobenzopurpurin **9** by ^{1}H NMR spectroscopy where three upfield resonances attributable to three ethyl groups on reduced pyrrole rings confirmed cyclization of the acrylate. As expected, resonances due to the acrylate protons were not evident in the spectrum of the product. C-13 NMR spectroscopy also gave a resonance at 140ppm which is diagnostic of the methine carbon of the purpurin ring system.[7] The more polar fraction gave a ^{1}H NMR spectrum very similar to that of **9** except one ethyl group was missing and resonances attributable to an ethylidene

functionality were present. The product was thus formulated as the derivative **10**. The visible absorption spectra of both **9** and **10** were typical of isobacteriochlorins with weak absorptions in the 600nm region.

Since electrophilic substitution of chlorins such as benzochlorin **3** is known to be directed to the more active adjacent *meso* position, it is not possible to generate the bacteriochlorin chromophore by this route. Thus the approach taken was to construct a porphyrin bearing both a *meso* acrylate and a *meso* acrolein group and to effect cyclization of both benzochlorin and purpurin groups at the same time.

The porphyrin needed for this reaction (**11**) was generated from octaethyl porphyrin (**1**, R=CH_2CH_3) by sequential treatment with nickel (II) acetate, Vilsmeier reagent and (carbethoxy methylene) triphenyl phosphorane to generate the acrylate group. Further reaction with the modified Vilsmeier reagent dimethyl aminoacrolein generated the acrolein moiety. This latter reaction gave the 5,10- disubstituted derivative **11** as the major isomer.

Treatment (of **11**) with trifluoroacetic acid under an inert atmosphere gave, after 2 hours at room temperature a major product having a visible absorption spectrum containing a Q band at 890nm. The



^{1}H NMR spectrum of the product included three upfield resonances indicative of three ethyls attached to reduced pyrrole rings, thus confirming that two pyrrole rings were reduced. Also present were resonances attributable to an ethylidene moiety similar to those previously observed in the ^{1}H NMR spectrum of **10**. Although two products are possible from this reaction, the isobacteriobenzopurpurin **13** and the bacteriobenzopurpurin **12**, the data are more consistant with the formulation of the product as **12**, particularly given the long red absorption band at 895nm. Finally, treatment of porphyrin **11** with concentrated sulfuric acid led to a different product distribution with the major product exhibiting a visible absorption band at 718nm. ^{1}H NMR spectroscopy indicated that one ethyl group had been lost from the structure, that only one pyrrole ring was reduced and that both benzochlorin and purpurin moieties were present. 2D COSY, C-13 and HETCOR spectroscopy confirmed these observations allowing the formulation of the product as that of **14**.

ACKNOWLEDGEMENT: We thank the National Institutes of Health for financial support under grant CA48733.

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SPECTROSCOPIC DATA:

12 NMR ($CDCl_3$): δ 8.74 (d, 1H, benzenoid H), 8.71, 7.98, 7.64 (3s, 2 meso H, purpurin H), 7.75 (t, 1H, benzenoid H), 7.53 (d, 1H, benzenoid H), 6.41 (q, 1H, $CH{=}C\underline{H}_3$), 4.46 (q, 2H, $CO_2C\underline{H}_2$), 3.52-3.26 (m, 8H, $C\underline{H}_2$ of ring ethyls), 2.40-2.33 (m, 6H, $C\underline{H}_2$ of ethyls), 2.12 (d, 3H, $CH{=}C\underline{H}_3$), 1.65-1.46 (m, 15H, $C\underline{H}_3$ of ring ethyls and ester), 0.34, 0.27, 0.04 (3t, 9H, $C\underline{H}_3$ of ethyls). UV-VIS (CH_2Cl_2): 895, 630, 585, 411. Mass: m/e 725. Analysis, Cal: $C_{44}H_{50}N_4O_2Ni.2H_2O$, C 69.48, H 6.80, N 7.57. Found: C 69.41, H 7.10, N 7.36.

14 NMR ($CDCl_3$): δ 9.20 (δ, 1H, benzenoid H), 8.93 (s, 1H, purpurin H), 8.38, 8.20 (2s, 2H, meso), 8.55 (d, 1H, benzenoid H), 7.90 (t, 1H, benzenoid H), 4.60 (q, 2H, $CO_2C\underline{H}_2$), 4.40 (s, 1H, NH), 3.80-3.60 (m, 12H, $C\underline{H}_2$ of ring ethyls), 3.15 (s, 1H, NH), 2.22 (m, 2H, $C\underline{H}_2$ of ethyl), 1.80-1.50 (m, 21H, 6 $C\underline{H}_3$ of ring ethyls, $C\underline{H}_3$ of ester), 0.20 (t, 3H, $C\underline{H}_3$-CH_2).UV-VIS (CH_2Cl_2): 718, 660, 615, 560, 444, 428, 388. Mass: m/e 641.

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