SYNTHESES OF MESO-AZACHLORINS AND MESO-AZABACTERIOCHLORINS§

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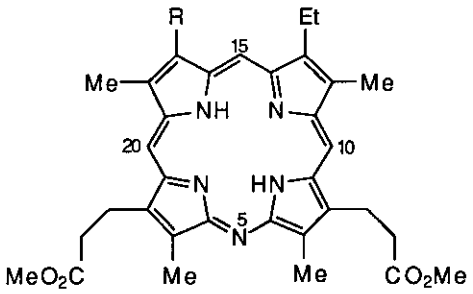
Abstract - Starting from azaporphyrins, new classes of chlorins and bacteriochlorins are synthesized using Diels-Alder or osmium tetraoxide reactions. Their strong absorption at long wavelength and easy synthesis suggests they may be promising potential candidates as sensitizers for use in photodynamic therapy of neoplasms.

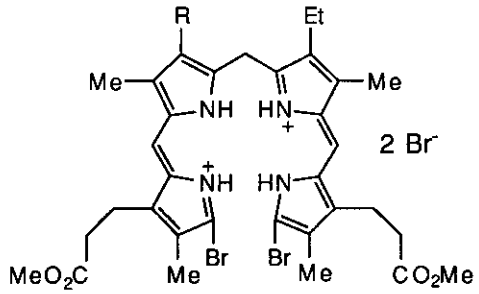
Montforts *et al.*[1] recently reported the preparation of 5-azachlorins from 5-azaprotoporphyrin-IX dimethyl ester by photo-oxygenation (the so-called photoprotoporphyrin reaction[2]). 5-Azaprotoporphyrin-IX dimethyl ester, in turn, was prepared from bilirubin using Fuhrhop's procedure.[3] Apart from the intrinsic interest generated by novel chromophores such as azaporphyrins, azachlorins, and potentially by azabacteriochlorins, they also have potential utility as long-wavelength sensitizers for use in photodynamic therapy, a new modality for treatment of cancer.[4] From detailed biological studies[5] it has been suggested that nitrogen atoms at the meso-positions of phthalocyanines might play a role in localization of the photosensitizer in tumor cells. However, it is still unclear whether all four meso-nitrogens are required in order to achieve biological activity characteristic of phthalocyanines.

In this paper we describe our synthetic work on azachlorins and azabacteriochlorins. In our approach, the azaporphyrins (**1**) and (**2**) were first prepared from the corresponding 1,19-dibromo-a,c-biladines (**3**) and (**4**) by following the literature method;[6,7] these were isolated in 50 to 55% yield. The 2-chloroethyl azaporphyrin (**1**) was

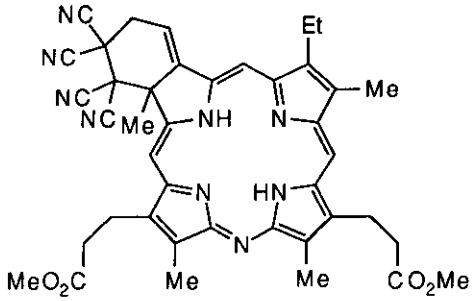
§ Dedicated to Dr. Arnold Brossi, on the occasion of his 70th birthday.



1 R = CH_2CH_2Cl
2 R = Et
5 R = $CH{=}CH_2$



3 R = CH_2CH_2Cl
4 R = Et



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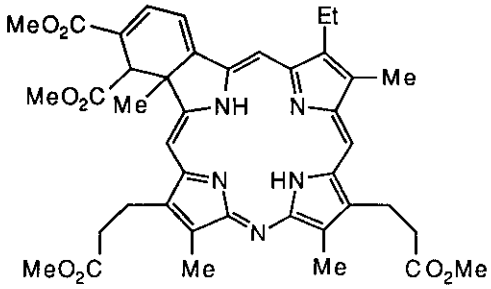

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then converted into its vinyl analogue (**5**) (λ_{max} 612 nm, Figure 1) by refluxing in 3% aqueous sodium hydroxide, followed by re-esterification with acidic methanol. A Diels-Alder reaction of **5** with tetracyanoethylene (TCNE) rapidly (after 2 h) gave the azachlorin (**6**) in 52% yield (λ_{max} 666 nm; Figure 1). A slower reaction took place when the dienophile was dimethyl acetylene-dicarboxylate (DMAD) and subsequent treatment with DBU[8] afforded the "benzoporphyrin-type" analogue (**7**), which possessed a strong absorption maximum at 686 nm (Figure 1). In a typical experiment, the azaporphyrin (**5**) (49 mg) was dissolved in toluene (50 ml), and DMAD (0.4 ml) was added. The reaction mixture was refluxed for ten days, the solvent was evaporated, and traces of DMAD were removed under high vacuum (0.5 mm Hg). The intermediate adduct (λ_{max} 666 nm) was redissolved in dichloromethane and DBU (0.2 ml) was added. The reaction mixture was stirred at room temperature for 30 min and the rearranged product showed a bathochromic shift of 20 nm (to 686 nm; Figure 1). After workup the product (**7**) was obtained in 21% yield, along with an unidentified side-product (λ_{max} 652 nm).

All the pyrroles and pyrromethanes used for the preparation of 1,19-dibromo-a,c-biladienes (**3**) and (**4**) were prepared by following standard methodology.[7]

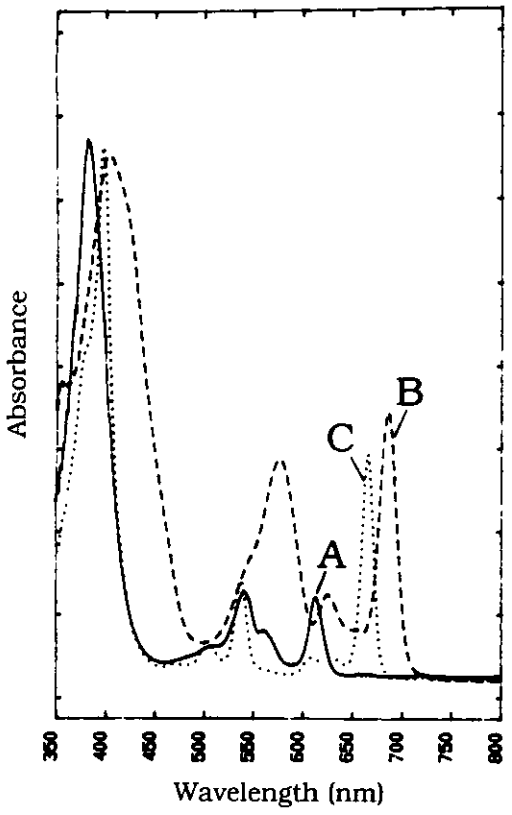


Figure 1: Optical spectra, in CH_2Cl_2 of A (——) azaporphyrin (**5**); B (– – –) azachlorin (**7**); and C (·····) azachlorin (**6**).

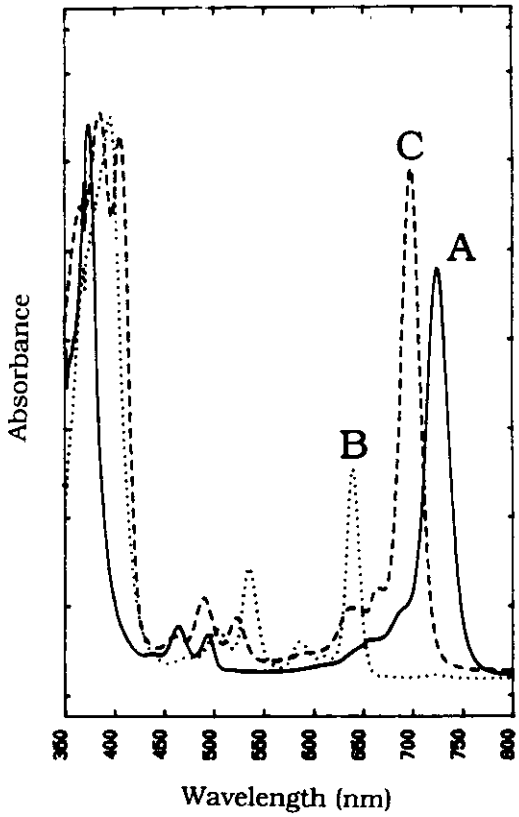
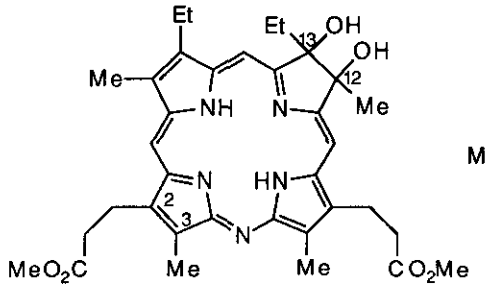


Figure 2: Optical spectra, in CH_2Cl_2 of A (——) azabacteriochlorin (**9**); B (·····) azaketochlorin (**10**); and C (– – –) azabacteriochlorin (**11**).

For the synthesis of both azachlorins and azabacteriochlorins, azaporphyrin (**2**) was treated with osmium tetraoxide. This chemistry has already been well-investigated in several porphyrin and chlorin systems.[9-12] Subsequent cleavage of the intermediate osmate ester with H_2S gas afforded mainly azachlorin-12,13-diol (**8**), with azachlorin-2,3-diol and azabacteriochlorintetraol (**9**) as minor contaminants. Acid treatment (H_2SO_4) of **8** produced the ethyl-migrated azaketochlorin (**10**) (λ_{max} 640 nm) *via* pinacol-pinacolone rearrangement in 40% yield,[13] along with a 20% yield of the corresponding methyl-migrated product (λ_{max} 652 nm). However, when azaporphyrin (**2**) was reacted with excess osmium tetraoxide, azabacteriotetraol (**9**) (with a strong absorption maximum at 724 nm, Figure 2) was isolated as the sole product. We have previously observed[14] that compounds in which hydrophilic groups are arranged on all sides of the molecule do not show any significant tumorcidal activity in photodynamic therapy; in contrast, sensitizers in which one side of the molecule is hydrophilic and the

other side is hydrophobic have generally shown better photosensitizing activity. Van Lier and Spikes[5] have reported similar observations in their experiments with sulfonated phthalocyanines. Thus, ketochlorin (**10**) was further reacted with osmium tetroxide following the reaction conditions discussed above. The reaction was monitored by spectro-photometry and the desired azabacteriochlorin-diol (**11**)[15] was isolated in 60% yield. Bacteriochlorin (**11**) has strong long wavelength absorbance at 698 nm (Figure 2).



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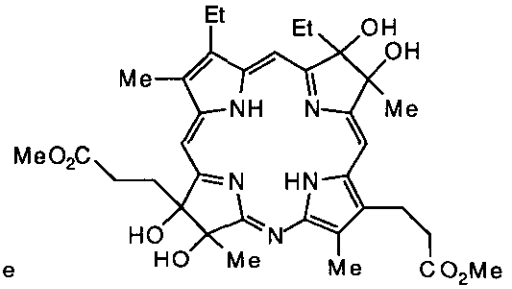

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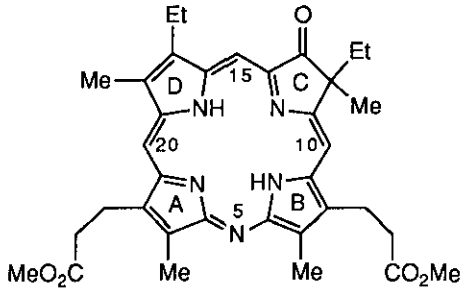

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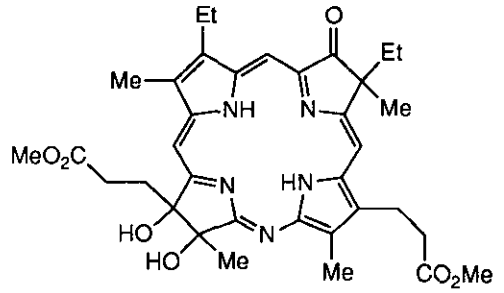

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Biological studies with these compounds and synthetic studies on diaza- and triaza-porphyrins and their chlorin and bacteriochlorin analogues, will be reported in due course.

ACKNOWLEDGMENTS

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13. The structure of azaketochlorin (**10**), mp 210-211°C, [and thus of azachlorin-diol (**8**)] was established by proton nmr (with NOE) spectroscopy (300 MHz; GE QE300): Compound (**10**) (using 5-aza nomenclature): δ ppm ($CDCl_3$) 9.76, 9.73, 9.01 (each 1H, s, 10,15,20-H); 4.24, 4.14 (each 2H, t, J = 7.7 Hz, 2,8-$C\underline{H}_2CH_2CO$); 3.95 (2H, q, J = 7.8 Hz, 17-$C\underline{H}_2CH_3$); 3.68, 3.64, 3.55, 3.51, 3.40 (each 3H, s, CH_3 and OCH_3); 3.17, 3.14 (each 2H, t, J = 7.7 Hz, 2,8-$CH_2C\underline{H}_2CO$); 2.72 (2H, q, J = 7.4 Hz, 12-$C\underline{H}_2CH_3$); 2.00 (3H, s, 12-CH_3); 1.75 (3H, t, J = 7.8 Hz, 17-$CH_2C\underline{H}_3$); 0.44 (3H, t, J = 7.4 Hz,12-$CH_2C\underline{H}_3$); -1.89, -1.92 (each 1H, br s, NH).

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15. Mp 75-76°C. Diastereomeric mixture. δ ppm ($CDCl_3$) 9.43, 8.83, 8.73 (each 1H, s, 10,15,20-H), 5.95, 4.50 (each 1H, br s, OH), 4.08, 3.08, (each 2H, t, J = 7.5 Hz, $C\underline{H}_2CH_2CO$), 3.79 (2H, q, J = 7.7 Hz, $C\underline{H}_2CH_3$), 3.65, 3.32, 3.27 (each 3H, s, CH_3), 3.64, 3.63 (each 1.5 H, s, OCH_3), 2.78 (4H, m, $CH_2C\underline{H}_2CO$), 2.59 (2H, m, $C\underline{H}_2CH_3$), 2.06 (3H, s, CH_3), 1.88, 1.86 (each 1.5 H, s, CH_3), 1.63 (3H, t, J = 7.7 Hz, $CH_2C\underline{H}_3$), 0.46 (3H, m, $CH_2C\underline{H}_3$), -0.71, -0.90 (each 1H, br d, NH).

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