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.

Montfons et al.1 recently reported the preparation of 5-azachlorins from 5-azaproporphyrin-IX dimethyl ester by
photo-oxygenation (the so-called photoproporphyrin reaction2). 5-Azaproporphyrin-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 studies5 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.
then converted into its vinyl analogue (5) ($\lambda_{\text{max}}$ 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 ($\lambda_{\text{max}}$ 666 nm; Figure 1). A slower reaction took place when the dienophile was dimethyl acetylene-dicarboxylate (DMAD) and subsequent treatment with DBU 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 ($\lambda_{\text{max}}$ 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 ($\lambda_{\text{max}}$ 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
For the synthesis of both azachlorins and azabacteriochlorins, azaporphyrin (2) was treated with osmium tetroxide. This chemistry has already been well-investigated in several porphyrin and chlorin systems.\textsuperscript{9-12} Subsequent cleavage of the intermediate osmate ester with H\textsubscript{2}S gas afforded mainly azachlorin-12,13-diol (8), with azachlorin-2,3-diol and azabacteriochlorintetraol (9) as minor contaminants. Acid treatment (H\textsubscript{2}SO\textsubscript{4}) of 8 produced the ethyl-migrated azaketochlorin (10) ($\lambda_{\text{max}}$ 640 nm) via pinacol-pinacolone rearrangement in 40% yield,\textsuperscript{13} along with a 20% yield of the corresponding methyl-migrated product ($\lambda_{\text{max}}$ 652 nm). However, when azaporphyrin (2) was reacted with excess osmium tetroxide, azabacteriotetraol (9) (with a strong absorption maximum at 724 nm, Figure 2) was isolated as the sole product. We have previously observed\textsuperscript{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\textsuperscript{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)\textsuperscript{15} was isolated in 60\% yield. Bacteriochlorin (11) has strong long wavelength absorbance at 698 nm (Figure 2).

\begin{center}
\includegraphics[width=\textwidth]{structures.png}
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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.

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REFERENCES

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 (CDCl₃) 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-CH₂CH₂CO); 3.95 (2H, q, J = 7.8 Hz, 17-CH₃CH₃); 3.68, 3.64, 3.55, 3.51, 3.40 (each 3H, s, CH₃ and OCH₃); 3.17, 3.14 (each 2H, t, J = 7.7 Hz, 2,8-CH₂CH₂CO); 2.72 (2H, q, J = 7.4 Hz, 12-CH₂CH₃) 2.00 (3H, s, 12-CH₃); 1.75 (3H, t, J = 7.8 Hz, 17-CH₂CH₃); 0.44 (3H, t, J = 7.4 Hz, 12-CH₂CH₃); -1.89, -1.92 (each 1H, br s, NH).
15. Mp 75-76°C. Diastereomeric mixture. δ ppm (CDCl₃) 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, CH₂CH₂CO), 3.79 (2H, q, J = 7.7 Hz, CH₂CH₃), 3.65, 3.32, 3.27 (each 3H, s, CH₃), 3.64, 3.63 (each 1.5 H, s, OCH₃), 2.78 (4H, m, CH₂CH₂CO), 2.50 (2H, m, CH₂CH₃), 2.06 (3H, s, CH₃), 1.88, 1.86 (each 1.5 H, s, CH₃), 1.63 (3H, t, J = 7.7 Hz, CH₂CH₃), 0.46 (3H, m, CH₂CH₃), -0.71, -0.90 (each 1H, br d, NH).

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