Mendeleev Commun., 2001, 11(6), 205–206

Synthesis of a vinyl-containing analogue of bacteriochlorophyll *a*

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10.1070/MC2001v011n06ABEH001519

3-Vinyl-3-deacetylbacteriopurpurin was synthesised for the first time, and the esters of vinylbacteriopurpurin were prepared by the addition of alcohols directly to the reaction of bacteriopurpurin with *p*-toluenesulfonic acid.

The search for new photosensitizers for the photodynamic therapy of cancer is now actively performed among natural chlorophylls and bacteriochlorophylls.[1]

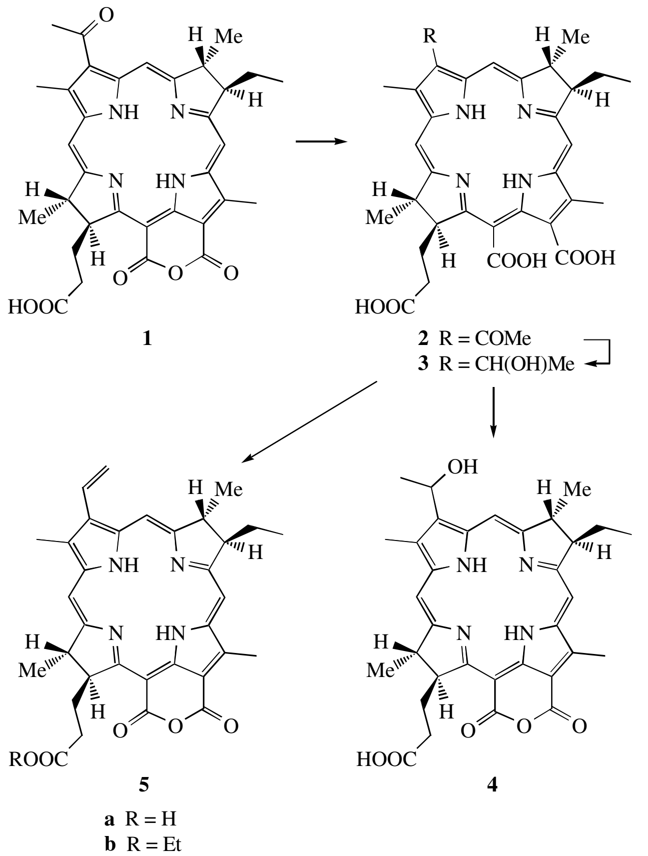
These two pigment classes are structurally similar but bacteriochlorins have the additionally hydrogenated pyrrole ring B and the acetyl rather than vinyl group at the 3-position of the macrocycle. Such structural changes of bacteriochlorins cause a significant improvement in their UV-spectroscopic properties, particularly, the bathochromic shift of the *Q*-band to 770 nm.

The introduction of an additional six-membered exocycle (*e.g.*, anhydride) into the main macrocycle leads to a further bathochromic shift (to 818 nm) of the major absorption band of bacteriopurpurin (BP).

The structure of bacteriopurpurin offers many ways to modify it chemically.[2,3] Hence, BP was chosen as a key compound to synthesise various photosensitizers in the bacteriochlorin series. We improved the stability of purpurin 18 derivatives by the conversion of an anhydride exocycle into an imide one.[4]

We synthesised the *N*-hydroxycycloimide of bacteriochlorin p_6 and demonstrated that the acetyl group is involved in the reaction of BP with hydroxylamine (as well as the anhydride ring) resulting in the formation of the corresponding oxime.

The aim of this work was to convert the acetyl group into vinyl to improve the selectivity of BP reactions. On the other hand, 3-vinylbacteriopurpurin is structurally similar to purpurin 18, which allows us to use the synthetic procedures that we developed for chlorophyll *a* earlier.[5,6]



Scheme 1

The vinyl group in the pyrrole ring A of **5a** was obtained from the α-hydroxyethyl group of **3** by treatment with *p*-toluenesulfonic acid (Scheme 1). The reduction of the acetyl group required temporary conversion of bacteriopurpurin **1** into bacteriochlorin **2**[7] because the treatment of BP with sodium borohydride leads not only to the formation of an alcohol but also to the conversion of the anhydride exocycle into the δ-lactone.[8]

Therefore, the anhydride ring was first opened by treatment with aqueous NaOH, which led to a hypsochromic shift of the *Q*-band to 770 nm. Triacid **2** was reduced by sodium borohydride to form alcohol **3** with an absorption maximum at 740 nm.

We discovered that treatment of **3** with hydrochloric acid in dioxane led to the anhydride exocycle closing without affecting the α-hydroxyethyl group of **4**, while treatment with *p*-toluenesulfonic acid led to 3-vinyl-3-deacetylbacteriopurpurin **5a**, which returns the major absoprtion band back to 783 nm.

We found that, as opposed to the formation of free acid **5a** in a chloroform solution, the addition of ethanol directly to the reaction mixture led to fast esterification of the propionic acid residue, which resulted in the formation of ester **5b**. The carboxyl group seems to possess such an enhanced activity due to the formation of an anhydride with *p*-toluenesulfonic acid.

Compound **5b** was obtained in 45% yield and characterised by HRMS and ^{1}H NMR spectroscopy.† The signals of the bacteriochlorin macrocycle *meso*-protons (10-H at δ 8.55, 5-H at δ 8.47 and 20-H at δ 8.32 ppm) were assigned using the data of 1D NOE experiments. The irradiation of the methyl groups at the 2- and 12-positions of the macrocycle led to NOE observation at 20-H and 10-H signals, respectively, while the irradiation of the vinyl group α-proton caused NOE at the 5-H *meso*-proton, which confirms their spatial proximity.

Finally, we analysed the influence of substituents on the spectroscopic characteristics of the bacteriopurpurins and com-

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† UV spectra were recorded in $CHCl_3$ using a Jasco-UV7800 spectrophotometer. The ^{1}H NMR spectra of $CDCl_3$ solutions were recorded using Bruker WM-250 and Bruker AM-300 NMR instruments and the DISNMR94 software. The 1D NOE experiments were carried out using the NOEFAST program, irradiation time was 1.5 s. Mass spectra were obtained on a VISION 2000 time-of-flight MS instrument by MALDI with 2,5-dihydroxybenzoic acid (DHB) as a matrix. The mass spectrum of **5b** was recorded using a Micromass Autospec mass spectrometer (EI, 70 eV, 200 °C).

Characteristics of the compounds obtained.

3: UV, λ_{max}/nm (relative intensities are given in parentheses): 379, 400, 510, 740 (1:0.9:0.5:0.85).

4: UV, λ_{max}/nm (relative intensities are given in parentheses): 364, 411, 536, 775 (1:0.8:0.6:0.6). MS, *m*/*z*: 584.2 (M^+).

5a: UV, λ_{max}/nm (relative intensities are given in parentheses): 364, 411, 539.5, 782 (1: 0.77: 0.35: 0.39).

5b: ^{1}H NMR, δ: 8.55 (s, 10-H), 8.47 (s, 5-H), 8.32 (s, 20-H), 7.73 (dd, 3^1-CH, *J* 12 Hz, *J* 18 Hz), 6.19 (dd, 3^2-CH_2-*cis*, *J* 18 Hz, *J* 1 Hz), 6.11 (dd, 3^2-CH_2-*trans*, *J* 12 Hz, *J* 1 Hz) 5.06 (d, 17-H, *J* 7 Hz), 4.25 (m, 18-H, *J* 7 Hz), 4.2 (m, 7-H), 4.05 (q, 17^5-CH_2, *J* 8 Hz), 3.95 (m, 8-H), 3.56 (s, 12-Me), 3.25 (s, 2-Me), 2.4 (m, 17^2-CH_2), 2.37 (m, 8^1-CH_2), 2.0 (m, 17^1-CH_2), 1.8 (d, 7-Me, *J* 7 Hz), 1.7 (d, 18-Me, *J* 7 Hz), 1.16 (t, 17^5-Me, *J* 8 Hz), 1.1 (t, 8^2-Me, *J* 6 Hz), 0.5 (s, NH), 0.0 (s, NH). UV, λ_{max}/nm, ($\varepsilon \times 10^{-3}$): 365 (41.2), 414.5 (20.4), 541.5 (15.3), 783 (16.0); MS, *m*/*z*: calc. for $C_{35}H_{38}N_4O_5$, 594.2657; found, 594.2842.

pared these characteristics with those of purpurin 18. The replacement of the α-hydroxyethyl group with vinyl, and then with acetyl, led to a bathochromic shift of the long-wave band in all these compounds. In the case of bacteriopurpurins, the above shifts were 7, 36 and 43 nm for (**4**)–(**5**), (**5**)–(**1**) and (**4**)–(**1**) pairs, respectively, while in the case of purpurin 18 and its derivatives these values were 4, 27 and 31 nm for analogous pairs.[9] Thus, the tetrahydroporphyrin macrocycle is highly sensitive to the introduction of different substituents; this property may be used for the synthesis of new photosensitizers based on bacteriochlorophyll *a*, which possess intense absorption at 800 nm.

This work was supported by the Russian Foundation for Basic Research (grant nos. 01-03-32543 and 00-15-97866). We are grateful to F. V. Toukach (N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences) for the NMR measurements.

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Received: 19th September 2001; Com. 01/1845