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Cyclic *N*-Hydroxyimides in a Series of Chlorins and Porphyrins

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Abstract: The first representatives of hydroxamic acids in the series of naturally-occurring chlorins were synthesised and their oxidation to porphyrins was studied.

Purpurin 18 (**1a**) is widely used for the synthesis of second generation sensitizers for cancer PDT.[1,2] The presence of an exocyclic anhydride ring in purpurin 18 causes considerable tension in the macrocycle and, therefore, results in the bathochromic shift of the longest wavelength band, which is used in cancer PDT, by approximately 30-35 nm compared to that of common chlorophyll derivatives. Unfortunately, purpurin 18 and related compounds are stable only in acid and neutral media while on dissolving in alkali, the anhydride ring easily opens, thus restoring the original spectral characteristics.[2] With this being so, a series of chemical transformations introduced by Smith and coworkers,[3] that affords the replacement of an oxygen in an anhydride ring with a nitrogen atom thus giving more stable cyclic imides with spectral characteristics being retained, is of particular interest.

In this communication we present a novel reaction, which makes it possible to perform a similar replacement in one step and in high yield. The reaction provides cyclic derivatives of hydroxamic acids, which for chlorins and porphyrins have not been described earlier.

The reaction proceeds in the presence of excess hydroxylamine in pyridine at room temperature (Scheme 1). As judged by TLC, no incidental byprocesses were observed such as reaction with ester group, which is characteristic of hydroxylamine.[4] The yield of resulting cyclic imide (**2b**) reached 91%, the second imide (**2a**) being obtained in lower yield, presumably due to losses during isolation. The structures of the products were proved by mass and electronic absorption spectra. The *N*-hydroxyimides demonstrated a considerable bathochromic shift of the major absorption band, e.g., for (**2a**) the major band was shifted by 20 nm in comparison with that of the starting purpurin, which is considerably larger than in the case of amides.[3] ^{1}H NMR spectra of (**2a**) and (**2b**) turned out to be rather non-informative, presumably due to the partial oxidation of the hydroxyimide group leading to the formation of free radicals.[5]

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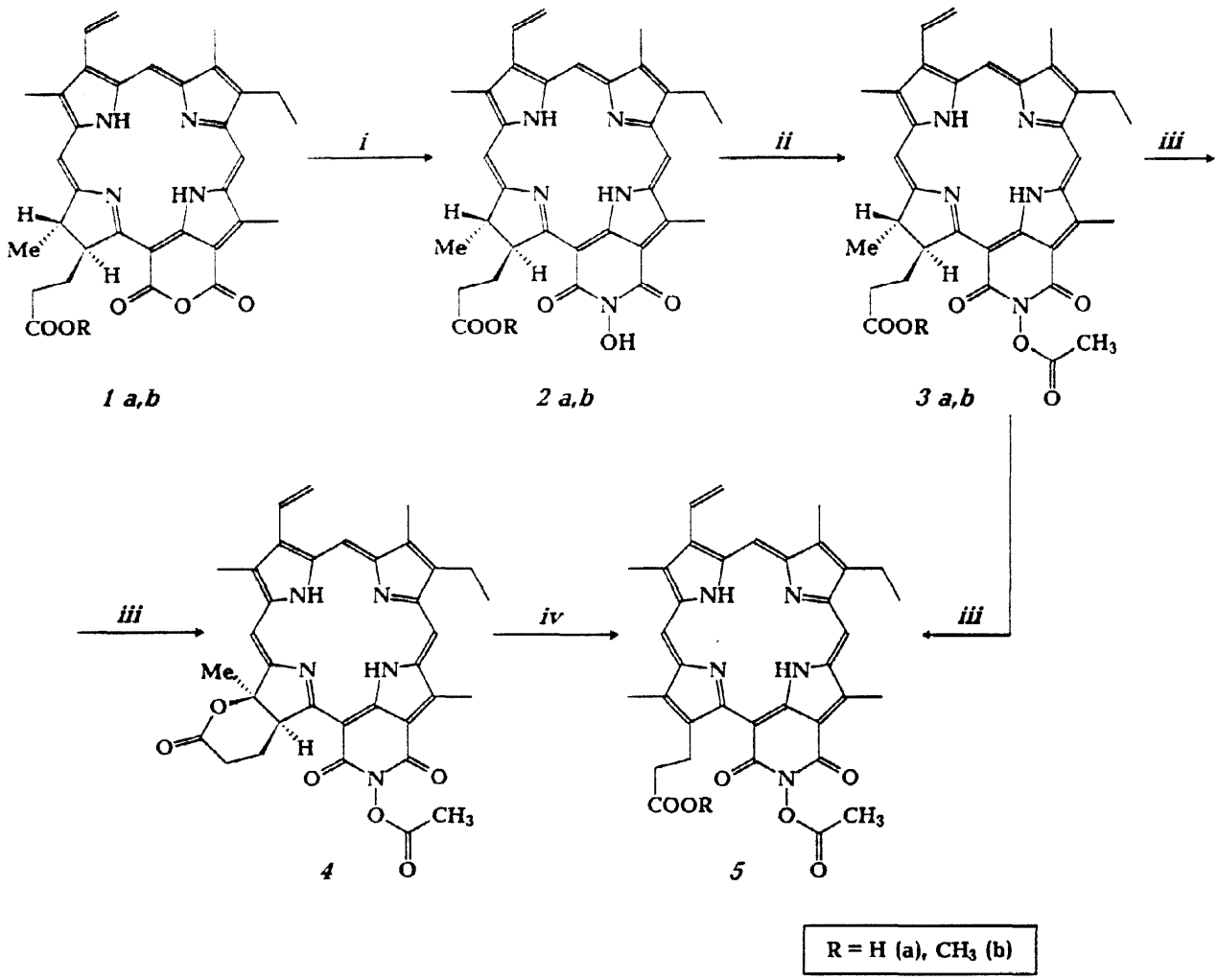

Scheme 1. Synthesis of hydroxamic acids on the basis of purpurin 18 and some of their chemical transformations. Reagents and conditions: I, NH_2OH·HCl, Py, 68% (2a), 91% (2b); ii, Ac_2O, $NaHCO_3$, dioxane, 69% (3a), 73% (3b); iii, DDQ, $CHCl_3$, 55% (4) from (3a), 45% (5) from (3b); iv, TFA, MeOH, 45% from (3b); all reactions were performed at 20 °C.

In order to test the chemical reactivity of the compounds obtained, we tried to acylate the hydroxyl group. It is known that hydroxamic acid can be readily alkylated and acylated.[5] If this reaction could be successfully applied to chlorins and porphyrins, it would open great possibilities for preparing a series of novel sensitizers. Acylation of *N*-hydroxyimides (**2a**) and (**2b**) was performed by treating them with acetic anhydride in dioxane. After purification, acylated derivatives (**3a**) and (**3b**) were obtained in 70% yield and were characterised by mass spectrometry, absorption spectroscopy and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum of (**3a**) showed not only signals characteristic of purpurin 18 (**1a**) but an additional signal δ 2.60 ppm, which corresponded to the methyl protons of the added acetyl group. Oxidation of chlorins (**3a**) and (**3b**) with DDQ gave interesting results. Treatment of (**3a**) with DDQ led not to the expected porphyrin (**5**) but to chlorin (**4**), which has an additional six-membered ring at the pyrrolic ring D. Only after treatment of this intermediate with TFA was porphyrin (**5**) obtained. In contrast, the methyl ester (**3b**) on oxidation gave

porphyrin (**5**) without formation of the intermediate lactone. These results are in good agreement with those we obtained earlier for chlorins with the six-membered anhydride ring, i.e., purpurin 18 and its 3-acetyl substituted analogue.[6] Therefore, the reaction found is of universal character and, presumably, can be observed in the case of other naturally-occurring chlorins that have the propionic acid residue at position 17. The ^{1}H NMR spectrum of (**4**) was similar to that of the δ-lactone, which we prepared earlier via oxidation of purpurin 18,[6] and showed only an additional signal of the 13^5 methyl group. On this basis we deduced the spatial structure of the exocyclic ring shown in Scheme 1.

Porphyrin (**5**) proved to be more stable than the purpuroporphyrins prepared earlier.[6] It was completely characterised by mass spectrometry and ^{1}H NMR spectroscopy. The visible region absorption spectra demonstrated the "*reverse etio-type*" analogous to cyclic N-alkylimides.[7]

Summarising, the synthesis of hydroxamic acids in the series of chlorins and purpurins opens new possibilities for preparing constrained macrocycles with exocyclic six-membered rings.

Characteristics of compounds obtained:[8]

(2a): *m/z* 579.7 (M^-); λ_{max}, nm, ($\varepsilon\cdot10^{-3}$): 424 (61.00), 487 (2.45), 516 (2.9), 557 (1.6), 662 (5.4) and 718 (25);

(3a): *m/z* 621.4 (100%, M^+), 562.6 (M-$OCOCH_3$); λ_{max}, nm, ($\varepsilon\cdot10^{-3}$): 419 (109.0), 483 (2.6), 513 (3.7), 552 (21.2), 654 (6.3) and 711 (39.1); δ_H 9.45 (s, 10-H), 9.21 (s, 5-H), 8.48 (s, 20-H), 7.80 (dd, 3^1-CH_3), 6.23 (dd, 3^2-CH_2), 6.14 (dd, 3^2-CH_2), 5.21 (dd, 17-H), 4.33 (q, 18-H), 3.73 (s, 12-CH_3), 3.55 (q, 8^1-CH_2), 3.27 (s, CH_3), 3.08 (s, CH_3), 2.62 (s, 13^5-CH_3), 2.45 (m, 17^1-CH_2), 1.98 (m, 17^2-CH_2), 1.70 (d, 18-CH_3), 1.62 (t, 8^2-CH_3) and 0.24 (br s, 2xNH);

(4): *m/z* 620.3 (100%, M+H), 562.2; λ_{max}, nm, ($\varepsilon\cdot10^{-3}$): 418 (110.0), 483 (4.6), 513 (5.6), 552 (23.7), 652 (7.5) and 708 (42.1); δ_H 9.68 (s, 10-H), 9.48 (s, 5-H), 8.77 (s, 20-H), 7.89 (dd, 3^1-CH_3), 6.31 (dd, 3^2-CH_2), 6.19 (dd, 3^2-CH_2), 5.61 (m, 17-H), 3.82 (s, 12-CH_3), 3.65 (q, 8^1-CH_2), 3.36 (s, CH_3), 3.18 (s, CH_3), 2.92 (m, 17^1-CH_2), 2.64 (s, 13^5-CH_3), 2.33 (m, 17^2-CH_2), 2.12 (s, 18-CH_3), 1.66 (t, 8^2-CH_3), -0.03 and -0.12 (br s, 2xNH);

(5): *m/z* 634.2 (100%, M+H); λ_{max}, nm, (relative intensities): 433, 534, 622 and 668 (1 : 0.01 : 0.08 : 0.1); δ_H 9.46 (s, *meso*-H), 9.43 (s, *meso*-H), 9.40 (s, *meso*-H), 7.88 (dd, 3^1-CH_3), 6.17 (dd, 3^2-CH_2), 6.10 (dd, 3^2-CH_2), 4.13 (q, 8^1-CH_2), 3.83 (t, 17^1-CH_2), 3.75 (s, 12-CH_3), 3.39 (s, $COOCH_3$), 3.37 (s, CH_3), 3.36 (s, CH_3), 3.14 (t, 17^2-CH_2), 2.70 (s, 13^5-CH_3), 1.66 (t, 8^2-CH_3), -2.06 and -2.35 (br s, 2xNH).

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8. ^{1}H NMR spectra were obtained on a Bruker MSL 200 in $CDCl_3$. Electronic absorption spectra were recorded on a Jasco 7800 in chloroform, extinction coefficients (ε) being given in 1 mol^{-1} cm^{-1}. Mass spectra were measured on an MSBKh instrument (SELMI, Sumy, Ukraine); ionisation was caused by ^{252}Cf fission products, and a time-of-flight monitoring ion analyser was employed.