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Synthesis of phosphorus-containing natural chlorins

Viktoriya S. Lebedeva,* Ramzes D. Ruziev and Andrey F. Mironov

M. V. Lomonosov Moscow State Academy of Fine Chemical Technology, 119571 Moscow, Russian Federation. Fax: +7 495 936 8901; e-mail: phsstr@gmail.com

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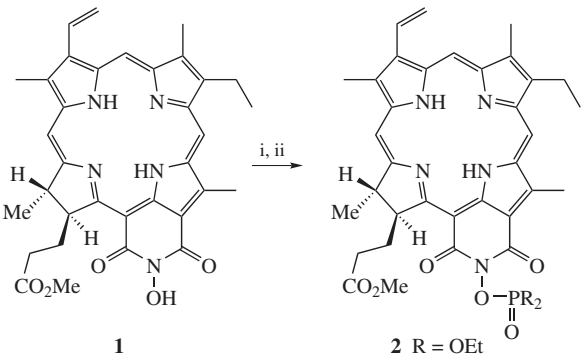
New phosphorus-containing derivatives of natural chlorins have been synthesised.

Water-soluble dihydroxyphosphonyl derivatives[1] and dialkyl- and diarylphosphonyl-containing compounds that can be coordinated with porphyrin metal complexes to give self-aggregating supramolecular assemblies[2] are of considerable current interest.

Among natural chlorins, compounds obtained from chlorophyll *a* are important due to the relative accessibility of this pigment and availability of convenient methods for modifying functional groups in the chlorin macrocycle.[3] Of special interest are chlorophyll *a* derivatives containing an additional six-membered cycloimide fragment at the main macrocycle.[4] The incorporation of this fragment results in a bathochromic shift of long-wave band Q by 40–45 nm towards the red region of the spectrum. This is very important in the development of photosensitisers for the photodynamic treatment of cancer since light having such wavelengths penetrates the tissues to a greater depth and allows a more efficient removal of deeply located tumours.[5]

Previously, we suggested a one-stage method for the preparation of chlorin p_6 *N*-hydroxycycloimide in > 90% yields by treatment of purpurin 18 with hydroxylamine.[6] It was of interest to use the hydroxy group in this cycloimide to obtain hitherto unknown phosphorus-containing chlorins and to study the photophysical properties complexation ability and biological activity of these compounds.

We found previously that the hydroxy group at the imide ring nitrogen atom has a sufficient reactivity to obtain alkyl and acyl derivatives.[7] However, the treatment of chlorin p_6 *N*-hydroxycycloimide methyl ester **1** with phosphorus oxychloride in the presence of triethylamine (Scheme 1) followed by hydrolysis did not allow us to isolate the expected chlorin p_6 dihydroxyphosphoryloxycycloimide, apparently, due to its lability. On the other hand, the treatment of the reaction mixture with ethanol, methanol or diethylamine in the presence of pyridine gave acceptable yields (47–55%) of cycloimides **2**–**4**. The structures of the products were confirmed by ^{1}H and ^{31}P NMR spectroscopy, mass spectrometry and electronic absorption spectroscopy.†



1

2 R = OEt
3 R = OMe
4 R = NEt_2

Scheme 1 *Reagents and conditions*: i, $POCl_3$, Et_3N; ii, EtOH, MeOH or $NHEt_2$, C_5H_5N.

† The electronic spectra of compounds **2**–**4** were recorded with a Jasco 7800 spectrophotometer at 400–800 nm in $CHCl_3$. The ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker DPX 300 spectrometer. The mass spectra were measured on a Vision 2000 instrument using the MALDI method combined with a time-of-flight analyzer.

For **2**: A solution of chlorin p_6 *N*-hydroxycycloimide methyl ester **1** (25 mg, 0.04 mmol) and triethylamine (5 μl, 0.04 mmol) in anhydrous dichloromethane (5 ml) was added dropwise to a solution of phosphorus oxychloride (6 μl, 0.06 mmol) in anhydrous dichloromethane (5 ml). The reaction mixture was stirred for 10 min at 25 °C; anhydrous ethanol (23 μl, 0.40 mmol) and pyridine (32 μl, 0.40 mmol) were added and stirring was continued for another 20 min at 25 °C. After that, the mixture was diluted with dichloromethane (5 ml) and washed with a sodium bicarbonate solution and water. The organic layer was separated and dried with sodium sulfate; the solvent was evaporated *in vacuo*. The residue was chromatographed on a plate with CHEMAPOL L 5/40 silica gel in a dichloromethane–methanol system (70:1). The yield of the target product **2** was 17 mg (55%). Electronic spectrum, λ_{max}/nm (relative intensities): 419, 482, 512, 551, 654, 710 (1:0.04:0.05:0.21:0.07:0.38). ^{1}H NMR, δ: 9.59 (s, 1H, 10-H), 9.31 (s, 1H, 5-H), 8.52 (s, 1H, 20-H), 7.85 (dd, 1H, 3^1-CH, *J* 19 and 12 Hz), 6.29 (dd, 1H, 3^2-CH_2, *J* 19 Hz), 6.18 (dd, 1H, 3^2-CH_2, *J* 12 Hz), 5.26 (d, 1H, 17-H, *J* 8 Hz), 4.73 (m, 4H, $POCH_2$), 4.35 (q, 1H, 18-H, *J* 8 Hz), 3.81 (s, 3H, 17^5-Me), 3.63 (s, 3H, 12-Me), 3.59 (q, 2H, 8^1-CH_2, *J* 8 Hz), 3.33 (s, 3H, 2-Me), 3.15 (s, 3H, 7-Me), 2.74 (m, 1H, 17^2-CH_2), 2.48 (m, 2H, 17^1-CH_2), 1.99 (m, 1H, 17^2-CH_2), 1.72 (d, 3H, 18-Me, *J* 8 Hz), 1.65 (t, 3H, 8^2-Me, *J* 8 Hz), 1.58 (m, 6H, $POCH_2\mathit{Me}$), 0.26 and 0.15 (2s, 1H each, NH). MS, *m/z*: 576.3 $[M - PO_2(OEt)_2]^+$, 700.3 $[M - Et]^+$, 730.4 $[M + H]^+$.

For **3**: Electronic spectrum, λ_{max}/nm (relative intensities): 418, 483, 513, 552, 654, 710 (1:0.03:0.04:0.019:0.07:0.36). ^{1}H NMR, δ: 9.54 (s, 1H, 10-H), 9.28 (s, 1H, 5-H), 8.50 (s, 1H, 20-H), 7.86 (dd, 1H, 3^1-CH, *J* 19 and 12 Hz), 6.25 (dd, 1H, 3^2-CH_2, *J* 19 Hz), 6.14 (dd, 1H, 3^2-CH_2, *J* 12 Hz), 5.25 (d, 1H, 17-H, *J* 8 Hz), 4.34 (q, 1H, 18-H, *J* 8 Hz), 4.32 and 4.29 (2d, 3H each, POMe, *J* 6 Hz), 3.76 (s, 3H, 17^5-Me), 3.58 (q, 2H, 8^1-CH_2, *J* 8 Hz), 3.56 (s, 3H, 12-Me), 3.30 (s, 3H, 2-Me), 3.11 (s, 3H, 7-Me), 2.68 (m, 1H, 17^2-CH_2), 2.45 (m, 2H, 17^1-CH_2), 2.00 (m, 1H, 17^2-CH_2), 1.72 (d, 3H, 18-Me, *J* 8 Hz), 1.64 (t, 3H, 8^2-Me, *J* 8 Hz), 0.28 and 0.18 (2s, 1H each, NH). ^{31}P NMR, δ: 0.65. MS, *m/z*: 576.4 $[M - PO_2(OMe)_2]^+$, 702.4 $[M + H]^+$.

For **4**: Electronic spectrum, λ_{max}/nm (relative intensities): 419, 482, 511, 550, 709 (1:0.05:0.06:0.19:0.35). ^{1}H NMR, δ: 9.52 (s, 1H, 10-H), 9.24 (s, 1H, 5-H), 8.51 (s, 1H, 20-H), 7.81 (dd, 1H, 3^1-CH, *J* 19 and 12 Hz), 6.24 (dd, 1H, 3^2-CH_2, *J* 19 Hz), 6.12 (dd, 1H, 3^2-CH_2, *J* 12 Hz), 5.24 (d, 1H, 17-H, *J* 8 Hz), 4.36 (q, 1H, 18-H, *J* 8 Hz), 3.78 (s, 3H, 17^5-Me), 3.69 (q, 2H, 8^1-CH_2, *J* 8 Hz), 3.59 (s, 3H, 12-Me), 3.47 (m, 8H, $PNCH_2Me$), 3.30 (s, 3H, 2-Me), 3.07 (s, 3H, 7-Me), 2.76 (m, 1H, 17^2-CH_2), 2.51 (m, 2H, 17^1-CH_2), 1.99 (m, 1H, 17^2-CH_2), 1.69 (d, 3H, 18-Me, *J* 8 Hz), 1.62 (t, 3H, 8^2-Me, *J* 8 Hz), 1.33 (m, 12H, $PNCH_2\mathit{Me}$), 0.04 and –0.08 (s, 1H each, NH). MS, *m/z*: 576.2 $[M - PO_2(NEt_2)_2]^+$.

The presence of signals of three *meso*-protons, vinyl, methyl (2-Me, 7-Me, 8^2-Me, 12-Me, 17^5-Me, 18-Me) and methylene (8^1-CH_2, 17^1-CH_2, 17^2-CH_2) protons, as well as 17-H and 18-H signals in the ^{1}H NMR spectra of cycloimides **2** and **3**, suggests that the chlorin macrocycle is retained. The additional four- and six-proton multiplets at δ 4.73 and 1.58 and three-proton doublets at δ 4.32 and 4.29 with intensity of three protons each were assigned to ethoxy and methoxy groups at the phosphorus atom, respectively. The ^{31}P NMR spectrum of compound **3** contained a signal at δ 0.65.

Compared to the spectrum of *N*-hydroxycycloimide methyl ester **1**, the ^{1}H NMR spectrum of cycloimide **4** also contained additional 8- and 12-proton multiplets at δ 3.47 and 1.33, which were assigned to ethyl groups at nitrogen atoms.

The mass spectrum of compound **2** contained a peak at *m*/*z* 730.4 assigned to $[M + H]^+$, as well as more intense peaks at *m*/*z* 700.3 and 576.3 assigned to the $[M – Et]^+$ and $[M – PO_2(OEt)_2]^+$ fragments, respectively. The spectrum of cycloimide **3** contained a peak at *m*/*z* 702.4 corresponding to $[M + H]^+$ and a peak at *m*/*z* 576.4 assigned to $[M – PO_2(OMe)_2]^+$. The mass spectrum of chlorin **4** only showed an intense peak with *m*/*z* 576.2 corresponding to the $[M – PO_2(NEt_2)_2]^+$ fragment.

Substitution for the hydroxy group at the nitrogen atom of the imide ring is accompanied by a hypsochromic shift of the *Q* band in the electronic spectra of cycloimides **2**–**4** from 718 to 709–710 nm.

Thus, compounds **2**–**4** are the first phosphorus-containing derivatives of natural chlorins; they may be of interest for subsequent studies on the biological activity of compounds with structures of this kind. Note that phosphorylation considerably expands the scope of possible chemical transformations of hydroxyl-substituted cycloimide derivatives of chlorin p_6.

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