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Alkylation of chlorin p_6 *N*-hydroxycycloimide with the use of 1,8-diazabicyclo[5.4.0]undec-7-ene

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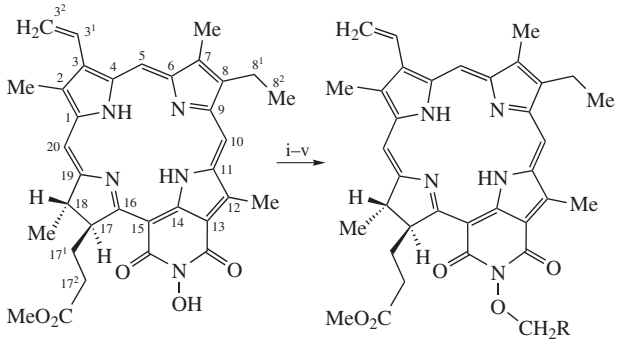
The hydroxyl group of *N*-hydroxycycloimide in a chlorin macrocycle is easily alkylated with haloalkanes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to give chlorin p_6 *N*-alkoxycycloimides in yields to 80%.

Natural chlorins, the derivatives of chlorophyll *a* having an intense absorption band at 660–665 nm, are widely used as photosensitizers for the photodynamic therapy of cancer.[1–3] Previously, we found that incorporation of an *N*-hydroxycycloimide fragment to the main chlorin macrocycle significantly improves the spectral characteristics of photosensitizers to shift the *Q* band to 718 nm into the so-called 'tissue transparency window', which makes it possible to remove larger and deeper-lying tumors.[4]

The presence of a hydroxyl group in chlorin **1** (Scheme 1), in turn, offers additional possibilities for the chemical modification of the molecule and a further improvement in the physicochemical and biological characteristics of this group of photosensitizers. In particular, the variation of a ratio between hydrophobic and hydrophilic fragments in the photosensitizer molecule can considerably affect their accumulation in the cell.[5–7] However, the known methods of the alkylation of chlorin p_6 *N*-hydroxycycloimide with diazomethane[4] or iodomethane in the presence of sodium hydride[3] cannot be extended to higher haloalkanes since they afford the target O-alkylated derivatives in low yields.

Herein, we report the successful alkylation of this hydroxyl group using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base having a good reputation in many organic reactions.[8–11] In fact, chlorin p_6 *N*-hydroxycycloimide **1** is readily alkylated with iodoalkanes C_1–C_3 in the presence of DBU even at room temperature to give the desired *N*-alkoxycycloimides **2**–**4** in yields higher than 80% (Scheme 1). The optimization showed that the best conditions involve the use of the alkylating agent as a solvent with a twofold excess of DBU.



1

2 R = H
3 R = Me
4 R = CH_2Me
5 R = CH_2Cl
6 R = CH_2Br

Scheme 1 *Reagents and conditions*: i, MeI; ii, $MeCH_2I$; iii, $MeCH_2CH_2I$; iv, $Cl(CH_2)_2Cl$ or v, $Br(CH_2)_2Br$; DBU, 25 °C, 0.75–4 h.

The structures of previously unknown compounds **3** and **4** were determined by ^{1}H NMR spectroscopy, mass spectrometry and electronic absorption spectroscopy.† The found constants of compound **2** were consistent with previously published data.[4] In the electronic spectra of the obtained compounds, an intense absorption maximum at 710–711 nm was retained.

The presence of the characteristic chemical shifts of three *meso*-protons, the protons of vinyl, methyl (2-Me, 7-Me, 8^2-Me, 12-Me, 18-Me) and methylene (8^1-CH_2, 17^1-CH_2, 17^2-CH_2) groups and the signals of 17-H and 18-H in the ^{1}H NMR spectrum of

† The electronic spectra were measured on a Jasco 7800 spectrophotometer in a range of 400–800 nm in $CHCl_3$. The ^{1}H NMR spectra in $CDCl_3$ were recorded on a Bruker DPX 300 spectrometer. The mass spectra were measured on a Vision 2000 instrument using the MALDI method in combination with a time-of-flight analyzer. Preparative TLC was performed on silica gel plates (brand name 60H).

13,15-N-*Methoxycycloimide of chlorin* p_6 *methyl ester* **2** *(general procedure)*. Iodomethane (2 ml) and DBU (6 μl, 0.034 mmol) were added to 10 mg (0.017 mmol) of the methyl ester of chlorin p_6 13,15-*N*-hydroxycycloimide **1**. The mixture was stirred at 25 °C for 45 min, diluted with chloroform (20 ml) and washed with water (3×150 ml); the organic layer was separated and dried with sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was chromatographed using a preparative TLC with a (70:5) mixture of chloroform and methanol. Yield 8.7 mg (85%). The constants found for compound **2** were consistent with previously published data.[4]

13,15-N-*Ethoxycycloimide of chlorin* p_6 *methyl ester* **3**: yield 83%. Electronic spectrum [λ_{max}/nm ($\varepsilon/10^3$)]: 420 (115.5), 512 (5.1), 551 (18.4), 655 (5.8), 710 (44.2). ^{1}H NMR, δ: 9.58 (s, 1H, 10-H), 9.35 (s, 1H, 5-H), 8.53 (s, 1H, 20-H), 7.88 (dd, 1H, 3^1-CH, *J* 18 and 12 Hz), 6.30 (dd, 1H, 3^2-CH_2, *J* 18 Hz), 6.17 (dd, 1H, 3^2-CH_2, *J* 12 Hz), 5.31 (d, 1H, 17-H, *J* 7 Hz), 4.58 (q, 2H, OCH_2Me, *J* 7 Hz), 4.33 (q, 1H, 18-H, *J* 7 Hz), 3.81 (s, 3H, CO_2Me), 3.65 (q, 2H, 8^1-CH_2, *J* 7 Hz), 3.58 (s, 3H, 12-Me), 3.34 (s, 3H, 2Me), 3.15 (s, 3H, 7-Me), 2.75 (m, 1H, 17^2-CH_2), 2.45 (m, 2H, 17^1-CH_2), 2.00 (m, 1H, 17^2-CH_2), 1.74 (d, 3H, 18-Me, *J* 7 Hz), 1.67 and 1.66 (2t, 2×3H, 8^2-Me and OCH_2Me, *J* 7 Hz), 0.12 and 0.09 (2s, 2×1H, NH). MS, *m/z*: 622.0 (M^+) (calc. for $C_{36}H_{39}N_5O_5$, *M* = 621.7).

13,15-N-*Propoxycycloimide of chlorin* p_6 *methyl ester* **4**: yield 80%. Electronic spectrum [λ_{max}/nm ($\varepsilon/10^3$)]: 420 (165.7), 482 (9.3), 512 (11.0), 550 (32.3), 652 (14.4), 710 (58.5). ^{1}H NMR, δ: 9.55 (s, 1H, 10-H), 9.32 (s, 1H, 5-H), 8.57 (s, 1H, 20-H), 7.86 (dd, 1H, 3^1-CH, *J* 18 and 12 Hz), 6.29 (dd, 1H, 3^2-CH_2, *J* 18 Hz), 6.18 (dd, 1H, 3^2-CH_2, *J* 12 Hz), 5.32 (d, 1H, 17-H, *J* 7 Hz), 4.50 (t, 2H, OCH_2CH_2Me, *J* 7 Hz), 4.36 (q, 1H, 18-H, *J* 8 Hz), 3.82 (s, 3H, CO_2Me), 3.64 (q, 2H, 8^1-CH_2, *J* 7 Hz), 3.59 (s, 3H, 12-Me), 3.34 (s, 3H, 2-Me), 3.14 (s, 3H, 7-Me), 2.75 (m, 1H, 17^2-CH_2), 2.43 (m, 2H, 17^1-CH_2), 2.11 (m, 2H, OCH_2CH_2Me), 2.00 (m, 1H, 17^2-CH_2), 1.73 (d, 3H, 18-Me, *J* 7 Hz), 1.66 (t, 3H, 8^2-Me, *J* 8 Hz), 1.25 (t, 3H, OCH_2CH_2Me, *J* 7 Hz), 0.18 and 0.08 (2s, 2×1H, NH). MS, *m/z*: 636.0 (M^+) (calc. for $C_{37}H_{41}N_5O_5$, *M* = 635.8).

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cycloimide **3** is indicative of the retention of a chlorin macrocycle. An additional quartet at 4.58 ppm with an intensity of two protons and a triplet at 1.66 ppm with an intensity of three protons observed in the spectrum were attributed to the protons of an ethoxy group at the nitrogen atom. Cycloimide **4** exhibited additional triplets due to methylene and methyl groups at δ 4.50 and 1.25 ppm, respectively, and a multiplet due to a methylene group at 2.11 ppm. The mass spectra of compounds **3** and **4** contained the peaks of molecular ions with *m*/*z* 622.0 (M^+) and 636.0 (M^+), respectively.

Similar conditions were used for the case with 1,2-dichloro- and 1,2-dibromoethanes resulting in haloethyl derivatives **5** and **6** in good yields.† In the ^{1}H NMR spectra of compounds **5** and **6**, additional signals due to the protons of 2-chloroethyl or 2-bromoethyl groups at δ 4.79 and 3.15 or 4.79 and 3.92 ppm, respectively, were observed along with the signals due to the protons of a chlorin macrocycle. The mass spectrum of compound **5** contains peaks with *m*/*z* 656.3 (M^+ + H) (69) and 658.3 (M^+ + H) (31), which correspond to the natural distribution of ^{35}Cl and ^{37}Cl ions. Peaks with *m*/*z* 699.1 (M^+) (50) and 701.1 (M^+) (50), which correspond to the natural distribution of ^{79}Br and ^{81}Br ions, were observed in the mass spectrum of compound **6**.

The synthesized chlorin p_6 *N*-alkoxycycloimides can be subsequently used for studying the effect of the length of an alkyl substituent on the photodynamic activity of cycloimides, and *N*-chloro- and *N*-bromoethoxycycloimides can be used for obtaining conjugates with other biologically active compounds.

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13,15-N-*(2-Chloroethoxy)cycloimide of chlorin* p_6 *methyl ester* **5**: yield 58%. Electronic spectrum [λ_{max}/nm (ε/10^3)]: 420 (118.6), 483 (9.6), 512 (10.7), 552 (26.3), 652 (12.7), 710 (45.7). ^{1}H NMR, δ: 9.65 (s, 1H, 10-H), 9.38 (s, 1H, 5-H), 8.62 (s, 1H, 20-H), 7.90 (dd, 1H, 3^1-CH, *J* 18 and 12 Hz), 6.33 (dd, 2H, 3^2-CH_2, *J* 18 Hz), 6.19 (dd, 2H, 3^2-CH_2, *J* 12 Hz), 5.33 (d, 1H, 17-H, *J* 8 Hz), 4.79 (t, 2H, OC*H*$_2$CH$_2$Cl, *J* 7 Hz), 4.38 (q, 1H, 18-H, *J* 8 Hz), 3.85 (s, 3H, CO_2Me), 3.69 (q, 2H, 8^1-CH_2, *J* 7 Hz), 3.60 (s, 3H, 12-Me), 3.38 (s, 3H, 2-Me), 3.19 (s, 3H, 7-Me), 3.15 (t, 2H, OCH$_2$C*H*$_2$Cl, *J* 7 Hz), 2.75 (m, 1H, 17^2-CH_2), 2.46 (m, 2H, 17^1-CH_2), 2.00 (m, 1H, 17^2-CH_2), 1.81 (d, 3H, 18-Me, *J* 8 Hz), 1.67 (t, 3H, 8^2-Me, *J* 7 Hz), 0.27 and 0.17 (2s, 2×1H, NH). MS, *m*/*z*: 656.3 (M^+ + H) (69), 658.3 (M^+ + H) (31) (calc. for $C_{36}H_{38}{}^{35}ClN_5O_5$, *M* = 655.3; for $C_{36}H_{38}{}^{37}ClN_5O_5$, *M* = 657.3).

13,15-N-*(2-Bromoethoxy)cycloimide of chlorin* p_6 *methyl ester* **6**: yield 71%. Electronic spectrum [λ_{max}/nm (ε/10^3)]: 420 (121.9), 482 (10.4), 512 (10.9), 552 (28.0), 652 (11.3), 711 (45.4). ^{1}H NMR, δ: 9.51 (s, 1H, 10-H), 9.26 (s, 1H, 5-H), 8.48 (s, 1H, 20-H), 7.85 (dd, 1H, 3^1-CH, *J* 18 Hz), 6.20 (dd, 2H, 3^2-CH_2, *J* 12 Hz), 5.25 (d, 1H, 17-H, *J* 8 Hz), 4.79 (m, 2H, OC*H*$_2$CH$_2$Br), 4.32 (q, 1H, 18-H, *J* 8 Hz), 3.92 (m, 2H, OCH$_2$C*H*$_2$Br), 3.76 (s, 3H, CO_2Me), 3.58 (q, 2H, 8^1-CH_2, *J* 7 Hz), 3.40 (s, 3H, 12-Me), 3.30 (s, 3H, 2-Me), 3.10 (s, 3H, 7-Me), 2.72 (m, 1H, 17^2-CH_2), 2.40 (m, 2H, 17^1-CH_2), 1.97 (m, 1H, 17^2-CH_2), 1.70 (d, 3H, 18-Me, *J* 8 Hz), 1.63 (t, 3H, 8^2-Me, *J* 7 Hz), 0.85 and 0.25 (2s, 2×1H, NH). MS, *m*/*z*: 699.1 (M^+) (50), 701.1 (M^+) (50) (calc. for $C_{36}H_{38}{}^{79}BrN_5O_5$, *M* = 699.2; for $C_{36}H_{38}{}^{81}BrN_5O_5$, *M* = 701.2).