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SYNTHESIS OF CHLORINS WITH A DISTAL VINYL GROUP

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A series of chlorins containing a vinyl group on the periphery of the chlorin ring that was attached by linkers of various length, potential monomers for synthesis of polymers containing chlorin via copolymerization, was synthesized from methylpheophorbide a.

Key words: methylpheophorbide a, chlorin e_6, chlorins with a distal vinyl group, monomers for copolymerization.

Porphyrins and their analogs grafted to polymers are promising photosensitizers for photodynamic sterilization of donor blood [1]. In particular, the synthesis of polymers with natural chlorins, especially the most abundant chlorophyll a and its derivatives, are of great interest. These compounds are attractive for synthesizing photosensitizers because, on one hand, they have good spectral properties and low toxicity [2] and, on the other, they have many reactive centers that enable various chemical transformations to be performed [3]. The vinyl group intrinsic to chlorophyll a and its derivatives can be used for copolymerization only with difficulty because it is bonded directly to the chlorin macrocycle and significant steric hindrances arise if it is used for the polymerization. A vinyl group distant from the macrocycle must be introduced into natural chlorin so that it can be used in copolymerization. Thus, the development of a method for synthesizing chlorins with a distal vinyl group is of great interest.

Chlorophyll a itself is rarely used as starting material for chemical transformations because of its poor stability and difficulties with preparing it pure.

Herein methylpheophorbide a (**1**), which is much more stable than chlorophyll a and is readily prepared pure while at the same time has the same reactive centers as chlorophyll a, is used as starting material for synthesizing chlorins with a vinyl group distant from the macrocycle. An allyl moiety was introduced on the periphery of the chlorin ring (**4**, **5**, **7**) by reactions at the exocycle and the 17-ester of **1**. Chemical transformations were used both for introducing the vinyl group on the periphery of the chlorin ring and for introducing a reactive center distant from the macrocycle.

The exocycle of chlorophyll a and its analogs, which have the same substituents in them, can be opened by primary and secondary amines [3]. This forms an amide bond at the 13-position. Substituents on the amine N atom end up bonded to the chlorin macrocycle. This reaction was used to synthesize from **1** chlorin e_6 13-amides with substituents of various hydrophilicity on the amide N atom [4, 5].

We synthesized chlorin e_6 13-amide (**5**), in which the vinyl group is bonded to the chlorin macrocycle by a 3-atom linker, by reacting **1** and allylamine. The action of certain amines on **1** is known to open the exocycle and convert the ester to an amide [5]. In this instance, this process would have been undesirable because introducing more than one distal vinyl group into chlorin could lead to formation of cross-linked polymers. The presence in the PMR spectrum of the main reaction product of singlets for the methyls of both esters and the relative intensities of the allyl protons led to the conclusion that undesired transformations of the esters into amides had not occurred under the reaction conditions. Analysis of the product mixture also did not detect products with additional amides, which indicated that the reaction was highly selective.

We used opening of the exocycle of **1** to prepare a chlorin with a vinyl that was more distant than that in **5**. An additional reactive center, a distal amine, was introduced onto the periphery of the macrocycle. Alkylation of this enabled an additional vinyl group to be conjugated. Chlorin with a distal amine (**6**) was synthesized by reacting ethylenediamine and **1** analogously to the amide synthesis described previously [4]. Compound **7** was synthesized by studying alkylation of the amine in **6** with allylchloride, allylbromide, and allyliodide. Acceptable alkylation yields were obtained for alkylation with allylbromide. Allylchloride and **6** did not react under these same conditions.

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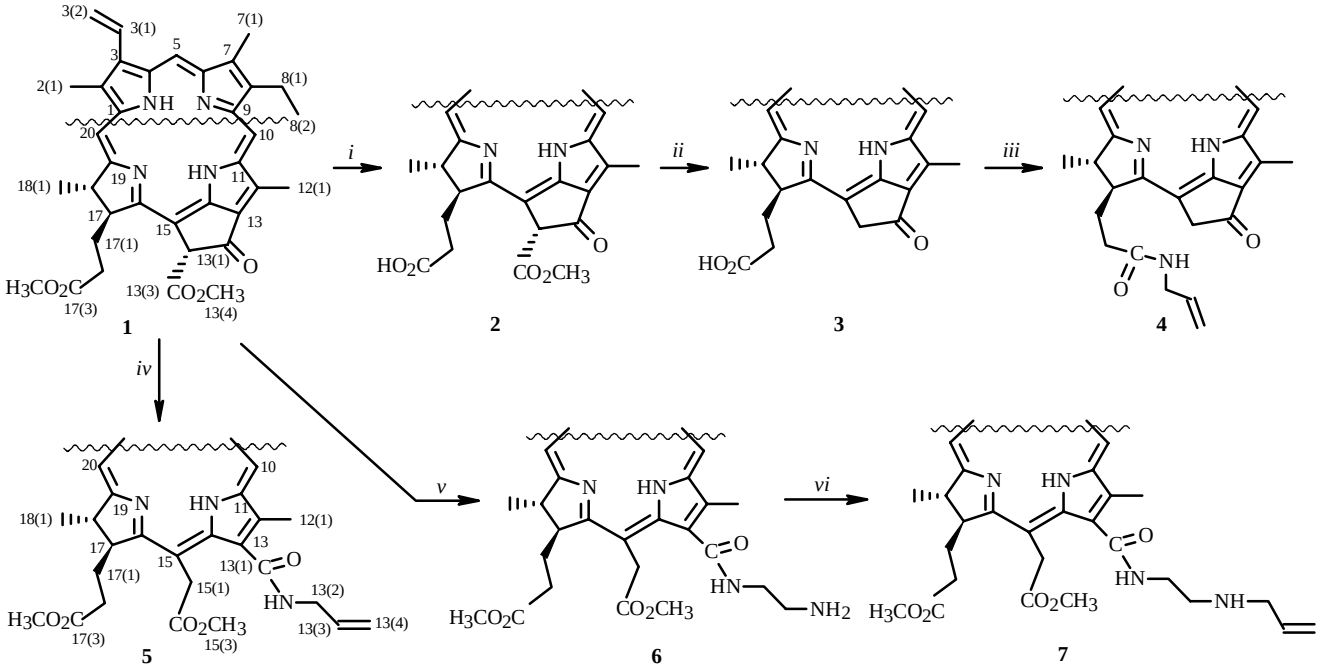

i. acetone, conc. HCl, 20-25°C, 22 h, yield 80%; *ii*. boiling in pyridine, 5 h, yield 78%; *iii*. Boc_2O (30 min at 0°C, CH_2Cl_2:pyridine), allylamine, 20-25°C; *iv*. allylamine, $CHCl_3$, 20-25°C; *v*. ethylenediamine, $CHCl_3$, 20-25°C; *vi*. allylbromide, sodium acetate, THF, boiling

Scheme 1.

A slightly shorter vinyl linker was conjugated in 17-[2-(*N*-allylcarbamoyl)]-substituted chlorophyll a derivatives. The reaction of the di-*t*-butylpyrocarbonate-activated carboxylic acid of the 17-propionate substituent with allylamine used pyropheophorbide a (**3**) instead of **2** because the exocycle could open to give chlorin with two distal vinyl groups in addition to the main product if **2** was used. In contrast with **2**, the exocycle of **3** cannot be opened under mild conditions by nucleophiles, which excludes this side reaction although the spectral properties of **2** and **3** are similar. Therefore, **2** was decarboxylated before reacting the carboxylic acid after acid-catalyzed hydrolysis of the ester of methylpheophorbide a. Despite the slightly shorter linker than in **7** through which the vinyl group in **4** is conjugated to the chlorin ring, the higher yield of **4** prepared from **1** makes this method preferable at this time for introducing the distal vinyl group.

The structures of all prepared compounds were confirmed by IR and NMR spectroscopy, which showed an allyl group in chlorins **4**, **5**, and **7**. The IR spectra of **4**, **5**, and **7** exhibited bands for C–H vinyl stretching vibrations (analogous vinyl vibrations were not observed in IR spectra of the starting chlorins). The PMR spectra of these chlorins contained multiplets for vinyl protons and multiplets for allyl methylene protons. Amide-I and amide-II vibration bands in IR spectra of **4** and **5** confirmed that they contained amides. Opening of the exocycle of **1** by allylamine during the synthesis of **5** was proved first by the absence in the IR spectrum of the reaction product of carbonyl vibrations of the exocycle **1** (1740 cm^{-1}) and, second, by the presence in the PMR spectrum of doublets for the 15-methylenes formed by exocycle opening.

Thus, we synthesized chlorins with a vinyl group conjugated to the macrocycle by linkers of various length that can be used as monomers for synthesizing polymers containing chlorins through copolymerization.

EXPERIMENTAL

PMR spectra of synthesized compounds in $CDCl_3$ or DMF-d_7 were recorded on Bruker AMX-400 instruments (working frequency 400 MHz); IR spectra, on a Specord M-80 in KBr disks. The course of reactions was monitored by TLC on Sorbfil plates. Products were purified by column chromatography over silica gel 100/400 (Lachema).

Methylpheophorbide a (1) was prepared from spirulina blue-green alga according to the literature method [6]; pheophorbide a (**2**) and pyropheophorbide a (**3**), by literature methods [7, 8]. Spectral properties of **1**-**3** were analogous to those described previously [4, 8].

Chlorin e_6 13-*N*-Alylamide-15,17-dimethylester (5). A solution of **1** (220 mg) in $CHCl_3$ (6 mL) was treated with allylamine (1 mL). The reaction mixture was stirred at room temperature for 4 h (TLC, elution by CCl_4:acetone, 4:1), diluted with $CHCl_3$ (40 mL), washed with water to remove allylamine until the rinsings were neutral, dried over anhydrous Na_2SO_4, and evaporated at reduced pressure. The solid was chromatographed over silica gel [elution by CCl_4:acetone (60:1) until unreacted **1** was completely removed then 20:1]. The effluent containing the main product was evaporated and reprecipitated from $CHCl_3$:pentane to afford **5**, 210 mg (90%), $C_{39}H_{45}N_5O_5$. IR spectrum (KBr, cm^{-1}): 1608 (chlorin band), 3097 (νC–H, vinyl), 1664 (amide-I), 1516 (amide-II), 1742 (νC=O ester).

PMR spectrum (DMF-d_7, δ, ppm, J/Hz): 9.90 (1H, s, H-10), 9.86 (1H, s, H-5), 9.23 (1H, s, H-20), 9.08 [1H, br.t, J = 5.4, NH-13(1)], 8.37 [1H, dd, J = 11.6 and 8.8, H-3(1)], 6.48 [1H, dd, J = 8.8 and 0.8, H(*trans*)-3(2)], 6.22-6.35 [1H, m, CH(Vi)-13(3)], 6.18 [1H, dd, J = 5.8 and 1.2, H(*cis*)-3(2)], 5.72 (1H, d, J = 18.8) and 5.42 (1H, d, J = 19.2 [CH_2-15(1)], 5.55 [1H, dd, J = 8.6 and 1.6, H(*trans*)-13(4)], 5.31 [1H, dd, J = 5.1 and 1.4, H(*cis*)-13(4)], 4.72 (1H, br.q, J = 7.2, H-18) 4.55 (1H, br.d, J = 8.4, H-17), 4.42-4.52 (1H, m) and 4.25-4.35 (1H, m) [CH_2-13(2)], 3.83-3.92 [2H, m, CH_2-8(1)], 3.78 [3H, s, CH_3-15(3)], 3.83 [3H, s, CH_3-17(4)], 3.60 [3H, s, CH_3-12(1)], 3.58 (3H, s, CH_3-2(1)], 3.37 [3H, s, CH_3-7(1)], 2.21-2.43 [2H, m, CH_2-17(1)], 1.68-1.84 [2H, m, CH_2-17(2)], 1.69-1.76 [6H, m, CH_3-18(1), CH_3-8(2)], -1.61 (1H, br.s, NH-I), -1.93 (1H, br.s, NH-III).

Pyropheophorbide a 17-*N*-Allylamide (4). A solution of **3** (200 mg) in CH_2Cl_2 (4 mL) and pyridine (2 mL) was treated with di-*t*-butylpyrocarbonate (200 mg), stirred at 0°C for 30 min, treated with allylamine (1 mL), stirred at room temperature for 1.5 h (TLC, elution by CCl_4:acetone, 4:1), diluted with $CHCl_3$ (30 mL), and washed with HCl (5%) to remove pyridine and allylamine, an excess of HCl, and water until the rinsings were neutral. The resulting solution was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The solid was chromatographed over silica gel with elution by CCl_4:acetone (15:1). The effluent containing the main product was evaporated and reprecipitated from $CHCl_3$ by pentane to afford **4**, 146 mg (72%), $C_{36}H_{39}N_5O_2$. IR spectrum (KBr, cm^{-1}): 1624 (chlorin band), 3100 (νCH, vinyl), 1669 (amide-I), 1556 (amide-II), 1696 (νC=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 9.24 (1H, s, H-10), 9.07 (1H, s, H-5), 8.48 (1H, s, H-20), 7.88 [1H, dd, J = 11.4 and 8.9, H-3(1)], 6.20 [1H, dd, J = 8.9 and 1.4, H(*trans*)-3(2)], 6.09 [1H, dd, J = 5.8 and 1.2, H(*cis*)-3(2)], 5.49-5.61 [1H, m, CH(Vi)-17(5)], 5.35 [1H, br.t, J = 5.2, NH-17(3)], 5.13 (1H, d, J = 19.6) and 4.97 (1H, d, J = 20) [CH_2-15(1)], 4.86-4.93 [2H, m, CH_2(Vi)-17(6)], 4.44 (1H, br.q, J = 6.5, H-18), 4.23 (1H, br.d, J = 7.2, H-17), 3.56-3.68 [2H, m, CH_2-17(4)], 3.42-3.53 [2H, m, CH_2-8(1)], 3.33 [3H, s, CH_3-12(1)], 3.22 [3H, s, CH_3-2(1)], 3.13 [3H, s, CH_3-7(1)], 2.53-2.65 (1H, m), 2.27-2.39 (1H, m), 2.11-2.22 (1H, m), and 1.87-1.95 (1H, m) [CH_2-17(1) and CH_2-17(2)], 1.74 [3H, d, J = 7.6, CH_3-18(1)], 1.56 [3H, t, J = 7.6, CH_3-8(2)], 0.36 (1H, br.s, NH-I), -1.78 (1H, br.s, NH-III).

Chlorin e_6 13-*N*-(2-Aminoethyl)-amide-15,17-dimethyl Ester (6). A solution of **1** (300 mg) in $CHCl_3$ (5 mL) was treated with ethylenediamine (0.6 mL), stirred at room temperature for 4 h (TLC, elution by $CHCl_3$:CH_3OH, 9:1), diluted with $CHCl_3$ (30 mL) and washed with water to remove ethylenediamine. The resulting solution was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The solid was chromatographed over silica gel [elution by CCl_3:acetone (20:1) until **1** was completely removed then $CHCl_3$:CH_3OH (10:1)]. The effluent containing the main product was evaporated and reprecipitated from $CHCl_3$ by pentane to afford **6**, 240 mg (73%). The spectral properties have been published [9]. IR spectrum (KBr, cm^{-1}): 1608 (chlorin band), 1524 (amide-I), 1636 (amide-II), 1742 (νC=O ester).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 9.89 (1H, s, H-10), 9.87 (1H, s, H-5), 9.23 (1H, s, H-20), 9.06 [1H, br.t, J = 5.7, NH-13(1)], 8.39 [1H, dd, J = 17.6 and 11.6, H-3(1)], 6.49 [1H, dd, J = 18.0 and 1.2, H(*trans*)-3(2)], 6.20 [1H, dd, J = 11.6 and 1.2, H(*cis*)-3(2)], 5.71 (1H, d, J = 18.4) and 5.42 (1H, d, J = 19.6) [CH_2-15(1)], 4.72 (1H, br.q, J = 8.2, H-18), 4.34 (1H, m, H-17), 3.8-4.0 [4H, m, CH_2-13(2), CH_2-13(3)], 3.70-3.80 [2H, m, CH_2-8(1)], 3.78 [3H, s, CH_3-15(3)], 3.64 [3H, s, CH_3-17(4)], 3.60 [3H, s, CH_3-12(1)], 3.59 [3H, s, CH_3-2(1)], 3.37 [3H, s, CH_3-7(1)], 3.24 [2H, br.t, J = 6.2, NH_2-13(3)], 2.20-2.70 [2H, m, CH_2-17(1)], 1.60-1.80 [2H, m, CH_2-17(2)], 1.70-1.73 [6H, m, CH_3-18(1), CH_3-8(2)], -1.61 (1H, br.s, NH-I), -1.93 (1H, br.s, NH-III).

Chlorin e_6 13-*N*-(2-(*N*-Allylamino)-ethyl)-amide-15,17-dimethyl Ester (7). A solution of **6** (150 mg) in THF (6 mL) was treated with freshly distilled allylbromide (2 mL) and anhydrous CH_3COONa (40 mg). The resulting mixture was refluxed for 1 h (TLC with elution by CCl_4:acetone, 4:1). When the reaction was finished, the mixture was diluted with $CHCl_3$ (40 mL)

and washed with water to remove sodium acetate. The resulting $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The solid was chromatographed over silica gel with elution by CCl_4:acetone (20:1). The effluent containing the main product was evaporated and reprecipitated from $CHCl_3$ by pentane to afford **7**, 49 mg (30%), $C_{41}H_{50}N_6O_5$. IR spectrum (ν, cm^{-1}): 1605 (chlorin band), 3079 (νC–H, vinyl), 1651 (amide-I), 1512 (amide-II), 1736 (νC=O ester).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 9.69 (1H, s, H-10), 9.62 (1H, s, H-5), 8.79 (1H, s, H-20), 8.07 [1H, dd, J = 11.6 and 9.3, H-3(1)], 6.33 [1H, dd, J = 8.8 and 1.2, H(*trans*)-3(2)], 6.12 [1H, dd, J = 5.7 and 1.4, H(*cis*)-3(2)], 5.78-5.91 [2H, m, NH-13(1), CH(Vi)-13(5)], 5.54 (1H, d, J = 18.4) and 5.27 (1H, d, J = 20) [CH_2-15(1)], 5.14-5.28 [2H, m, CH_2(Vi)-13(6)], 4.46 (1H, br.q, J = 7.2, H-18), 4.38 (1H, br.d, J = 5.2, H-17), 3.94-4.06 [2H, m, CH_2-13(4)], 3.73-3.84 [4H, m, CH_2-13(2), CH_2-13(3)], 3.53-3.67 [2H, m, CH_2-8(1)], 3.73 [3H, s, CH_3-15(3)], 3.61 [3H, s, CH_3-17(4)], 3.56 [3H, s, CH_3-12(1)], 3.48 [3H, s, CH_3-2(1)], 3.30 [3H, s, CH_3-7(1)], 2.84-2.88 [1H, m, NH-13(3)], 2.50-2.62 (1H, m), 2.08-2.27 (3H, m) [CH_2-17(1) and CH_2-17(2)], 1.72 [3H, t, J = 8, CH_3-8(2)], 1.25 [3H, d, J = 7.2, CH_3-18(1)], -1.57 (1H, br.s, NH-I), -1.79 (1H, br.s, NH-III).

The yield of **7** from alkylation of **6** by allyliodide under analogous conditions was 5%. Alkylation of **6** by allylchloride under these conditions was unsuccessful.

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