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OPENING OF THE PHORBIN EXOCYCLE BY WEAK O-NUCLEOPHILES. STUDY AND OPTIMISATION OF FREE CHLORINE e_6 SYNTHESIS METHODS

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Abstract. *The article considers issues concerning the reaction of exocycle opening in phorbin molecules (on the example of methylpheophorbide a) under the O-nucleophiles - water and alcohols action. According to the author, under certain conditions relatively weak nucleophiles as water and alcohols can cause the opening of the exocycle in the molecule of methylpheophorbide a with the formation of chlorine derivatives e_6. The study of this reaction, in addition, reveals new synthetic methods to obtain chlorine e_6 esters of different degrees of substitution, and eventually - free chlorine e_6 in the form of triacids. Free chlorine is a valuable photosensitiser for photodynamic therapy (PDT), and a starting compound for the preparation of other photosensitizers. The article also discusses possible synthetic approaches to obtain free chlorine e_6.*

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Introduction

Some medical issues remain topical and unresolved even in the 21st century. These are, in particular, the issues of cancer and antibiotic-resistant bacterial infections [1-8]. This fact predetermines the constant search for new effective and at the same time maximally safe ways to solve these problems [7]. Photodynamic therapy (PDT) is one of the most promising methods aimed at combating both cancer diseases and pathogenic bacterial microflora; a method associated with the use of photosensitisers (PS) [7-10]. A photosensitizer is usually an organic dye with the ability to selectively accumulate in tumour tissues or bacterial cells. Moreover, during irradiation with light of a certain wavelength, it generates active (singlet) oxygen. Active oxygen, in turn, destroys surrounding tumour tissues or bacterial cell organelles [7]. Since singlet oxygen is generated only in the place of photosensitizer accumulation during

its laser irradiation. The healthy tissues around the tumour or the focus of bacterial infection are not affected [7]. However, photosensitisers have a number of requirements (simultaneous water- and fat-solubility (amphiphilicity), ability to absorb light quanta in the red and near-infrared regions of the spectrum, efficient generation of singlet oxygen and other reactive oxygen species, tropism to tumour cells, low toxicity and phototoxicity, high rate of elimination from the body), etc. Indeed, very few of them can be realised through one chemical compound only. Thus, there is no "ideal photosensitizer" [7]. Therefore, scientist are in the constant search for new photosensitisers - natural and synthetic ones.

Semisynthetic derivatives of natural chlorophyll - derivatives of phorbins, as well as amides and esters of chlorine e_6 (both in free form and as conjugates with various monomeric biomolecules and biopolymers) are very promising asphotosensitisers [11-16]. Nevertheless, even these compounds still do not fully satisfy the whole set of requirements for photosensitisers. Therefore, the search for new ways of their synthesis and modification continues. It is also a challenge to obtain free chlorine e_6 in pure form by standard methods, such as alkaline hydrolysis of its esters or methylpheophorbide *a*. It produces a mixture of similar compounds which must be separated [17].

The initial compound for the preparation of chlorine $e_6$various derivatives is methylpheophorbide *a*. It is obtained from natural chlorophyll *a* in two steps. The first stepis demetallisation (removal of the magnesium ion by hydrochloric acid), and the second one is transesterification (replacement of the phytol residue with a methyl group at position 17 by methanol-sulphuric acid (5% vol.)). In order to obtain chlorine e_6 derivatives from methylpheophorbid e_a, it is necessary to open the phorbinexocycle. The exocycle opening reaction is a nucleophilic substitution at the carbonyl carbon atom at position 13(1) [18]. The tendency of the exocycle to open under the action of nucleophilic reagents is primarily due to the removal of steric stresses (distortion of valence angles in the exocycle and repulsion of closely located bulk substituents at positions 17 and 13(2)) during the reaction. It also concerns with the peculiarities of the process mechanism (the possibility of negative chargedelocalisation in the carboanion formed by heterolytic bond breaking 13(1)-C-13(2)-C) [16].

The reaction of exocycle opening has been studied quite well on the example of the methylpheophorbide *a* interaction with amines acting as N-nucleophiles [18, 19]. The spatial structure of amine (the degree of the nitrogen atom shielding by substituents) and the electronic structure of the macrocycle (the presence of electron-acceptor substituents should hypothetically facilitate the reaction) have a significant influence on reaction proceeding [18]. In this case, the steric factor plays a dominant role and cannot be compensated by the electronic one. Hence, primary, and secondary aliphatic amines react smoothly. In case of secondary amines, the substituents at the nitrogen atom should not be more voluminous than the *n*-propyl group [18]. Moreover, the process characterized by the excesses of amines (100-200-fold). At the same time, there are studies [20, 21] describing the opening of the exocycle by bulk amine molecules with minimum excesses. However, the use of more stringent

conditions for the reaction of exocycle opening (boiling in toluene instead of room temperature) causes reaction direction changing. Furthermore, amidation of the exocycleester group occurswithout its opening [18].

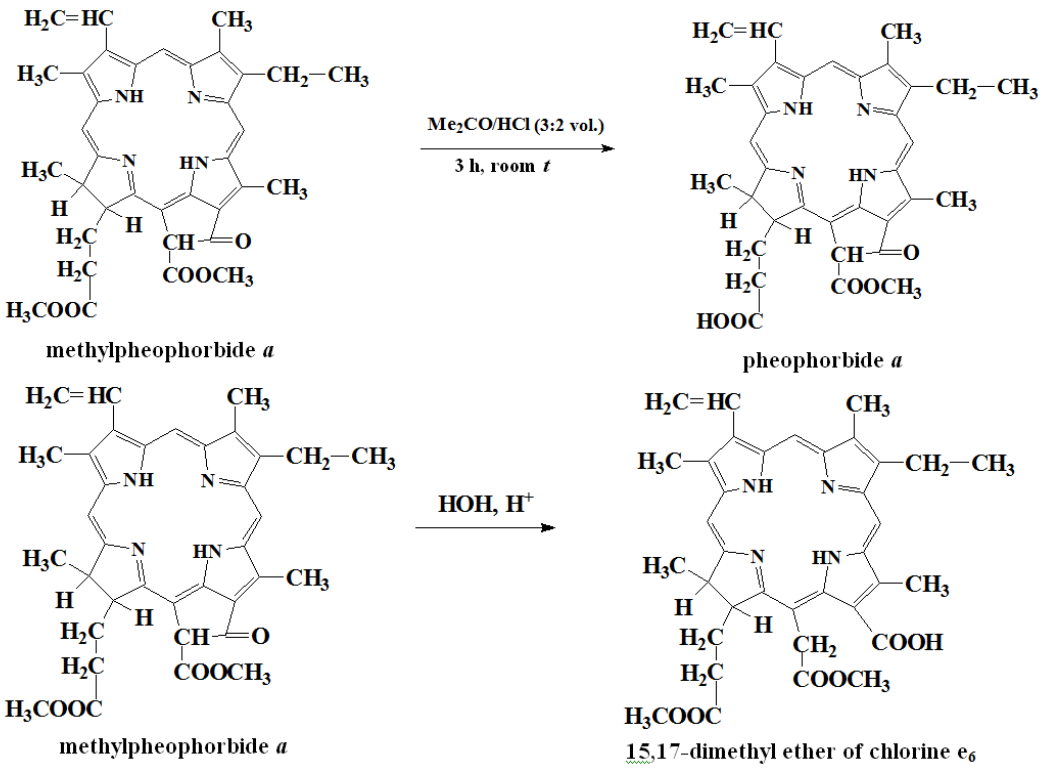
The opening of the exocycle by O-nucleophiles in methylpheophorbide *a* and its derivatives has been described in the literature [22, 23]. However, those O-nucleophiles should be by very strong ones (in particular, sodium methylate). Alkaline hydrolysis of phorbin derivatives ispreparatively inexpedient. Therefore, it causes the formation of a difficult-to-separate mixture of free chlorine e_6 and its methyl esters with various degrees of substitution [18]. For preparation of trimethyl ether of chlorine e_6, treatment of such mixtures with diazomethane is usually used [22, 23]. Their preparation is associated with certain difficulties (relatively inaccessible reagents) and risks (starting substances for the synthesis, particularly N-nitrosomethylurea, are carcinogenic, and diazomethane itself is poisonous and explosive). The trimethyl ether of chlorine e_6 can be obtained by treatment of methylpheophorbide *a* with sodium methylate [22]. It is also formed by the action of potassium hydroxide solution in methanol on methylpheophorbide *a* in pyridine [24] or tetrahydrofuran. Water, although in trace quantities, was found to be a weak nucleophile, when interacting with phorbines under certain conditions, can form exocycle opening products. Pheophorbide *a* also undergoes exocycle opening upon treatment with potassium hydroxide in the THF-methanol system at room temperature to form 17-carboxy-13,15-dimethyl ether of chlorine e_6.

Free chlorine e_6 is formed along with other products when a solution of methylpheophorbide *a* in THF is treated with aqueous potassium hydroxide solution at boiling. One of the by-products is chlorine e_4. It is a product of a single decarboxylation of chlorine e_6 at position 15 of the macrocycle. The decarboxylation reaction of chlorine e_6 is described in the literature [25]. It proceeds upon heating of chlorine e_6 in basic media.

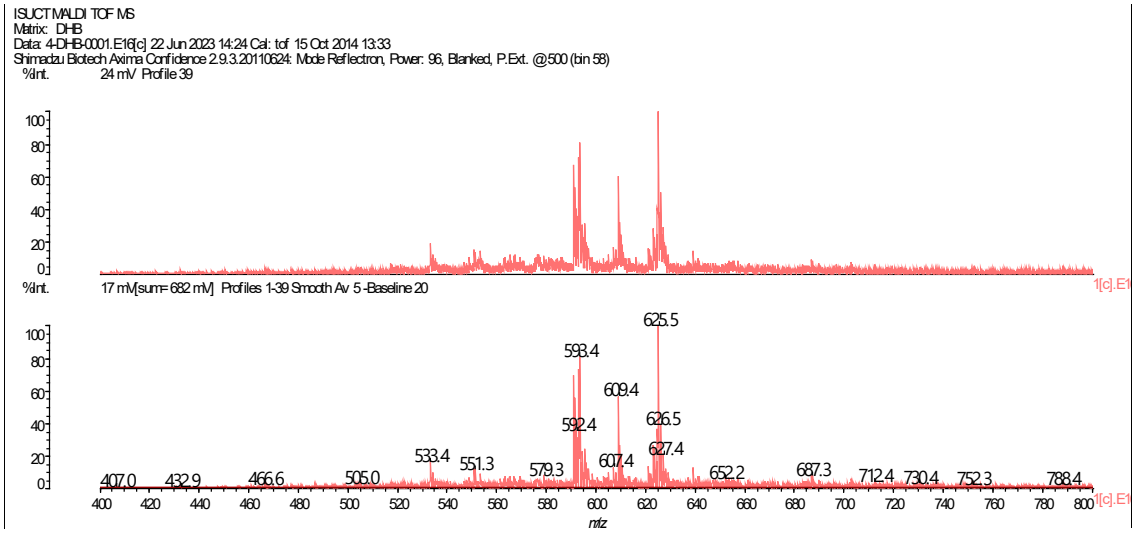
Experimental part

Methylpheophorbide *a* was prepared according to [26]. The solvents were purified by generally accepted methods. Methanol was dried by distillation over magnesium metal; tetrahydrofuran and chloroform were distilled after soaking over potassium hydroxide and sodium sulphate, respectively. Acetone was subjected to distillation with a deflagmator. Potassium hydroxide and hydrochloric acid were used without prior preparation. Mass spectra were recorded using an Axima Confidence time-of-flight tandem mass spectrometer with matrix-assisted ionisation (MALDI TOF) (Shimadzu, Japan). 2,5-dihydroxybenzoic acid (DHB) and α-cyano-4-hydroxycinnamic acid (CHCA) were used as matrix. ^{1}H NMR spectra were recorded on an Avance-500 spectrometer (Bruker, Germany) with an operating frequency of 500 MHz at 293 K.

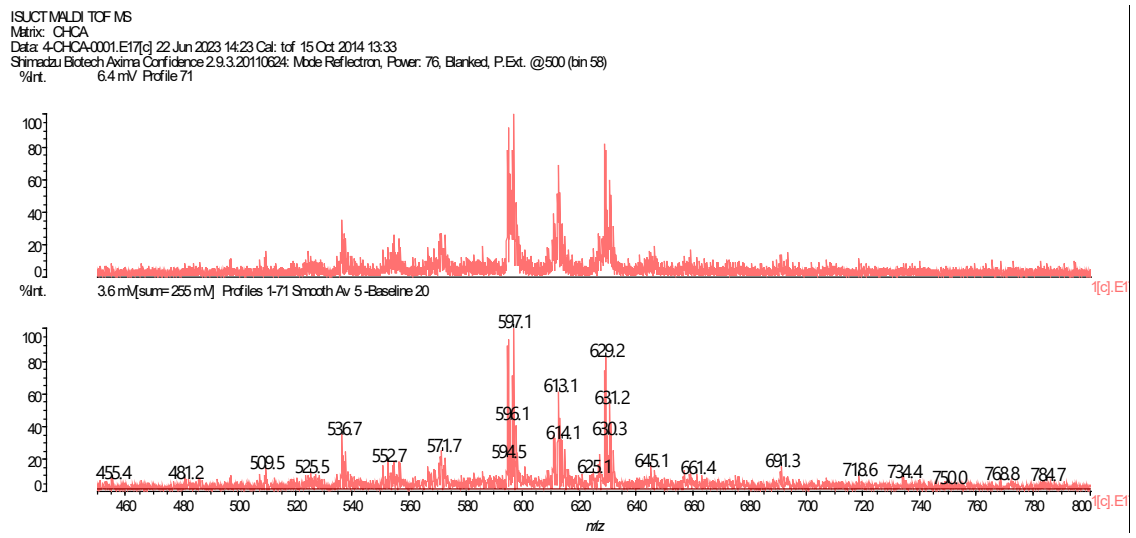
1. Study of methylpheophorbide *a* hydrolysis in an acidic medium.



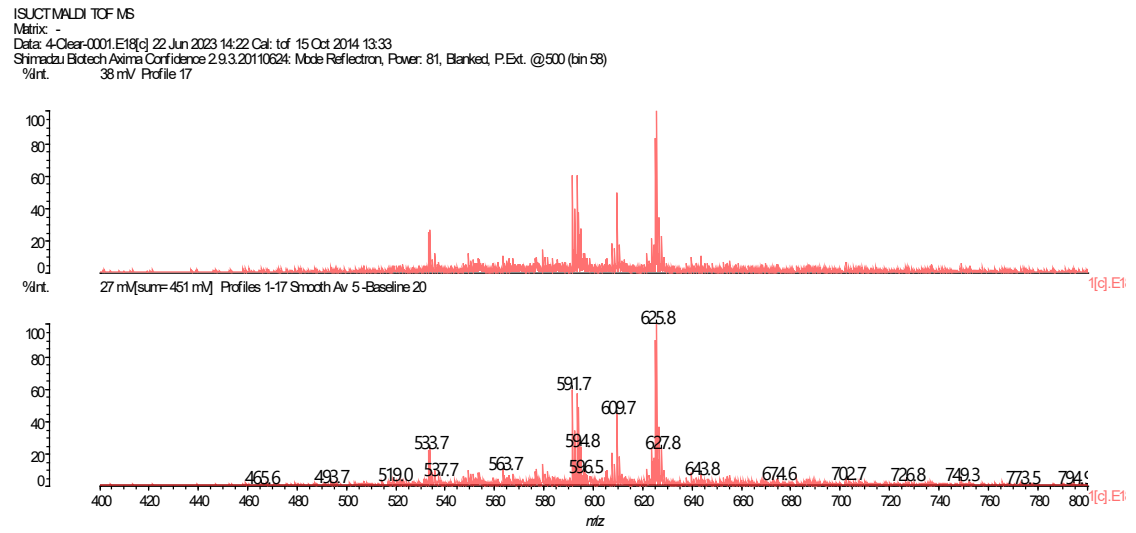
We dissolved methylpheophorbide *a* (200 mg, 0.329 mmol) in 6 ml of acetone. We added 4 ml of concentrated hydrochloric acid to the resulting solution. We stirred the reaction mixture at room temperature for 4 h, followed by extraction with chloroform and methanol, and washing the organic layer with water. TLC (silica gel, dichloromethane - methanol (10% vol.)) of the reaction mixture after extraction shows, in addition to the main zones (pheophorbide *a* as the main product and traces of unreacted initial methylpheophorbide *a*), also the presence of a green-coloured hard-to-suspend fraction. We performed column chromatography of the obtained product in silica gel using chloroform-methanol mixtures (2-20% vol.) as eluent. The green-coloured fraction released the column last and was washed off with chloroform - methanol (20% vol.) mixture. According to mass spectrometry data, this fraction is a mixture of free chlorine e_6 and its methyl esters of different degrees of substitution. However, the predominant component of the mixture is dimethyl ester of chlorine e_6 (M = 625) (Fig. 1). Logically, it is 15,17-dimethyl ether of chlorine e_6 with a free carboxyl group at position 13, at the exocycle opening site; the exocycle opening agent is water. The mixture also contains the monomethyl ester of chlorin e_6 (M = 611) (see Fig. 1), apparently being a 15-monomethyl ester, since the 17-$COOOCH_3$-group undergoes acid hydrolysis more readily than the 15-$COOCH_3$-group. This follows from numerous experimental data on the preparation of 17-monocarboxylic derivatives of chlorine e_6 13-amides of 15-monomethyl ethers, as well as pheophorbide obtained by selective hydrolysis of the 17-$COOOCH_3$-group in the methylpheophorbide molecule to the 17-COOH-group while retaining the 15-$COOCH_3$-fragment. Finally, free chlorine e_6 corresponds to the 597 signal present in the mass spectra (see Fig. 1).



DHB



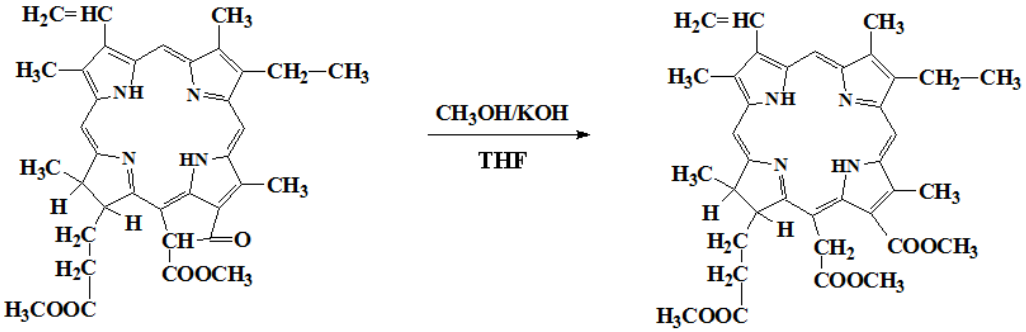
CHCA



Without matrix

Fig. 1. Mass spectra of the "green fraction" on and without different matrices

2. Synthesis of 13,15,17-trimethyl ether e_6 chlorine.



We dissolved methylpheophorbide *a* (121.6 mg, 0.2 mmol) in 6 ml of tetrahydrofuran. We dissolved potassium hydroxide (336 mg, 6 mmol) in 12 ml of methanol. We added the potassium hydroxide solution to the solution of methylpheophorbide *a*; the reaction mixture turned green. We added chloroform and water to the reaction mixture; there was a separation into two layers. The lower coloured organic layer was separated and washed off with water. Column chromatography of the crude product obtained was performed in silica gel using chloroform-methanol mixture (1% vol.) as eluent. The first fraction (green colour) represents the target product. It is confirmed by mass spectrometry (M = 640) (Fig. 2) and ^{1}H-NMR data.

13,15,17-Trimethyl ether of chlorine e_6. Dark green powder. Yield 89.6 mg (70%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ, ppm: 9.71 (s, 1H, 10-H), 9.58 (s, 1H, 5-H), 8.76 (s, 1H, 20-H), 8.08 (dd, 1H, 3(1)-H), 6.37 (dd, 1H, 3(2)-H-*trans*), 6.16 (dd, 1H, 3(2)-H-*cis*), 5.37 (d, 1H, 15(1)-CH), 5.26 (d, 1H, 15(1)-CH'), 4.47 (dd, 1H, 18-H), 4.42 (d, 1H, 17-H), 4.28 (s, 3H, 13-$COOCH_3$), 3.84 – 3.76 (overlapping m + s, sums. 5H, 8(1)-CH_2, 15(3)-CH_3), 3.66 (s, 3H, 12(1)-CH_3), 3.60 (s, 3H, 17(4)-CH_3), 3.49 (s, 3H, 2(1)-CH_3), 3.32 (s, 3H, 7(1)-CH_3), 2.58 (m, 1H), and 2.22 (m, 2H): 17(1)-CH_2, 17(2)-CH_2; 1.80–1.71 (overlapping d + t + m, sums. 7H, 8(2)-CH_3, 18(1)-CH_3, 17-CH_2), -1.28 (s, 1H, 21-NH), -1.44 (s, 1H, 23-NH).

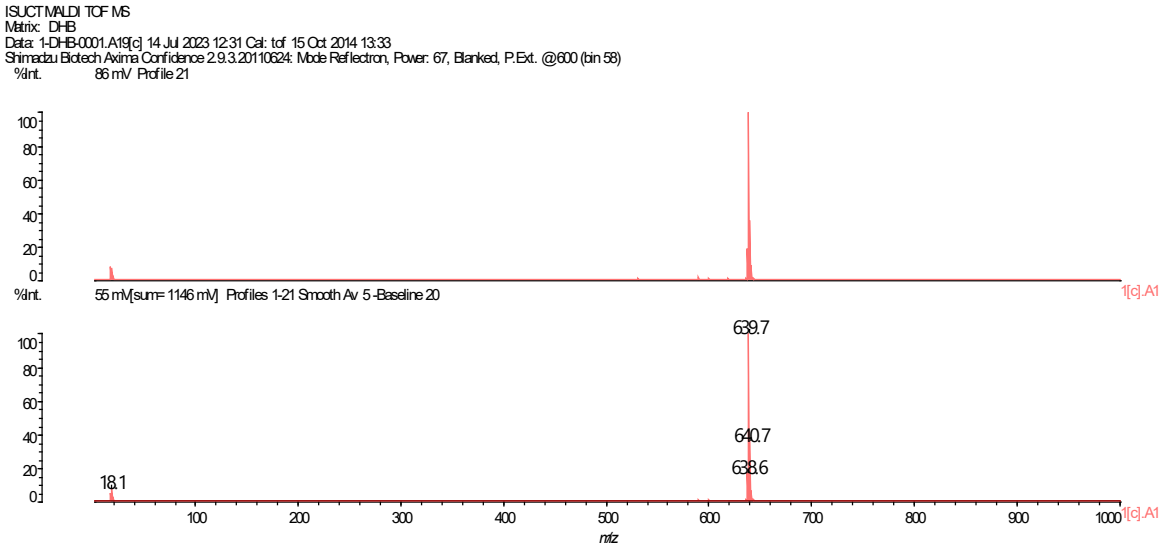


Fig. 2. Mass-spectrum of 13,15,17-trimethyl ether e_6 chlorine

According to mass spectrometry, mono- and dimethyl esters of chlorine e_6 are also formed in trace amounts as by-productsa (M = 612 and 625, respectively) (Fig. 3). They can be

easily separated chromatographically (washed off the column only by high concentrations of methanol up to 100%).

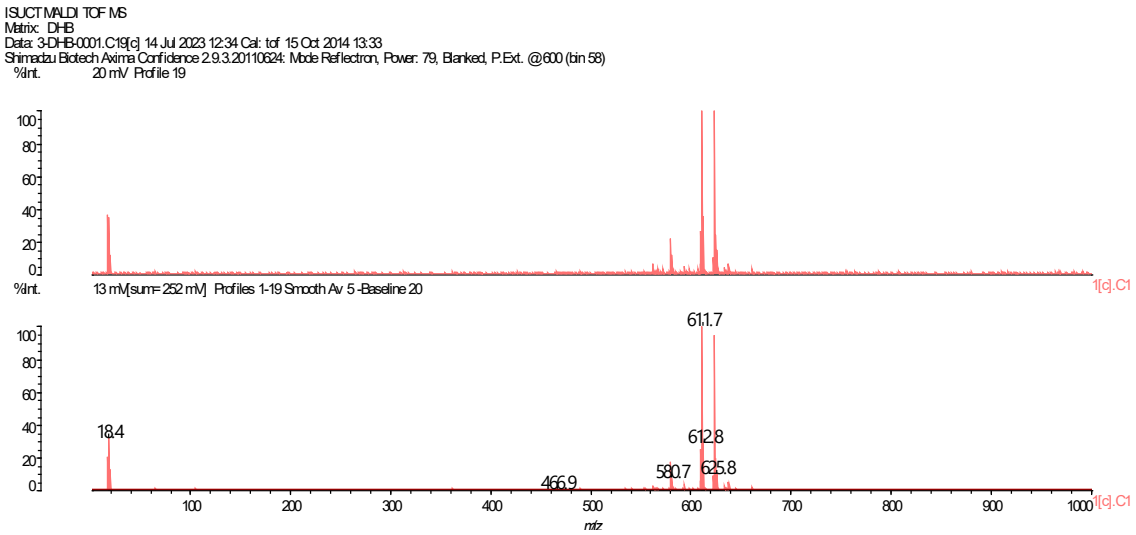
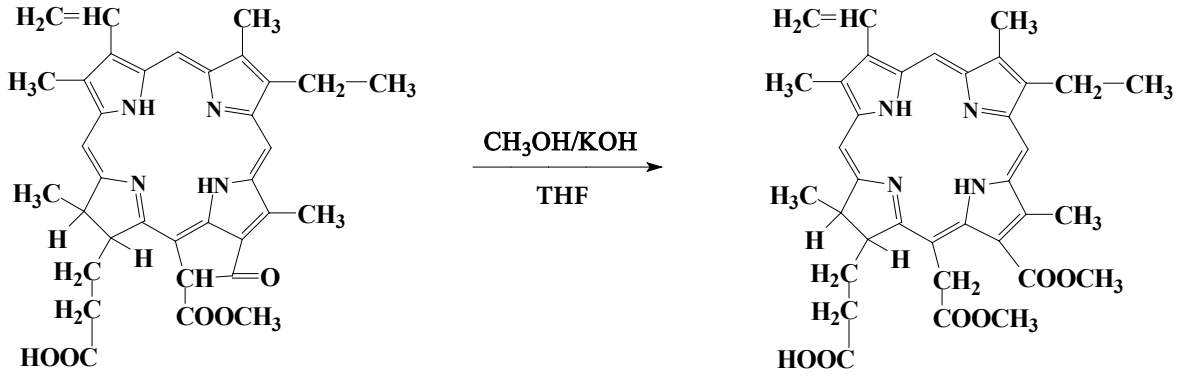


Fig. 3. Mass spectrum of a mono- and dimethyl ester mixture of chlorine e_6

3. Synthesis of 17-carboxy-13,15-dimethyl chlorine ester e_6.



We dissolved pheophorbide *a* (59.4 mg, 0.1 mmol) in 4 ml of tetrahydrofuran and potassium hydroxide (145.9 mg, 2.6 mmol) in 6 ml of methanol. We added the alkali solution to the pheophorbide solution. We diluted the resulting solution (green colour) with water and neutralised it with a calculated amount of dilute hydrochloric acid (0.2 ml of HCl in 20 ml of water). It resulted by coloured precipitation, which was filtered on a paper filter, dried at room temperature, and subjected to column chromatography in silica gel using chloroform-methanol mixture (2% vol.) as eluent. According to mass spectrometry data and ^{1}H-NMR (M = 626.1 (Fig. 4), first green-coloured fraction represents the target product.

17-Carboxy-13,15-dimethyl ether of chlorine e_6. Dark green powder. Yield 21.1 mg (34%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ, ppm: 9.71 (s, 1H, 10-H), 9.58 (s, 1H, 5-H), 8.77 (s, 1H, 20-H), 8.08 (dd, 1H, 3(1)-H), 6.37 (dd, 1H, 3(2)-H-*trans*), 6.16 (dd, 1H, 3(2)-H-*cis*), 5.34 (d, 1H, 15(1)-CH), 5.28 (d, 1H, 15(1)-CH'), 4.46 (overlapping d + dd, sums. 2H, 18-H, 17-H), 4.26 (s, 3H, 13-$COOCH_3$), 3.80 (qu, 2H, 8(1)-CH_2), 3.76 (s, 3H, 15(3)-CH_3), 3.59 (s, 3H, 12(1)-CH_3), 3.49 (s, 3H, 2(1)-CH_3), 3.31 (s, 3H, 7(1)-CH_3), 2.62, and 2.22 (both – m, sums. 4H, 17(1)-CH_2, 17(2)-CH_2), 1.77 (d, 3H, 8(2)-CH_3), 1.73 (t, 3H, 18(1)-CH_3), -1.45 (s, 1H, 23-NH).

As a by-product, monomethyl ether of chlorine e_6 (M = 612) is also formed. It was washed off from the column (together with residual amounts of the target product) by chloroform-methanol mixture (1:1 vol.), as can be seen from mass spectrometry data (Fig. 5).

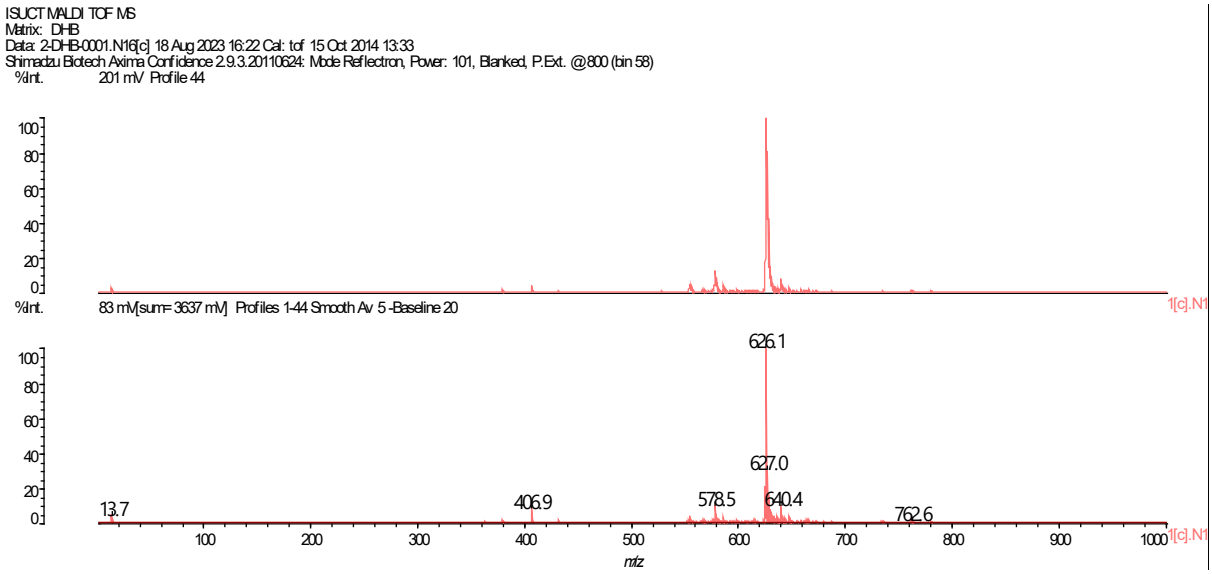


Fig. 4. Mass-spectrum of 17-carboxy-13,15-dimethyl chlorine ester e_6

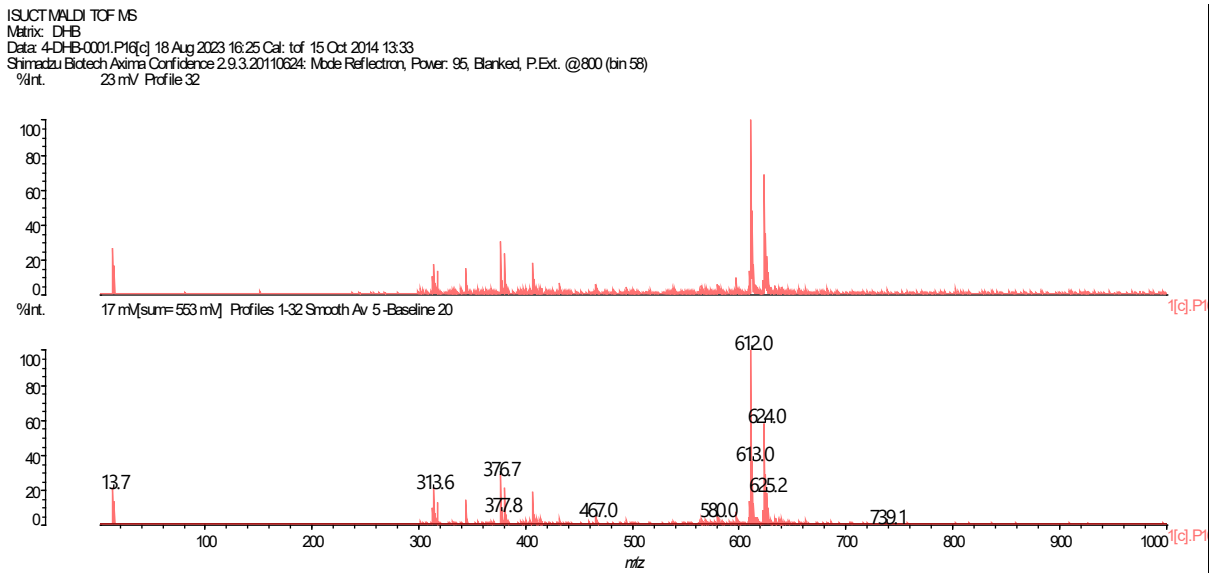
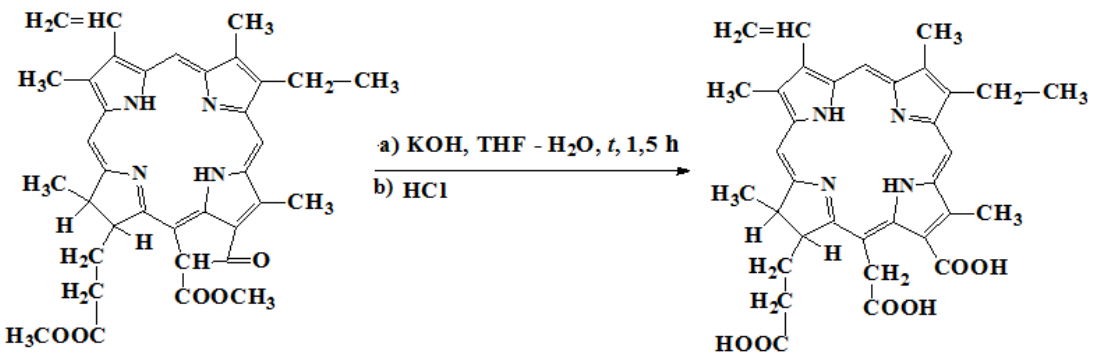


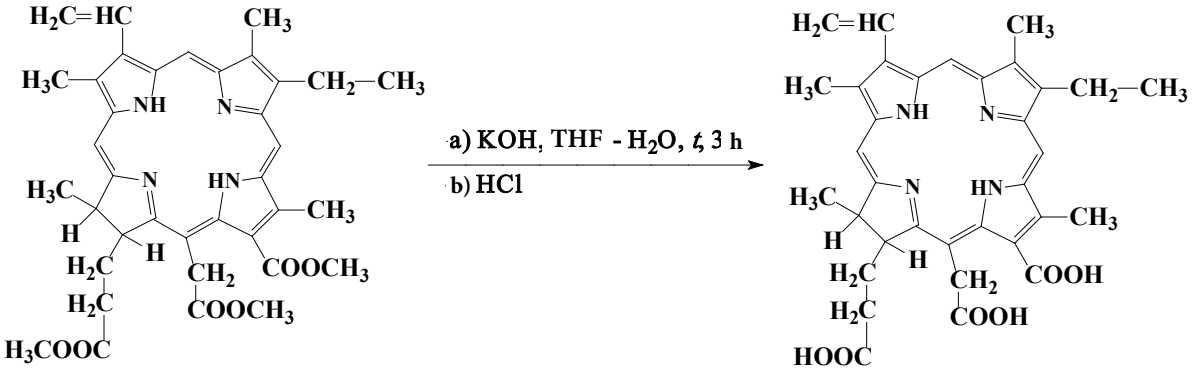
Fig. 5. Mass spectrum of the side fraction in the synthesis of 17-carboxy-13,15-dimethyl ether of chlorine e_6

4. Synthesis of chlorine e_6 from methylpheophorbide *a*.



Methylpheophorbide *a* (121.6 mg, 0.2 mmol) was dissolved in 10 mL of tetrahydrofuran; potassium hydroxide (3.36 g, 60 mmol) was dissolved in 10 ml of water. We added the alkali solution to the macrocyclic compound. We boiled the reaction mixture with a reflux condenser for 1.5 h, diluted it with water, and neutralised it with dilute hydrochloric acid (5 ml $HCl_{conc.}$ In 50 ml water). The precipitate was filtered and dried at room temperature. Column chromatography of the obtained product was performed in silica gel using chloroform-methanol mixtures as eluent. Chlorine e_6 elutes from the column in a wide range of concentrations of methanol in chloroform. Indeed, the largest amount is washed off by chloroform-methanol mixture 1:1 vol. (at lower concentrations of methanol mainly by-products are washed off). Note, after column chromatography, chlorine e_6 still contains some impurities; the yield of such "crude" chlorine e_6 was 29.9 mg (25%).

5. Synthesis of chlorine e_6 from 13,15,17-trimethyl ether of chlorine e_6.



We dissolved 13,15,17-Trimethyl ether of chlorine e_6 (192.0 mg, 0.3 mmol) in 15 ml of tetrahydrofuran and potassium hydroxide (5.04 g, 90 mmol) in 15 ml of water. We added the alkali solution to the macrocyclic compound. We boiled the reaction mixture with a reflux condenser for 3 h, diluted it with water, and neutralised it with dilute hydrochloric acid (7,5 ml $HCl_{conc.}$ in 75 ml water). The precipitate was filtered and dried at room temperature. Column chromatography of the obtained product was performed in silica gel using chloroform-methanol mixtures as eluent. . Indeed, the largest amount chlorine e_6 was eluted from the column with a 1:1 vol. chloroform-methanol mixture; the yield of "raw" chlorine was 19.0 mg (10.6%).

Results and discussion

The technique of ester group hydrolysis at position 17 (in the system acetone - hydrochloric acid 10:2 vol., 24 h of stirring at room temperature) was initially used for the synthesis of 17-monocarboxy derivatives of chlorine e_6 13-amides of 15-monomethyl ethers from the corresponding 13-amides of 15,17-dimethyl ethers of chlorine e_6 [28]. A modified version of this technique is also well-known - acetone - hydrochloric acid ratio 3:2 vol., stirring time - 3 h (at room temperature) [29]. According to ^{1}H-NMR, both variants give 17-monocarboxy derivatives as the main product without affecting the 15-complex ester group

and exocycle (in the case of phorbines). However, increasing the time of the modified method up to 4 h causes partial opening of the exocycle in the molecule of methylpheophorbide *a*, despite the main product of the reaction remainspheophorbide *a*. Under similar conditions, pheophorbide *a* (acetone - hydrochloric acid 1:1 vol., 5 h stirring at room temperature) also forms chlorine derivatives in trace amounts. However, contrary to theoretical expectations, methylpheophorbide *a* reacts easily, although it is a more electron-saturated compound compared to pheophorbide proper and contains more ester groups.

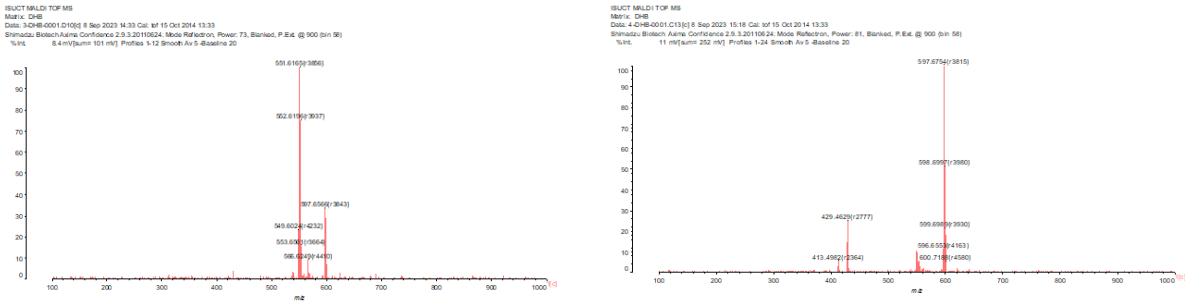
The possibility of principal opening the phorbinexocycle even with such a weak nucleophile as water suggests the process is to be more efficient with the use of stronger nucleophiles. Therefore, we attempted to conduct the opening of the exocycle in the molecule of methylpheophorbide *a* using a solution of an alkali, potassium hydroxide, in methanol. The possibility of simultaneous hydrolysis of ester groups was also assumed. However, methylpheophorbide *a* is very poorly soluble in methanol. Therefore, an organic solvent inert with respect to alkali, tetrahydrofuran (THF), was added to the reaction mixture to increase its solubility. The reaction mixture acquired a bright green colour at the transition of methylpheophorbide *a* into solution. It indicated the opening of the exocycle. TLC of the product isolated by extraction showed as the main product a nonpolar fraction of bright green colour. It moves with the solvent front already at minimum concentrations of methanol (0.5-1% vol.), which is used as eluent in its mixtures with chloroform. In case of monocarboxylic derivatives, the polarity of the product should have been higher, which indirectly supported the formation of trimethyl ester of chlorine e_6. Subsequently, the formation of trimethyl ether of chlorine e_6 was confirmed by mass spectrometry and ^{1}H-NMR data. The signal of the phorbinexocycle proton at 6.28 m.d. disappears and the signal of an additional methyl group at 4.28 m.d. appears in the ^{1}H-NMR spectrum of the product in $CDCl_3$. Hydrolysis of ester groups requires more stringent conditions (larger excesses of alkali, presence of water in solution, elevated temperature), but is complicated by side processes (in particular, decarboxylation of formed chlorine e_6).

We expected that the 13,15,17-trimethyl ether of chlorine e_6 would prove to be the most convenient precursor of free chlorine e_6 (in the form of a triacid).This substance contains three very chemically similar ester groups, that are supposed to undergo hydrolysis under almost identical conditions (unlike phorbines, which contain different reaction centres - at least an exocycle and an ester group).However, experiment shows at longer time of hydrolysis process (3 h in comparison with 1.5 h in case of methylpheophorbide *a*) trimethyl ether of chlorine e6 gives less yield of the target product (chlorine e_6) and more by-products in comparison with methylpheophorbide a. It is confirmed by mass spectrometry (Fig. 6). In addition, chlorine e_6 even after column chromatography still contains the impurities and requires additional purification.

Acid amides can react with nitrous acid formed in the reaction medium from sodium nitrite and mineral acid (most often hydrochloric one). In this process, free acids are obtained from the acid amides.

Fraction 1 ($CHCl_3$ - 20% vol. MeOH) Fraction 2 ($CHCl_3$ - 50% vol. MeOH)

Methylpheophorbide *a*



13,15,17-Trimethyl ether of chlorine e_6

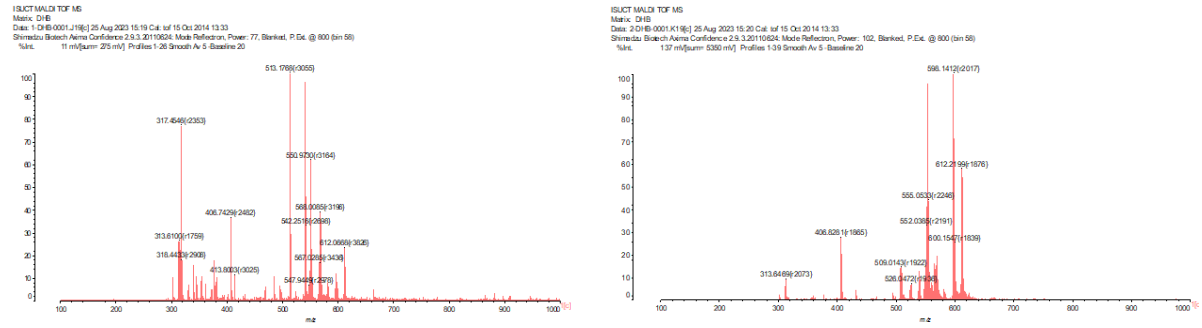


Fig. 6. Mass spectra of the main fractions obtained during the alkaline hydrolysis of methylpheophorbide *a* and 13,15,17-trimethyl ether of chlorine e_6 with potassium hydroxide in the "tetrahydrofuran" system

Hypothetically, chlorine triamide e_6 under such conditions should form free chlorine e_6, and 13-monoamide 15,17-dimethyl ether of chlorine e_6 - the corresponding 13-monocarboxy derivative. However, when we try to use chlorine e_6 amides for these purposes, the formation of the corresponding carboxy derivatives is not observed. Moreover, electrophilic substitution in the macrocycle occurs to form a mixture of different 20-substituted derivatives. Product with molecular weight corresponding to isomeric NO^2- or ONO-derivatives predominates in the mixture when using excess $NaNO_2$; while using a stoichiometric amount of nitrite in the mixture remains a significant amount of the initial unreacted amide, containing impurity products of 20-substitution in the macrocycle. According to $_1$H-NMR spectroscopy, the signals of all protons, except 20-H, are obtained split, with major signals correspond to the initial amide of chlorine e_6. Since the products of 20-substitution do not contain a proton in the indicated position of the macrocycle, they do not give a signal in the $_1$H-NMR spectrum.

Conclusions

We have demonstrated phorbinexocycle opening not only by strong O- and N-nucleophiles, but also by such relatively weak O-nucleophiles as alcohols and water. We have studied the conditions for the formation of chlorine e_6 and its methyl esters upon treatment of phorbines with potassium hydroxide under various conditions. We have considered possible alternative methods for the preparation and purification of free chlorine e_6.

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