Synthesis of Polyfunctional Chlorines Based on Methylpheophorbide *a* and Its Analogues

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Abstract

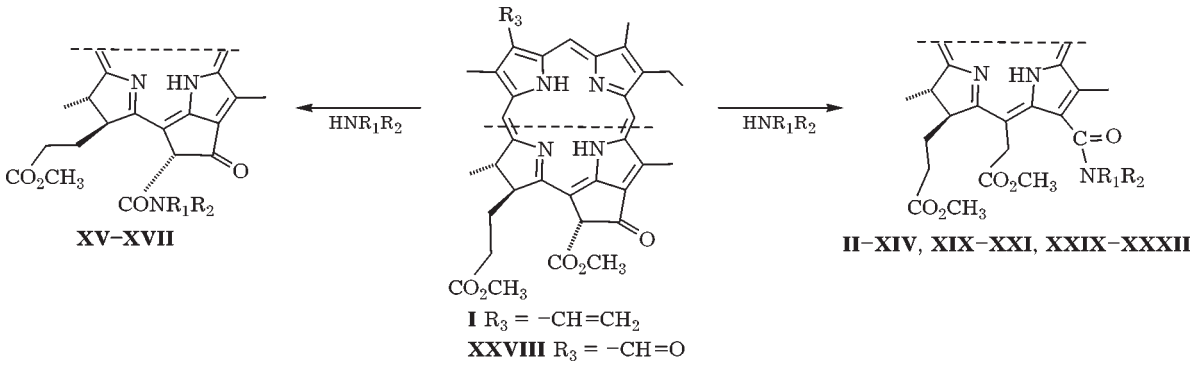
Methylpheophorbide *a* use as an initial compound for obtaining potential antineoplastic preparations is considered. A possibility to carry out some reactions with the participation of main reaction centres of methylpheophorbide *a* such as exocycle, vinyl group, and propionate substituent for the preparative purposes is demonstrated. The use of the reactions of the main reaction centres provides an opportunity for obtaining porphyrin compounds of the very manifold structure. All of the compounds obtained have a chlorine pharmacophor in the structure of the molecule providing their activity as photosensitizers for photodynamic therapy of oncological and other diseases.

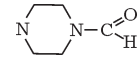
Key words: methylpheophorbide *a*, chlorophyll *a*, chlorine e_6

INTRODUCTION

Porphyrins exhibit a number of unique properties and play a significant role in animate nature. The uniqueness of this class of compounds induces an interest with respect to them from the standpoint, for example, of revealing the role of porphyrins incorporated into complex protein complexes, of using them as medical products, semiconductors, *etc.* In this connection, new efficient and economical methods for obtaining porphyrins are under development, both synthetic ones, and the originating from naturally occurring sources such as phytogenous raw material, blood, oil. In particular, the derivatives of chlorophyll *a* obtained from various phytogenous raw material can serve as initial compounds for the synthesis of biologically active substances: diagnostic and antineoplastic preparations for oncology, wound-healing preparations, *etc.* [1–7]. For establishing the dependence between the structure and biological activity and for performing the synthesis of new biologically active compounds, of a great interest is the development of efficient methods for introducing additional substituents at the periphery of the chlorine macrocycle. In obtaining medical preparations, a special attention of researchers is attracted by simple (for performing) reactions those allow them to obtain simultaneously a wide range of compounds. On the one hand, such approach allows the researchers to select the most active compounds; on the other hand, the simplicity of synthesis provides a serious advantage in obtaining the compounds on the scales necessary for significantly more profound tests and use in clinical practice. Methylpheophorbide *a* (**I**) represents one of the most accessible and, at the same time, the most suitable compounds for obtaining chemical modifications of chlorophyll *a* derivatives (Scheme 1). Due to the presence of a number of reaction centers (exocycle, vinyl group, *etc.*) in the molecule, methylpheophorbide *a* could be used for the synthesis of chlorines with the very manifold substituents at the periphery of the macrocycle.

In order to introduce various fragments at the periphery of the chlorine cycle one could use the reaction of compound **I** exocycle cleavage under the action of amines resulted in the formation of corresponding 13(1)-amides of chlorine e_6 (see Scheme 1) [8–15]. After the performing of such interaction, there are fragments attached to the nitrogen atom belonging to amine at the periphery of the chlorine mac-

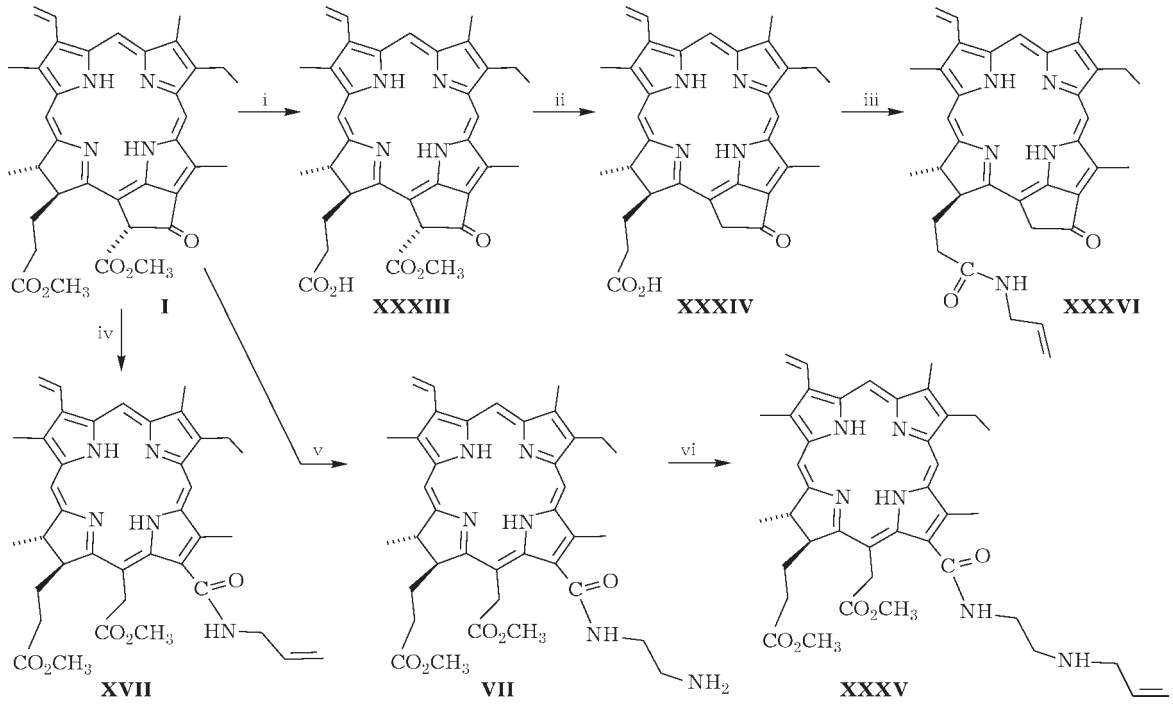


Compound	NR_1R_2	Compound	NR_1R_2
R_3 = −CH=CH_2		R_3 = −CH=CH_2	
II	$NHCH_3$	**XVIII**	$N(C_2H_5)_2$
III	$NHCH_2CH_3$	**XIX**	$NH(CH_2)_3CH_3$
IV	NH_2	**XX**	$NH(CH_2)_5CH_3$
V	$NHNH_2$	**XXI**	$NH(CH_2)_7CH_3$
VI	$NHCH_2CH_2OH$	**XXII**	$NHCH_2Ph$
VII	$NHCH_2CH_2NH_2$	**XXIII**	
VIII	$NHCH_2CH_2CH_2NH_2$	**XXIV**	
IX	$N(CH_3)_2$	**XXV**	$N((CH_2)_3CH_3)_2$
X		**XXVI**	$N((CH_2)_5CH_3)_2$
XI	$NHCH_2CH_2CH_2OH$	**XXVII**	$N((CH_2)_7CH_3)_2$
XII	$NHCH_2CH_2CH_2OH$		
XIII	$NHCH_2CH(OH)CH_2OH$	R_3 = −CH=O	
XIV	$NH(CH_2)_2O(CH_2)_2X$ (X = OH; NH_2; $N(CH_3)_2$)	**XXIX**	$NHCH_3$
XV	$NHCH_2CH_2CH_2N(CH_2CH_2OX)_2$ (X = H; CH_3; Ac)	**XXX**	$N(CH_3)_2$
XVI	$NH(CH_2)_2O(CH_2)_2O(CH_2)_2OX$ (X = H; CH_3)	**XXXI**	$NHCH_2Ph$
XVII	$NHCH_2CH=CH_2$	**XXXII**	$N(CH_2CH_3)_2$

Scheme 1.

rocycle. So, the reaction of **I** with methylamine [8] and ethylamine [9] results in the formation of 13-N-alkylamides **II** and **III**, respectively. The opening of methylpheophorbide **I** exocycle can be also achieved under the action of ammonia and hydrazine resulting in the formation of compounds **IV** and **V**, respectively, in the latter case the cleavage reaction occurs as a by-process accompanying the reduction of the vinyl group [10]. In a similar manner 13-amides of chlorine e_6 with various hydrophylic and hydrophobic substituents (**VI**–**XVI**) were synthesized [11–13].

A remote vinyl group introduction at the periphery of the chlorine macrocycle has been performed (through the action of allylamine, for example, compound **XVII** was obtained) [14]. These chlorines could be used as monomers in order to obtain porphyrin-containing polymers *via* copolymerization [4]. In the synthesis of



(i): acetone, conc. HCl, 20–25 °C, 22 h, the yield of 80 %; (ii): boilinf in pyridine, 5 h, the yield of 78 %; (iii): Boc_2O (30 min at 0 °C, CH_2Cl_2–pyridine), allylamine, 1 h, 20–25 °C, 1 h, the yield of 70 %; (iv): allylamine, $CHCl_3$, 20–25 °C, 1 h, the yield of 90 %; (v): ethylenediamine, $CHCl_3$, 20–25 °C, 2 h, the yield of 76 %; (vi): allylbromide, sodium acetate, THF, boiling, 1 h, the yield of 30 %.

Scheme 2.

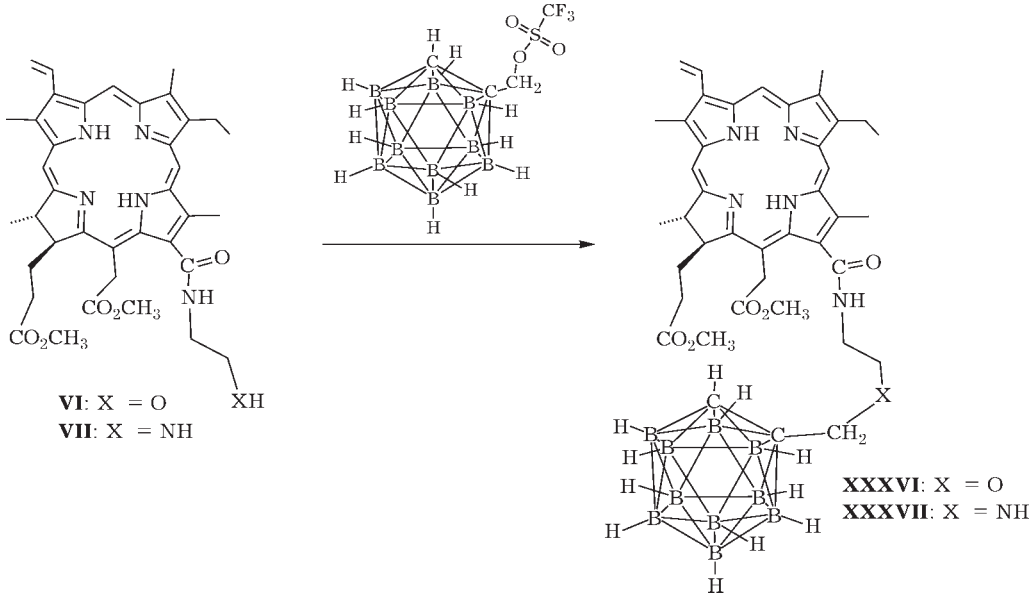
chlorines with a remote vinyl group, the cleavage of exocycle under the action of amines has been used not only for direct introduction of the allyl fragment, but also for introducing an additional reaction centre at the periphery of the chlorine cycle such as an amino group distant from the macrocycle, which amino group alkylation allows adding a supplementary vinyl group (Scheme 2) [14]. The chlorine with a remote amino group **VII** has been synthesized through the reaction between ethylenediamine and methylpheophorbide *a* **I**. In order to obtain compound **XXXV**, chlorine **VII** amino group alkylation processes with the use of allylchloride, allylbromide and allyliodide were studied. Plausible yield values for the product of alkylation were obtained in the case of alkylation with allylbromide. A somewhat shorter bridge attaches the vinyl group in the case of 17-[2(N-allylcarbamoyl)] substituted amide derivatives of chlorophyll *a*. For the reaction of the carboxyl group belonging to the 17-propionate substituent with allylamine activated by di-*tert*-butylcarbonate, pyropheophorbide *a* **XXXIV** was used instead of pheophorbide *a* **XXXIII** (see Scheme 2). It is connected with the fact that in the case of compound **XXXIII**, besides the basic reaction, there could be an undesirable cleavage exocycle observed resulting in the formation of chlorine with two remote vinyl groups. In contrast to exocycle **XXXIII**, the exocycle of pyroderivative **XXXIV** cannot be opened under soft conditions under nucleophylic action, which excludes a side reaction to occur. Notwithstanding the fact that there is a little shorter (as compared to clorine **XXXV**) bridge wherethrough the vinyl group is attached to the chlorine cycle within amide **XXXVI**, a higher yield of compound **XXXVI** with the obtaining from methylpheophorbide *a* **I** allows one to consider this variant of the introduction of a remote vinyl group to be the most preferable way.

The introduction of additional reaction centres at the periphery of the chlorine macrocycle with the use of methylpheophorbide *a* reactions with amines could be also applied in order to construct other, more complicated molecules. So, the synthesis of chlorine dimers

has been carried out through acylation of the amino group of compound **VIII** [15]. By means of alkylation of the hydroxy and amino groups of compounds **VI** and **VII**, the addition of carborane fragment was possible to carry out [7]. (These compounds are promising from the standpoint of realizing various binary antineoplastic strategies, in particular, the combinations of photodynamic and boron based neutron capture therapy for oncological diseases.) Corresponding carboranyl triflate (1-trifluoromethanesulphonyl methyl-*o*-carborane) was used as an alkylation agent (Scheme 3).

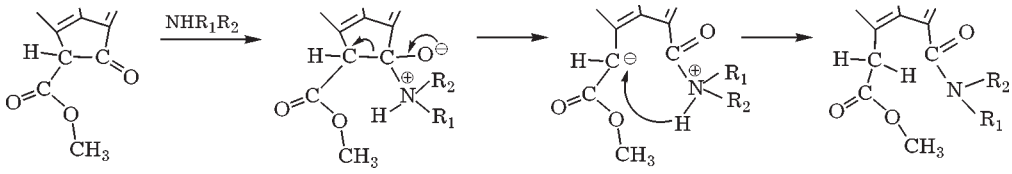
Thus, the cleavage of exocycle of methylpheophorbide *a* **I** and its analogues under the action of amines could be used both for one-stage introduction of necessary fragments during the formation of chlorine e_6 13-amides, and for the construction of more complicated molecules with the use of the reactions of functional groups introduced. Notwithstanding the appeal of "a one-stage variant" and its popularity, it is difficult to designate the margins of this reaction applicability in the preparative chemistry of chlorophylls and their derivatives basing on known data from the literature, both from the standpoint of the influence of amine and substrate structure, and from the viewpoint of the reaction conditions. The exocycle cleavage reaction under the action of amines is usually carried out at room temperature during 1–48 h; chloroform, methylene chloride or THF being used as solvents. The mechanism of exocycle cleavage for methylpheophorbide *a* **I** and its analogues under the action of amines represents the reaction of nucleophylic substitution at the carbonyl carbon atom located in the position 13(1) (Scheme 4).

The course of this reaction, as well as all similar reactions of carbonyl compounds, is influenced by the value of partial negative charge at the unshared electron pair of the nitrogen atom, as well as the size, structure and the number of substituents at the nitrogen atom those determine the steric availability of the unshared electron pair and the spatial difficulties in the formation of an sp^3 hybridized intermediate [16]. Moreover, the reactivity of the substratum is influenced by the features of its structure. In particular, additional electron accepting substituents in the chlorine macrocycle those cause an increase in the partial positive



Compound	Conversion level, %	Yield, %	Reaction conditions
X = O	35	15	Boiling in THF, sodium acetate, 1.5 h
X = NH	100	20	The same

Scheme 3.



Scheme 4.

charge at the carbonyl carbon atom located in the position 13(1), promote exocycle cleavage due to a more ready interaction with amine at the first stage. So, the studies on the kinetics for the reactions of chlorophylls *a* and *b* and corresponding pheophytines with amines demonstrate that the *b*-series derivatives having the electron accepting aldehyde group, exhibit a higher reaction rate [17, 18]. Thus, the data on the reaction mechanism available from the literature given and on the reaction use in the preparative chemistry can allow one to reveal only the factors influencing the reactivity of both the participants of this interaction. However, to forecast the result of the reaction as well as the possibility of obtaining either derivative e_6 of chlorine basing on the structure the reacting amine seems to be hardly possible.

TABLE 1

Methylpheophorbide *a* **I** interaction with primary and secondary amines (see Scheme 1)

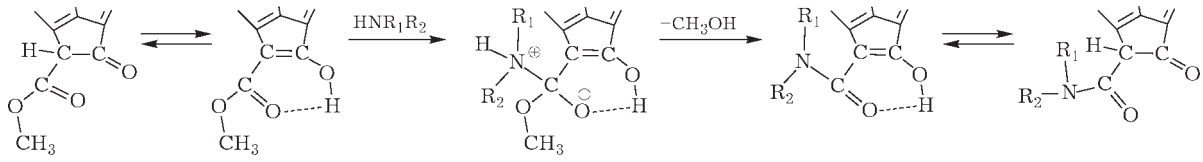
Reaction conditions	Amine	Reaction result
Benzene, room temperature, 5 min	Piperidine	Yield of 13-amide **XXIII** amounting to50 %
Benzene, boiling, 0.5–1.5 h	Diethylamine	Reaction does not occur
	Benzylamine	Yield of 13-amide **XXII** amounting to 47 %
	Dibutylamine, dihexylamine, dioctylamine, aniline, 2-aminopyridine, cyclohexylamine, *tert*-butylamine	Reaction does not occur
	Formylpiperazine	Yield of 13-amide **XXIV** amounting to 30 %
THF, room temperature, 24 h (10–20 min for *n*-butylamine)	*n*-Butylamine	Yield of 13-amide **XIX** amounting to 60 %
	n-Hexylamine	Yield of 13-amide **XX** amounting to 34 %
	n-Octylamine	Yield of 13-amide **XXI** amounting to 32 %
	Benzylamine	Yield of 13-amide **XXII** amounting to 5 %
	Dibutylamine, dihexylamine, dioctylamine, aniline, 2-aminopyridine, cyclohexylamine, *tert*-butylamine	Reaction does not occur
THF, boiling, 0.5–1.5 h	Diethylamine	Yield of 13-amide **XVIII** amounting to 40 %
	Dibutylamine, dihexylamine, dioctylamine, aniline, 2-aminopyridine, cyclohexylamine, *tert*-butylamine	Reaction does not occur
	Benzylamine	Yield of 13-amide **XXII** amounting to 17.5 %
DMFA, boiling, 1–1.5 h	Dibutylamine Dihexylamine Dioctylamine	Amidation of ester group at the position 13(2) occurring (formation of amides **XXV–XXVII**)
	Aniline, 2-aminopyridine, cyclohexylamine, *tert*-butylamine	Reaction does not occur
Toluene, boiling, 1–1.5 h	Dibutylamine Dihexylamine Dioctylamine	Amidation of ester group at the position 13(2) occurring (formation of amides **XXV–XXVII**)
	Aniline, 2-aminopyridine, cyclohexylamine, *tert*-butylamine	Reaction does not occur

In order to establish the margins of applicability for the reaction of exocycle cleavage in methylpheophorbide *a* **I** under the action of amines during one-stage preparative obtaining of 13-amides of chlorine e_6, we studied the interaction of **I** with amines with various structure under different conditions (see Scheme 1, Table 1) [21]. For the reaction we have chosen amines with different values of electronic density at unshared electron pair of the amine nitrogen atom, different steric availability and various sizes of substituents at the nitrogen atom of the amine (see Scheme 1, formation reactions for compounds **XVIII**–**XXVII)**.

Besides methylpheophorbide *a* **I**, we investigated the interaction of the some amines with methylpheophorbide *d* **XXVIII** (compounds **XXIX**–**XXXI**) those have the electron accepting group located in the position 3 of the macrocycle.

As one would expect (taking into account the reaction mechanism), the reactivity of amines in the reaction under investigation is essentially reduced due to the increase in steric difficulties of unshared electron pair at the amine nitrogen atom as well as the decrease in the electronic density thereat (see Table 1). A comparative analysis of the results obtained for the reaction between methylpheophorbide *a* **I** and primary or secondary amines indicates that there is a prevailing influence of steric factors (such as spatial availability of unshared electron pair of the nitrogen atom and steric hindrance in the formation of an sp^3 hybridized intermediate) upon the reactivity of amines. Irrespective of the size of an alkyl radical, primary amines use to react under much softer conditions than secondary amines (except for dimethylamine). So, butylamine reacts much faster and under much softer conditions than diethylamine which is isomeric with respect to the former. An increased reactivity of piperidine in comparison with other secondary amines also indicates a prevailing influence of the steric factor: the cyclization of an alkyl chain, to all appearance, could cause a decrease in the probability of forming the conformations wherein the unshared electron pair located at the nitrogen atom appears shielded, which causes the reactivity of amine to rise steeply. Moreover, due to the restriction of the conformational mobility of alkyl chains there is a reduction of steric hindrance observed with respect to the formation of an sp^3 hybridized intermediate.

In a similar manner as piperidine, a high reactivity in the reaction with methylpheophorbide *a* **I** is exhibited by morpholine [11, 12]. The increase in the size of a substituent at the nitrogen atom of the amine (a much longer alkyl chain in hexylamines and octylamines, the benzene ring in benzylamine) also does not promote the reaction to occur, though the influence of this factor is less considerable. It is interesting that dibutialmine, in contrast with octylamine isomeric with respect to the former, uses to react with methylpheophorbide *a* **I** very hardly. In case that one succeed in involving this substance in the reaction, no exocycle cleavage occurs, but an amidation of the ester group at the position 13(2) is observed to proceed with the formation of corresponding 13(2) amide **XXV**. Taking into account a considerable steric availability of the ester group of a substituent at the position 17, one would expect that this group could react with amine. However, the amidation proceeds with the participation with a much more sterically hindered ester group of the exocycle. The hindrances are exhibited, for example, in the reaction of methylpheophorbide *a* **I** hydrolysis catalyzed by acid (see Scheme 2). On keeping compound **I** in the mixture of acetone with concentrated HCl one can observe hydrolyzing the ester group of the substituent located at the position 17 to occur; whereas no hydrolytic products from the ester group located at the position 13(2) are observed [19]. A higher reactivity of 13(2)-carbomethoxyl group as compared to that for the ester group of the substituent located at the position 17 could be caused by the activation of the former in the process of intramolecular hydrogen bond formation within the enolic form of methylpheophorbide *a* **I** (Scheme 5), which facilitates the nucleophylic attack of the ester group by dibutylamine. This assumption is supported by the fact that there is no amidation observed under boiling with dibutylamine in toluene for the only ester group of methylpyropheophorbide *a* **XXXIV** (Scheme 6); this ester group with respect to many reactions is close in reactivity to the carbomethoxyl group of the substituent located at the position 17 of methylpheophorbide *a* **I**. Dihexylamine and dioctylamine use to react in a similar fashion.

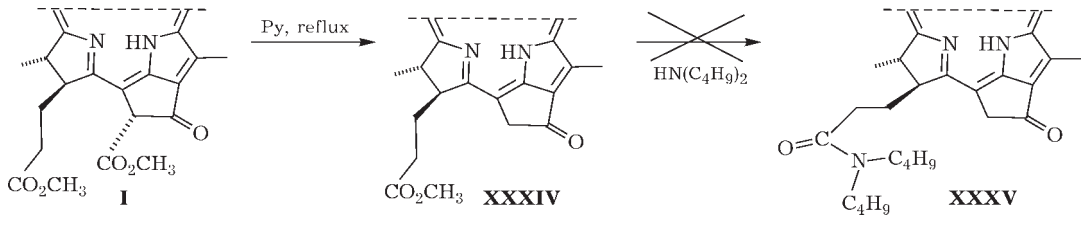


Scheme 5.

The results of the studies on compound **I** interaction with dialkylamines having different size of alkyl substituents allow one to assume that an increase in the size of the substituent at the nitrogen atom of amine exerts the greatest effect mainly on the possibility to form an sp^3 hybridized transition state, rather than on the steric availability of the unshared electronic pair at the nitrogen atom. Even in the case of those amines those do not cause the exocycle cleavage, a big size of the substituent does not exclude any possibility for the nucleophylic attack, which occurs in the process of 13(2)-amide group amidation.

The reactivity of amine and exocycle are also influenced by the distribution of electronic density within the molecules of a reagent of a substrate. A decrease in the electronic density of unshared electron pair at the nitrogen atom of amine prevents the exocycle from cleavage. So, in the case of aromatic amines (aniline, 2-aminopyridine) no reaction with methylpheophorbide *a* **I** occurs even under the most severe conditions. In spite of the fact that kinetic measurements indicate a considerable increase in the reactivity of exocycle with introducing an electron accepting aldehyde group into the macrocycle [17, 18], the authors have not succeeded in revealing any significant advantages in preparative obtaining of 13-amides as switching from methylpheophorbide *a* **I** to methylpheophorbide *d* **XXVIII**.

The substitution of the vinyl group located at the position 3 by an electron accepting aldehyde group does not result in so much increasing the exocycle reactivity that its cleavage would be possible with sterically hindered or aromatic amines. We found none example for amine that could not exhibit exocycle cleavage for methylpheophorbidea *a* **I** under either conditions entering into a similar reaction with methylpheophorbide *d* **XXVIII**. The absence of such examples, to all appearance, could be caused by a prevailing influence of the steric factor upon reactivity of compounds in the reaction under consideration. The toughening of reaction conditions (for example, due to its carrying out under boiling instead of room temperature and due to an increase in the boiling temperature of a solvent) in many cases promotes carrying out the reaction. However, to achieve exocycle cleavage due to toughening the conditions in the cases when the molecule is prevented from this transformation by the features of amine or substrate structure, as a rule, is not possible. So, with carrying out the reaction between methylpheophorbide *a* **I** and benzylamine at room temperature, irrespective of a solvent (chloroform, benzene, THF), corresponding amide **VI** either is not formed at all (as is the case with the reaction in benzene media), or the reaction of its formation proceeds very slowly and this fact, to all appearance, may results in the lowest (3–6 %) yield of amide **VI** (for the reaction running in chloroform and THF media). At the same time the reaction between methylpheophorbide *a* **I** and benzylamine under boiling in benzene resulted



Scheme 6.

in the obtaining of amide **VI** with a quite satisfactory yield, whereas in the cases of dibutylamine, dihexylamine, dioctylamine, aniline and 2-aminopyridine one have not succeeded in performing the reaction of exocycle cleavage.

A considerable effect on the course of the reaction is exerted by a solvent, too; however, to establish the character of this influence basing on the data available seems to be hardly possible. So, diethylamine does not react with methylpheophorbide *a* **I** under boiling in benzene, whereas corresponding amide has been obtained with the yield amounting to 40 % in the case of THF At the same time, for the reaction with benzylamine the maximal yield is observed upon performing the reaction in benzene medium, twice exceeding the compound yield obtained under boiling in THF. Hence, in order to determine optimum conditions for carrying out the reaction, the choice of the most suitable solvent should be carried out by means of an experiment. In all the cases when one succeed in performing the exocycle cleavage reaction, in order to obtain a satisfactory amide yield value, a multifold molar excess of amine should be used. A decrease in the amine amount results in increasing the reaction time as well as in a considerable reduction of the yield of amides, whereas the toughening of conditions does not result in any rise of the reaction product yield. So, under boiling of methylpheophorbide *a* **I** with an equimolar amount of hexylamine a difficult to separate mixture is formed consisting of four, at least, components instead of the only product formed in the reaction with the excess of amine. However, at a room temperature the conversion level of methylpheophorbide *a* **I** under these conditions is very low even after several days of running the reaction. A high molar excess of amine required for using in the reaction (besides the reactivity of amine and of a substrate) causes considerable restrictions for the application of this reaction in chemical modifying of natural chlorines.

Thus, the data presented in [21] allow us to reveal the major factors limiting the possibility of performing one-stage synthesis of chlorine e_6 13-amides with a prescribed substituent. The experimental data obtained by authors of [21] could form a basis for forecasting the results of preparative one-stage synthesis of chlorine e_6 13-amide derivatives with the participation of amines having different structure. So, for all secondary amines with the substituents located at the nitrogen atom those are identical in size or more bulky than the *n*-butyl group, as well as for primary amines wherein the amino group is bound with the secondary or tertiary carbon atom, the cleavage of exocycle could not be observed, but one would expect the direction of the reaction to change.

The increase in the reactivity of secondary amines is promoted by a decrease in the conformational mobility of the substituents at the nitrogen atom, for example, due to the cyclization of the chains consisted of methylene groups. In this connection, only rather simple substituents could be introduced using a one-stage process (for example, hydrophobic alkyl groups), and the increase in the size of the substituent at the nitrogen atom of amine might cause a considerable lowering of the yield of 13-amide. As a consequence, high yield values for chlorine e_6 13-amides in performing the reaction with complicated molecules are improbable even when this amino group is attached to primary carbon atom ($-CH_2NH_2$ fragment). The reduction of the electronic density value of the unshared electron pair of the amine nitrogen atom (inherent in aromatic amines) impedes not only the cleavage of exocycle, but also the amidation of the ester group at the position 13(2). The introduction of electron accepting groups with the purpose of increasing the partial positive charge at the carbonyl carbon atom located at the position 13(1) promoting the nucleophylic attack, most likely, could not give any considerable advantages in the obtaining of 13-amides, since possible steric barriers in the reaction running would level the action this favorable factor to a considerable extent. The toughening of reaction conditions in many cases promotes the exocycle cleavage, however, also in this case a cosiderable improvement could be achieved only for amines with rather small-sized substituents at the nitrogen atom (for secondary amines the substituents should not be more bulky than ethyl) or with any restrictions in conformational mobility (for example, due to the formation of a cycle from alkyl chains). In the case of primary amines, rigid fragments comparable in size with benzyl, or unbranched

hydrocarbon chains (up to octyl) are considered to be suitable as substituents. Such amines should have a higher boiling point, since a temperature elevation is often required for performing the reaction.

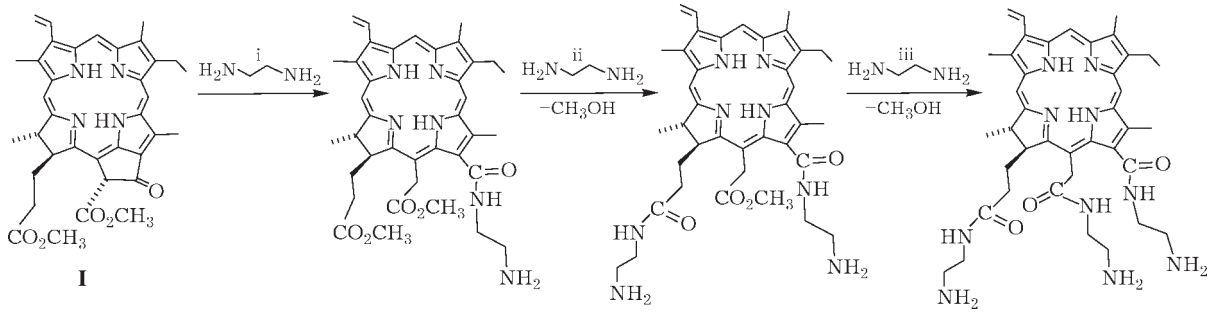
As it was mentioned earlier, the cleavage of exocycle in methylpheophorbide *a* **I** and its analogues under the action of amines could be applied in order to introduce additional reactive functional groups whose reactions might be used in the construction of more complicated molecules. Such approach represents a promising alternative with respect to one-stage introduction of bulky and complicated substituents, which is by no means always the practicable case.

In order to synthesize polyfunctional chlorines, the cleavage of exocycle under the action of amines could be used in combination with the reactions of other functional groups. The authors of [22] studied the interaction of compound **I** with ethylenediamine. It has been demonstrated that the reaction between ethylenediamine and amide **VII** without solvent results in the amidation of its ester groups, and at the same time the reaction is first of all entered by the ester group of the substituent located at the position 17 (Scheme 7).

The derivatives of chlorophyll are used as initial compounds for the synthesis of antineoplastic preparations, mainly photosensitizers for photodynamic therapy of oncological diseases. The introduction of a metal into the coordination sphere of chlorines results in changing their biological activity and in occurring new biological properties. So, an effect of dark toxicity with respect to malignant neoplastic cells has been quite recently found out for some zinc and nickel complexes of naturally occurring chlorines. The authors of [23] investigated the interaction of some chlorophyll *a* derivatives with nickel acetate and acetylacetonate under various conditions (see Table 1) and synthesized nickel complexes of these chlorines (Scheme 8).

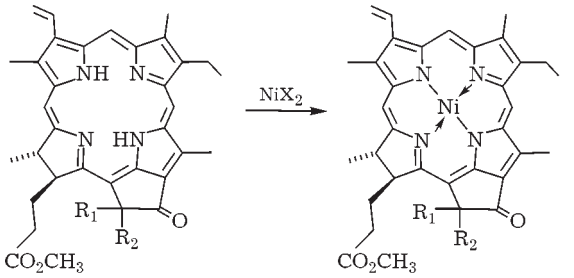
It has appeared that the synthesis of nickel complexes of natural chlorines proceeds efficiently under boiling of initial ligand with nickel acetylacetonate in toluene medium. In should be mentioned that under these conditions one succeed in obtaining the nickel complex with such an unstable ligand as methylpheophorbide *a*. Of particular interest is the fact that the chlorine reaction with an equimolar amount of nickel acetylacetonate results in gaining a good yield of the complexes, whereas for synthesizing them one uses to involve into reaction a multifold excess of the metal salt. Data presented in Table 2 indicate that the yield of complexes is influenced in a complicated manner by a great number of various factors, the most essential among those them consisting in the ligand stability under the reaction conditions.

The introduction of tertiary amino groups at the periphery of the chlorine macrocycle is of a considerable interest from the standpoint of the synthesis of cationic photosensitizers for photodynamic therapy of various diseases. The alkylation of tertiary amino groups results in the formation of corresponding salts of tetrasubstituted ammonium. It is known [24], that the bis-N,N(dimethylamino)methane can be used for the introduction of the dimethylaminomethyl groups into various molecules as well as for the generation of dimethylaminomethyl

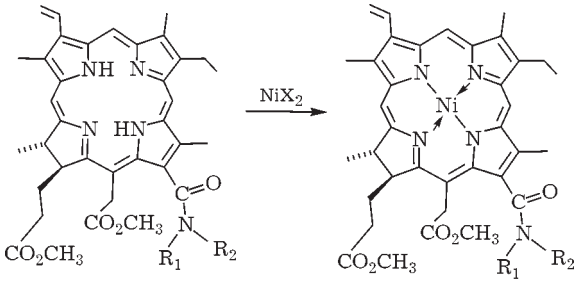


(i): ethylenediamine, $CHCl_3$, 20 °C, 3 h; (ii): ethylenediamine, 20 °C, 20 h; (iii): ethylenediamine, 20 °C, 40 h without isolation of intermediate mono- and diamides.

Scheme 7.



X = OAc, AcAc
R_1 = H; R_2 = CO_2CH_3 (**I**) and (Ni-**I**)
R_1 = OH; R_2 = CO_2CH_3 (**XLI**) and (**Ni-XLI**)
R_1 = R_2 = H (**XXXIV**) and (**Ni-XXXIV**)



X = OAc, AcAc
R_1 = R_2 = CH_3 (**IX**) and (Ni-**IX**)
R_1 = CH_3; R_2 = H (**II**) and (Ni-**II**)

Scheme 8.

cation (Scheme 9). Similar cation is formed in a Mannich reaction.

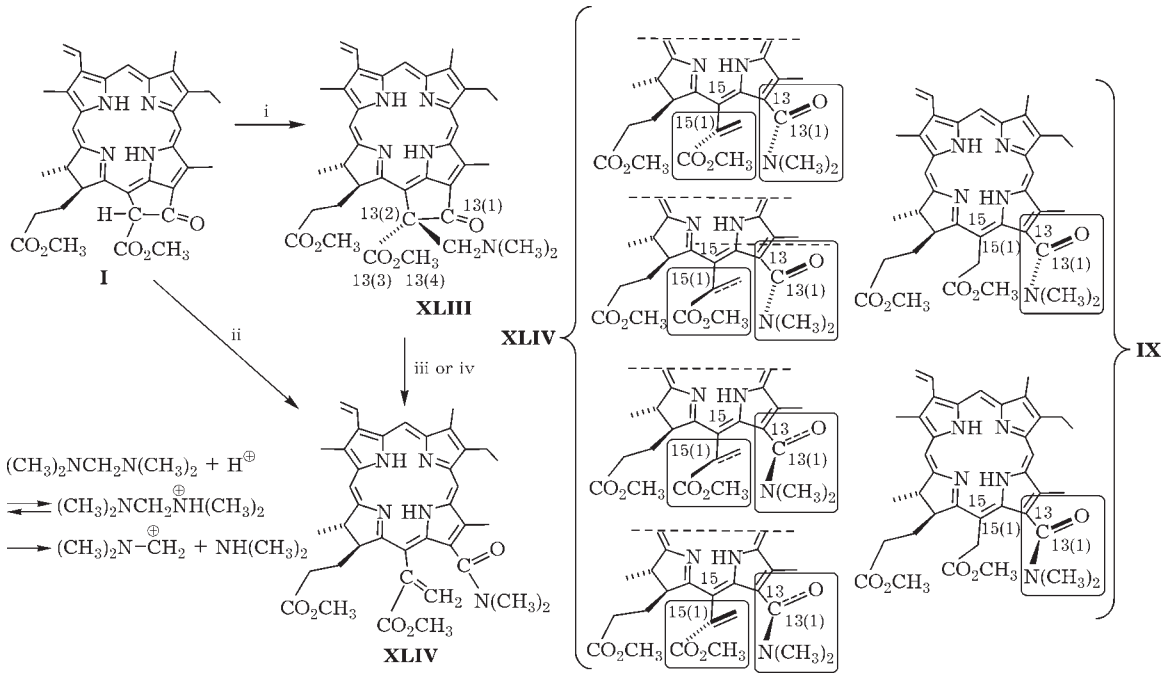
The authors of [25–27] investigated the interaction of bis-N,N(dimethylamino)methane with methylpheophorbide *a* **I** under various conditions (see Scheme 9). It has appeared that the reaction of aminomethylation at α-position with respect to the keto group of exocycle **I** occurs in the mixture of THF with acetic acid at 10–12 °C with the formation of 13(2)-dimethylamino derivative XLIII. It is interesting to note that the aminomethylation of methylpheophorbide *a* **I** occurs in a stereoselective fashion with the formation of the only compound such as 13(2)R-diastereomer. The stereoselectivity of the reaction could be explained by some features of the substrate structure. To all appearance, the enolic form of **I** is not strictly flat, whereas the carbomethoxylgroup is somewhat displaced into a transoid position with respect to the methylpropionate substituent located at the position 17 due to mutual repulsion of these substituents. In this connection, in the case of electrophilic attack on the multiple bond of the enolic species, its opposite side is sterically more accessible. As a result, only one diastereomer is formed, with dimethylaminomethyl substituent located on one side of the plane of the chlorine macrocycle with 17-propionate fragment.

On prolonged keeping 13(2)-dimethylaminomethyl derivative **XLIII** at a room temperature in the mixture of THF with acetic acid the derivative **XLIII** undergoes isomerization resulting in the formation of 13-dimethylamide derivative **XLIV** of chlorine e_6 with the fragment of methyl ester of acrylic acid located at the position 15 (see Scheme 9). The compound obtained exists in the form of four isomers. To all appearance, there are atropoisomers realized with different relative positioning of the planes of the chlorine macrocycle, the amide group at the position 13 and the fragment of methylacrylate at the position 15. The occurrence of four atropoisomers for compound **XLIV** could be caused by a hindrance of the rotation around such bonds as (13)C–(13(1))C and (15)C–(15(1))C (see Scheme 9). A similar phenomenon was observed in the studies on chlorine e_6 derivatives with tertiary amide groups located at the position 13, such as chlorine e_6 13-NN-dimethylamide-15,17-dimethyl ester **IX**. These compounds exist as two isomers those differ from each other in a relative positioning of the chlorine macrocycle and 13-amide

TABLE 2

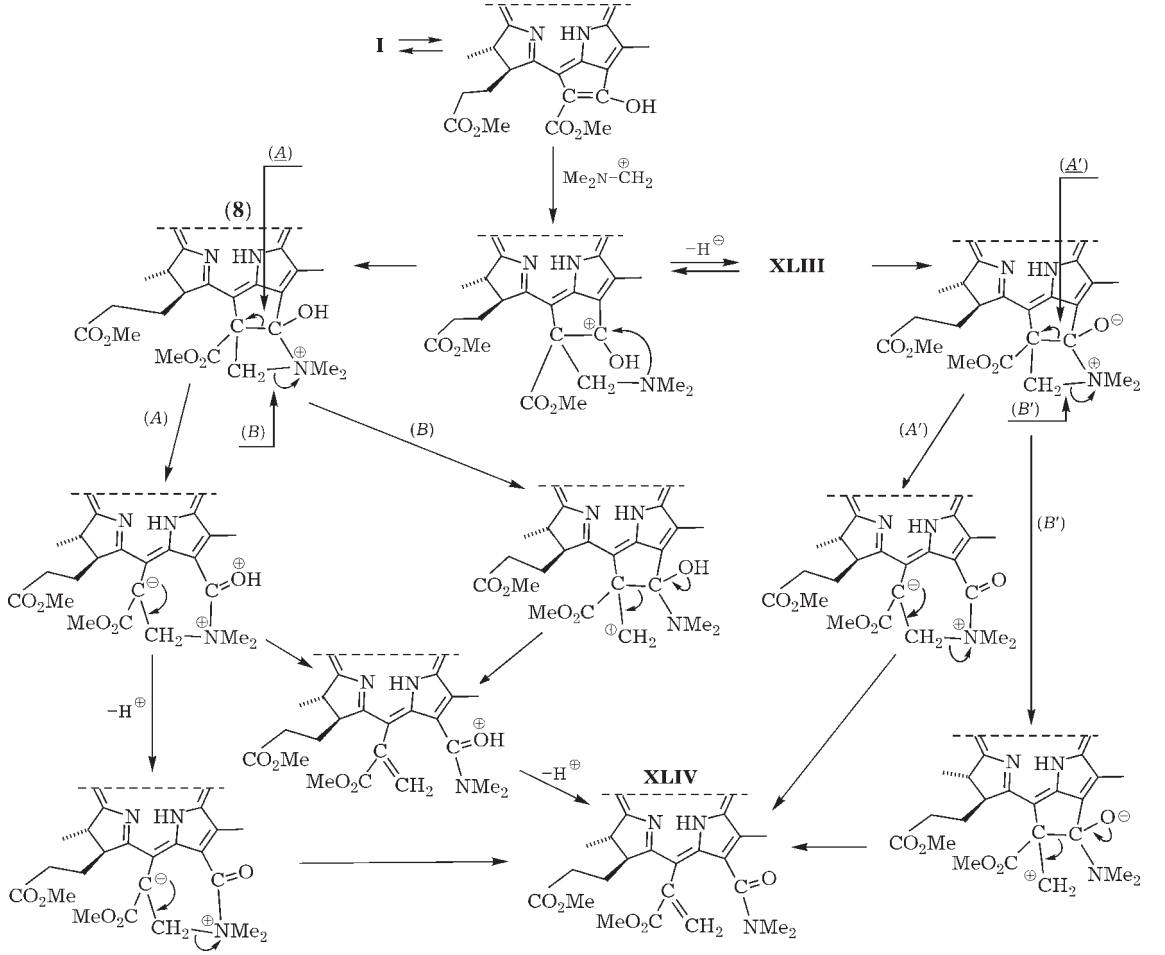
Conditions of synthesis and the yield of nickel complexes for chlorophyll *a* derivatives

Complexes	Yield, %	
	$Ni(OAc)_2$, AcOH, boiling	$Ni(AcAc)_2$, toluene, boiling
(Ni-**I**)	0	10
(Ni-**XLI**)	60	65
(Ni-**XXXIV**)	45	78
(Ni-**II**)	25	69
(Ni-**IX**)	21	70

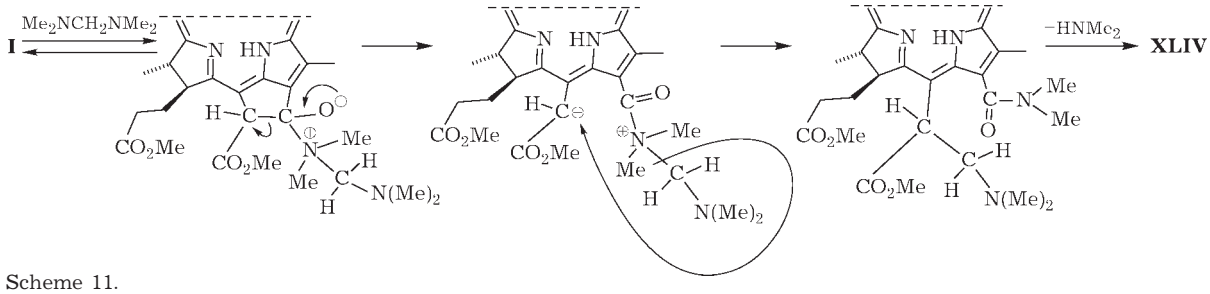


(i): **II**, THF–AcOH, 10–12 °C, 24 h; (ii): **II**, THF, boiling during 8 h; (iii): THF–AcOH, 48 h, room temperature; (iv): THF, boiling.

Scheme 9.



Scheme 10.



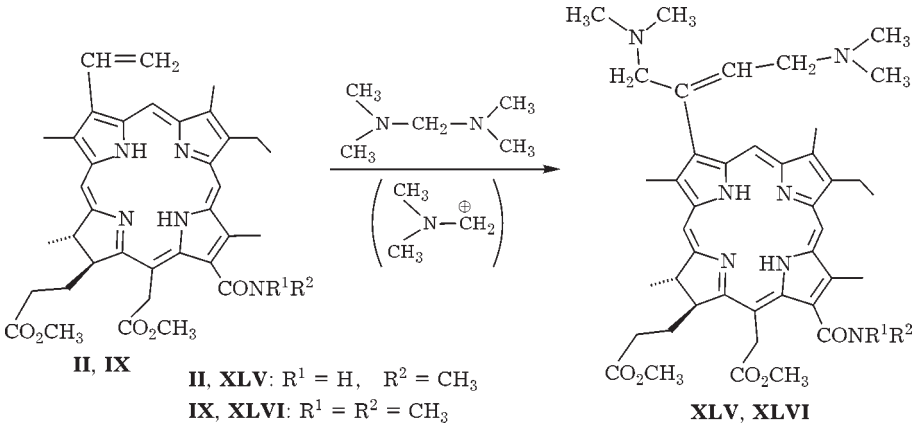
Scheme 11.

group [11, 12] (see Scheme 9). Possible mechanisms proposed for the formation of compound **XLIV** are presented in Schemes 10 (mechanism 1) and 11 (mechanism 2). The first mechanism includes the formation of the product of compound **XLIII** aminomethylation and its subsequent isomerization. The second mechanism consists in a nucleophilic attack on 13(1)-carbonyl carbon atom with the subsequent cleavage of exocycle, dimethylaminomethyl cation migration and dimethylamine molecule splitting out, which results in the formation of a multiple bond of the methacryl substituent.

Thus, the action by bis-N,N(dimethylamino)methane on methylpheophorbide *a* **I** depending on conditions could result in the obtaining of substances undescribed earlier such as 13(2)-N,N-dimethylaminomethyl derivative of methylpheophorbide *a* **XLIII** and 13-dimethylamide derivative **XLIV** of chlorine e_6 with the fragment of methyl ester of acrylic acid located at the position 15. The latter could be obtained either immediately from compound **I**, or from the product of its aminomethylation **XLIII**. Bis-N,N(dimethylamino)methane could be used also for aminomethylation of the vinyl group [26]. Under more severe reaction conditions (the mixture of THF with acetic acid under boiling chlorines with two N,N-dimethylaminomethyl substituents in the vinyl group are formed with a high yield (Scheme 12).

CONCLUSION

So, methylpheophorbide *a* **I** could be efficiently used as a parent compound for obtaining potential biologically active substances. Due to the presence of several reaction centres (exocycle, vinyl group, propionate substituent) in the molecule of methylpheophorbide *a*, it is possible to obtain porphyrin compounds of the very manifold structure. All the compounds obtained have a chlorine pharmacophor in the structure of the molecule providing their activity as photosensitizers for photodynamic therapy of oncological and other diseases.



II, **IX**

II, **XLV**: $R^1 = H$, $R^2 = CH_3$

IX, **XLVI**: $R^1 = R^2 = CH_3$

XLV, **XLVI**

Scheme 12.

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