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The Search for New Synthetic Photosensitizers

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Abstract— The results of studies on the synthesis of photosensitizers conducted the last 10 years in frame of health care programs funded by the Moscow Government are reported.

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Phthalocyanines and related compounds are one of the most popular class of organic functional dyes. Over the past 25 years, numerous reviews and monographs have been published on the synthesis, properties and applications of these compounds [1], including their using as photosensitizers for photo-dynamic therapy [23]. Research programs funded by the Moscow Government included a wide range of synthetic works of both technological and research character.

This review presents the most interest scientific results of the synthetic work.

Nucleophilic Substitution in Tetrachlorophthalonitrile as the Way to New Hexadecasubstituted Phthalocyanines

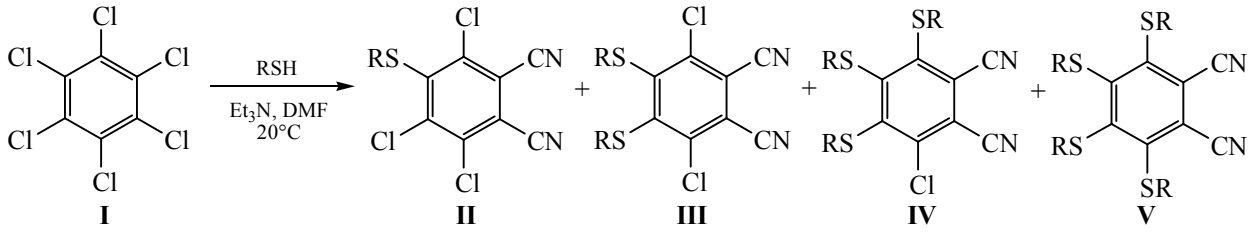
Substituted phthalonitriles are the most popular starting compounds for the obtaining of corresponding substituted phthalocyanines, and nucleophilic substitution of leaving group are most commonly used for their synthesis [2]. It is possible to introduce various substituents (alkoxy and aryloxy groups, alkyl- and arylsulfanyl substituents, amino groups and others) by substitution generally a halogen atom or a nitro group in the phthalonitrile benzene ring. Commercially available 3- and 4-nitrophthalonitriles commonly used as the starting reagents as well as monohalogen substituted phthalonitriles (e.g., rather exotic 3-bromo-5-*tert*-butyl-phthalonitrile [3]), which allow to obtain asymmetrical mono- (di-) substituted phthalonitriles and randomeric mixture of tetra- (octa-) substituted phthalocyanines ultimately.

Phthalonitriles carrying two substituent groups provide more synthetic capabilities. For example, symmetric 4,5-dibromo [4] and 3,6-bis(trifluoromethylsulfonyloxy)phthalonitrile [5] allow to introduce eight symmetrically located substituents in phthalocyanine. Nitro groups in 3,5-dinitrophthalonitrile may be sequentially replaced by two different nucleophiles, but regioselectivity of the first substitution is low [6]. Substitution in 4-bromo-5-nitrophthalonitrile takes place with an excellent chemoselectivity [7]: bromine atom is substituted first [8] and remaining nitro group may be replaced by the same [9] or other nucleophile [10].

Very attractive substrates in terms of synthetic possibilities are tetrahalogeno substituted phthalonitriles. All four fluorine atoms in tetrafluorophthalonitrile can be replaced by nucleophiles such as alkoxy or aryloxy group [11] but selectivity of substitution of less number of fluorine atoms has not been shown. That is why commercially available tetrachlorophthalonitrile is very promising in this point of view. In principle, all four chlorine atoms therein may be substituted with the same or sequentially with various nucleophiles in different ratios, and grate variety of structures can be achieved in this way. However, to our surprise, prior to our work we could not find the publications on the systematic study of nucleophilic substitution of the halogen atoms in tetrahalogenophthalonitrils except patents [12].

† Deceased.

Table 1. Reaction of tetrachlorophthalonitrile **I** with S-nucleophiles



I **II** **III** **IV** **V**

Nucleophil, R	1 : RSH	Yield, %			
		II	**III**	**IV**	**V**
a. Ph	1 : 1	28	20.6	–	–
	1 : 2	–	92.0	–	–
	1 : 3	–	25.2	26.7	36.4
	1 : 4	–	–	–	93.0
b. *t*-Bu	1 : 1	29	23.4	–	–
	1 : 2	–	91.4	–	–
	1 : 3	–	22.7	26.3	40.0
	1 : 4	–	–	–	90.2
c. *n*-Bu	1 : 2	–	91.0	–	–
	1 : 4	–	–	–	95.0
d. *n*-$C_{10}H_{21}$	1 : 2	–	87.4	–	–
	1 : 4	–	–	–	89.3

It should be noted that the exhaustive substitution of halogen atoms in tetrahalogeno substituted phthalonitriles may lead to only one reaction product. In the case of substitution of two halogen atoms theoretically possible formation of four substances: products of substitution of halogen atoms in the positions 3,5; 4,5; 3,6 and/or 3,4. In all patents found only symmetrically disubstituted phthalocyanines and corresponding phthalonitriles were mentioned (for example 3,6-dichloro-4,5-bis(phenylsulfanyl)-phthalonitrile), but the structures of the products were not strictly proved.

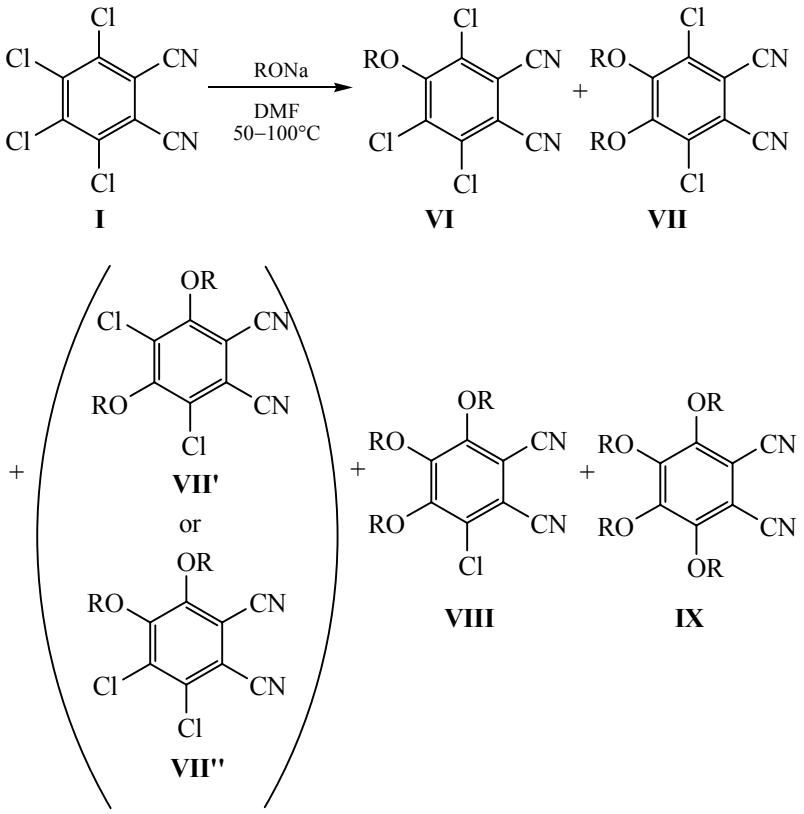
The principal aim of the study was to determine the possibilities of substitution of a certain and maximum number of chlorine atoms in tetrachlorophthalonitrile with different nucleophiles and the study of the regioselectivity of substitution.

For S-nucleophiles aryl and alkylthiols were used [13]. It has been shown that the highest selectivity of the substitution is reached when tetrachlorophthalonitrile **I** and the thiol ratio is 1 : 2 and 1 : 4, when two or four chlorine atom are substituted, respectively (Table 1). X-ray diffraction analysis of phthalonitrile **IIIa** proved that the first two chlorine atoms are substituted at position 4 and 5 of the benzene ring. When the ratio of the reagents is 1 : 1 and 1 : 3, a mixture of three substances: starting phthalonitrile **I,** mono- **II** and disubstituted phthalonitriles **III** in the first case or di- **III**, tri- **IV** and tetrasubstituted phthalonitriles **V** in the second case. Obviously, lower selectivity at last two ratios is associated with a significant difference in the reactivity of chlorine atoms in the positions 4 and 3 of benzene rings, and similar reactivity of chlorine atoms in the positions 4 and 5 of unsubstituted and monosubstituted phthalonitrile, respectively, or in positions 3 and 6 of di- and tri-substituted phthalonitrile, respectively.

Interaction of phthalonitrile **I** with aryl-oxides as O-nucleophiles is studied on examples of phenolate and 3-pyridylate anions in DMF [14]. The reaction of phthalonitrile **I** with one of these nucleophiles requires harder conditions, and does not proceed so selectively in respect of both the product number and regioselectivity. Nevertheless it is possible to choose the reaction conditions (temperature and reactant ratio) at which each product – mono- to tetrasubstituted – predominantly or exclusively forms (Table 2).

Regioselectivity of substitution of the first chlorine atom is as high as for the S-nucleophiles while the regioselectivity of the second chlorine substitution

Table 2. Reaction of tetrachlorophthalonitrile **I** with O-nucleophiles



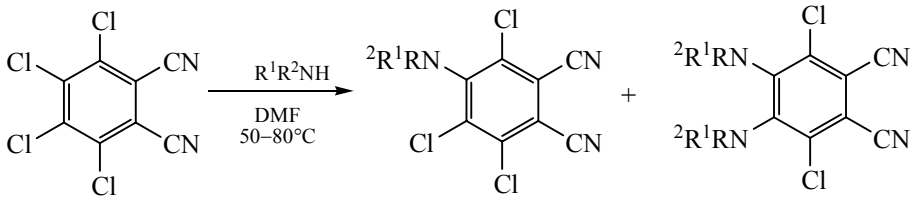
Nucleophil, R	1 : RONa	Reaction temperature, °C	Yield, %				
			VI	**VII**	**VII'** or **VII''**	**VIII**	**IX**
a. Ph	1 : 1	50°C	29.2	–	–	–	–
	1 : 2		53.4	10.5	–	–	–
	1 : 3		19.2	45.3	–	10.0	–
	1 : 4		–	30.5	–	36.5	–
		100°C	–	–	–	60.5	–
b. 3-PyO	1 : 2	50°C	13.0	22.0	16.2	9.1	–
	1 : 4		–	7.8	5.2	49.9	–
		100°C	–	–	–	59.8	–
	1 : 6		–	–	–	–	65.0[a]

[a] In DMSO, product **IXb** (mp 113–115°C) is not previously published.

depends on the structure of the nucleophile. In the reaction with phenoxide the only disubstitution product is 3,6-dichloro-4,5-diphenoxyphthalonitrile **VIIa**, whereas in the case of pyridylate one of unsymmetrical disubstituted products **VIIb'** or **VIIb''** along with the product **VIIb** (structure proved by XRD) is formed in ratio ~2 : 3.

As N-nucleophiles we used aniline and aliphatic primary and secondary amines [15]. Only with the use of cyclic secondary amines it was possible to replace two chlorine atoms in phthalonitrile **I**, in all other cases only one chlorine atom was replaced. All reactions in this case led to single regioisomer (symmetric while disubstituted) indicating a high regioselectivity. By analogy with the reactions involving S- and O-nucleophiles, we believe that the substitution occurs at position 4 and 5. Generally, maximum yields 60–65% were achieved when using 10-fold excess of amine (Table 3).

Table 3. Reaction of tetrachlorophthalonitrile **I** with N-nucleophiles



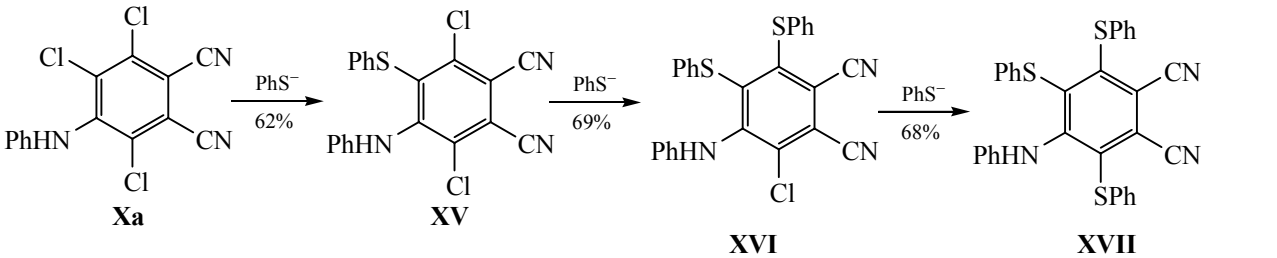
I **X** **XI**

Nucleophil	R^1	R^2	Base	1 : Amine	Yield, %	
					X	**XI**
a	Ph	H	–	1 : 10	65.0	–
b	*n*-C_8H_{17}	H	K_2CO_3	1 : 4	54,8	–
c	Et	Et	–	1 : 10	60,0	–
d	Bu	Bu	–	1 : 10	64.3	–
e	$(CH_2)_2O(CH_2)_2$		–	1 : 10	–	65.5
f	$(CH_2)_5$		–	1 : 10	–	61.7

Action of C-nucleophiles (malonate, dimedone or malononitrile) leads to the replacement of only one chlorine atom in the 4 position (according to XRD of malonate **XII**) [16]. In the case of dimedone the reaction is not stopped and the intermediate product undergoes intramolecular O-substitution with the formation of two regioisomeric dibenzofuran derivatives **XIV'** and **XIV''** similar to that observed in the interaction β-dicarbonyl compounds with 4-bromo-5-nitrophthalonitrile [17] (Scheme 1).

The remaining chlorine atoms in all obtained phthalonitriles can also be substituted in the next step. In particular, in all products of N- [18] and C-substitution [16], they can be smoothly replaced with S-nucleophile.

However, in case of aryloxy products **VI–VIII** using of S-nucleophiles in the second step results in aryloxy substitution also. Conversely, by the selection of conditions, we managed to replace the two remaining chlorine atoms in the bis(phenylsulfanyl) substituted phthalonitriles **IIIa** to pyridyloxy groups [18]:

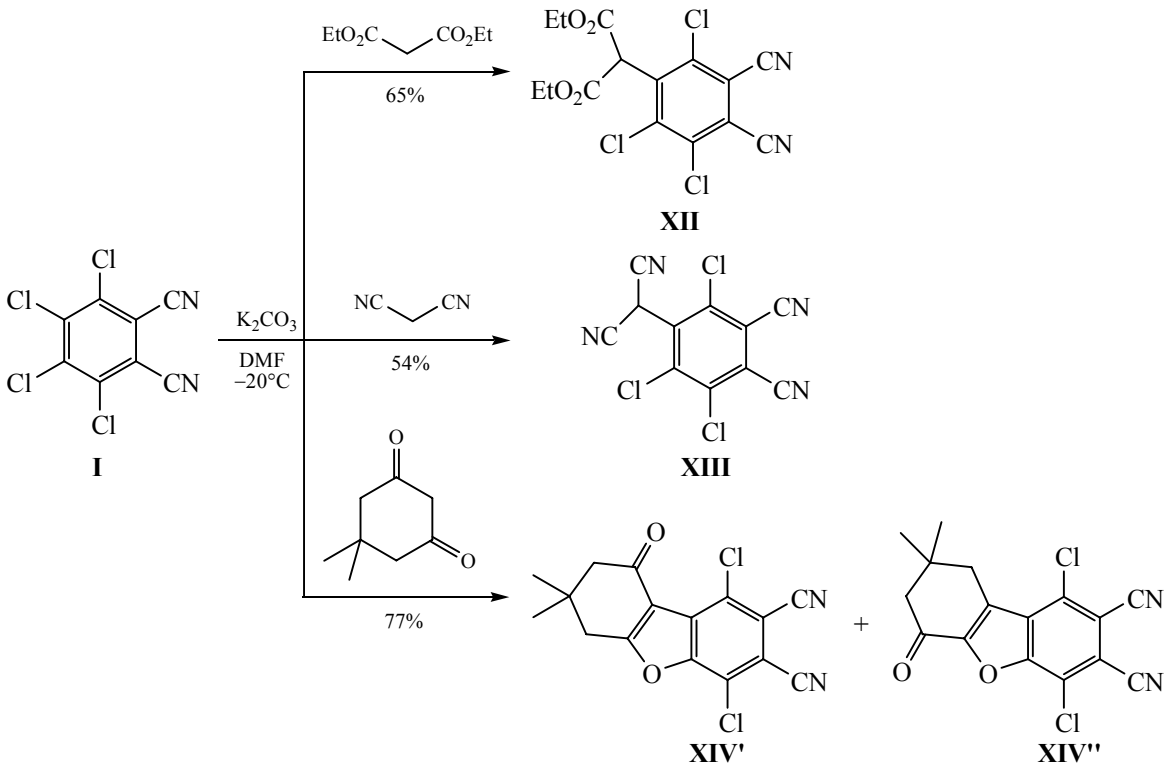


Xa **XV** **XVI** **XVII**

From the obtained tetrasubstituted phthalonitriles we synthesized phthalocyanine complexes of various metals [13–16, 19]. The diagram in Fig. 1 shows that, on the basis of one common synthon — tetrachlorophthalonitrile — various substituted phthalocyanines can be purposefully synthesized, and their absorption maxima cover a significant part of the red and near-infrared range of spectrum.

Several synthetic phthalocyanines were tested as a photosensitizer for photodynamic therapy in the form of micellar solutions in the presence of nonionic

Scheme 1.



surfactants. It was shown that zinc octakis(alkylsulfanyl)-octachlorophthalocyanines are effective photosensitizers for photodynamic therapy of cancer [20, 21].

Not only liposoluble but water-soluble phthalocyanines also could be prepared from tetrachlorophthalonitrile. Thus, we obtained water-soluble polycationic phthalocyanines with the number of cationic groups from 4 to 12 by quaternization of pyridyloxy groups of complexes obtained from phthalonitriles **VIb–VIIIb** with methyl iodide [22]. In aqueous solutions of these complexes increasing number of

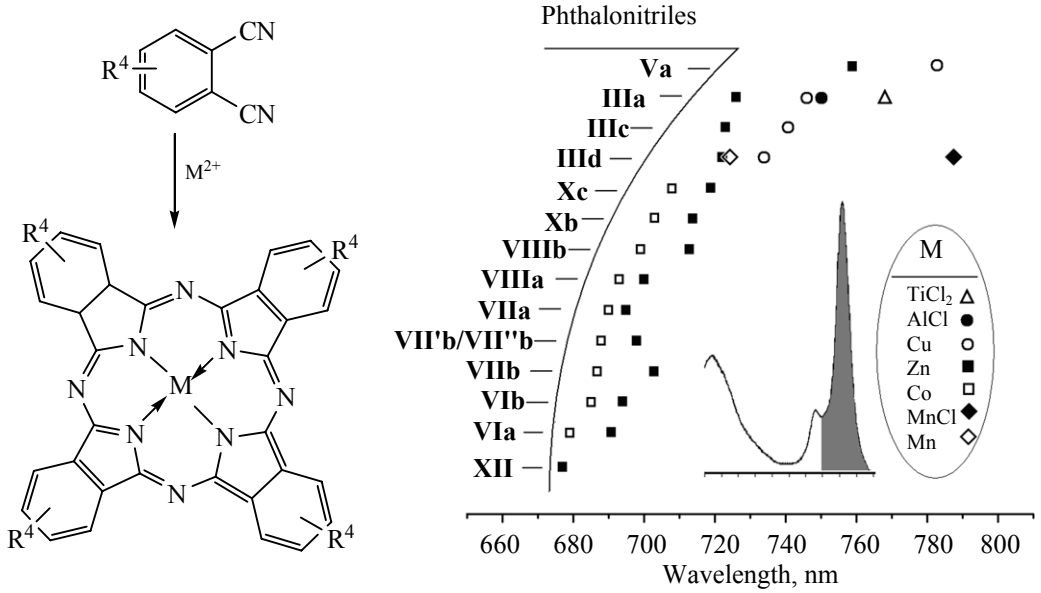
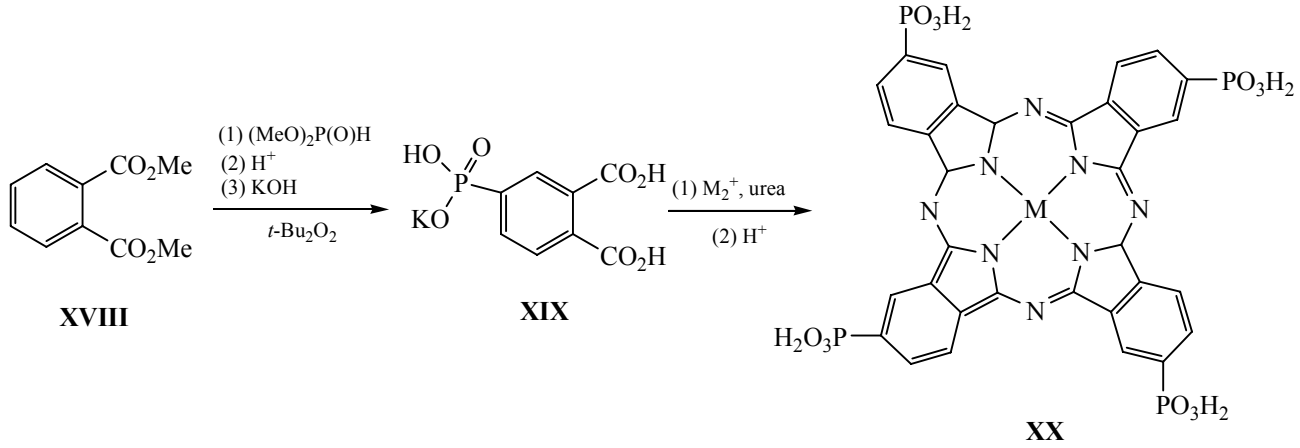


Fig. 1. UV-Vis *Q*-band maximums of hexadecasubstituted phthalocyanines.

Scheme 2.



XVIII **XIX** **XX**

cationic groups shifts equilibrium of aggregation towards the monomer up to the complete disappearance of the aggregates. It was also shown that the change of organic to aqueous solution does not affect the position of the longwave band maximum in the electronic spectra of these complexes.

Synthesis of Water-Soluble Photosensitizers

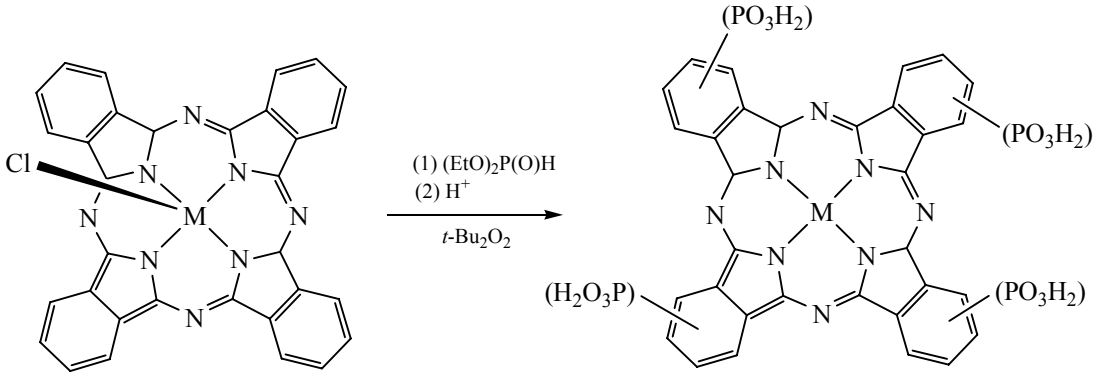
The use of water-soluble photosensitizers is one of the approaches for creating a drugs for photodynamic therapy, which allows to simplify the formulation. As an example it could be mentioned the first reported synthetic photosensitizer for photodynamic therapy and photoluminescent diagnosis Photosens (hydroxy aluminum sulfophthalocyanine), which preparation and use in clinical practice has been described in the reviews [23]. Other example - metal-free sulfophthalocyanine (Phthalosens) [24] which has several advantages over its predecessor and now is prepared for clinical trials. Below the results of studies on the synthesis of water-soluble phthalocyanines and related compounds bearing other ionogenic groups summarized.

Phthalocyanines containing phosphonate groups. The introduction of ionic groups in the macrocycle of phthalocyanine complexes provides their solubility in water which allows to prepare a formulation as aqueous solution. In particular, this approach is implemented in creating Photosense (aluminum sulfophthalocyanine) [23]. Other functionalities also can be introduced in macrocycle to impart water solubility, for example anionic carboxy [25–31] or a cationic ammonium groups [22, 32–34].

A very small number of works are devoted to the preparation and investigation of phthalocyanines with phosphonate groups due to little variety of available correspondingly functionalized phthalogenes. Thus, by substitution of iodine in 4-iodophthalonitrile by the reaction with diethyl phosphite in the presence of palladium catalyst and a base diethyl 3,4-dicyanophenylphosphonate was obtained [35]. The same phthalonitrile was prepared by substituting the bromine in the 4-bromophthalonitrile under the action of triethyl phosphite in the presence of $NiCl_2$ as a catalyst [36]. Single example of phthalonitrile with a phosphonate group in side chain was synthesized by substitution of nitro group in 4-nitrophthalonitrile [37]. In addition, phthalocyanines with a phosphonate group in side chains were obtained by functionalization of other substituted phthalocyanines – by Heck reaction from iodosubstituted phthalocyanine and diethyl vinylphosphonate [38a] or by alkenylation of hydroxy groups in tetrahydroxyphthalocyanine [38b].

The first phthalogene containing a phosphonate group in the benzene ring and used for the phthalocyanine synthesis was monopotassium salt of 4-phosphonophthalic acid **XIX** [39]. This salt was prepared by a multistage reaction including phosphorylation of *o*-xylene using P_2O_5 under high temperature, transformation of the resulting 3,4-dimethylphenylphosphonic acid into phosphonylchloride with $POCl_3$ and PCl_5, photochemical chlorination of methyl groups with chlorine and subsequent oxidation by $KMnO_4$. We have developed a more simple method for synthesis of this phthalogene comprising direct oxidative phosphorylation of dimethyl phthalate **XVIII** with dimethyl phosphite in the presence of di-*tert*-butyl peroxide [40] followed by acid hydrolysis of the resulting product and transformation the resulting acid into monopotassium salt **XIX** (Scheme 2).

Scheme 3.



XXI

Despite the moderate yield of analytically pure phthalogene **XIX** (~25%), the benefits of this "one-pot" method are the smaller number of chemical steps, the exclusion of highly toxic reagents and labor-intensive operations. Yields of copper and cobalt complexes of tetraphosphonophthalocyanine **XX** obtained from the salt **XIX** in the presence of urea in a high boiling solvent are 70 and 80%, respectively. Note, that the aluminum complex was obtained with a very low yield (~7%) and gallium complex was obtained only in a trace by this scheme.

As it turned out, this method is suitable for direct phosphorylation of phthalocyanines, and in this case of aluminum and gallium complexes corresponding phosphonates **XXI** were obtained in 40–45% yield [41] (Scheme 3). The products were obtained as a mixture of phthalocyanines with different degree of substitution and different position of phosphonic groups in macrocycle, however this disadvantage is compensated by the possibility of adjusting of the phosphonic groups average number in the macrocycle varying the duration of the reaction. Thus, during the phosphorylation of gallium phthalocyanine in diethyl phosphite for 2–3, 6, or 10 h, the products with an average degree of substitution of 1, 3 and 4 were obtained, correspondingly.

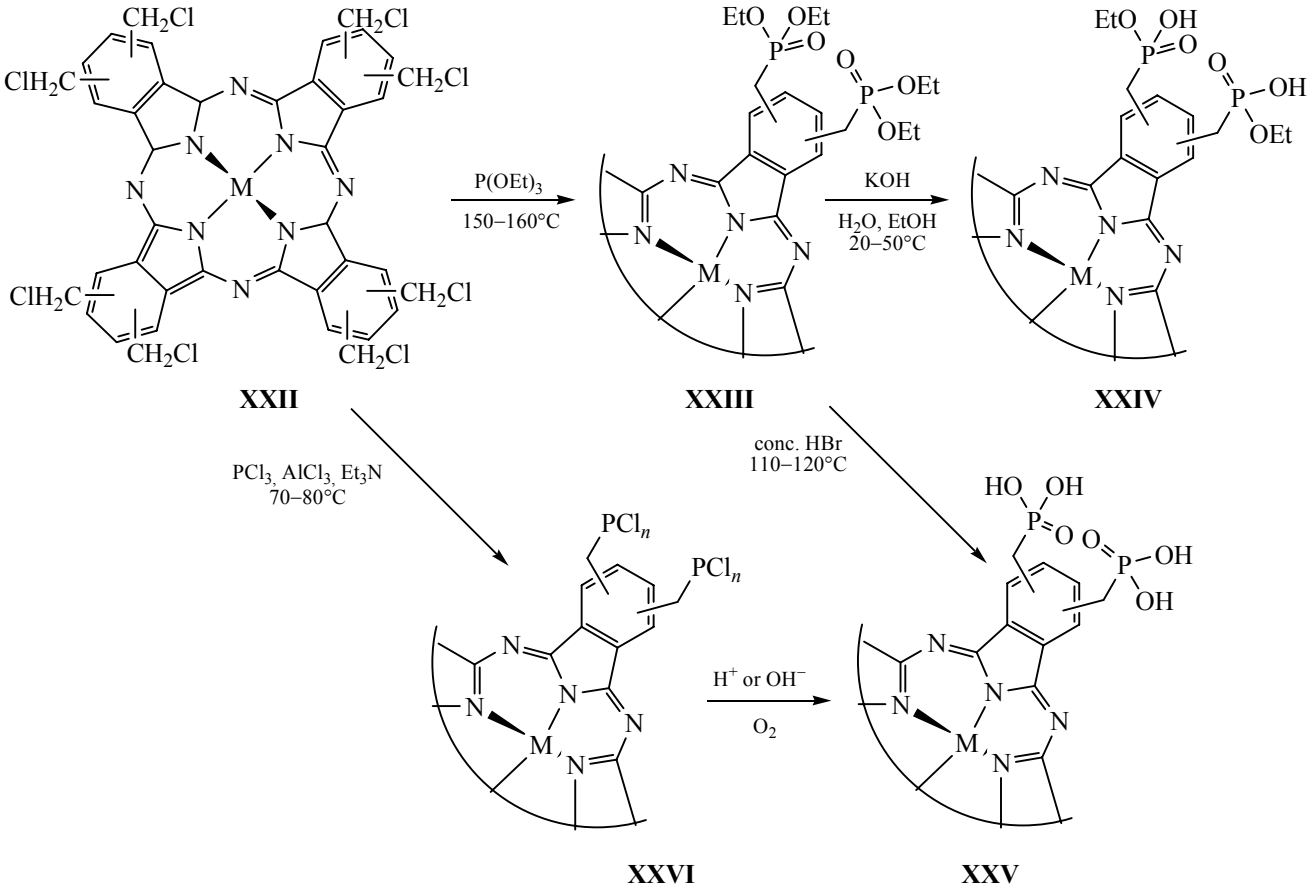
We have developed a general approach to the preparation of phthalocyanines containing up to eight phosphonomethyl groups or their esters by the transformation of chloromethyl groups of available chloromethyl substituted phthalocyanines **XXII** [42] by the Michaelis–Arbuzov reaction [43] (Scheme 4).

This approach is applicable to a wide range of phthalocyanine metal complexes (M = AlX, Zn, SnX_2, SiX_2, TiO) and allows to obtain phthalocyanines **XXIII** with an average number of phosphonate groups from 2 to 8 in yields not less than 55%. By hydrolysis of diester groups under mild alkaline conditions it is possible to prepare half ester compounds **XXIV** in high yields. Complete hydrolysis occurs at much more severe conditions by boiling in concentrated hydrobromic acid wherein the complexes of certain metals undergo a degradation which reduces yields of the free acids **XXV** to 17–30%.

The apparent advantage of this group of highly substituted photosensitizers is the almost complete absence of aggregation in aqueous solutions and a noticeable bathochromic shift of the long-wavelength absorption band. Thus, the absorption maximum of aluminum complex **XXIII** is 698 nm with a molar absorption coefficient higher than 10^5 M^{-1} cm^{-1}, and aluminum complex **XXIV** has even larger bathochromic shift. Analysis of toxicity revealed that the complex **XXIV** belongs to the third class of hazardous substances. Some of the proposed photosensitizers were tested in vitro and in vivo and showed good results both in terms of their efficiency and of the rate of excretion of the drug from the body.

To avoid the severe hydrolysis conditions, we have elaborated an alternative method for synthesis of free acids **XXV**. This method consisted in converting of chloromethyl derivatives **XXII** first in (two- or trichlorophosphino)methyl substituted complexes **XXVI** which are easily converted into the free acids **XXV** under the action of water or under acidic or alkaline hydrolysis on air [44]. This method is attractive also because the possibility of preparation from intermediate **XXVI** of other phosphonic acid

Scheme 4.



XXII **XXIII** **XXIV**

XXVI **XXV**

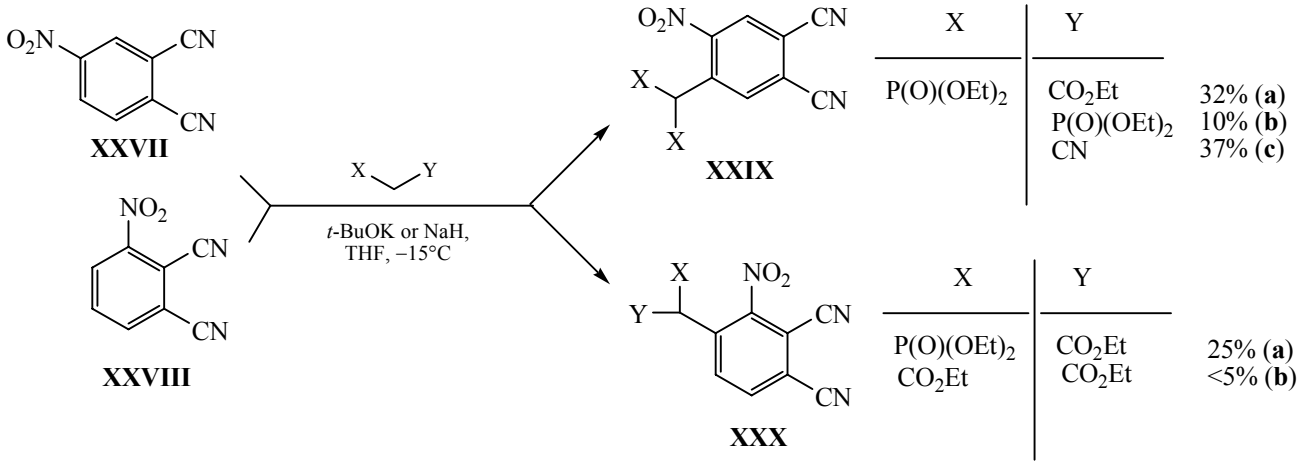
derivatives such as amides or esters with delicate alcohol or amine residues.

Following just the same approach, authors of [45] from mono- and bis(bromomethyl) substituted phthalonitriles obtained the corresponding phthalonitriles with phosphonate groups, which were successfully transformed into complexes with four and eight phosphonate groups.

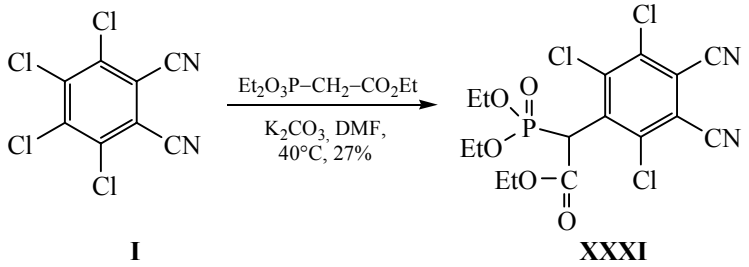
In course of this work on the synthesis of substituted phthalocyanines with phosphonate group in the side chain, we investigated the reaction of aromatic C-nucleophilic substitution. This reaction is repeatedly used for the preparation of substituted phthalonitriles. Thus, under the action of alkyl malonate anions on 4-nitrophthalonitril [46, 47] or 4,5-dichlorophthalonitril [48] the corresponding dicyanophenylmalonates were obtained as a result of the *ipso*-substitution of a nitro group or a chlorine atom. Interaction of β-dicarbonyl compounds with 4-bromo-5-nitrophthalonitrile led to C-nucleophilic substitution of the bromine atom and subsequent enolization and O-substitution of nitro group eventually resulted in the formation of dibenzofurane derivatives [49]. At the same time, reaction of dimedone and 4-nitrophthalonitrile in the presence of a base leads to oxidative substitution of a hydrogen atom in the *ortho*-position to the nitro group and further to cyclization similar to the above-mentioned for 4-bromo-5-nitrophthalonitrile [49]. Therefore, in the course of the study we had to figure out the possibility and the direction of the interaction of C-nucleophiles bearing with a phosphonate group [50].

The interaction between the 4-nitro- (**XXVII**) or 3-nitrophthalonitrile (**XXVIII**) with triethyl phosphonoacetate, or tetraethyl diethoxyphosphorylacetonitrile in the presence of base leads, in contrast to the interaction with the malonate, to the products not of ipso but oxidative substitution of the hydrogen atom to form products **XXIX** and **XXX**, respectively (Scheme 5). Product yields in this transformation (even in optimized for product **XXIXa** conditions) do not exceed 37%.

Scheme 5.



Scheme 6.



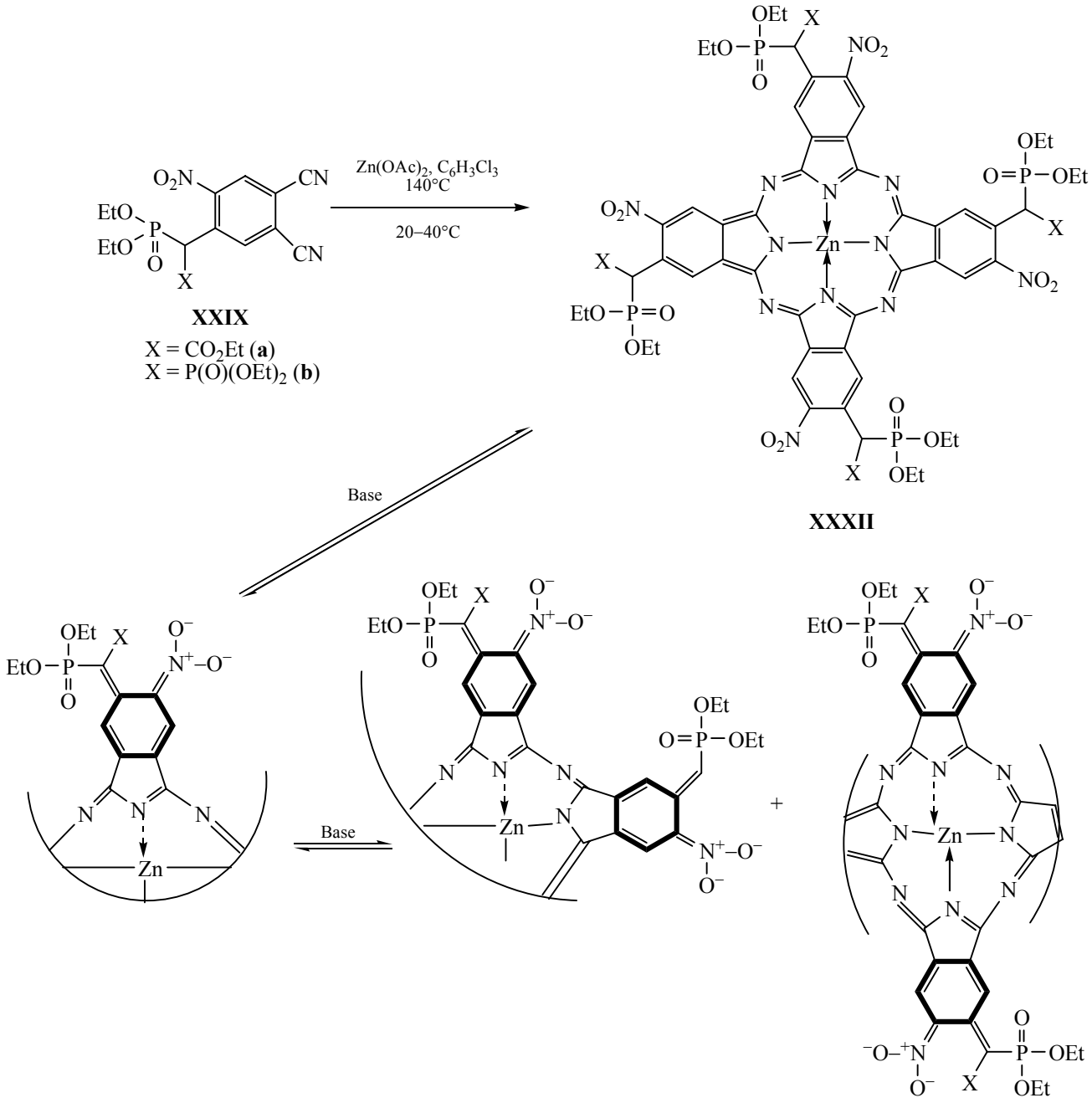
It should be noted that, unlike the 4-nitrophthalonitrile **XXVII,** its 3-isomer **XXVIII** has not been reported as a substrate in C-nucleophilic substitution. Perhaps our attempt to introduce a substrate **XXVIII** into the reaction with diethyl malonate "illuminates" this fact: from a complex mixture of products only starting dinitrile **XXVIII** was isolated but containing the product of oxidative substitution **XXXb** as impurity.

Reaction of tetrachlorophthalonitrile **I** with triethyl phosphonoacetate leads to substitution of only one chlorine atom in position 4 (according to XRD) with formation of phosphonate **XXXI** (Scheme 6). No increasing of an amount of the nucleophile nor re-involvement of the phosphonate **XXXI** in the reaction led to the second chlorine substitution. Perhaps, the reason of such inactivity is high acidity of methine group of the product **XXXI** which leads to its competitive deprotonation in reaction conditions. Resulting carbanion conjugates with the benzene ring and deactivates the latter one to further nucleophilic attack.

All the phosphonates **XXIX**–**XXXI** are easily deprotonated even by weak bases to form a conjugated carbanions, that detected by the appearance of an intense bright red color of the solution. Probably due to their high acidity we did not find conditions for tetramerization of phthalogenes **XXIXc**, **XXXa, XXXb,** and **XXXI**. However, template tetramerization of phthalonitriles **XXXa, XXXb** results in the formation of target phthalocyanines **XXXIIa, XXXIIb** (Scheme 7).

These phthalocyanines have an unprecedented property related with increased CH-acidity of methine group *ortho*-positioned to the nitro group: addition of bases leads to successive and reversible shift of long wavelength band maximum in electronic absorption spectra from ~700 to 815 nm and further to 870 nm (Fig. 2). We believe that for these complexes deprotonation of CH groups leads to the formation of local chromophore systems that exclude one or two benzene rings from phthalocyanine aromatic system. As a result, chlorin- and/or (iso)bacteriochlorin-like aromatic systems are formed which have bathochromically shifted band of the chromophore with respect to the original system, just like tetraazachlorins and tetraaza(iso)bacteriochlorins which absorb at much longer wavelength region than tetraazaporphines [51].

Scheme 7.



Octacarboxyphthalocyanines and their conjugates. The presence of carboxy groups in the phthalo-cyanine macrocycle gives convenient opportunity for tuning its physical and chemical properties by obtaining water soluble salts, functional derivatives (esters, amides and imides) and conjugates with natural or synthetic molecules.

Phthalocyanines with four or eight carboxy groups in the macrocycle are known for quite long time. 2,9,16,23-Tetracarboxyphthalocyanines are usually prepared by tetramerization of trimellitic anhydride in the presence of urea and a metal salt [26, 27]. Another method of their preparation as well as their esters and amides includes tetramerization of 3,4-dicyanobenzoic acid [52] or its functional derivatives [28].

2,3,9,10,16,17,23,24-Octacarboxyphthalocyanines are of great interest because, firstly, they retain the molecular symmetry of the unsubstituted phthalo-

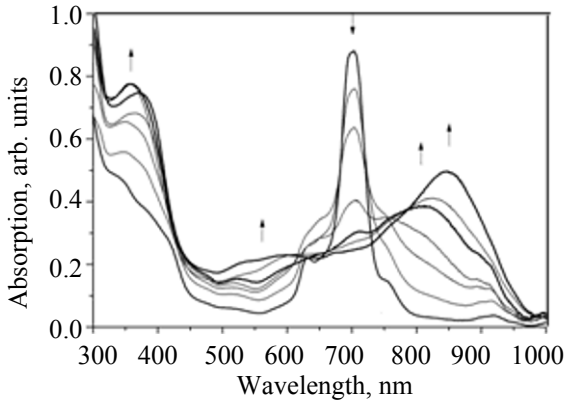


Fig. 2. Changes in absorbtion spectrum of complex **XXXIIa** in DMF on adding 1,8-diazabicyclo[5.4.0]undec-7-en.

cyanine while tetrasubstituted analogs consist of a mixture of positional isomers, and secondly, their salts form true solutions in aqueous media and their lipophilic derivatives are less prone to aggregation in organic solvents. The main method of their preparation is the tetramerization of symmetrical derivatives of pyromellitic acid – its dianhydride or 1,2,4,5-tetracyanobenzene in the presence of metal salts [53] (Scheme 8). However, in this case the product of the reaction represents a mixture of both monomeric complexes **XXXIII** and polymeric phthalocyanines. Separation of target mononuclear complex from the polymers, especially from low molecular weight oligomers could be achieved with a laborious column chromatography. This method is time consuming and the yield of the product is only 5–20% depending on the nature of the central metal atom. The selective synthesis of the metal-free product **XXXIII** (M = HH) by tetramerization of 1,2,4,5-tetracyanobenzene under carefully controlled conditions has been reported, but low yield and low accessibility of the starting compound limit the application of this method.

By another approach unsymmetrical derivatives of pyromellitic acid are used as starting compounds for the synthesis of **XXXIII**, namely 4,5-dicyano-phthalimide [28, 54] and 4,5-bis(alkoxycarbonyl)-phthalonitriles [28, 30, 31]. The advantages of this method are selectivity, high yields of desired octa-carboxyphthalocyanine derivatives and the possibility of obtaining both metal complexes and metal-free macroligands. However, in this case starting phthalo-genes are also difficult to prepare, that limits the application of this method.

We have developed a method for preparing the starting 4,5-bis(alkoxycarbonyl)phthalonitriles from commercially available and cheap pyromellitic anhydride [25] (Scheme 9).

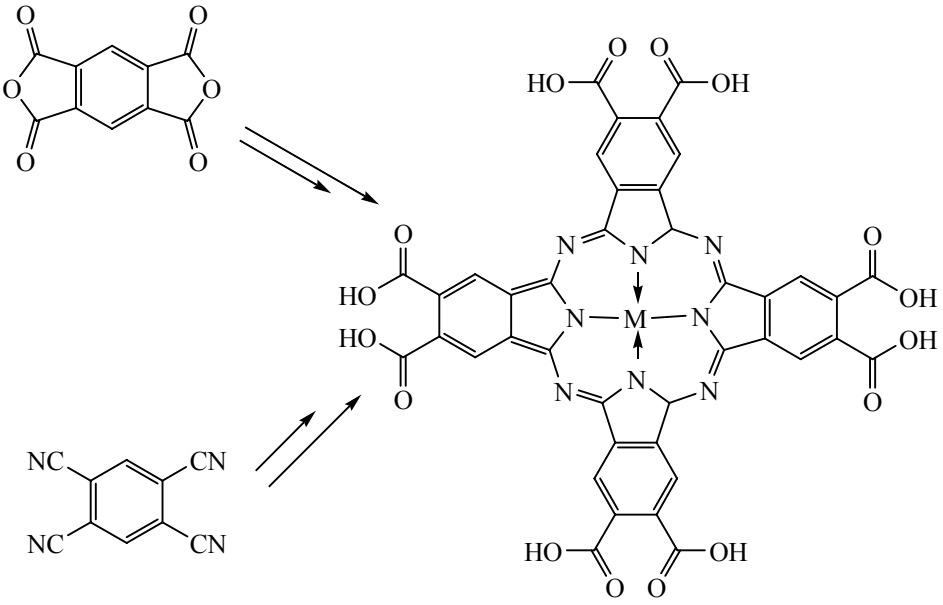
According to this method 4,5-bis(ethoxycarbonyl) phthalimide **XXXV** was prepared from triethyl ester **XXXIV** (easily obtained in a high yield from pyromellitic anhydride [55]). The phthalimide **XXXV** was converted to diethyl 4,5-dicyanophthalate **XXXVI** in two simple steps with overall yield of 60–65% starting from pyromellitic anhydride. For comparison, related dialkyl 4,5-dicyanophthalates were obtained in ~12% overall yield starting from *o*-xylene including such steps as oxidation with potassium permanganate and cyanation with toxic copper(I) cyanide [31].

As a part of the health care program of the Moscow Government, we have prepared a number of octa-carboxyphthalocyanines **XXXIII** and their conjugates with biologically important molecules in order to study their biological activity. Thus, aluminum (M = AlOH) and zinc (M = Zn) octacarboxyphthalocyanines in the form of their sodium salts were found to be promising photosensitizers for photodynamic therapy due to the efficient generation of reactive oxygen species [56]. Good results were obtained in the so-called "dark" therapy for cobalt complex (M = Co, Teraphthal®), which catalyzes formation of reactive oxygen species in the presence of ascorbic acid in the absence of light [57]. Zinc and cobalt complexes are also effective as sonosensitizers for sonodynamic therapy of cancer [58]. It was shown that the manganese complexes (M = MnOH, MnOAc) are of interest as a contrast agent for magnetic resonance therapy of oncological diseases [59].

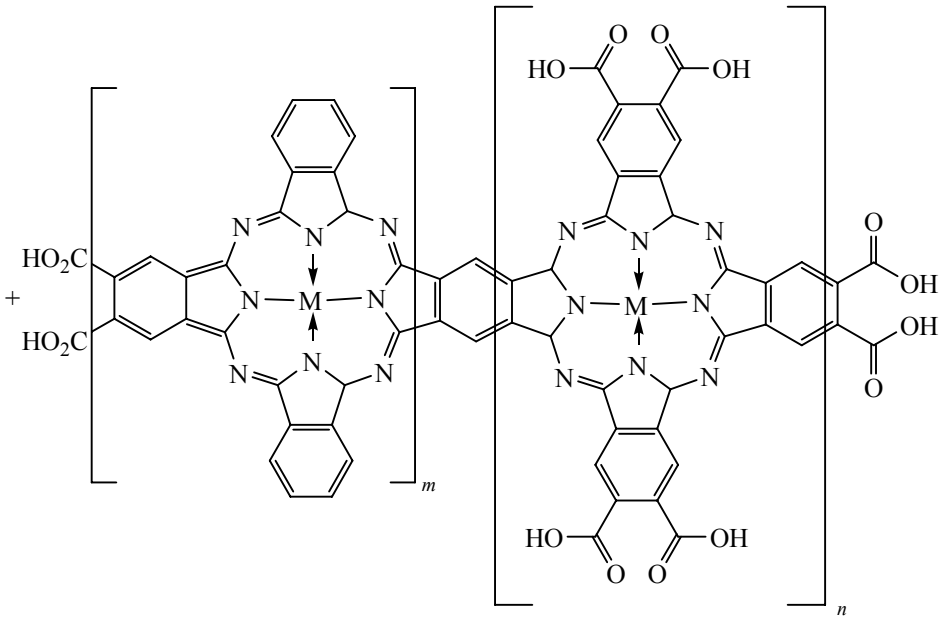
It was shown that sodium salts of **XXXIII** form strong associates of controlled composition with cationic octakis(pyridiniummethyl)phthalocyanines due to their anionic character. Their catalytic activity greatly depends both on the composition and the central metal nature of cationic and anionic components [60].

Iron and cobalt tetracarboxyphthalocyanines are able to form strong conjugates with oligonucleotides that can be used for the oxidative modification of single stranded DNA fragments with molecular oxygen in the presence of reducing agent or with hydrogen peroxide. The catalytic activity of the conjugate can be increased by the addition of a third component – phthalocyanine with positively charged substituents,

Scheme 8.



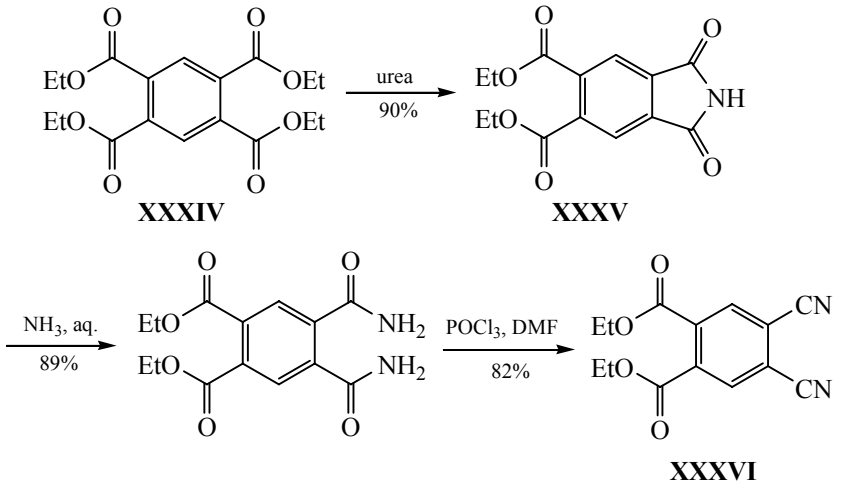
XXXIII



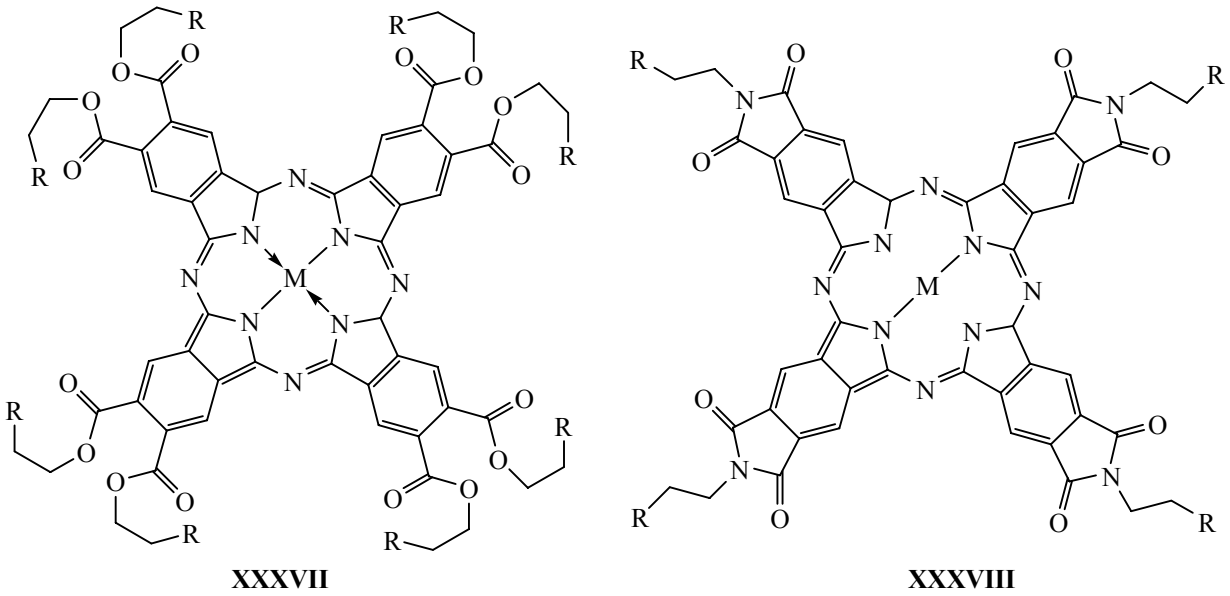
which forms an associate with a molecule of tetracarboxyphthalocyanine [61].

By functionalization of carboxy complexes **XXXIII** we obtained a number of their derivatives – esters and imides bearing small biologically important molecules of cationic or anionic character as substituents (Scheme 10). Thus, zinc, cobalt, iron and hydroxyaluminum 2,3,9,10,16,17,23,24-octakis(2-chloroethoxycarbonyl)phthalocyanines **XXXVIIa** were obtained by reaction of tetraanhydrides of metal complexes **XXXIII** with 2-chloroethanol. After quaternization with tertiary amines such as trimethylamine, 2-dimethylaminoethanol, *N,N*-diethylethylenediamine and *N,N*-dimethylglycine water-soluble conjugates of the cationic type **XXXVIIb–XXXVIIe** were obtained [62, 63]. Reaction of the above mentioned tetraanhydrides with *N,N*-diethyl-

Scheme 9.



Scheme 10.



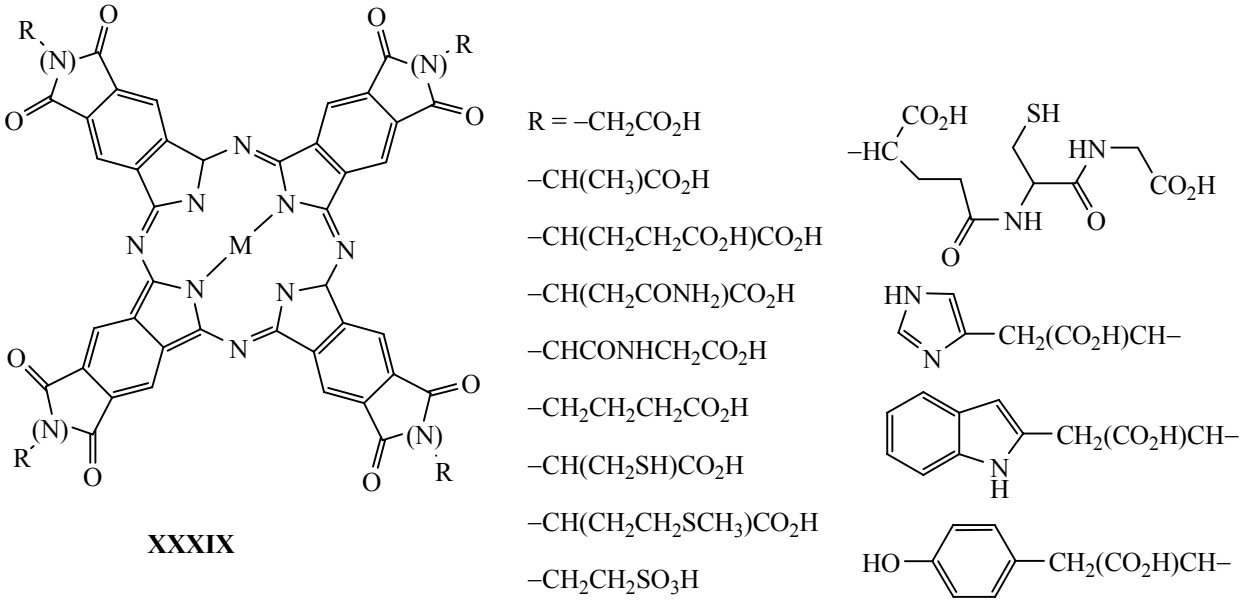
XXXVII: R = Cl (**a**), $N^+Me_3Cl^-$ (**b**), $N^+(Me)_2CH_2CH_2OH\ Cl^-$ (**c**), $N^+(Et)_2CH_2CH_2OH\ Cl^-$ (**d**), $N^+(Me)_2CH_2COOH\ Cl^-$ (**e**), M = AlOH, Co, Zn, Fe; **XXXVIII**: R = $N(Et)_2$ (**a**), $N^+(Et)_2\,I^-$ (**b**), $N^+(Et)_3CH_2H_5SO_4^-$ (**c**), $N^+(Et)_2MeCH_3SO_4^-$ (**d**), $N^+(Et)_2MeCH_3C_6H_4SO_3^-$ (**e**), $N^+(Et)_2Me(CH_3)_2PO_4^-$ (**f**), M = AlOH, Co, Zn, Fe.

ethylenediamine lead to (2-diethylaminoethyl)substituted tetraimides **XXXVIIIa** (M = Co, Zn, AlOH, Fe), which are starting compounds for the new series of water-soluble cationic covalent conjugates **XXXVIIIb–XXXVIIIf**, namely, its quaternary salts with methyl iodide , methyl tosylate, dimethyl and diethyl sulfate, trimethyl phosphate [64].

A number of water-soluble covalent conjugates of anionic type were prepared by the reaction of the tetraanhydrides **XXXIII** with amino acids, in particular α-amino acids or their ethyl esters (in the case of glycine) according to the published procedure [65]. Mono-, di-, tri- and tetraconjugates **XXXIX** can be obtained by varying the ratios of reactants, temperature and reaction time (Scheme 11).

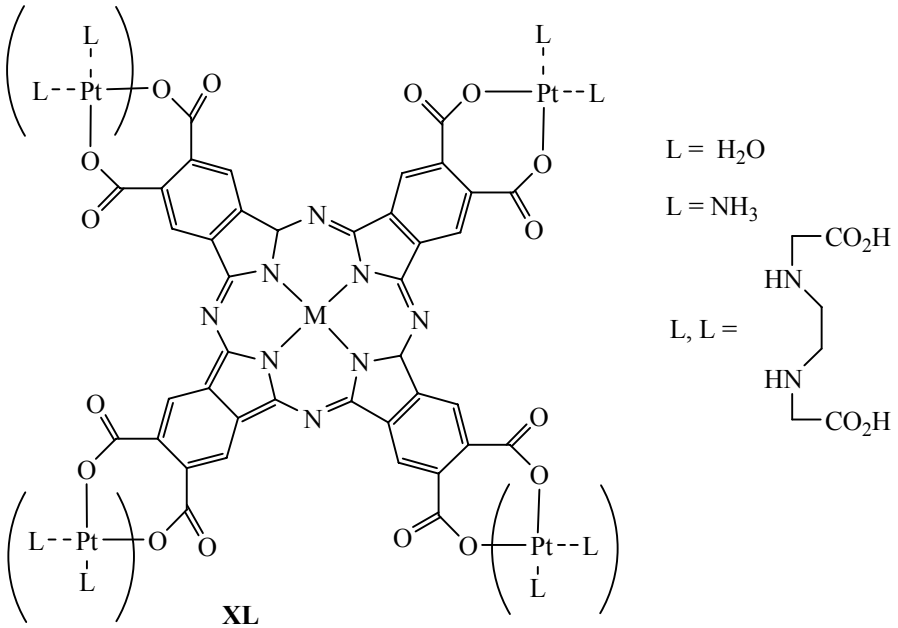
To date the conjugates with series of natural and synthetic amino acids (glycine, histidine, alanine and β-alanine, cysteine, asparagine, tyrosine, tryptophan, methionine, glutamic acid, α-aminoadipic acid, folic acid, γ-aminobutyric acid), the dipeptide (glycyl-

Scheme 11.



XXXIX

Scheme 12.

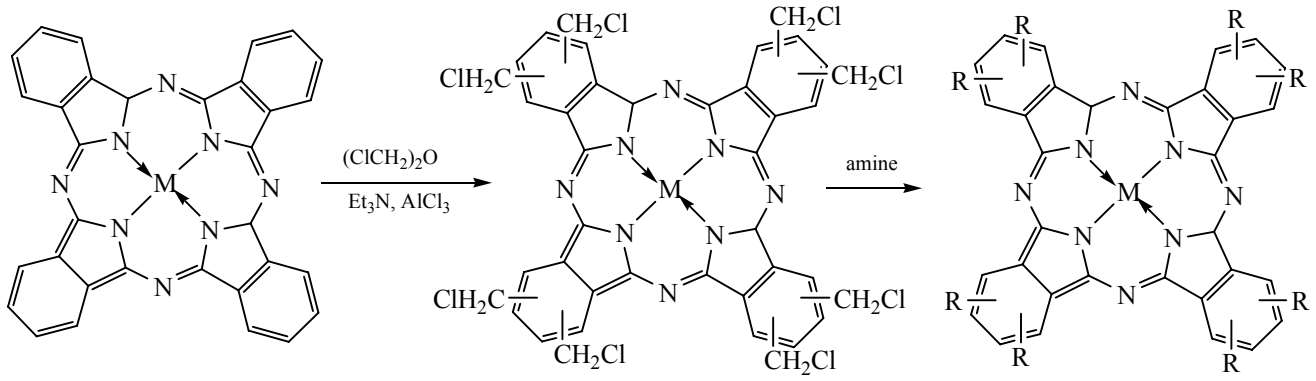


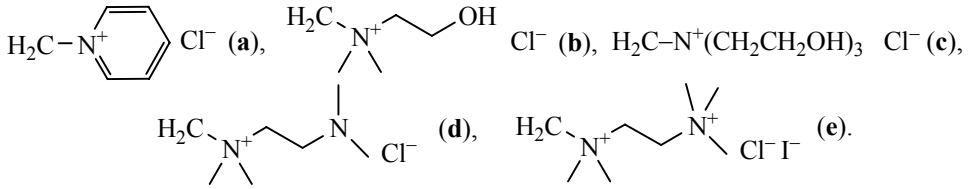
XL

glycine), the tripeptide (glutathione) and sulfo-analog of *α*-amino acid taurine were prepared. The most interesting of these compounds, primarily for the catalytic ("dark") therapy are conjugates with glycine, sarcosine [26] and taurine [63, 66].

Complexes **XXXIII** may be used for the synthesis of exocyclic covalent conjugates with other metals, such as Pt (II). These conjugates combine the properties of a photosensitizer for photodynamic therapy (or "dark" catalytic therapy) with cytotoxic properties of platinum(II) compounds which are used in cancer chemotherapy. To date the covalent conjugates of Pt(II) with octacarboxyphthalocyaninatocobalt **XL** (M = Co) [67], zinc **XL** (M = Zn) [68] and aluminum **XL** (M = AlOH) [69] with the

Scheme 13.





number of exocyclic coordination centers from 1 to 4 were prepared (Scheme 12).

Cationic phthalocyanines. Cationic tetrapyrrole compounds attract attention of researchers because they exhibit a much higher activity compared with the anionic or neutral structures in antimicrobial PDT [70]. Above we already mentioned the approach which allows to obtain phthalocyanines with cationic substituents: quaternization of pyridyloxy substituted phthalocyanines [22] or esters of carboxyphthalocyanines with tertiary amino group in ester moiety **XXXVIIa**, **XXXVIIIa** [62–64].

We have also used the approach based on quaternization of chloromethyl substituted phthalocyanines **XXII** [42] with suitable tertiary amines [71, 72] (Scheme 13). As in the preparation of phosphonomethyl substituted phthalocyanines **XXIII–XXVI**, in this case a mixture of compounds **XLI** is formed, which can be characterized only by the average number of cationic groups in the macrocycle. However, this approach has several significant advantages, namely: the low cost of the target substance; possibility of using the same starting material to obtain both cationic and anionic phthalocyanines (see above); easy regulation of cationic groups number in macrocycle by varying of the reaction conditions: reagents ratio, temperature and reaction time; easy varying of central metal atom and quaternary centers design; using as starting materials of substituted phthalocyanines and removal of the cationic sites from the macrocycle to side chain [73].

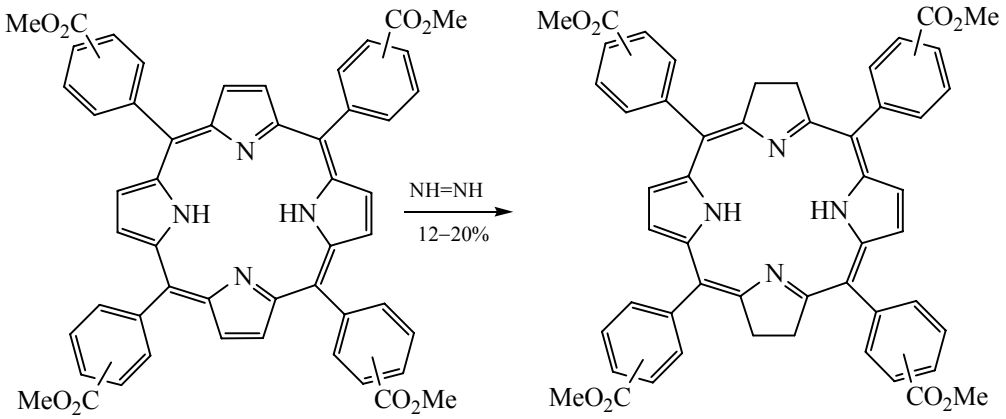
Having carried out an extensive screening, we established the influence of some structural factors of these photosensitizers, such as number of cationic substituents in the macrocycle [34], type of metal and design of the substituent [33, 74], on the antimicrobial photodynamic efficiency. Optimal antimicrobial photosensitizer – zinc octacholinylphthalocyanine (**XLIb**, M = Zn), now known as Cholosens – has been chosen. It has a wide range of photodynamic activity and can be applied not only in antimicrobial PDT [71, 75], but also in the treatment of cancer [72, 76].

Attachment of chloromethyl substituted phthalocyanines to the surface and subsequent quaternization leads to cationic photosensitizers attached to solid carrier. They also may serve as heterogeneous antimicrobial photosensitizers for photodynamic therapy [73, 77].

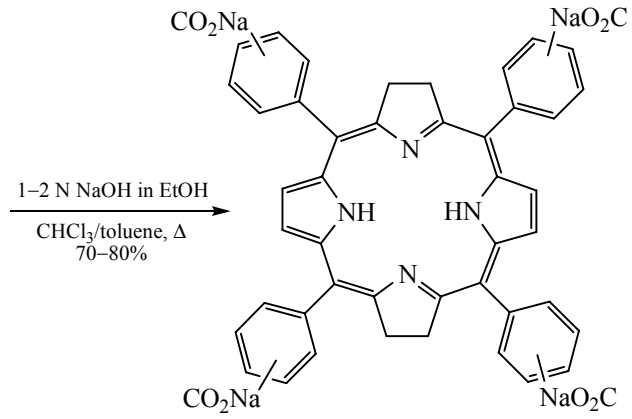
Water-Soluble *meso*-Tetraarylbacteriohlorines

Hydrogenated derivatives of porphyrins - chlorins and bacteriochlorins – are widely studied because their representatives are component of some the important natural compounds. These macrocycles with strong

Scheme 14.



XLII **XLIII**



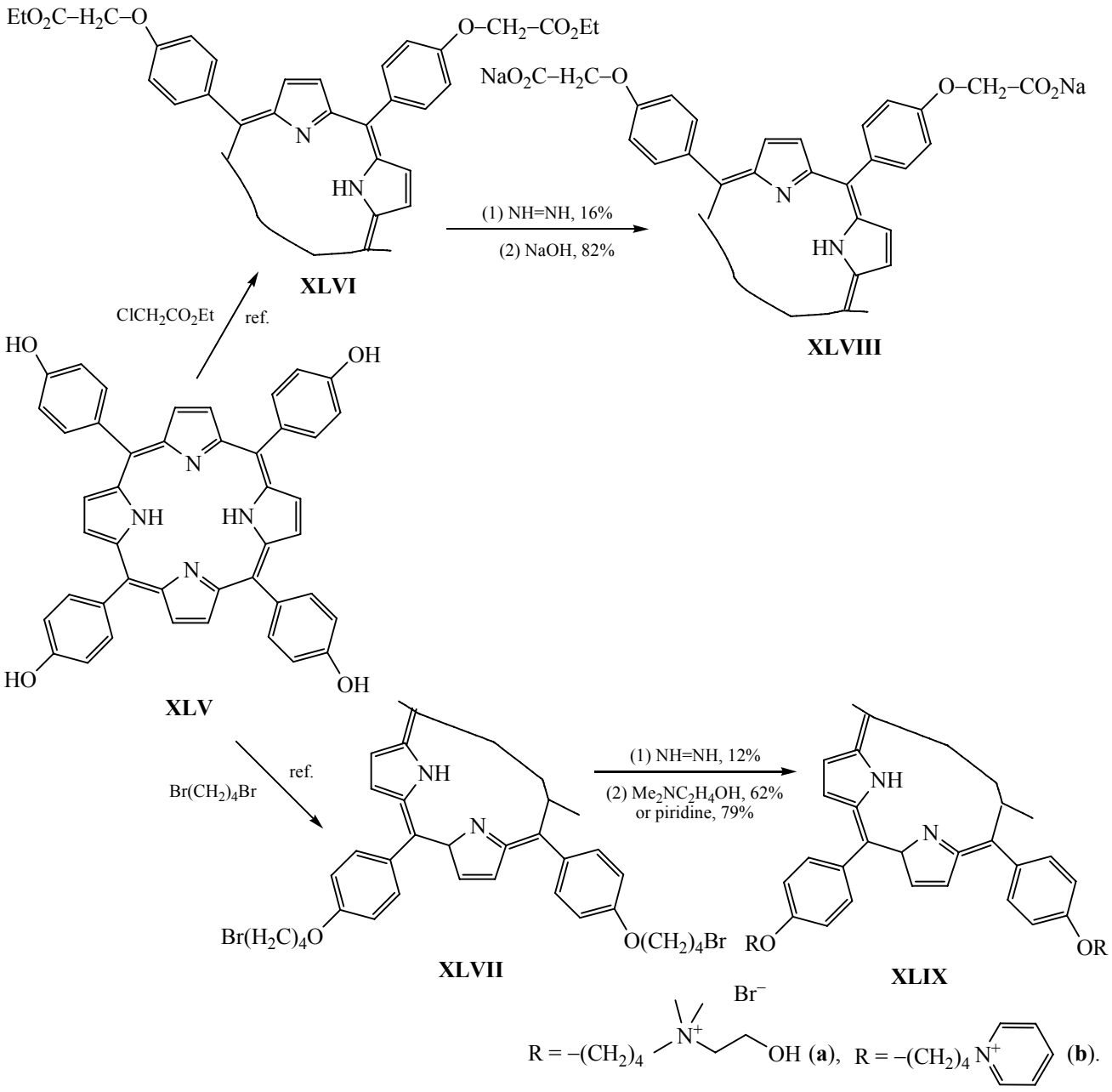
XLIVa (*meta*)
XLIVb (*para*)

absorption in the red and near IR spectral region are widely studied as a second-generation photosensitizers for photodynamic therapy of cancer [78]. Bacteriochlorins are of particular interest as they are characterized by intense absorption in the "therapeutic window" (720-800 nm) which use allows to increase the efficiency PDT due to the deeper penetration of radiation to the tumor. However, the use of many bacteriochlorins is limited due to their high hydrophobicity that requires the use of photosensitizer delivery systems to the cell membrane. It means that search of new methods for the synthesis of hydrophilic bacteriochlorin derivatives is rather actual problem.

We have synthesized a number of *meso*-tetraaryl substituted bacteriochlorins having a phenyl group with pro-cationic or pro-anionic substituent or a pyridine moiety. A simple and convenient method developed by Whitlock et al. [79] has been used for their synthesis which based on reduction of the corresponding porphyrins with diimide formed *in situ* from *p*-toluenesulfonylhydrazide in the presence of potassium carbonate in boiling pyridine, sometimes with minor modifications. Thus, the reduction of tetrakis-3- or 4-(methoxycarbonyl)phenyl substituted porphyrins **XLII** lead to bacteriochlorins esters **XLIII** with moderate yields (20%), which are hydrolyzed to the sodium salt **XLIV** in good yields [80] (Scheme 14).

Convenient common synthon to prepare both cationic and anionic bacteriochlorins proved to be tetrakis(4-hydroxyphenyl)porphyrin **XLV**. It gives starting porphyrins **XLVI** [81] and **XLVII** [82] bearing pro-anionic or pro-cationic group, respectively, by interaction with ethyl chloroacetate or 1,4-dibromobutane (Scheme 15). They are reduced with diimide to the corresponding bacteriochlorins, then hydrolysis of ester groups with sodium hydroxide

Scheme 15.

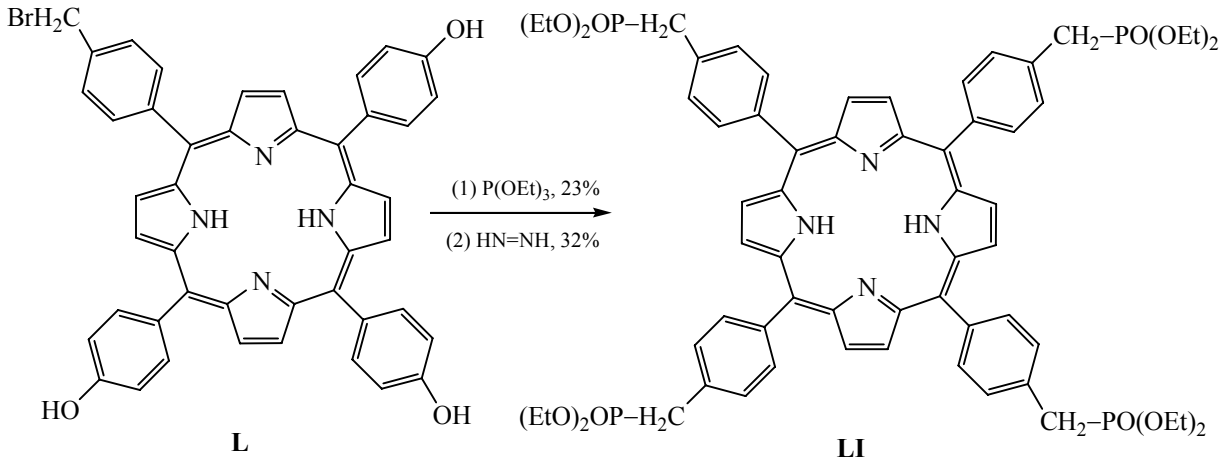


or interaction of alkylbromide groups with tertiary amines smoothly resulted to bacteriochlorins with distanced from the macrocycle carboxy or quaternary ammonium groups **XLVIII** and **XLIX**, respectively [83] (Scheme 15).

For preparation of bacteriochlorins with phosphonate groups we used the Michaelis–Arbuzov reaction by analogy with phthalocyanines (see above). Thus, on heating of bromomethyl substituted tetraphenylporphyrin **L** with triethylphosphite corresponding tetraphosphonate was isolated in moderate yield which gave bacteriochlorin with four phosphonate groups **LI** by reduction with diimide [84] (Scheme 16).

Only 3-pyridylsubstituted bacteriochlorine **LIIIa** was formed in good yield (40%) by reduction of tetrapyridylporphyrins **LII** with diimide (Scheme 17). Its 4-pyridyl analogue **LIIIb** was obtained with a very

Scheme 16.



L **LI**

low yield, due to, apparently, very poor solubility of the parent compound in the reaction medium. Alkylation of the product **LIIIa** with methyl iodide, methyl tosylate [85], ethyl chloroacetate or 1,4-dibromobutane yields tetracationic bacteriochlorins **LIVaa–LIVad** with yields of 60–70% [86]. The presence of terminal bromine in the alkyl chains of compounds **LIVac** allows further quaternization with increasing number of the cationic centers to eight. The reaction of compound **LIVac** with tertiary amines results in formation of octacationic bacteriochlorins **LIVae**, **LIVaf** with yields higher than 80% [87] (see Scheme 17).

Only cadmium complex **LV** (M = Cd) was obtained by reaction of tetrapyridylsubstituted product **LIIIa** with acetates or acetylacetonates of different transition metals (Cd, Zn, Mg, AlX, Pd) in various solvents in the presence of bases or without them. The zinc complex **LV** (M = Zn) was synthesized quantitatively by transmetallation *via* refluxing of cadmium complex with zinc acetylacetonate in a mixture of chloroform/methanol. The tetracationic zinc complexes **LVIaa**, **LVIab** were prepared from this last zinc complex by interaction with methyl iodide or methyl tosylate. Alternatively last two complexes were obtained from metal-free analogue **LIIIa** by quaternization and consequent metallation. In contrast to **LIIIa**, quaternary salts **LIVaa–LIVac**, **LIVaf** formed zinc complexes **LVIaa–LVIac**, **LVIaf** *via* direct metallation with zinc acetylacetonate with good yields [88].

The bacteriochlorins synthesized were tested *in vitro* and *in vivo* in P.A. Herzen Moscow Institute of Oncology for evaluation of their photodynamic activity. It was found that some of them have high photobiological activity (inhibition of tumor growth and response rate were 100% for **LIVac** and **LIVaf**), and can be used as photosensitizers for PDT of cancer.

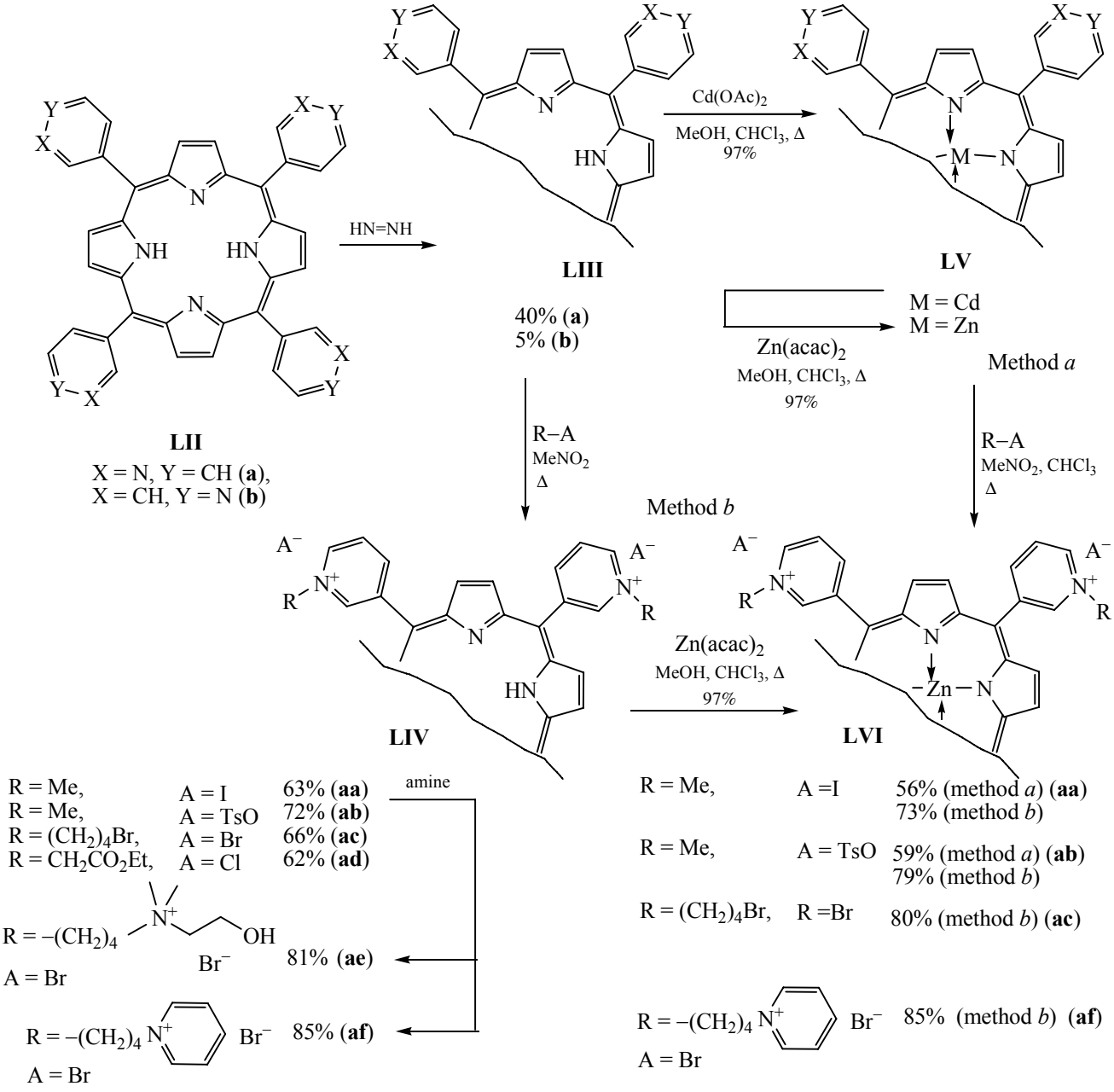
Synthesis of Tetraazachlorins, Tetraaza(iso) bacteriochlorins, and Their Derivatives

Until recently, tetraazaporphyrins were much less studied compounds in comparison with other classes of tetrapyrrolic compounds like a porphyrins or phthalocyanines due to their low availability. In the last three decades rather a lot of information about the synthesis and properties of substituted tetraazaporphyrins were appeared and described in the numerous reviews [89]. Formal hydrogenation of the double bond of one of tetraazaporphyrin pyrrolic units leads to tetraazachlorin, hydrogenation of two opposite pyrrolic units leads to tetraazabacteriochlorin, and hydrogenation of two adjacent units leads to tetraazaisobacteriohlorin.

The hydrogenated derivatives of tetraazaporphyrins were almost not studied at the beginning of our work because of the lack of practical methods of their synthesis. The only one article devoted to the synthesis of alkylsubstituted tetraazachlorin was published in 1958 [90], while tetraazabacteriochlorin and tetraazaisobacteriochlorin were unknown. Meanwhile, due to the intense absorption in the red and near-IR regions of the spectrum these compounds are of interest as second generation photosensitizers for PDT as absorbing in the "therapeutic window."

We have designed two general methods for tetraazachlorins, tetraazabacteriohlorins and tetraazaisobacteriohlorins synthesis in the course of works supported by the Moscow City Government [51].

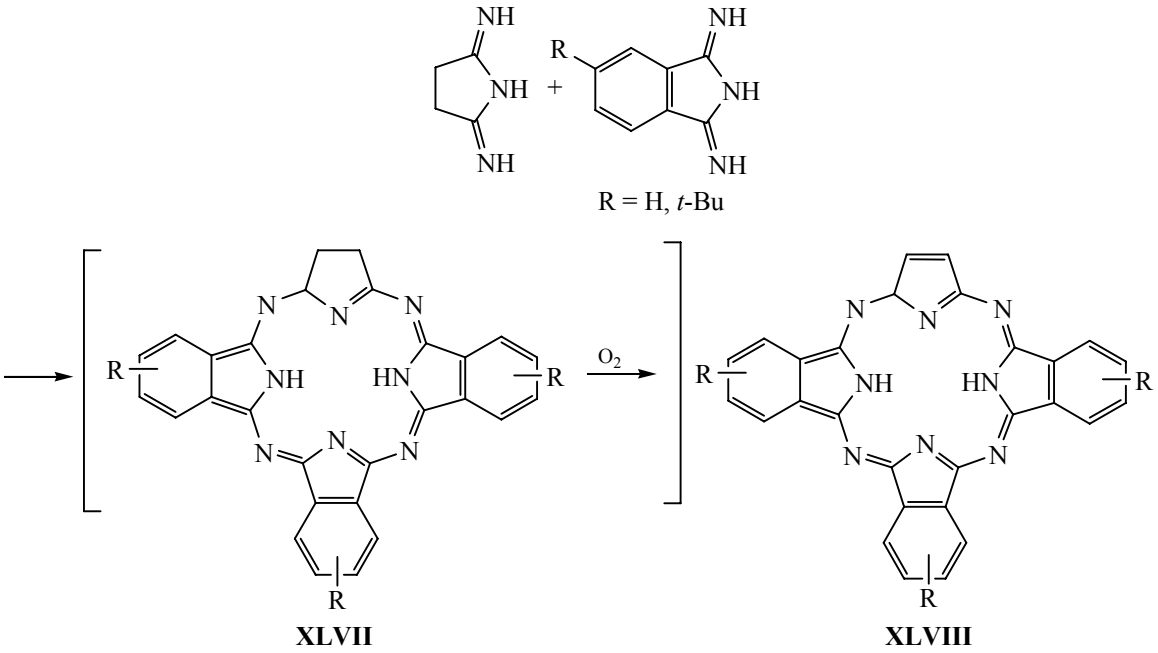
Scheme 17.



Mixed condensation with saturated phthalogenes. The first attempt of a mixed condensation of phthalogenes with different levels of saturation was described by Linstead et al. in 1955 [90]. Indeed, reaction of succinimidine with 1,3-diimidoisoindoline or its *tert*-butylsubstituted derivative [92] led to tribenzotetraazachlorins **LVII** as intermediates, but they proved to be unstable to air oxidation and as a result only corresponding tribenzotetraazaporphyrins **LVIII** were isolated (Scheme 18).

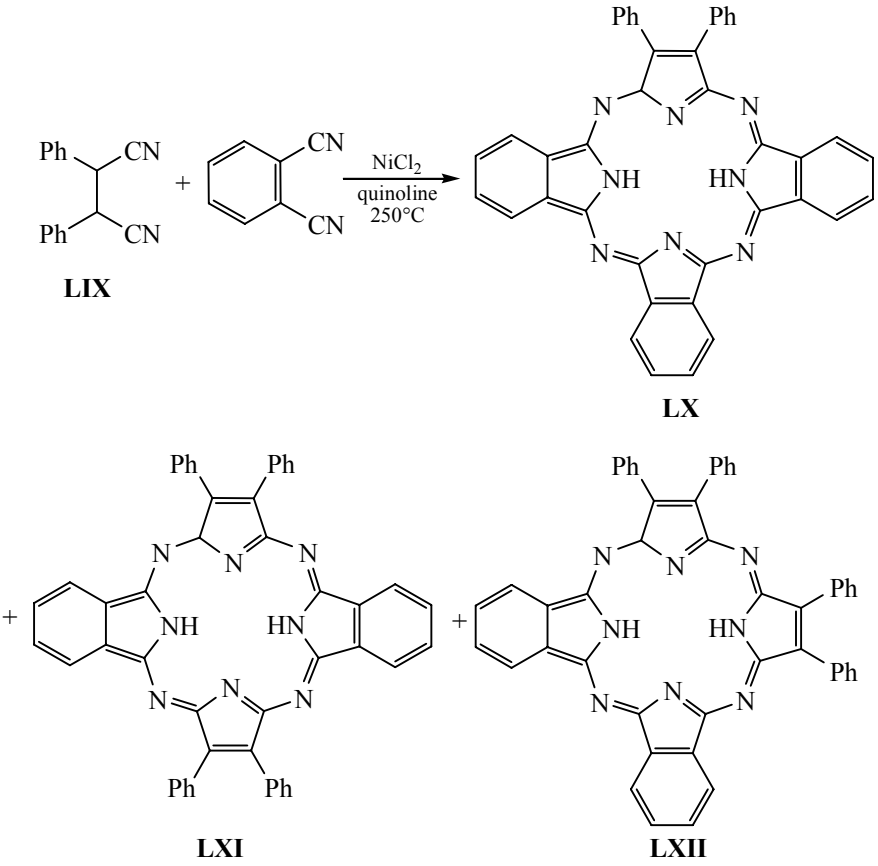
We have investigated the mixed condensation of phthalonitrile with substituted succinonitriles as saturated components and the influence of the position and number of substituents in the succinonitrile on stability of obtained benzofused hydrogenated derivatives of tetraazaporphyrins was studied.

Scheme 18.



XLVII **XLVIII**

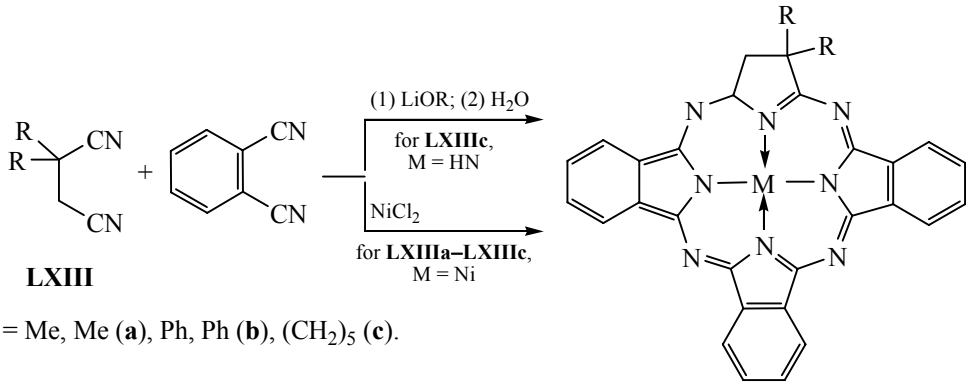
Scheme 19.



LIX **LX**

LXI **LXII**

Scheme 20.



LXIII

R, R = Me, Me (**a**), Ph, Ph (**b**), $(CH_2)_5$ (**c**).

LXIV

The mixture of the diphenyltribenzo- **LX** and two isomeric tetraphenyldibenzotetraazaporphyrins **LXI** and **LXII** was isolated as a minor products in the interaction of 2,3-diphenylsuccinonitrile **LIX** and phthalonitrile with nickel chloride in quinoline (major product was nickel complex of phthalocyanine) (Scheme 19). The corresponding tetraazachlorin was recorded on UV-vis spectrum of the reaction mixture by the characteristic long-wavelength absorption band with a maximum of absorption ~730 nm. Thus, the presence of two vicinal substituents in succinonitrile does not prevent the oxidation of intermediate tetrapyrrolic compounds with saturated bonds to the corresponding benzotetraazaporphyrins.

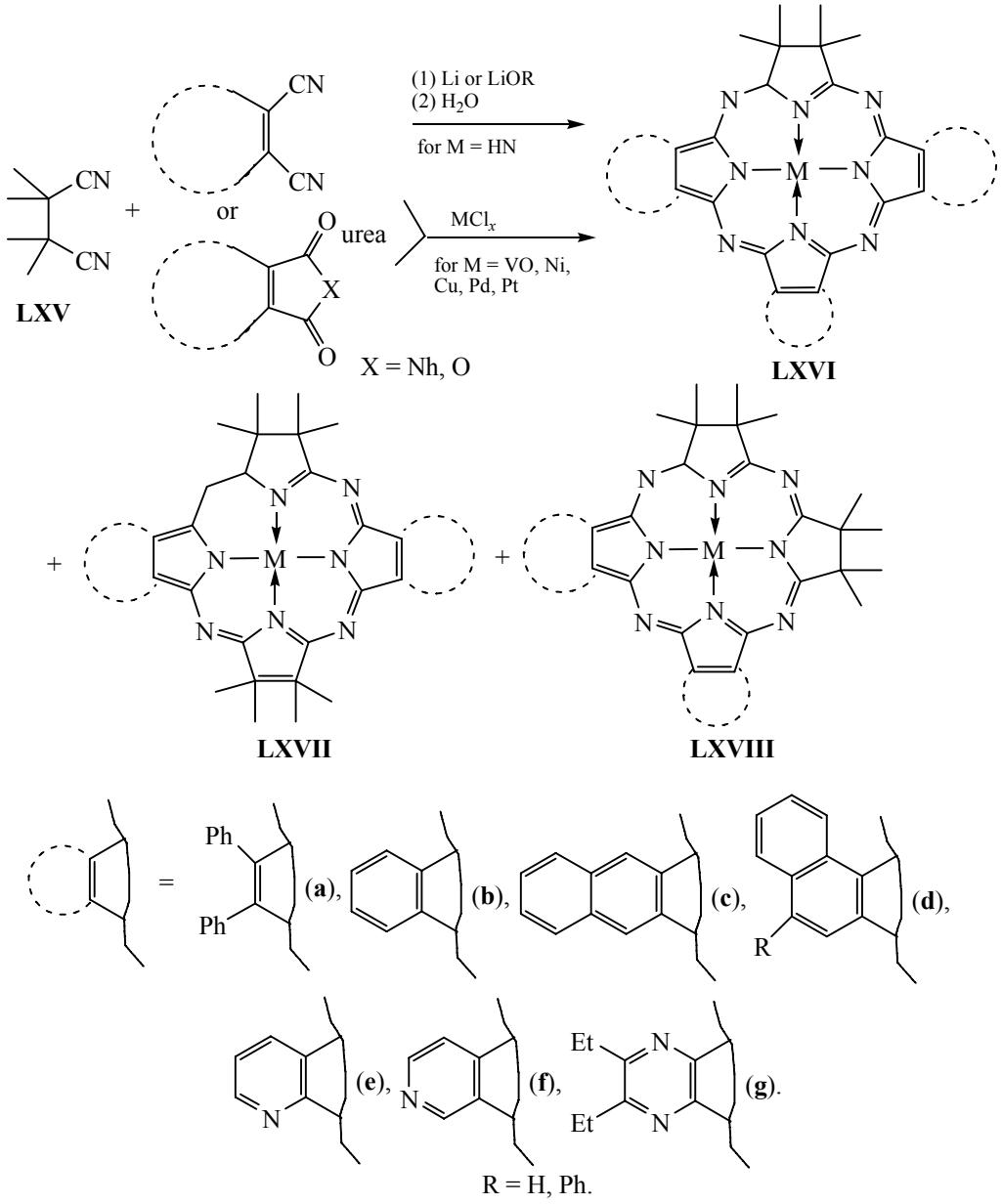
More productive proved to be use of 2,2-disubstituted succinonitriles **LXIII** because dehydrogenation of target annulated hydrogenated derivatives of tetraazaporphyrins can be possible only with stipulation migration of substituents. So, nickel complexes **LXIVa–LXIVc** (M = Ni) were obtained by heating of the phthalonitriles and nickel chloride in quinoline and were isolated with yields of up to 9%. In contrast, the metal-free β-spiromacrocycle **LXIVc** (M = HH) were obtained with low yield (~2%) by boiling phthalonitriles and lithium dimethylaminoethoxide in dimethylaminoethanol (Scheme 20).

With increase of reaction time or during chromatography purification on alumina or silica one of phenyl or methyl groups of nickel complex **LXIVb** (M = Ni) and **LXIVa** (M = Ni) was migrated to neighboring β-pyrrolic carbon atom by similar to retropinacol rearrangement, and the subsequent oxidation give tribenzotetraazaporphyrins **LX** or its dimethyl analogue.

Oxidation-stable derivatives of tetraazachlorin were obtained using the tetramethylsuccinonitril **LXV** as saturated component. In this case, the transformation of a single bond into a double bond is possible only by elimination of methyl groups in the pyrroline fragment of product. Derivatives of aromatic and heteroaromatic 1,2-dicarboxylic acid – dinitriles, anhydrides and imides – were used as the unsaturated components, and diphenylfumaronitril was used as well. Metal-free tetraazachlorins **LXVI** (M = HH) were obtained by mixed condensation of dinitriles in boiling dimethylaminoethanol in the presence of lithium dimethylaminoethoxide with yields from 1.5 to 4%. Condensation of phthalogenes with metal salts in the presence of ammonium molybdate as a catalyst in boiling quinoline or sulfolane leads to tetraazachlorin **LXVI** with rather higher yield; moreover, in this conditions tetrahydroderivatives – tetraazabacteriochlorins **LXVII** and **LXVIII** – were also obtain for the first time (Scheme 21).

The main product of the reaction in all cases was the corresponding symmetric tetraazaporphyrin or tetraarenotetraazaporphyrin derivative – the result of the predominant tetramerization of unsaturated phthalogene. Due to structural features, in particular, the presence of quaternary carbon atoms with methyl groups out of the macrocycle plane, hydrogenated macrocycles **LXVI**, **LXVII,** and **LXVIII** have good solubility in organic solvents and are rather easily separated from the derivatives of tetraazaporphyrins. Tetraazachlorin **LXVI** was the main product in each case of hydrogenated derivatives synthesis, but for some of them rather fairly high yield of tetraazachlorins was achieved as a result of structure and

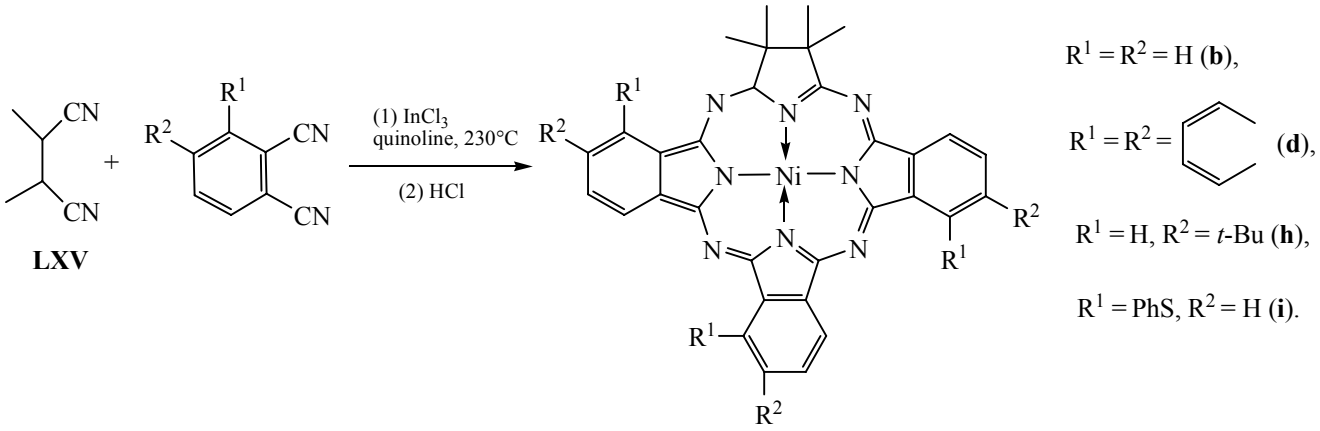
Scheme 21.



conditions optimization (molar ratio, temperature and reaction time). Thus, nickel tribenzotetraazachlorin complex **LXVIb** (M = Ni) was obtained in a yield of more than 20% by using phthalonitrile as unsaturated component. In the same time an imide or anhydride of naphthalene-2,3-dicarboxylic acid are preferable to use to achieve the best yield ~22% of nickel complex with three linearly condensed naphthalene moieties **LXVIc** (M = Ni) [93]. Products with two saturated bonds **LXVII** and **LXVIII** are formed in a much smaller amount. Nevertheless in some cases they were not only isolated in an amount of 2% for **LXVII** and 4% for **LXVIII**, but also all possible randomers were separated and characterized for tetraazachlorins **LXVId** (R = H) and **LXVIe, LXVIef** [94].

Significantly increased yield of metal-free tetraazachlorins **LXVIa, LXVIb, LXVId** was achieved while condensing of the precursors with different hydrogenation levels in the presence of indium chloride as a template [95] (Scheme 22). Condensation of succinonitrile **LXV** with different

Scheme 22.



LXVI

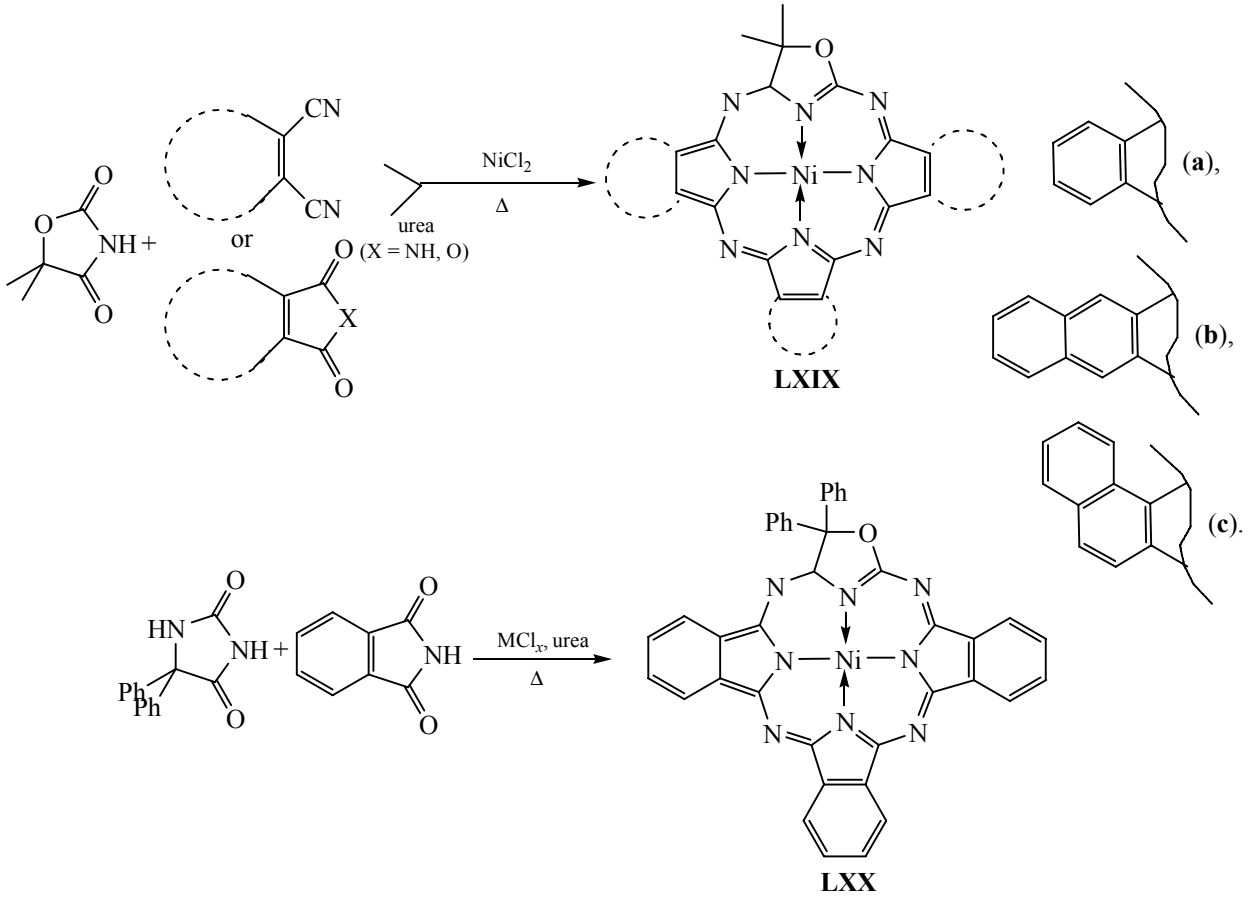
phthalonitriles and subsequent demetallation of intermediately formed indium complexes with hydrochloric acid leads to the formation of metal-free triarenotetraazachlorins **LXVI** (M = HH) in 40% yield. This approach opens up opportunities for the synthesis of various tetraazachlorins including the compounds unavailable by lithium method and thus makes them highly accessible to researchers.

Saturated component may be a heterocyclic also. In this case the introduction of heteroatoms (O, N) in β-position of hydrogenated pyrrollic unit of the macrocycle stabilizes it in comparison with β,β-disubstituted carbocyclic analogues **LXIVa, LXIVb**. Thus, reaction of 5,5-dimethyloxazolidine-2,4-dione or 5,5-diphenylimidazolidin-2,4-dione with derivatives of phthalic, naphthalene-1,2- or -2,3-dicarboxylic acid and nickel chloride leads to stable nickel complexes of corresponding β-oxatetraazachlorins **LXIX** [96] or β-azatetraazachlorin **LXX** [97] with yields of 4–8% (Scheme 23).

[n + 2] Cycloaddition reaction. It is known that two peripheral double bonds of tetraazaporphyrins **LXXa** as well as in porphyrin are quasi-isolated from conjugation system of the macrocycle and can react as double bonds of alkenes. For example, Cβ=Cβ bond of tetraazaporphyrins undergoes reaction of dihydroxylation with OsO_4 [98]. This feature of porphyrins is widely used for preparation of chlorins and bacteriochlorins *via* cycloaddition reactions [99]. Analogous cycloaddition reactions of tetraazaporphyrins have not been studied probably because of the difficult accessibility of the simplest representative of this series – unsubstituted tetraazaporphyrin **LXXIa**. Until recently its the best method of synthesis was Linstead's method [100]. This method, based on the reaction of the unstable at elevated temperatures maleonitrile with magnesium propoxide in boiling propyl alcohol followed by demetallation of magnesium complex with acetic acid and resulted in 11% yield of product. We have described a simple and convenient method of synthesis of tetraazaporphyrin by condensation of commercially available succinonitrile in the presence of lithium dimethylaminoethylate in boiling dimethylaminoethanole with simultaneous oxidation of intermediate formed hydroderivatives with atmospheric oxygen in 16% yield [101].

Synthetic behavior of tetraazaporphyrin **LXXIa** in Diels–Alder reaction (or [4 + 2] cycloaddition) were studied with two types of dienes: linear arenes (anthracenes and tetracene) [102] and cyclopentadienes [103]. On heating **LXXIa** in boiling chlorobenzene with an excess of anthracene **LXXIIa**, alkyl substituted anthracenes **LXXIIb,c** or tetracene **LXXIId** only mono-adduct was obtained namly tetraazachlorin **LXXIII** with a yield of up to 71% (with a small amount of bis-adduct, tetraazabacteriochlorin **LXXIVd** in the case of the more reactive tetracycle **LXXIVd**) (Scheme 24). Increasing temperature of reaction in case di-*tert*-butylanthracene **LXXIIc** leads to the formation of a mixture of monoadduct **LXXIIIc** and bis-adduct **LXXVc** (yield 21%) with a small amount of bis-adduct **LXXIVc**. Reaction proceeds more selectively in the presence $AlCl_3$ as a catalyst. In this case, in the reaction mixture along with

Scheme 23.

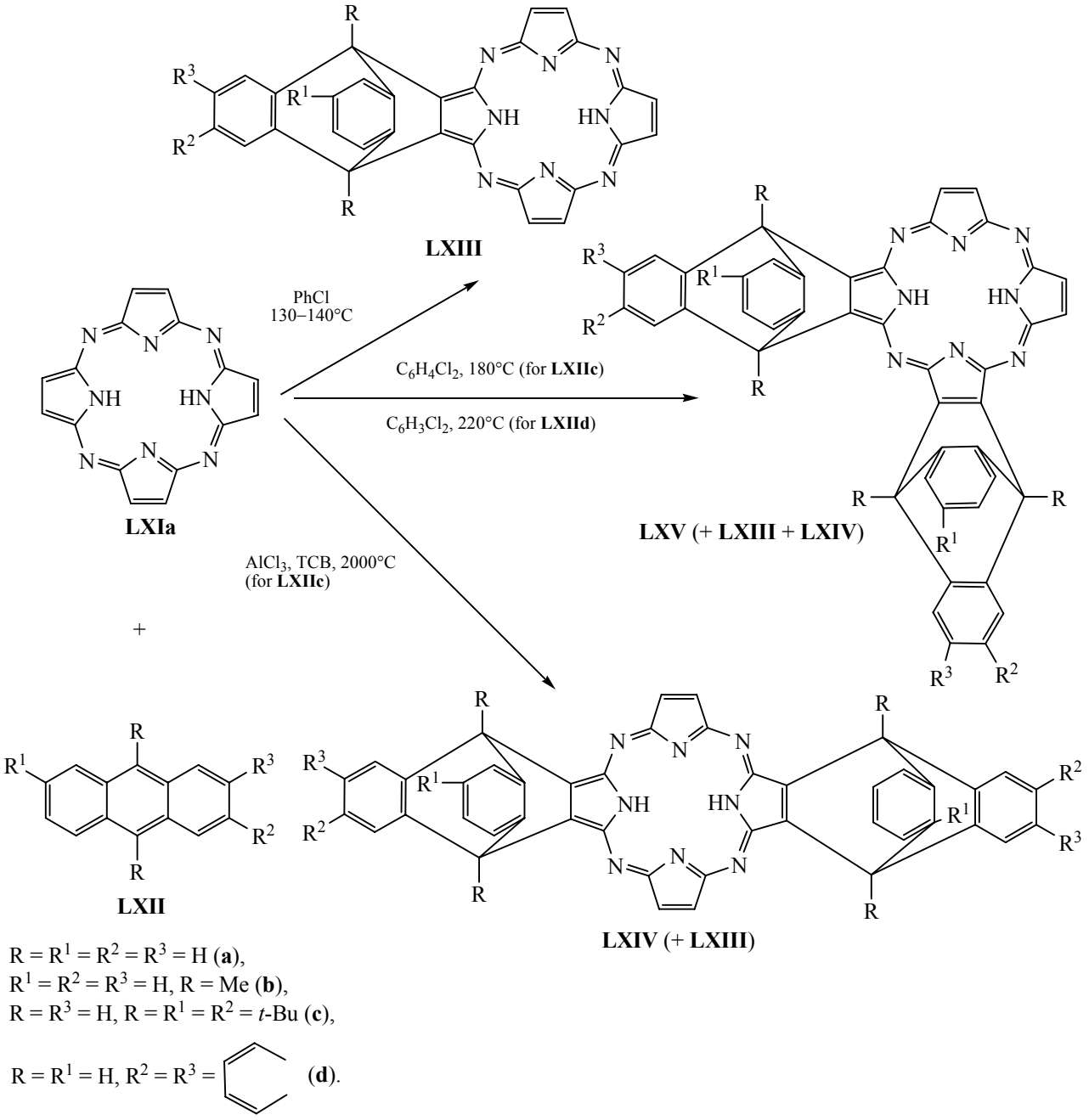


tetraazachlorin **LXXIIIc** only bis-adducts of tetraazabacteriohlorin **LXXIVc** formed, which can be isolated in 35% yield. In the case of tetracene **LXXIId** carrying out the reaction in boiling trichlorobenzene bis-adducts **LXXIVd** and **LXXVd** were obtained with yields of 16.5% and 25.5%, respectively. Bis-adducts **LXXIVc, LXXIVd** and **LXXVc, LXXVd** were separated chromatographically into two groups of stereoisomers containing macrocycles with transoid and cysoid position of two dibenzobarellenic units in respect of macrocyclic plane.

Heating of tetraazaporphyrin **LXXIa** with an excess of cyclopentadienes **LXXVI** also leads to formation of mono-adducts **LXXII** or a mixture of mono-adducts **LXXII** and bis-adducts **LXXVIII** and **LXXIX** (Scheme 25). The structure and yield of products depend on the activity of the dienes, the molar ratio of the reactants and the reaction temperature. Interaction between tetraazaporphyrin **LXXIa** and cyclopentadiene **LXXVIa** or hexachlorocyclopentadiene **LXXVIb** at 140–150°C leads to selective formation of tetraazachlorins **LXXVIIa, LXXVIIb** with high yields: 63% and 47%, respectively. The temperature increase to 220°C in case diene **LXXVIb** leads to formation the bis-adducts **LXXVIIIb** and **LXXVIXb** with 7% and 0.5% yields, respectively, in addition to mono-adduct **LXXVIIb**. Under the similar conditions in case of diene **LXXVIc** yield of bis-adduct **LXXVIIIc** increases to 28% and the maximum yield for the bis-adduct **LXXVIXc** was 0.7%.

The [3 + 2] cycloaddition reaction smoothly proceeds for unsubstituted tetraazaporphyrin as well as its tetra- and octasubstituted derivatives [102]. The mono- and bis-adducts **LXXX** and **LXXXI** were obtained by heating **LXXIa-d** with azomethine ylide (generated *in situ* from paraformaldehyde and sarcosine) (Scheme 26). Selective formation of mono- or bis-adduct can be operated by variation the molar ratio of reactants and temperature of reaction. Thus, mixture of tetraazachlorin **LXXXa** (47%) and

Scheme 24.



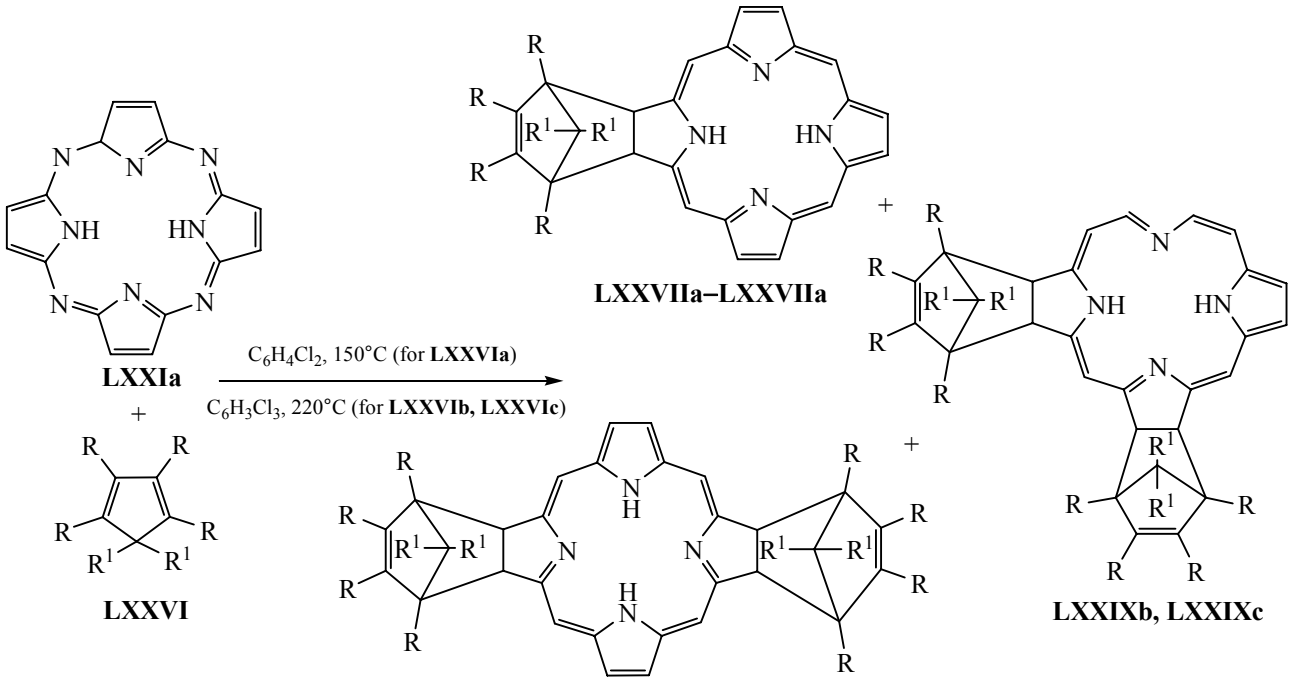
R = R^1 = R^2 = R^3 = H (**a**),
R^1 = R^2 = R^3 = H, R = Me (**b**),
R = R^3 = H, R = R^1 = R^2 = *t*-Bu (**c**),

R = R^1 = H, R^2 = R^3 = (**d**).

tetraazaisobacteriochlorin **LXXXIa** (18%) was obtained by heating of tetraazaporphyrin **LXXIa** and the azomethine ylide in a molar ratio of 1 : 2 at 130°C. Yield of the bis-adduct increases to 55% with increasing of both the molar ratio to 1 : 3 and reaction temperature to 150°C. Reactivity of tetraphenyltetraazaporphyrin **LXXIb** in [3 + 2] cycloaddition is comparable to reactivity of unsubstituted tetraazaporphyrin **LXXIa**. For octasubstituted derivatives **LXXIc**, **LXXId** the higher reaction temperature is required which leads to decrease of total yields of the hydrogenated tetraazaporphyrin derivatives.

The tetraazaporphyrin **LXXIa** similarly reacts with nitrones, an another type of dipolar compounds. In case of nitrones as well as azomethine ylide, only

Scheme 25.



R = R^1 = H (**a**), R = R^1 = Cl (**b**), R = Cl, R^1 = MeO (**c**).

tetraazachlorin **LXXXII** (51%) (molar ratio of reagents of 1 : 5) or a mixture of tetraazachlorin **LXXXII** and tetraazabacteriochlorin **LXXXIII** (molar ratio of reagents 1 : 10) may be prepared changing the molar ratio of the reagents. It should be noted that both types of dipolar reagents produce only one of the two possible regioisomers of bis-adduct: tetraazaisobacteriochlorin or tetraazabacteriochlorin, but different for azomethine ylides and nitrones.

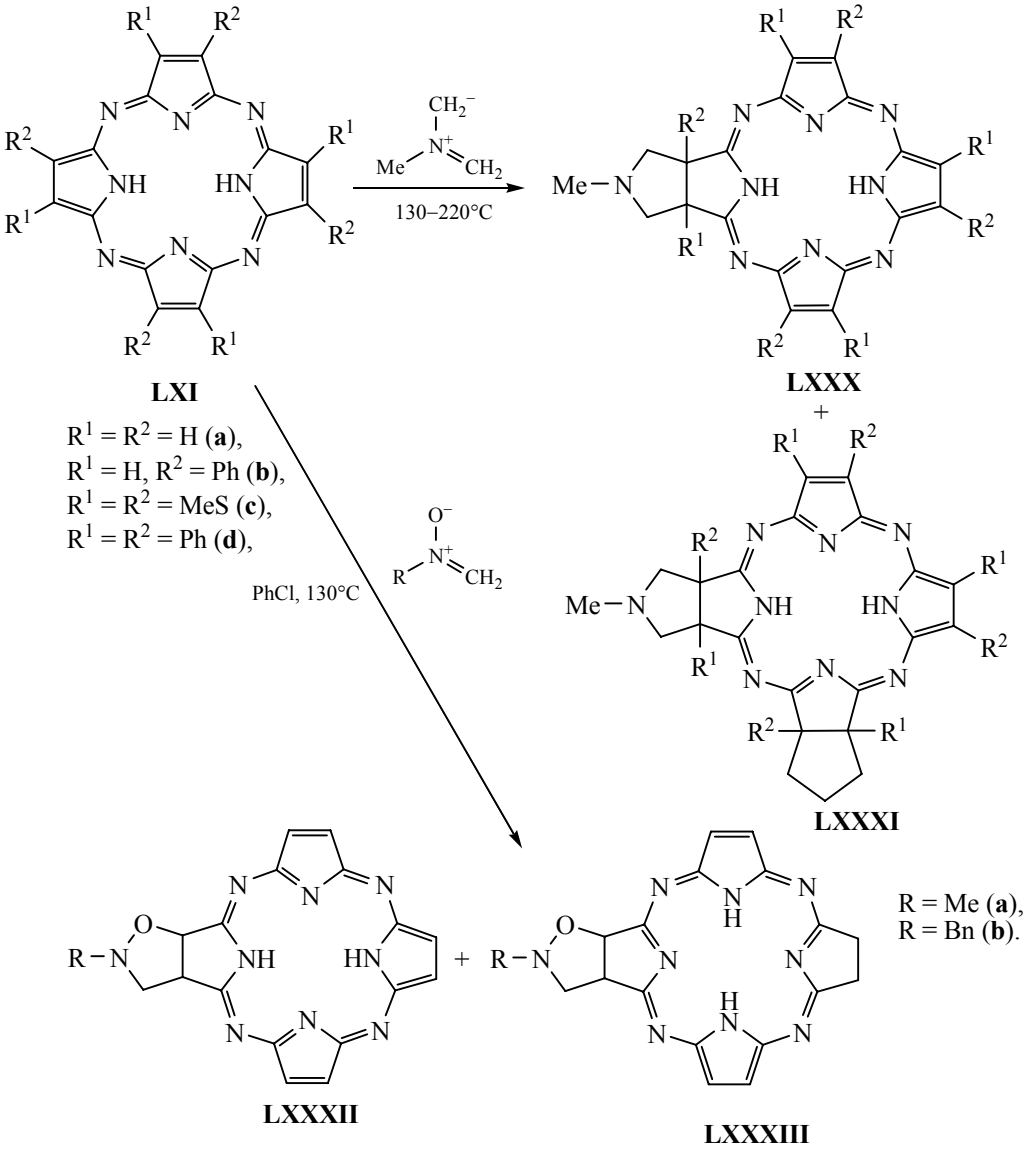
Despite the presence of vicinal hydrogens at the saturated bond, hydrogenated tetrapyrroles **LXXX–LXXXIII** are sufficiently stable to oxidation and can be isolated from the reaction mixture as individual compounds by column chromatography. At the same time tribenzotetraazachlorins **LXXXIV** (yield 10–20%) obtained from tribenzotetraazaporphyrin **LVIII** and azomethine ylide (Scheme 27) are much less stable and partially oxidized during of chromatographic purification. Obviously, the less resistance of these compounds to oxidation caused by the tendency to form of a more expanded aromatic conjugate system of tribenzotetraazaporphyrin as compared with unsubstituted tetraazaporphyrin **LXXIa**.

Reaction of [3 + 2] cycloaddition has been used for the synthesis of the conjugate **LXXXV,** which consist from one porphyrin and one tetraazachlorin fragments (yield ~30%) [104] (Scheme 28).

Finally, we have shown the use of [2 + 1] cycloaddition reaction of carbene to the double bond of tetraazaporphyrin. In contrast with previously described types of cycloaddition this reaction for porphyrins compounds weakly studied and has never been described for tetraazaporphyrins. Interaction of tetraazaporphyrin **LXXI**a with carbene generated *in situ* from ethyl diazoacetate in the presence of cobalt 2,9,16,23-tetra-*tert*-butylphthalocyanine as a catalyst led to the corresponding tetraazachlorin **LXXXVI** in ~4% yield without formation of bis-adducts [105] (Scheme 29).

Thus, we have developed two methods for preparation of the hydrogenated derivatives of tetraazaporphyrins — tetraazachlorins, tetraazabacteriochlorins, and tetraazaisobacteriochlorins: mixed condensation of phthalogenes with different levels of saturation and cycloaddition reactions to the peripheral double bonds of tetraazaporphyrins. These methods can be provide

Scheme 26.

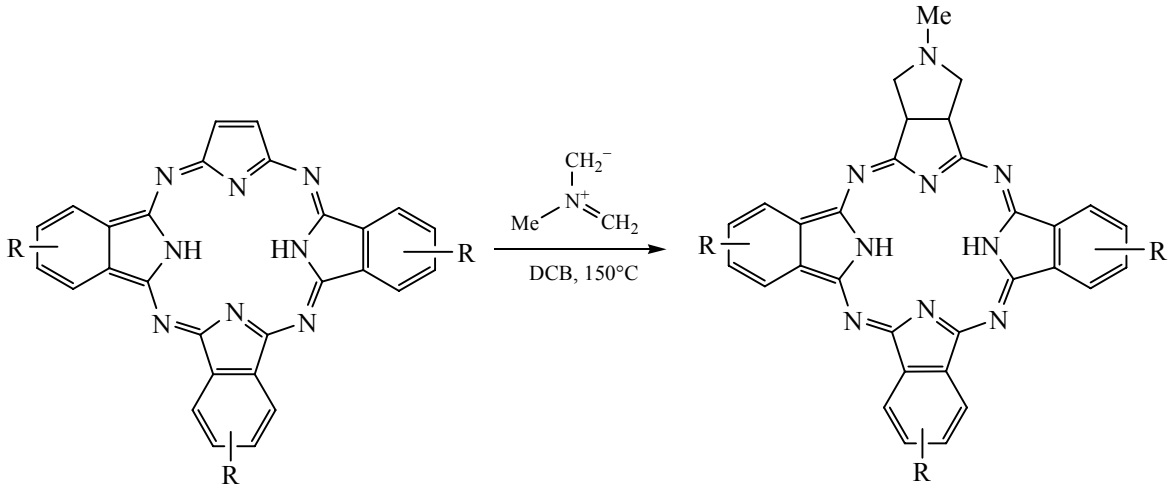


preparation of a previously unknown tetrapyrrolic compounds for scientific investigations.

The influence of hydrogenation level and additional benzene rings on UV-vis spectra of the obtained tetrapyrrolic compounds were discussed in the review [51]. Tetraazachlorins are of great interest as perspective photosensitizers in the near IR region of the spectrum due to the intense absorption of *Q*-band in the region at 700–800 nm. However, most of the synthesized tetraazachlorins with required spectral properties are insoluble in water, therefore it is necessary either to transform them to water soluble forms or use a special delivery system for their medical applications. But, chemical transformation of water insoluble tetraazachlorins to soluble derivatives could significantly change their spectral properties, as well as applying delivery system cannot assure the preservation of photochemical properties of tetraazachlorins due to their possible aggregation in solution.

We have investigated the spectral properties of several fluorescent chlorins, in particular tetramethyltribenzotetraazachlorine **LXVI** (M = HH), solubilized in aqueous micellar solutions of nonionic surfactant (Cremophor EL, Tween 80, Pluronic F-68, etc.). [106].

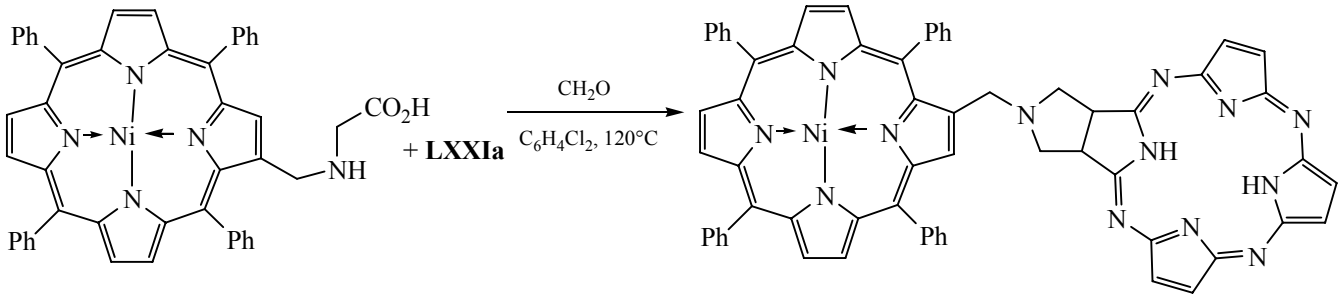
Scheme 27.



LVIII **LXXXIV**

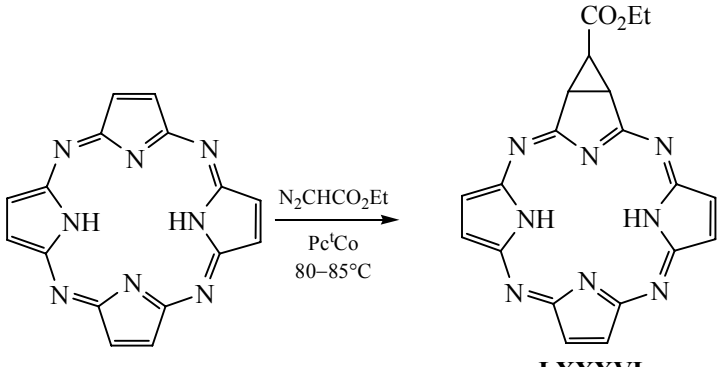
R = H (**a**), R = *t*-Bu (**b**).

Scheme 28.



LXXXV

Scheme 29.



LXXIa **LXXXVI**

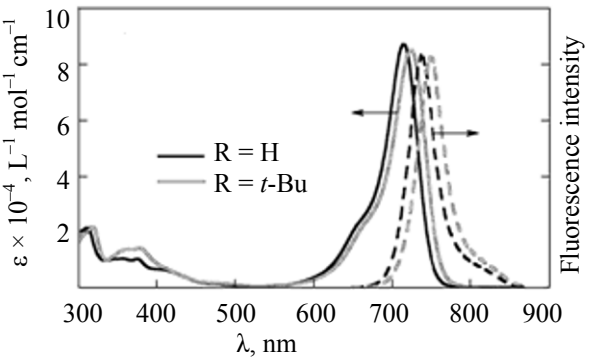


Fig. 3. Absorbtion and fluorescence spectra of dibenzoaza-BODIPY 88 in chloroform.

The resulting compositions represents a complex supramolecular systems, and the formation of non-fluorescent non-photoactive "face-to-face" aggregates would be expected due to combined intermolecular interactions between the components of tetraazachlorin/surfactant/water system. The study showed that Cremophor EL provides a high content of photoactive tetraazachlorin monomer in micellar solution and stability of the composition during its storage, while possessing a moderate toxicity. Moreover, the solubilization technology used allows to achieve high degree of incorporation of tetraazachlorins keeping the spectral properties of the corresponding monomers, even in the case of tetraazachlorins having a low solubility in the surfactant and prone to strong aggregation.

In vitro study of the interaction of solubilized tetrazachlorine **LXVI** (M = HH) with cancer cells has found direct proportional relationship between degree of photosensitizer monomer state in micellar solutions and the amount of the fluorescent photoactive photosensitizer accumulated in the cells – the main factor which determines the level of photoinduced cytotoxicity of the photosensitizer. Thus, the spectral-luminescent properties of lipophilic photosensitizer solubilized with nonionic surfactants could be used for prediction of its photodynamic activity *in vivo*, which is important for the screening of new photosensitizers.

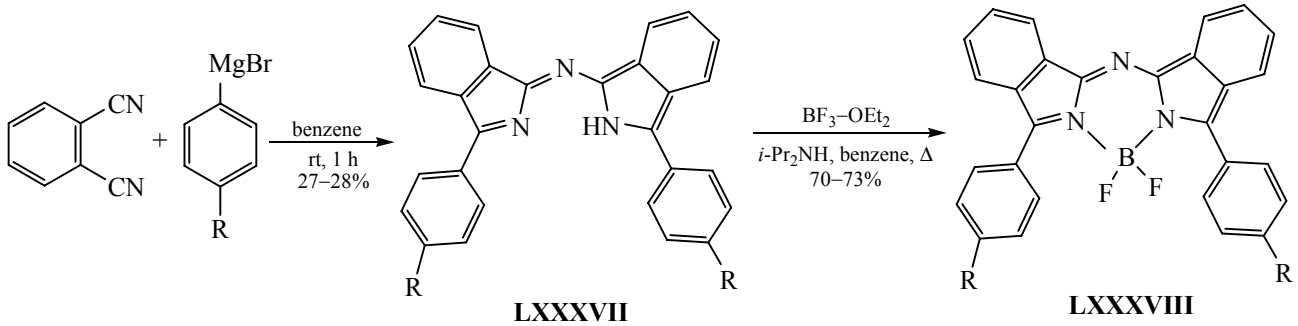
Studies on photodynamic activity of a number of tetraazachlorins in aqueous micellar solutions of nonionic surfactants (Cremophor EL or Proxanol 268) *in vitro* and *in vivo* have demonstrated that these compounds represent a new class of effective photosensitizers in near IR range and can be used for the treatment of deeper tumors tissue by photodynamic therapy [107].

Dibenzoanalogues of aza-BODIPY

Dyes that absorb in the red and near-infrared regions of the spectrum are attracted growing interest due to their application in various fields of science and technology, for example, to create an information storage device or as molecular markers in biological studies [108]. Along with other classes of dyes growing interest has been shown to dyes called BODIPY (BOronDIPYrromethene or 4,4-difluoro-3a,4a-diaza-4-bora-*s*-indacene) [109] due to their intense absorption and fluorescence, high stability in polar solvents and at different pH values [110].

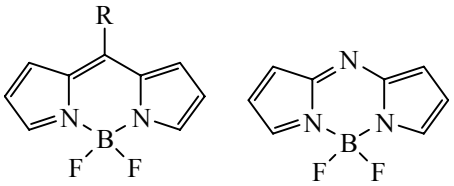
In chemistry of these complexes an important task is to develop methods of changing the structure, which allows shifting the long wave absorption maximum to the red or near infrared region. Different methods of structural modification have been tried including introduction to the structure of BODIPY of electron-withdrawing substituents, giving greater rigidity to structure and expansion of π-system [111]. It was

Scheme 30.



R = H, *t*-Bu, MeO.

found that the substitution of the bridging carbon atom for the nitrogen leads to a marked bathochromic shift of the absorption and luminescence bands without decreasing in intensity. Suitability of aza-BODIPY as photosensitizers for photodynamic therapy has also been demonstrated [112].



BODIPY aza-BODIPY

Carrying out investigations in the field of phthalocyanine analogues, we studied in details previously reported interaction of phenylmagnesium bromide with phthalonitriles [113]. On a number of examples we demonstrated that this interaction leads to the extended due to benzoannulating π-system of 3,3'-diaryldiisoindolylazene **LXXXVII** in moderate yields (~30%). Reaction of this product with boron trifluoride etherate in the presence of diisopropylamine proceeds smoothly to form dibenzoaza-BODIPY **LXXXVIII** [114] (Scheme 30).

As we expected, dyes **LXXXVIII** absorb and fluorescent in the near infrared region of the spectrum (Fig. 3) and have pronounced photodynamic activity against solid form of sarcoma S-37 in mice [21].

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