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Improved Method of 5,10,15,20–Tetrakis(4–hydroxyphenyl)–porphyrins Synthesis

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Dedicated to Academician Irina P. Beletskaya on the occasion of her Anniversary

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5,10,15,20-Tetrakis(4-hydroxyphenyl)porphyrin and 5,10,15,20-tetrakis(4-hydroxy-3-methoxyphenyl)porphyrin were synthesized in the 3 solvents mixture by Adler-Longo method. The porphyrin purification was carried out by ethyl acetate extraction.

Keywords: *meso*-Tetraarylporphyrins, extraction, Soxhlet extractor, electron spectra.

Улучшенный метод получения 5,10,15,20–тетракис(4–гидроксифенил)порфиринов

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Посвящается академику Ирине Петровне Белецкой по случаю её юбилея

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Синтезированы 4-гидроксизамещенные тетрафенилпорфирины прямой конденсацией пиррола с соответствующими замещенными бензальдегидами в условиях модифицированного метода Адлера, и усовершенствованы методы выделения и очистки.

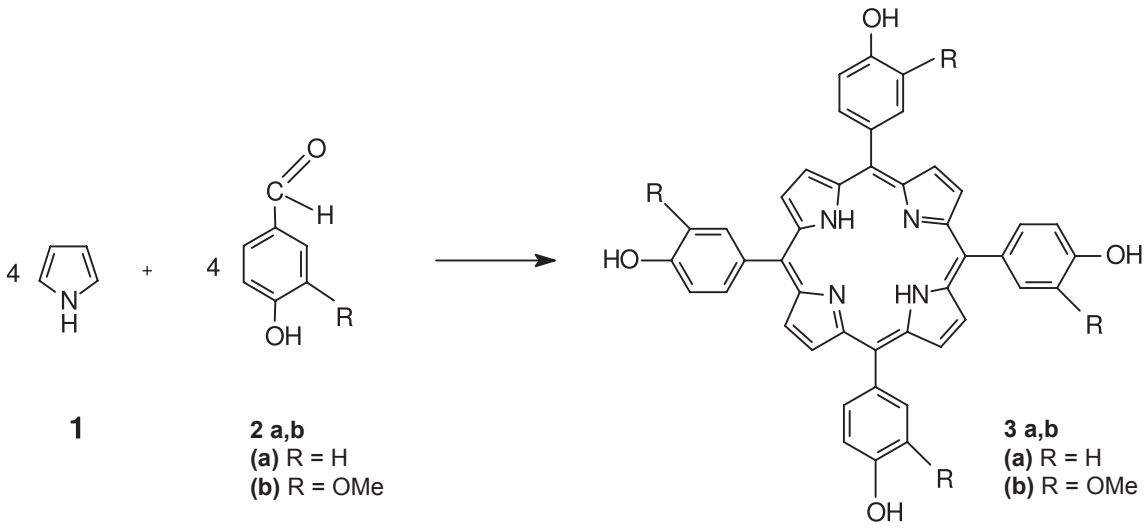
Ключевые слова: *мезо*-Тетраарилпорфирины, экстракция, аппарат Сокслета, электронные спектры.

The great interest of porphyrin chemistry is caused by their unique physical and chemical properties that allows to use them in optoelectronics, as semiconductors, sensors, catalysts, model compounds for studying the electrons and energy transfer processes, and also in medicine in diagnostics and therapy of malignant tumors, as antimicrobic remedies, at cardiovascular violations, *etc*.

The special place among porphyrins is taken by their numerous synthetic derivatives.[1] First of all, it is connected with their availability, high stability, the possibility of various chemical transformations, and also the unique ability to give chelate complexes with the majority of elements of the Periodic system and to form the complex structures of energy transformation on their basis.

The *meso*-aryl substituents presence in the porphyrins allows to carry out the immobilization on polymeric matrixes,[2,3] the linkage to the surface of gold nanoparticles,[4] the receiving of hybrids with DNA oligonucleotides,[5] *etc*. For these purposes the symmetric tetrakis(4-hydroxyphenyl)-porphyrin is widely used. Many researchers addressed to the synthesis of this compound, its isomers and analogs throughout the big period of time. So in the Treibs paper[6] this porphyrin was received with the yield of 9.7 % from 4-hydroxybenzaldehyde and pyrrole in AcOH-pyridine mixture (2:1) at air bubbling, and the vanillin derivative was received with 7.5 % yield.

Proceeding from tetraphenylporphyrin 3-hydroxy derivative and the subsequent reduction to the chlorin,



Scheme 1.

the drug Foskan was developed for PDT.[7] However tetra(hydroxyphenyl)porphyrins are generated with rather low yields and the reaction is accompanied by formation of a large amount of difficultly separable impurities.

One of the alternative approaches to the synthesis of the similar compounds was the demethylation of *m*- and *p*-methoxysubstituted porphyrins by aniline hydrochloride or 60 % HBr.[8]

The essential contribution to the synthesis of this porphyrin was made by the chinese scientists[9] who used at the synthesis the triple mixture of EtCOOH-AcOH-$PhNO_2$ (2:1:1) solvents where the nitrobenzene was performing the oxidant role. The porphyrin yield came to 35.7 %. Later it was succeeded to increase to 43 % using a columnar chromatography on the silica gel.[10]

The purpose of this work consisted in finding effective purification conditions for symmetric tetraarylporphyrins. The porphyrins synthesis was carried out by well-known methods using the monopyrrole condensation (Scheme 1). In contrast to the earlier applied chromatography methods of purification the crude product extraction by ethyl acetate in the Soxhlet extractor led to the process simplification, reduction of the solvents consumption and reduction of the expenditure of time for carrying out the process.

To avoid the chromatography purification, we used an extraction by ethyl acetate in the Soxhlet extractor for the purification of the crude product. The porphyrin was passing to the solution, and the black product which visually remind of the coal, was remaining in the Soxhlet thimble. The porphyrin yield came to 56 %. Its more hydrophobic derivative on the basis of vanillin was received with the yield of 24.8 %. The substances structure was confirmed by the mass spectra data, UV-vis spectroscopy (Table 1), and the identity was confirmed by TLC and HPLC data.

Experimental

Pyrrole, propionic acid and ethyl acetate are refluxed at atmospheric pressure. Hexane, petroleum ether, nitrobenzene and acetic acid are used without additional purification. Electronic

Table 1. UV-vis spectra of 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (literary data and own results).

Literary source	Reaction conditions	Yield, %	Solvent (UV-vis)	Electron spectra, λ_{max}, nm ($\varepsilon\times10^{-3}$)				
				Soret	IV	III	II	I
Treibs [4-OH]TPP[6]	AcOH- pyridine	9.7	EtOH	415 (468)	513 (16.22)	546 (6.03)	588 (4.68)	645 (3.09)
Semeikin[8]	Demethylation of OCH_3-groups	84	Py	426 (439)	521 (14.4)	561 (12.9)	598 (4.7)	656 (6.2)
Sun[9]	EtCOOH-AcOH-$C_6H_5NO_2$	35.7	CH_2Cl_2	417	513	551	592	646
Bragina[10]	EtCOOH-AcOH-$C_6H_5NO_2$	43	AcOEt	417 (270)	514 (11.28)	548 (7.94)	590 (5.13)	645 (4.89)
Compound **3a**	EtCOOH-AcOH-$C_6H_5NO_2$	56	AcOEt	419 (286)	517 (11.63)	554 (8.01)	592 (5.23)	650 (3.62)
Treibs[6] TPP with vanillin	AcOH-pyridine	7.5	EtOH	422 (339)	518 (17.4)	557 (11.5)	595 (5.63)	653 (5.76)
Compound **3b**	EtCOOH	24.8	EtOH	421 (305)	519 (16.2)	558 (10.7)	593 (5.3)	651 (5.1)

absorption spectra (UV-vis) are registered on a spectrometer Jasco 7800 (Japan). Mass spectra are measured on a Brucker Ultraflex TOF (Germany). Reaction course, as well as individuality of the synthesized compounds, are controlled by TLC on Silufol UV-254 plates (Chemapol, Czech Republic) in the ethyl acetate – petroleum ether system (2:1). HPLC is carry out on a Waters Breeze chromatograph on a Nova-Pack column (18.4 μm, 4.6×150 mm). Porphyrin 3a is elute by a 20 % A – 80 % B mixture (eluent A: water; eluent B: acetone-acetonitrile, 6:4) in 7 min., further 100 % B, the stream speed is 1 ml/min. A strip is detected at 400 nanometers.

*5,10,15,20-Tetrakis(4-hydroxyphenyl)porphyrin (**3a**)*. Nitrobenzene (4 ml), 8 ml of propionic acid, 4 ml of glacial acetic acid are mixed in the 50 ml three-neck flask and refluxed during 30 min with the Liebig condenser. 4-Hydroxybenzaldehyde (**2a**) (91 mg, 0.746 mmol) is dissolved in 5 ml of propionic acid, and dropped in the reactionary mixture. At the same time 50 mg (0.746 mmol) of pyrrole (**1**) mixed with 4 ml of nitrobenzene is slowly dropped. The mixture is refluxed during 1.5 h with the Liebig condenser, cooled, blew through by air within 30 min, 10 ml of petroleum ether (40-60 °C) is flowed, then the mixture is left in the refrigerator for the night. The precipitate is filtered, washed by petroleum ether. The purification is carried out using the Soxhlet extractor with ethyl acetate as a solvent. Yield 71 mg (56 %). Brilliant crystals are dark blue color. R_f 0.47. UV-vis (ethanol) λ_{max} nm: 419 (286), 517 (11.63), 554 (8.01), 592 (5.23), 650 (3.62). Mass spectrum, *m/z*: 678.15 [M]+, account for 678.74; RT 12.217 min, content of the main substance - 94 %.

*5,10,15,20-Tetrakis(4-hydroxy-3-methoxyphenyl)porphyrin (**3b**)*. Vanillin (**2b**) (334 mg, 2 mmol) is refluxed in 15 ml of propionic acid in the 50 ml two-neck flask. Then the solution of 140 mg (2.09 mmol) of pyrrole (**1**) in 8 ml of propionic acid is dropped during 15 min. The reaction mixture is refluxed during 30 min, cooled to the room temperature and allowed to stay at -18 °C for the night. The precipitate is filtered and washed by petroleum ether. The extraction by ethyl acetate in the Soxhlet extractor is used for the purification of the porphyrin obtained. Yield 99 mg (24.8 %). R_f 0.6. *m/z*: 798.8 $[M]^+$, account for 798.29. UV-vis λ_{max} nm: 421 (305), 519 (16.2), 558 (10.7), 593 (5.3), 651 (5.1).

On the ground of the carried out research it was shown that tetraarylporphyrins can be successfully purified, passing the chromatography purification, using extraction in the Soxhlet extractor.

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