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Synthesis and Study of New Nitrogen-Containing Heterocycles Based on Glycoluril Derivatives

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Abstract—Functionalization of some cyclic bisureas (glycolurils) and their methylol derivatives was investigated with the goal to obtain new azaheterocycles. The modification of tetra-*N*-methylglycoluril gave unknown before tetra-*N*-methylbisimidazolium tetrachloride and provided a possibility of the synthesis therefrom of glycoluril tetrafluoro derivatives.

Keywords: glycolurils (bisureas), tetra-*N*-methylglycoluril (mebicar), tetra-*N*-methylbisimidazolium tetrachloride, antioxidant activity

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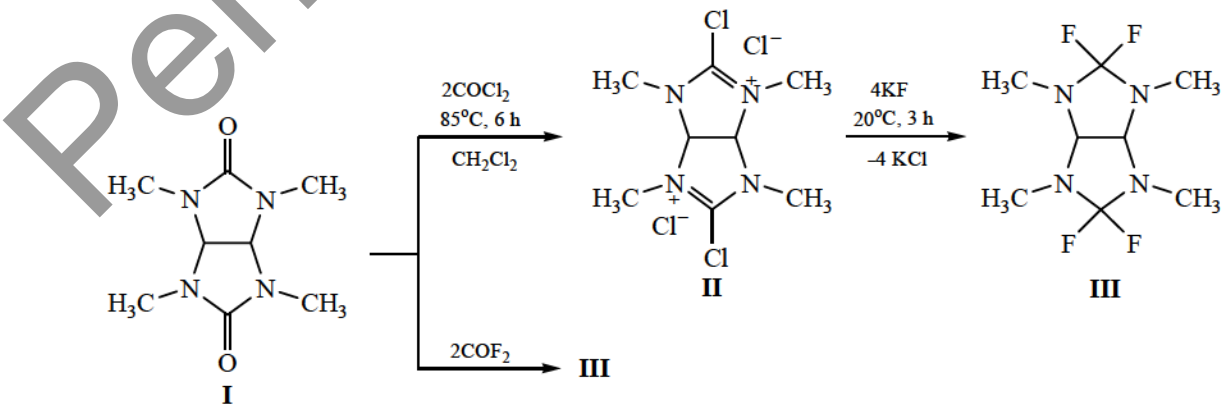
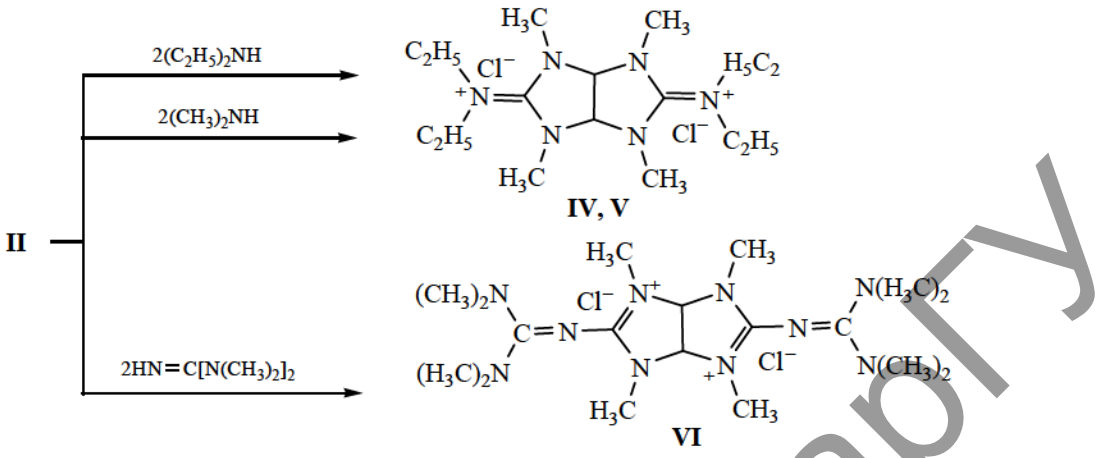
Glycoluril (2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione) and its derivatives are applied in various fields of industry. They are used at water purification as disinfectors, as burning inhibitors at paper manufacturing [1]. The resins containing glycoluril are used at dyes and coatings preparation. Glycoluril derivatives are widely used in the production of hardening polymer compositions, psychotropic agents [2, 3], explosives, and as prolonged fertilizers [4].

Glycoluril is a bicyclic substrate extremely attractive for further functionalization with the goal of synthesis and investigation of new azaheterocycles [5]. A high interest to glycoluril and its derivatives is due to a wide potential of chemical modification of the compounds [6, 7]. In extension of the research in this direction [8, 9] in the present work new possibilities of chemical modification of some glycoluril derivatives were studied, in particular, of 2,4,6,8-tetramethyl-

Scheme 1.



Scheme 2.



2,4,6,8-tetraazabicyclo[3.3.0]octane-3,7-dione (1,3,4,6-tetramethylglycoluril, mebicar) **I** [10].

Thus, the reaction of 1,3,4,6-tetramethylglycoluril **I** with phosgene in methylene chloride led to formation of before unknown glycoluril tetra-*N*-methylbisimidazolium tetrachloride **II**.

It is known that the introduction of a halogen atom, chlorine or fluorine, into the molecule of potential biologically active compound instead of, e.g., the carbonyl oxygen may cause a change or even strengthening of the biological activity [11]. To obtain the fluorine-containing derivatives of glycoluril, the reaction of compound **II** with potassium fluoride was carried out. The reaction proceeded in anhydrous acetonitrile and led to formation of tetra-*N*-methyltetrafluoroglycoluril **III**. The alternative method for preparation of tetra-*N*-methyltetrafluoroglycoluril **III** is the reaction of glycoluril **II** with COF_2.

The reaction progress was monitored by ^{19}F NMR spectroscopy. In the ^{19}F NMR spectrum of compound **III** there was a signal at 70.9 ppm corresponding to four fluorine atoms.

Aiming to obtain new potential biologically active compounds, functionalization of glycoluril tetra-*N*-methylbisimidazolium tetrachloride **II** was performed with amines of various structures. Thus, tetramethylguanidine, dimethyl- and diethylamines were applied. The reaction was performed at room temperature in anhydrous methylene chloride. The obtained compounds **IV**–**VI** were crystalline.

The synthesized compounds **I**–**V** were examined for antioxidant activity. The results are presented in the table. The data illustrate that the activity of compounds **II**, **IV**, **V** is higher than the activity of trolox used as a reference.

As a result of the performed research new derivatives of glycoluril were prepared; some of them show high antioxidant activity.

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker DRX-300 and Jeol ECX-400 spectrometers, internal reference TMS. ^{19}F NMR spectra (376 MHz) were registered on a Jeol ECX-400 instrument, internal reference $CFCl_3$. Mass spectra were obtained on a Varian Saturn 2000K instrument. Elemental analysis was done on a Eurovector-EA3000 apparatus (Italy). Melting points were determined on a Boetius and MP50 Melting Point System.

2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]-octane-3,7-dione (I) was prepared by the known procedure [10].

2,5-Dichloro-1,3,4,6-tetramethyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazol-1,4-diylium dichloride (II). To a solution of tetramethylglycoluril **I** (1.0 g, 0.005 mol) in CH_2Cl_2 was added with stirring 2.5 g, (0.025 mol) of $COCl_2$. The reaction mixture was heated for 2 h at 50–60°C. The solvent was distilled off; the residue was washed with diethyl ether (3–4 times) and dried in argon. Yield 0.8 g (67%), mp 235–237°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.95 s (12H, CH_3), 4.91 s (2H, CH). Mass spectrum: *m*/*z* 308. Found, %: C 31.36; H 4.32; N 18.47; Cl 45.91. $C_8H_{14}N_4Cl_4$. Calculated, %: C 31.17; H 4.55; N 18.18; Cl 46.10.

Coefficients of antioxidant activity of glycoluril and its derivatives

Compound	C_w, mol/L	K, μmol L^{-1} min^{-1}	K_{av}
Glycoluril	4.5×10^{-5}	55.9	64.0
		66.1	
		59.7	
		78.2	
		60.1	
I	4.5×10^{-5}	77.28	87.104
		81.56	
		75.69	
		120.74	
		80.25	
II	4.5×10^{-5}	130.0	138.99
		139.64	
		126.8	
		138.9	
		159.6	
IV	4.5×10^{-5}	156.6	161.59
		170.2	
		166.38	
		154.26	
		160.5	

2,2,5,5-Tetrafluoro-1,3,4,6-tetramethyloxyhydroimidazo[4,5-*d*]imidazole (III). *a*. A mixture of compound **II** (99.74 g, 0.590 mol) and potassium fluoride (102.84 g, 1.770 mol) in anhydrous acetonitrile was heated at 85°C under nitrogen for 6 h. After cooling inorganic salts were separated from the reaction mixture, the residue was distilled. Yield 88.5 g (62%), mp 47°C (37 mmHg). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.52 s (12H, CH_3), 3.05 s (2H, CH). ^{19}F NMR spectrum ($CDCl_3$): δ_F 70.9 ppm. Mass spectrum: *m*/*z* 242. Found, %: C 39.43; H 5.98; N 23.37; F 31.22. $C_8H_{14}N_4F_4$. Calculated, %: C 39.67; H 5.79; N 23.14; F 31.40.

b. COF_2 (16.5 g, 0.25 mol) was passed through a solution of compound **II** (9.9 g, 0.05 mol) in anhydrous acetonitrile under argon at continuous stirring at 25°C; the reaction progress was monitored by ^{19}F NMR. After distilling off the solvent, the residue was distilled in a vacuum. Yield 8.2 g (68%), mp 47°C (37 mmHg).

***N*,*N*'-{1,3,4,6-Tetramethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diylidene}bis(*N*-ethylethanoaminium) dichloride (IV).** Diethylamine (0.9 g, 0.006 mol) was added dropwise to compound **II** (0.7 g, 0.003 mol) at room temperature in anhydrous methylene chloride for 3 h. The solvent was distilled off; the formed crystals were washed with anhydrous diethyl ether and dried. Yield 1.8 g (67%), mp 198°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.83 s (12H, CH_3), 5.12 s (2H, CH). Mass spectrum: *m*/*z* 381. Found, %: C 50.48; H 8.66; N 22.37; Cl 18.41. $C_{16}H_{34}N_6Cl_2$. Calculated, %: C 50.39; H 8.92; N 22.05; Cl 18.64.

***N*,*N*'-{1,3,4,6-Tetramethyltetrahydroimidazo[4,5-*d*]imidazole-2,5(1*H*,3*H*)-diylidene}bis(*N*-methylmethanoaminium) dichloride (V)** was prepared similarly from 0.6 g (0.003 mol) of **II** and 0.7 g (0.006 mol) of dimethylamine. Yield 0.8 g (67%), mp 235°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.95 s (12H, CH_3), 4.91 s (2H, CH). Mass spectrum: *m*/*z* 325. Found, %: C 44.52; H 8.21; N 25.63; Cl 21.59. $C_{12}H_{26}N_6Cl_2$. Calculated, %: C 44.31; H 8.00; N 25.85; Cl 21.85.

2,5-Bis{[bis(dimethylamino)methylidene]amino}-1,3,4,6-tetramethyl-3,3a,6,6a-tetrahydroimidazo[4,5-*d*]imidazole-1,4-diylium dichloride (VI) was prepared similarly from 0.8 g (0.003 mol) of **II** and 0.9 g (0.006 mol) of tetramethylguanidine. Yield 1.8 g (57%), mp 204.9°C. ^{1}H NMR ($CDCl_3$), δ, ppm: 2.92 s (12H, CH_3), 5.08 s (2H, CH). Mass spectrum: *m*/*z* 465. Found, %: C 46.65; H 8.39; N 30.38; Cl 15.02. $C_{18}H_{38}N_{10}Cl_2$. Calculated, %: C 46.45; H 8.17; N 30.11; Cl 15.27.

Antioxidant activity was determined by the method of cathodic voltammetry (process of oxygen electro-reduction). Trolox was used as a reference.

Experimental procedure included obtaining the voltammogram of cathodic electro-reduction of oxygen with the help of an analyzer connected to PC. The electrochemical cell consisted of a glass vessel filled with a solution of background electrolyte with an indicator glass-carbon electrode immerged in it, a silver chloride electrode of comparison, and a silver chloride auxiliary electrode. 0.1 M solution of sodium perchlorate in ethanol was used as a background solution.

Antioxidant activity of the investigated sample was estimated by the kinetic criterion of antioxidant activity K (μmol L^{-1} min^{-1}), which reflects the amount

of the oxygen forms reacted with the sample in time and is determined by the following equation:

$$K = c(O_2)/t(1 - I_i/I_o),$$

where $c(O_2)$ is the concentration of oxygen in the starting solution without the investigated sample, μmol L^{-1}; I_i is the value of limiting current of oxygen electro-reduction, μA; I_o is the value of limiting current of oxygen electro-reduction in the absence of the investigated sample in a solution, μA; t is the time of the process, min.

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