

## Tetrazoles: LII.\* Synthesis of Functionally Substituted Tetrazoles from Benzene-1,3,5-tricarboxylic Acid Derivatives

M. V. Zatsepina, T. V. Artamonova, and G. I. Koldobskii

St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia  
e-mail: koldobsk@tu.spb.ru

Received September 14, 2007

**Abstract**—*N,N,N'*-Triarylbenzene-1,3,5-tricarboximidoyl chlorides reacted with sodium azide under conditions of phase-transfer catalysis to give functionally substituted tetrazoles whose subsequent functionalization led to complex heterocyclic structures which may be regarded as first-generation tetrazole-containing dendrimers.

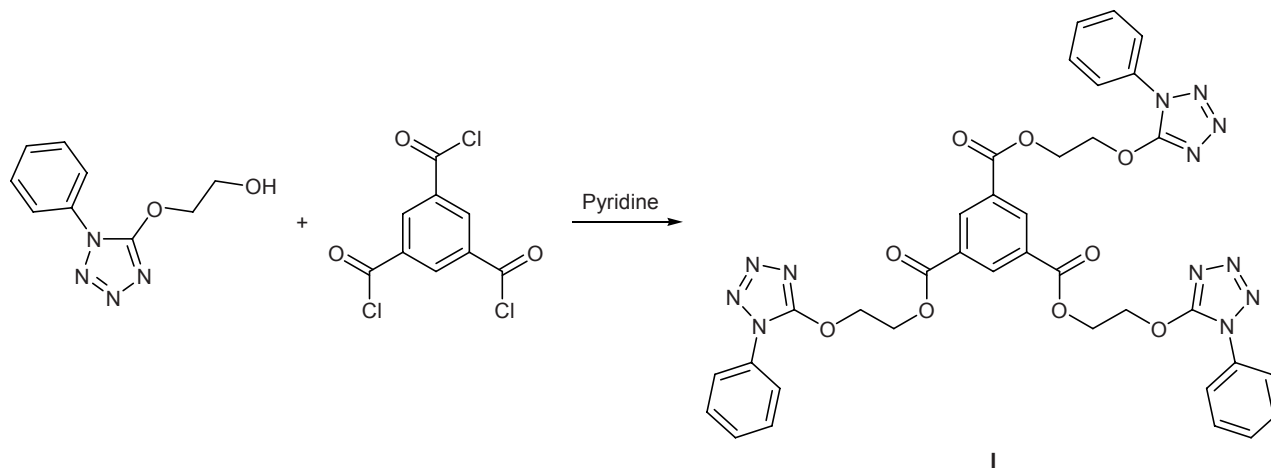
**DOI:** 10.1134/S1070428008040180

In continuation of our studies on the synthesis and properties of functionally substituted tetrazoles [1–5], we have developed an approach to complex heterocyclic structures including three and more tetrazole rings; these structures could be used for the preparation of tetrazole-containing dendrimers. Analysis of possible ways for solving this problem led us to select benzene-1,3,5-tricarboxylic acid derivatives which were successfully used in the synthesis of various functionally substituted tetrazoles. In the first step of our study we showed that acylation of 2-(1-phenyl-1*H*-tetrazol-5-yloxy)ethan-1-ol with benzene-1,3,5-tricarbonyl trichloride in the presence of pyridine gives tris-[2-(1-phenyl-1*H*-tetrazol-5-yloxy)ethyl] benzene-1,3,5-tricarboxylate (**I**) (Scheme 1).

We then tried to obtain functionally substituted tetrazoles from the corresponding *N,N,N'*-triarylbenzene-1,3,5-tricarboxamides via sequential transformation of these compounds into imidoyl chlorides and treatment of the latter with sodium azide under conditions of phase-transfer catalysis. As a result, we isolated a number of heterocyclic structures **IIa–IIe** containing three tetrazole ring (Scheme 2). The oxidation of compound **IIc** with sodium dichromate in sulfuric acid smoothly afforded tricarboxylic acid **III** (Scheme 3) which was then converted into the corresponding *N*-aryl triamides **Va** and **Vb** (Scheme 4).

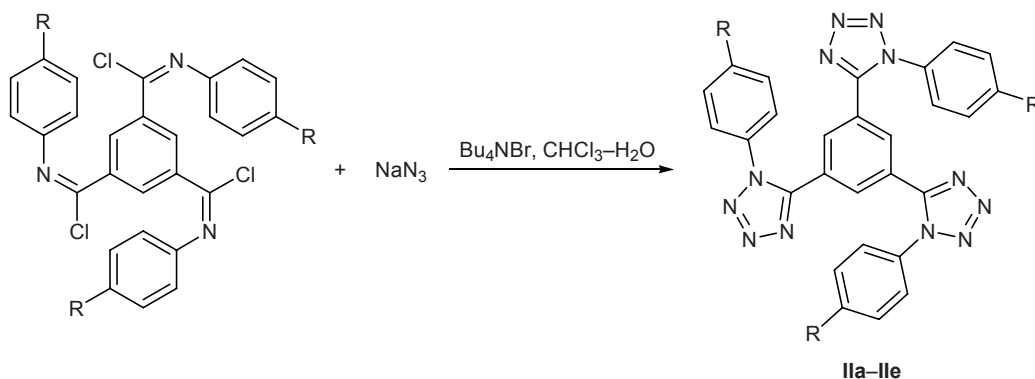
Using amide **Vb** as starting compound we obtained complex heterocyclic system **VI** which includes six tetrazole rings (Scheme 5).

Scheme 1.



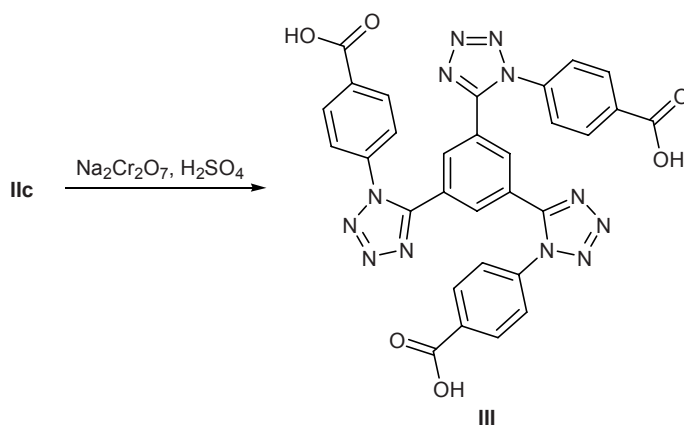
\* For communication LI, see [1].

Scheme 2.



R = MeO (a), EtO (b), Me (c), H (d), Br (e).

Scheme 3.



Thus the use of benzene-1,3,5-tricarboxylic acid as base structural unit opens the way to tetrazole-containing dendrimers of the first generation.

#### EXPERIMENTAL

The IR spectra were recorded on a Shimadzu FTIR-8400s spectrometer from samples prepared as KBr pellets. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured on a Bruker WM-400 spectrometer in  $\text{DMSO}-d_6$  unless otherwise stated.

2-(1-Phenyl-1*H*-tetrazol-5-yloxy)ethan-1-ol was synthesized according to the procedure described in [6]. *N,N',N''*-Triarylbenzene-1,3,5-tricarboxamides were prepared as reported [7] and were converted into the corresponding imidoyl chlorides by treatment with thionyl chloride at 75–80°C over a period of 2 h [8].

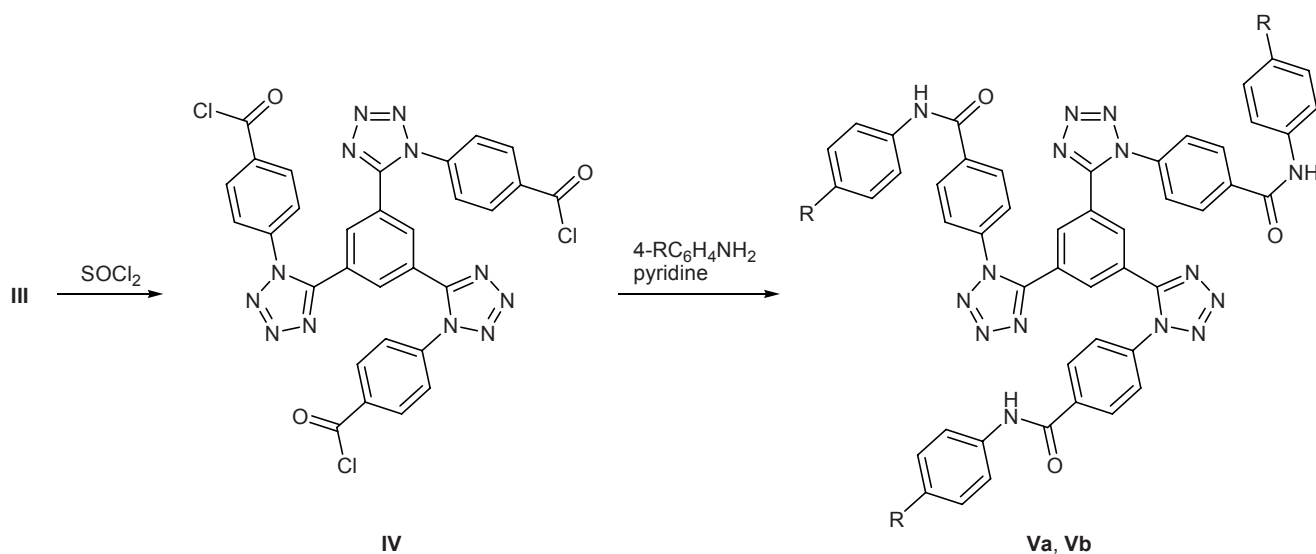
***N,N',N''*-Tris(4-methoxyphenyl)benzene-1,3,5-tricarboxamide.** Yield 91%, mp 281–282°C (from DMF–MeCN, 1:2). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 828, 911, 1032, 1109, 1176, 1245, 1301, 1325, 1412, 1462, 1511, 1595, 1606, 1648, 2834, 2932, 2953, 3064, 3131,

3209, 3263.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.97 s (9H,  $\text{CH}_3$ ), 7.14 d (6H,  $\text{H}_{\text{arom}}$ ), 8.06 d (6H,  $\text{H}_{\text{arom}}$ ), 8.99 s (3H,  $\text{H}_{\text{arom}}$ ), 10.80 s (3H, NH). Found, %: C 67.92; H 5.31; N 7.88.  $\text{C}_{30}\text{H}_{27}\text{N}_3\text{O}_6$ . Calculated, %: C 68.56; H 5.18; N 8.00.

***N,N',N''*-Tris(4-ethoxyphenyl)benzene-1,3,5-tricarboxamide.** Yield 87%, mp 272–273°C (from DMF–MeCN, 1:2). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 826, 922, 1045, 1115, 1174, 1242, 1303, 1394, 1412, 1477, 1511, 1595, 1606, 2872, 2933, 2977, 3071, 3132, 3272.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.51 t (9H,  $\text{CH}_3$ ), 4.20 q (6H,  $\text{CH}_2$ ), 7.12 d (6H,  $\text{H}_{\text{arom}}$ ), 8.09 d (6H,  $\text{H}_{\text{arom}}$ ), 9.05 s (3H,  $\text{H}_{\text{arom}}$ ), 10.94 s (3H, NH). Found, %: C 69.59; H 5.97; N 7.26.  $\text{C}_{33}\text{H}_{33}\text{N}_3\text{O}_6$ . Calculated, %: C 69.83; H 5.86; N 7.40.

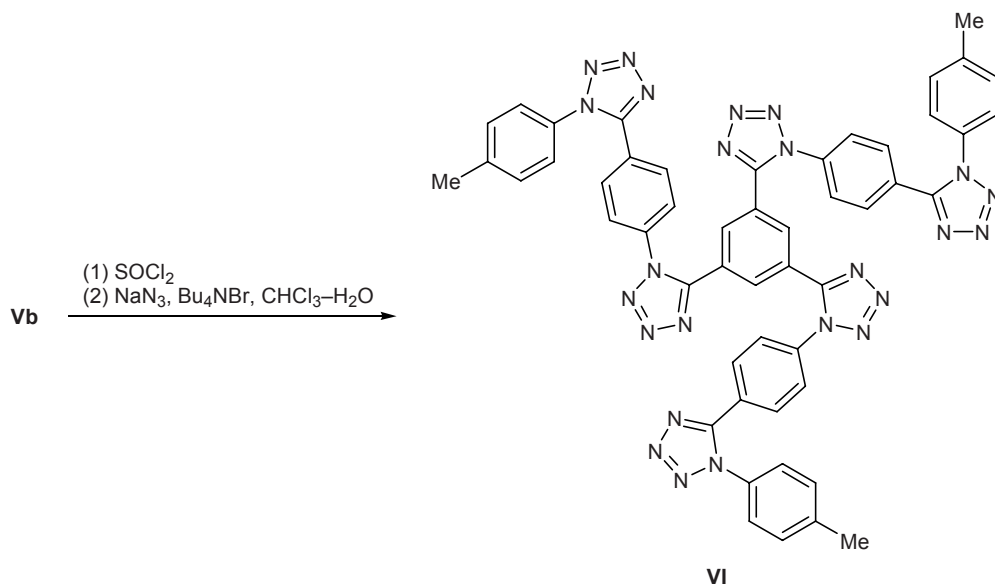
***N,N',N''*-Tris(4-methylphenyl)benzene-1,3,5-tricarboxamide.** Yield 90%, mp 297–298°C (from DMF– $\text{H}_2\text{O}$ , 5:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 811, 913, 1010, 1071, 1262, 1299, 1322, 1404, 1448, 1514, 1536, 1606, 1646, 2866, 2920, 3056, 3119, 3193, 3235.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.30 s (9H,  $\text{CH}_3$ ),

Scheme 4.



R = MeO (a), Me (b).

Scheme 5.



7.20 d (6H, H<sub>arom</sub>), 7.88 d (6H, H<sub>arom</sub>), 8.86 s (3H, H<sub>arom</sub>), 10.76 s (3H, NH). Found, %: C 75.64; H 5.94; N 8.81. C<sub>30</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub>. Calculated, %: C 75.45; H 5.70; N 8.80.

***N,N',N''*-Triphenylbenzene-1,3,5-tricarboxamide.** Yield 96%, mp 326–327°C (from DMFA-H<sub>2</sub>O, 5:1) [7]. IR spectrum, ν, cm<sup>-1</sup>: 690, 753, 1257, 1320, 1444, 1497, 1544, 1599, 1650, 3064, 3285. <sup>1</sup>H NMR spectrum, δ, ppm: 7.13–7.81 m (15H, H<sub>arom</sub>), 7.68 s (3H, H<sub>arom</sub>), 10.57 s (3H, NH). Found, %: C 74.51; H 4.88; N 9.77. C<sub>27</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>. Calculated, %: C 74.47; H 4.86; N 9.65.

***N,N',N''*-Tris(4-bromophenyl)benzene-1,3,5-tricarboxamide.** Yield 89%, mp 285–286°C (from DMF-H<sub>2</sub>O, 5:1). IR spectrum, ν, cm<sup>-1</sup>: 819, 1011, 1073, 1174, 1258, 1292, 1317, 1394, 1487, 1517, 1536, 1595, 1649, 3056, 3116, 3235, 3263. <sup>1</sup>H NMR spectrum, δ, ppm: 7.55 d (6H, H<sub>arom</sub>), 7.78 d (6H, H<sub>arom</sub>), 8.69 s (3H, H<sub>arom</sub>), 10.74 s (3H, NH). Found, %: C 48.51; H 2.73; N 6.32. C<sub>27</sub>H<sub>18</sub>Br<sub>3</sub>N<sub>3</sub>O<sub>3</sub>. Calculated, %: C 48.25; H 2.70; N 6.25.

**Tris[2-(1-phenyl-1*H*-tetrazol-5-yloxy)ethyl] benzene-1,3,5-tricarboxylate (I).** Benzene-1,3,5-tricarboxonyl trichloride, 1.39 mmol, was slowly added to

a solution of 4.85 mmol of 2-(1-phenyl-1*H*-tetrazol-5-yloxy)ethan-1-ol in 5 ml of pyridine under stirring at 30–35°C. The mixture was stirred for 3 h at 20°C, diluted with 100 ml of water, and stirred for 15 min, and the precipitate was filtered off, washed with water (50 ml), and dried in air. Yield 0.72 g (67%), mp 54–56°C (from EtOAc–EtOH, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 759, 905, 930, 1021, 1029, 1100, 1133, 1231, 1297, 1329, 1400, 1450, 1505, 1563, 1596, 1730, 2890, 2961, 3071, 3078.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 5.32 t (6H,  $\text{CH}_2$ ), 5.49 t (6H,  $\text{CH}_2$ ), 7.95–8.22 m (15H,  $\text{H}_{\text{arom}}$ ), 9.25 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 56.06; H 4.12; N 21.92.  $\text{C}_{36}\text{H}_{30}\text{N}_{12}\text{O}_9$ . Calculated, %: C 55.81; H 3.90; N 21.70.

**1,3,5-Tris[1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl]benzene (IIa).** A solution of 5.95 mmol of *N,N,N'*-tris(4-methoxyphenyl)benzene-1,3,5-tricarboximidoyl trichloride in 30 ml of chloroform was slowly added to a mixture of 20.81 mmol of sodium azide, 0.5 mmol of tetrabutylammonium bromide, and 25 ml of water. The mixture was stirred for 8 h at 20°C, and the organic phase was separated, washed with water (30 ml), dried over magnesium sulfate, and evaporated under reduced pressure. Yield 2.0 g (89%), mp 255–256°C (from MeCN–EtOH, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 837, 897, 1025, 1046, 1064, 1104, 1172, 1255, 1304, 1423, 1449, 1514, 1590, 1607, 2840, 2935, 2963, 3007, 3081.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.96 s (9H,  $\text{CH}_3$ ), 7.29 d (6H,  $\text{H}_{\text{arom}}$ ), 7.62 d (6H,  $\text{H}_{\text{arom}}$ ), 8.23 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 59.71; H 4.11; N 28.23.  $\text{C}_{30}\text{H}_{24}\text{N}_{12}\text{O}_3$ . Calculated, %: C 60.00; H 4.03; N 27.99.

Compound **IIb** was synthesized in a similar way.

**1,3,5-Tris[1-(4-ethoxyphenyl)-1*H*-tetrazol-5-yl]benzene (IIb).** Yield (85%), mp 192–193°C (from MeCN–EtOH, 1:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 838, 899, 920, 1047, 1109, 1172, 1257, 1305, 1393, 1423, 1442, 1475, 1514, 1589, 1608, 2897, 2935, 2980, 3078.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.35 t (9H,  $\text{CH}_3$ ), 4.10 q (6H,  $\text{CH}_2$ ), 7.04 d (6H,  $\text{H}_{\text{arom}}$ ), 7.34 d (6H,  $\text{H}_{\text{arom}}$ ), 7.91 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 61.42; H 4.31; N 25.91.  $\text{C}_{33}\text{H}_{30}\text{N}_{12}\text{O}_3$ . Calculated, %: C 61.67; H 4.70; N 26.15.

**1,3,5-Tris(1-phenyl-1*H*-tetrazol-5-yl)benzene (IIc).** A solution of 5.95 mmol of *N,N,N'*-triphenylbenzene-1,3,5-tricarboximidoyl chloride in 30 ml of chloroform was slowly added at 20°C to a mixture of 20.81 mmol of sodium azide, 0.5 mmol of tetrabutylammonium bromide, and 25 ml of water. The mixture was stirred for 8 h at 20°C, and the precipitate was filtered off, washed with water (100 ml), and dried at 50°C. Yield 2.2 g (73%), mp 264–265°C (from MeCN–

EtOAc, 3:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 762, 788, 900, 1018, 1074, 1113, 1264, 1442, 1497, 1517, 1596, 3055, 3067.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.39–7.62 m (15H,  $\text{H}_{\text{arom}}$ ), 7.88 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 63.57; H 3.54; N 33.35.  $\text{C}_{27}\text{H}_{18}\text{N}_{12}$ . Calculated, %: C 63.52; H 3.55; N 32.92.

Compounds **IIc** and **IIe** were synthesized in a similar way.

**1,3,5-Tris[1-(4-methylphenyl)-1*H*-tetrazol-5-yl]benzene (IIc).** Yield 71%, mp 267–268°C (from DMF–MeCN, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 816, 896, 1002, 1015, 1066, 1105, 1270, 1423, 1446, 1489, 1515, 2867, 2921, 3057, 3077.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.60 s (9H,  $\text{CH}_3$ ), 7.55 s (12H,  $\text{H}_{\text{arom}}$ ), 8.22 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 64.97; H 4.11; N 30.51.  $\text{C}_{30}\text{H}_{24}\text{N}_{12}$ . Calculated, %: C 65.21; H 4.38; N 30.42.

**1,3,5-Tris[1-(4-bromophenyl)-1*H*-tetrazol-5-yl]benzene (IIc).** Yield 79%, mp 299–300°C (decomp., from DMF). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 833, 894, 1000, 1009, 1071, 1099, 1270, 1404, 1446, 1486, 1511, 1587, 3059, 3068, 3090.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.71 d (6H,  $\text{H}_{\text{arom}}$ ), 7.97 d (6H,  $\text{H}_{\text{arom}}$ ), 8.29 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 43.30; H 2.15; N 22.78.  $\text{C}_{27}\text{H}_{15}\text{Br}_3\text{N}_{12}$ . Calculated, %: C 43.40; H 2.02; N 22.49.

**4,4',4''-[Benzene-1,3,5-triyltris(1*H*-tetrazol-5,1-diyl)]tribenzoic acid (III).** Sulfuric acid (94%), 8 ml, was slowly added to a mixture of 4.16 mmol of tetrazole **IIc**, 24.97 mmol of sodium dichromate, and 8 ml of water under stirring at 18–20°C. The mixture was stirred for 3 h at 110°C, cooled to 18–20°C, and poured into 100 ml of an ice–water mixture. The precipitate was filtered off, washed with 5% sulfuric acid (3×30 ml) and water (3×30 ml), and dissolved in 50 ml of 5% aqueous sodium hydroxide. The solution was filtered and acidified with concentrated hydrochloric acid to pH 2, and the precipitate was filtered off, washed with water (3×30 ml), and dried at 50°C. Yield 1.8 g (67%), mp >300°C (from DMF–EtOH, 1:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 772, 785, 865, 1000, 1013, 1039, 1062, 1105, 1174, 1271, 1385, 1416, 1446, 1513, 1570, 1605, 1641, 1712, 3076.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 7.31 s (3H,  $\text{H}_{\text{arom}}$ ), 7.32 d (6H,  $\text{H}_{\text{arom}}$ ), 7.86 d (6H,  $\text{H}_{\text{arom}}$ ).  $^{13}\text{C}$  NMR spectrum,  $\delta_{\text{C}}$ , ppm: 125.7, 126.1, 131.2, 132.1, 133.9, 137.0, 152.3, 166.7. Found, %: C 55.64; H 3.01; N 25.86.  $\text{C}_{30}\text{H}_{18}\text{N}_{12}\text{O}_6$ . Calculated, %: C 56.08; H 2.82; N 26.16.

**4,4',4''-[Benzene-1,3,5-triyltris(1*H*-tetrazol-5,1-diyl)]tribenzoyl trichloride (IV).** A mixture of 0.78 mmol of compound **III**, 3 ml of thionyl chloride, and one drop of DMF was stirred for 2 h at 75–80°C.

Excess thionyl chloride was removed under reduced pressure, and the residue was treated with petroleum ether (3×20 ml). Yield 0.48 g (89%). Trichloride **IV** thus obtained was brought into further syntheses without additional purification.

**4,4',4''-[Benzene-1,3,5-triyltris(1*H*-tetrazol-5,1-diyl)]tris[*N*-(4-methoxyphenyl)benzamide] (Va).** Trichloride **IV**, 0.62 mmol, was slowly added to a solution of 2.17 mmol of 4-methoxyaniline in 5 ml of pyridine under stirring at 30–35°C. The mixture was stirred for 3 h at 20°C, 100 ml of 5% hydrochloric acid was added, the mixture was stirred for 15 min, and the precipitate was filtered off, washed with water (50 ml), and dried at 50°C. Yield 0.22 g (59%), mp 197–200°C (from DMF–EtOH, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 761, 828, 896, 1030, 1104, 1176, 1247, 1322, 1414, 1441, 1512, 1534, 1599, 1607, 1656, 2836, 2935, 3002, 3072, 3301.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 3.73 s (9H,  $\text{CH}_3$ ), 6.92 d (6H,  $\text{H}_{\text{arom}}$ ), 7.59 d (6H,  $\text{H}_{\text{arom}}$ ), 7.65 d (6H,  $\text{H}_{\text{arom}}$ ), 8.04 d (9H,  $\text{H}_{\text{arom}}$ ), 10.31 s (3H, NH). Found, %: C 63.68; H 4.11; N 21.32.  $\text{C}_{51}\text{H}_{39}\text{N}_{15}\text{O}_6$ . Calculated, %: C 63.94; H 4.10; N 21.93.

**4,4',4''-[Benzene-1,3,5-triyltris(1*H*-tetrazol-5,1-diyl)]tris[*N*-(4-methylphenyl)benzamide] (Vb)** was synthesized in a similar way. Yield 0.36 g (64%), mp 193–195°C (from DMF–EtOH, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 760, 813, 857, 895, 1000, 1012, 1102, 1261, 1298, 1321, 1405, 1444, 1514, 1606, 1652, 2855, 2921, 2950, 2950, 3031, 3193, 3307.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 2.89 s (9H,  $\text{CH}_3$ ), 7.72 d (6H,  $\text{H}_{\text{arom}}$ ), 7.97 d (6H,  $\text{H}_{\text{arom}}$ ), 8.16 d (6H,  $\text{H}_{\text{arom}}$ ), 8.52 d (9H,  $\text{H}_{\text{arom}}$ ), 9.74 s (3H, NH). Found, %: C 66.94; H 4.09; N 23.15.  $\text{C}_{51}\text{H}_{39}\text{N}_{15}\text{O}_3$ . Calculated, %: C 67.32; H 4.32; N 23.09.

**5,5',5''-[Benzene-1,3,5-triyltris(1*H*-tetrazol-5,1-diyl)-4,1-phenylene]tris[1-(4-methylphenyl)-1*H*-tetrazole] (VI).** Tris-imidoyl chloride prepared from amide **Vb**, 0.38 mmol, was dissolved in 30 ml of chloroform, and the solution was slowly added to

a mixture of 1.35 mmol of sodium azide, 0.5 mmol of tetrabutylammonium bromide, and 25 ml of water. The mixture was stirred for 8 h at 20°C, and the organic phase was separated, washed with water (30 ml), dried over magnesium sulfate, and evaporated under reduced pressure. Yield 0.23 g (61%), mp 187–189°C (from DMF–EtOAc, 2:1). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 752, 820, 848, 897, 1000, 1061, 1101, 1138, 1179, 1268, 1435, 1475, 1514, 1613, 2855, 2923, 3048, 3070, 3075.  $^1\text{H}$  NMR spectrum (acetone- $d_6$ ),  $\delta$ , ppm: 2.41 s (9H,  $\text{CH}_3$ ), 7.42 d (6H,  $\text{H}_{\text{arom}}$ ), 7.50 d (6H,  $\text{H}_{\text{arom}}$ ), 7.61 d (6H,  $\text{H}_{\text{arom}}$ ), 7.80 d (6H,  $\text{H}_{\text{arom}}$ ), 8.10 s (3H,  $\text{H}_{\text{arom}}$ ). Found, %: C 62.51; H 3.72; N 34.41.  $\text{C}_{51}\text{H}_{36}\text{N}_{24}$ . Calculated, %: C 62.19; H 3.68; N 34.13.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 08-03-00342).

## REFERENCES

1. Myznikov, L.V., Roh, J., Artamonova, T.V., Hrabalek, A., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2007, vol. 43, p. 765.
2. Artamonova, T.V., Zatssepina, M.V., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 1318.
3. Koldobskii, G.I., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 469.
4. Zatssepina, M.V., Artamonova, T.V., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 1056.
5. Zatssepina, M.V., Hrabalek, A., Artamonova, T.V., and Koldobskii, G.I., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 1834.
6. Gol'tsberg, M.A. and Koldobskii, G.I., *Khim. Geterotsikl. Soedin.*, 1996, no. 11/12, p. 1515.
7. Lewis, F.D., Long, T.M., Stern, C.L., and Liu, W., *J. Phys. Chem. A.*, 2003, vol. 107, p. 3254.
8. Koldobskii, G.I., Nikonova, I.V., Zhivich, A.B., Ostrovskii, V.A., and Poplavskii, V.S., *Zh. Obshch. Khim.*, 1992, vol. 62, p. 194.