

Dedicated to Full Member of the Russian Academy of Sciences
V.A. Tartakovskii on the 70th Anniversary of His Birth

Tetrazoles: XLIII.* Polydentate Tetrazole-Containing Ligands for Biomimetic Studies**

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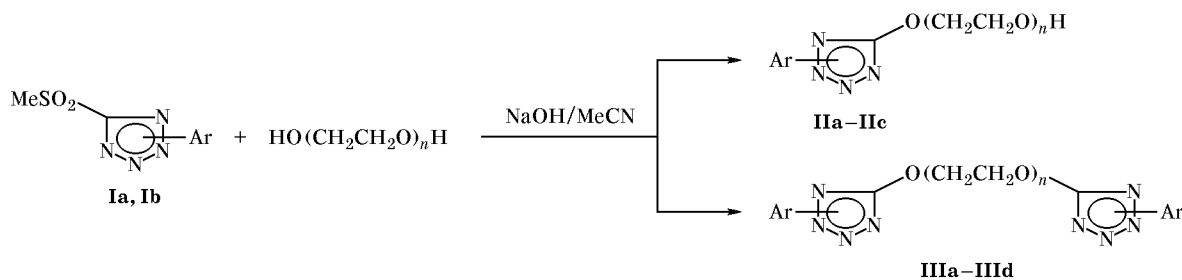
Abstract—1(2)-Aryl-5-methylsulfonyltetrazoles react with ethylene glycol, di- and triethylene glycols, and tris(2-hydroxyethyl)amine in acetonitrile in the presence of sodium hydroxide to give tetrazole-containing ethers. The products can be used as polydentate ligands for biomimetic studies.

While continuing our search for optimal methods of preparation of polydentate tetrazole-containing ligands, as well as of tetrazole derivatives exhibiting antituberculous activity, we have studied the reactivity of 1(2)-aryl-5-methylsulfonyltetrazoles toward such nucleophiles as ethylene glycol, di- and triethylene glycols, and tris(2-hydroxyethyl)amine. We previously showed that 1(2)-aryl-5-methylsulfonyltetrazoles react with simple monobasic alcohols in the presence of bases to give the corresponding 1(2)-aryl-5-alkoxy-

tetrazoles in high yields [1–3]. The rate of nucleophilic replacement of the methylsulfonyl group in such substrates is strongly determined by the position of the aryl substituent in the heteroring: It increases in going from 2- to 1-substituted compounds, in keeping with their electronic structure [4].

Reactions of 1(2)-aryl-5-methylsulfonyltetrazoles with polyatomic functionally substituted alcohols as nucleophiles were not discussed previously. We have found that 5-methylsulfonyl-1-phenyltetrazole (**Ia**)

Scheme 1.



I, Ar = 1-phenyl (**a**), 2-(4-nitrophenyl) (**b**); **II**, Ar = 1-phenyl, *n* = 1 (**a**); Ar = 2-(4-nitrophenyl), *n* = 2 (**b**), 3 (**c**); **III**, Ar = 1-phenyl, *n* = 1 (**a**); Ar = 2-(4-nitrophenyl), *n* = 1 (**b**), 2 (**c**), 3 (**d**).

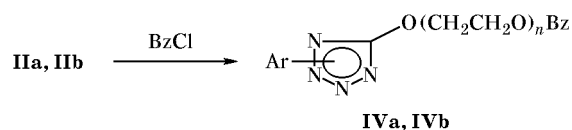
* For communication XLII, see [1].

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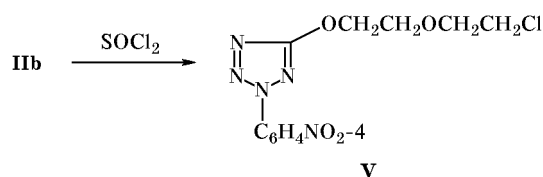
and 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole (**IIb**) react with ethylene, diethylene, and triethylene glycols in the presence of sodium hydroxide to give the corresponding tetrazole-containing ethers in good yields (Scheme 1). The reactions occur at 20°C in acetonitrile, and both mono- and disubstitution products can be obtained, depending on the reactant ratio. The replacement of methylsulfonyl group in tetrazole **IIb** by the action of di- and triethylene glycols is characterized by a higher rate, as compared to the reaction with ethylene glycol. This may be due to catalytic effect of di- and triethylene glycols, which is usually observed in nucleophilic substitution processes [5].

Tetrazole-containing alcohols **IIa** and **IIb** readily undergo acylation with benzoyl chloride. Treatment of compound **IIb** with thionyl chloride yields the corresponding halogen derivative (Scheme 2).

Scheme 2.



IV, Ar = 1-phenyl, $n = 1$ (**a**); 2-(4-nitrophenyl), $n = 2$ (**b**).



1-Aryl-5-methylsulfonyltetrazoles react with tris-(2-hydroxyethyl)amine under the same conditions as with the above polyatomic alcohols. As expected, the reactivity of the nitrophenyl-substituted tetrazole was higher (Scheme 3).

Thus, we have developed a procedure for the synthesis of tetrazole-containing polydentate ligands

which may be used for preparation of coordination compounds with iron and other transition metals. In addition, the products obtained are expected to exhibit antituberculous activity, as was found experimentally for some other tetrazole-containing ethers [6]. Finally, tetrazoles **V**, **VIa**, and **VIb** may be used in the synthesis of dendrimers, following both convergent and divergent schemes [7].

EXPERIMENTAL

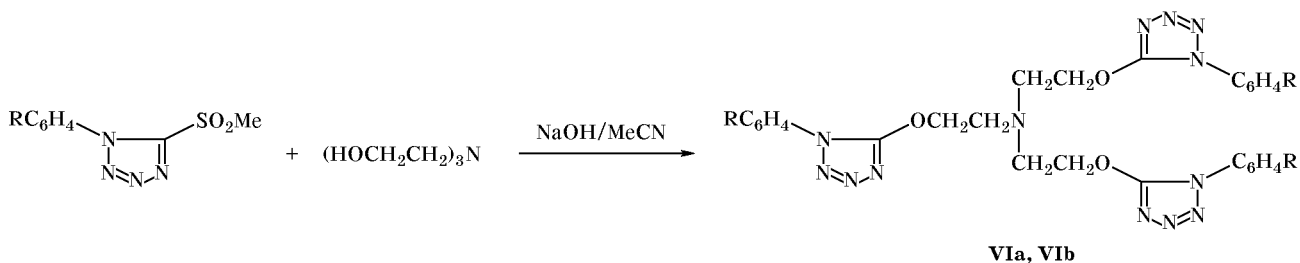
The IR spectra were recorded on a UR-20 spectrometer in KBr; the IR spectrum of **VIb** was obtained on a Perkin-Elmer Spectrum BX-1000 instrument. The ^1H NMR spectra were measured on a Bruker AC-200 spectrometer. The purity of the products was checked by TLC on Silufol UV-254 plates, using chloroform as eluent.

5-Methylsulfonyl-1-phenyltetrazole (**Ia**), 5-methylsulfonyl-1-(4-nitrophenyl)tetrazole, and 5-methylsulfonyl-2-(4-nitrophenyl)tetrazole (**IIb**) were synthesized as described in [1–3]. The procedure for preparation of 2-(1-phenyltetrazol-5-yloxy)ethanol (**IIa**) was reported in [8].

2-[2-[2-(4-Nitrophenyl)-5-tetrazolyloxy]ethoxy]ethanol (IIb). Sodium hydroxide, 40 mmol, was added to a solution of 0.74 mmol of tetrazole **IIb** and 40 mmol of diethylene glycol in 10 ml of acetonitrile. The mixture was stirred for 6 h at 20°C and diluted with 50 ml of water, and the precipitate was filtered off. Yield 0.2 g (89%), mp 75–76°C (from ethanol). IR spectrum, ν , cm^{-1} : 920, 1000, 1040, 1060, 1070, 1120, 1150, 1220, 1250, 1320, 1350, 1380, 1450, 1470, 1505, 1540, 1570, 1600, 3100, 3550. ^1H NMR spectrum (CDCl_3), δ , ppm: 3.7 m (4H, $\text{OCH}_2\text{CH}_2\text{OH}$), 4.0 t (2H, $\text{OCH}_2\text{CH}_2\text{OCH}_2$), 4.7 t (2H, NCOCH_2), 8.3–8.4 m (4H, H_{arom}). Found, %: C 44.65; H 4.52; N 23.78. $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}_5$. Calculated, %: C 44.75; H 4.40; N 23.73.

2-[2-[2-(4-Nitrophenyl)-5-tetrazolyloxy]ethoxy]ethoxy]ethanol (IIc) was synthesized in

Scheme 3.



VI, R = H (**a**), 4- NO_2 (**b**).

a similar way. Reaction time 5 h. Yield 90%, mp 62–63°C (from ethanol). IR spectrum, ν , cm^{-1} : 900, 920, 940, 960, 1000, 1040, 1070, 1100, 1120, 1150, 1210, 1250, 1290, 1320, 1350, 1390, 1450, 1510, 1540, 1560, 1610, 1620, 2890, 2930, 3100, 3140, 3490. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 3.4–3.7 m (8H, $\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$), 3.9 t (2H, $\text{NCOCH}_2\text{CH}_2\text{O}$), 4.5 s (1H, OH), 4.7 t (2H, NCOCH_2), 8.2–8.5 m (4H, H_{arom}). Found, %: C 46.24; H 5.13; N 20.78. $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_6$. Calculated, %: C 46.02; H 5.01; N 20.65.

1,2-Bis(1-phenyl-5-tetrazolyloxy)ethane (IIIa). Sodium hydroxide, 8.8 mmol, was added to a solution of 8.8 mmol of tetrazole **Ia** and 4.2 mmol of ethylene glycol in 15 ml of acetonitrile. The mixture was stirred for 20 h at 20°C and diluted with 150 ml of water, and the precipitate was filtered off. Yield 1.03 g (70%), mp 179–180°C (from DMF). IR spectrum, ν , cm^{-1} : 910, 985, 1030, 1050, 1085, 1105, 1150, 1190, 1255, 1295, 1300, 1335, 1360, 1410, 1455, 1505, 1575, 1605, 1745, 2870, 2930, 3080. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 4.92 s (4H, CH_2), 7.32–7.62 m (10H, H_{arom}). Found, %: C 55.11; H 3.92; N 31.81. $\text{C}_{16}\text{H}_{14}\text{N}_8\text{O}_2$. Calculated, %: C 54.84; H 4.04; N 31.73.

Tetrazoles **IIIb–IIIc** were synthesized by a similar procedure.

1,2-Bis[2-(4-nitrophenyl)-5-tetrazolyloxy]ethane (IIIb). Reaction time 13 h. Yield 0.15 g (71%), mp 180–181°C (from aqueous DMF). IR spectrum, ν , cm^{-1} : 860, 925, 980, 995, 1035, 1050, 1065, 1085, 1110, 1180, 1205, 1220, 1320, 1345, 1450, 1505, 1535, 1555, 1605, 2865, 2930, 3105, 3135. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 4.90 s (4H, CH_2), 8.25–8.50 m (8H, H_{arom}). Found, %: C 43.66; H 2.79; N 31.90. $\text{C}_{16}\text{H}_{12}\text{N}_{10}\text{O}_6$. Calculated, %: C 43.63; H 2.73; N 31.82.

Bis[2-[2-(4-nitrophenyl)-5-tetrazolyloxy]ethyl] ether (IIIc). Reaction time 10 h. Yield 78%, mp 188–189°C (from acetonitrile–DMF, 1:1). IR spectrum, ν , cm^{-1} : 900, 930, 1000, 1050, 1060, 1100, 1120, 1220, 1270, 1320, 1340, 1350, 1450, 1480, 1500, 1550, 1580, 1600, 1620, 2940, 3100, 3140. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 3.90 t (4H, CH_2OCH_2), 4.6 t (4H, NCOCH_2), 8.20–8.40 m (8H, H_{arom}). Found, %: C 44.59; H 3.60; N 28.84. $\text{C}_{18}\text{H}_{16}\text{N}_{10}\text{O}_7$. Calculated, %: C 44.65; H 3.31; N 28.93.

1,2-Bis[2-[2-(4-nitrophenyl)-5-tetrazolyloxy]ethoxy]ethane (IIIId). Reaction time 5 h. Yield 82%, mp 169°C (from acetonitrile). IR spectrum, ν , cm^{-1} : 900, 1000, 1040, 1050, 1060, 1110, 1120, 1130,

1210, 1260, 1290, 1320, 1340, 1370, 1390, 1440, 1470, 1505, 1530, 1570, 1600, 1620, 2900, 2930, 3090, 3110, 3130. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 3.6 s (4H, $\text{OCH}_2\text{CH}_2\text{O}$), 3.9 t (4H, $\text{NCOCH}_2\text{CH}_2$), 4.6 t (4H, NCOCH_2), 8.25–8.50 m (8H, H_{arom}). Found, %: C 45.51; H 3.97; N 26.48. $\text{C}_{20}\text{H}_{20}\text{N}_{10}\text{O}_8$. Calculated, %: C 45.47; H 3.78; N 26.51.

2-(1-Phenyl-5-tetrazolyloxy)ethyl benzoate (IVa). Benzoyl chloride, 1.4 mmol, was added to a solution of 1.3 mmol of 2-(1-phenyl-5-tetrazolyloxy)ethanol in 5 ml of pyridine. The mixture was stirred for 5 h at 20°C, 30 ml of water was added, and the precipitate was filtered off, washed with water (2×20 ml), and dried in air. Yield 0.2 g (53%), mp 64–65°C (from ethanol). IR spectrum, ν , cm^{-1} : 930, 980, 1030, 1060, 1080, 1130, 1180, 1280, 1310, 1400, 1450, 1500, 1570, 1608, 1730, 2860, 2930, 2960. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 4.90 t (2H, CH_2OCO), 4.70 t (2H, CH_2O), 7.50–8.0 m (10H, H_{arom}). Found, %: C 61.85; H 4.32; N 17.98. $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3$. Calculated, %: C 61.93; H 4.52; N 18.06.

2-[2-[2-(4-Nitrophenyl)-5-tetrazolyloxy]ethoxy]ethyl benzoate (IVb) was synthesized in a similar way. Yield 63%, mp 73–74°C (from ethanol). IR spectrum, ν , cm^{-1} : 910, 940, 1000, 1030, 1040, 1130, 1210, 1290, 1350, 1400, 1440, 1450, 1500, 1540, 1560, 1600, 1710, 2830, 2870, 3000. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 3.8–3.9 m (4H, $\text{OCH}_2\text{CH}_2\text{O}$), 4.3 t (2H, CH_2), 4.75 t (2H, CH_2OCO), 7.40–7.60 m (5H, C_6H_5), 8.25–8.50 m (4H, C_6H_4). Found, %: C 54.09; H 4.18; N 17.63. $\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}_6$. Calculated, %: C 54.14; H 4.26; N 17.54.

2-[2-[2-(4-Nitrophenyl)-5-tetrazolyloxy]ethoxy]ethyl chloride (V). Thionyl chloride, 0.73 mmol, was added at 0–2°C to a solution of 0.34 mmol of compound **IIb** in 1 ml of pyridine. The mixture was stirred for 15 min at 0°C and for 1 h at 20°C and was poured into 30 ml of water. The precipitate was filtered off, washed with water (2×20 ml), and dried in air. Yield 0.1 g (85%), mp 63–65°C (from ethanol). IR spectrum, ν , cm^{-1} : 930, 960, 1000, 1030, 1060, 1120, 1200, 1270, 1320, 1360, 1450, 1480, 1510, 1550, 1570, 1600, 2950, 3100, 3140. ^1H NMR spectrum (DMSO- d_6), δ , ppm: 3.75–4.10 m (6H, CH_2), 4.50 t (2H, CH_2), 8.25–8.50 m (4H, H_{arom}). Found, %: C 42.12; H 3.82; N 22.41. $\text{C}_{11}\text{H}_{12}\text{ClN}_5\text{O}_4$. Calculated, %: C 42.11; H 3.83; N 22.33.

Tris[2-(1-phenyl-5-tetrazolyloxy)ethyl]amine (VIa). Sodium hydroxide, 3.8 mmol, was added to a solution of 3.8 mmol of 5-methylsulfonyl-1-phenyl-tetrazole (**Ia**) and 1.2 mmol of tris(2-hydroxyethyl)-

amine in 15 ml of acetonitrile. The mixture was stirred for 26 h at 20°C, 150 ml of water was added, and the precipitate was filtered off and dried in air. Yield 0.49 g (70%), mp 111–112°C (from ethanol). IR spectrum, ν , cm^{-1} : 870, 890, 920, 940, 980, 1010, 1030, 1050, 1080, 1100, 1140, 1190, 1295, 1305, 1320, 1360, 1365, 1400, 1460, 1505, 1570, 1600, 2860, 2900, 2940, 2980, 3080. ^1H NMR spectrum ($\text{DMSO-}d_6$), δ , ppm: 3.10 s (6H, CH_2), 4.58 s (6H, CH_2O), 7.32–7.67 m (15H, H_{arom}). Found, %: C 55.74; H 4.77; N 31.11. $\text{C}_{27}\text{H}_{27}\text{N}_{13}\text{O}_3$. Calculated, %: C 55.77; H 4.64; N 31.32.

Tris[2-[1-(4-nitrophenyl)-5-tetrazolyloxy]ethyl]amine (VIb) was synthesized in a similar way. Reaction time 5 h. Yield 85%, mp 152°C (from DMF–ethanol, 1:1). IR spectrum, ν , cm^{-1} : 892, 909, 953, 1007, 1038, 1108, 1130, 1188, 1235, 1290, 1311, 1338, 1394, 1420, 1443, 1502, 1526, 1566, 1598, 1612, 2826, 3092, 3118, 3439. ^1H NMR spectrum (CDCl_3), δ , ppm: 3.50 t (6H, CH_2), 4.70 t (6H, CH_2O), 7.9–8.25 m (12H, H_{arom}). Found, %: C 45.21; H 3.52; N 31.31. $\text{C}_{27}\text{H}_{24}\text{N}_{16}\text{O}_9$. Calculated, %: C 45.25; H 3.35; N 31.28.

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