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Synthesis of 1,8-Di(pyrazol-1-yl)-3,6-dioxaoctane and Its Derivatives

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Abstract—From pyrazole, 3,5-dimethylpyrazole, and 1,8-dibromo-3,6-dioxaoctane in a superbasic medium KOH–DMSO the corresponding 1,8-di(pyrazol-1-yl)-3,6-dioxaoctanes were synthesized and converted into iodo-, nitro-, amino-, and formylderivatives.

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Ligands containing several pyrazole rings are capable of complex formation with transition metals ions exhibiting catalytic and fluorescent properties and a biological action [1]. Bis(pyrazol-1-yl)alkanes, bidentate chelate-forming ligands, are sufficiently well understood, but compounds with more complex linkers between the pyrazole rings are described in few publications [2].

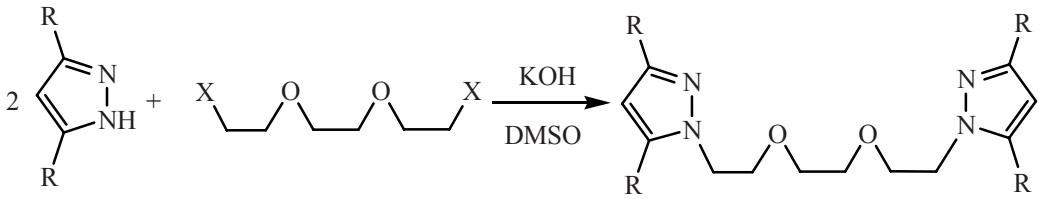
We report here on the first synthesis of pyrazole-containing chelate-forming ligands with a diether linker between the heterocycles, 1,8-di(pyrazol-1-yl)-3,6-dioxaoctane (**Ia**) and 1,8-bis(3,5-dimethylpyrazol-1-yl)-3,6-dioxaoctane (**Ib**). Compounds **Ia** and **Ib** were synthesized in a superbasic medium KOH–DMSO (Scheme 1). This method was formerly applied to the synthesis of di(pyrazol-1-yl)alkanes [3, 4] and alos to the alkylation of nitrogen heterocycles [5].

The alkylation of 3,5-dimethylpyrazole with 1,8-dichloro-3,6-dioxaoctane was carried out at 80°C in the superbasic environment (Scheme 1), and the reaction completed within 22 h. At the use of 1,8-dibromo-3,6-dioxaoctane the reaction was faster (see the table) presumably due to the higher nucleofugal ability of bromine compared to chlorine. At room temperature the reaction time with 1,8-dibromo-3,6-dioxaoctane was 24 h. Thus the temperature significantly affected the duration of the synthesis. Yet the temperature and the character of the alkylating agent did not essentially influence the yield of compound **Ib** (see the table).

Compound **Ia** was obtained from pyrazole and 1,8-dibromo-3,6-dioxaoctane under similar conditions. As seen from the table, the presence of methyl substituents in the pyrazole ring weakly affected the activity of the heterocycle in the alkylation along Scheme 1.

The variation of the properties of the pyrazole-

Scheme 1.



Ia, Ib

X = Cl, Br; R = H (**a**), Me (**b**).

containing ligands can be achieved by introducing into their structure of versatile functional groups. We obtained iodo-, formyl-, nitro-, and aminoderivatives of compounds synthesized. The choice of the functional groups was based on their high reactivity and the ability to form polymers. For instance, the iodine in the position *4* of the pyrazole ring of di(pyrazol-1-yl)methanes is easily replaced by the other functional groups and also enters into the condensation leading to oligomers [6].

The oxidative iodination of compound **Ib** was performed using the system I_2–HIO_3–H_2SO_4 in acetic acid (Scheme 2). The process resulted in the formation of diiododerivative **II** in 67% yield. This iodinating system was previously applied to the synthesis of iododerivatives of N-alkylpyrazoles [7].

Pyrazole-containing dialdehydes are also capable of forming polycondensation products with diamines [8]. The formylation of compound **Ib** was performed by Vilsmeier reaction (Scheme 2) at 100°C. The yield of dialdehyde **III** reached 65%.

The pyrazole nitroderivatives are interesting because of their biological activity. The investigations performed in [9] suggest that nitropyrazoles should possess antimicrobial properties and would be promising analogs of currently applied nitroimidazoles.

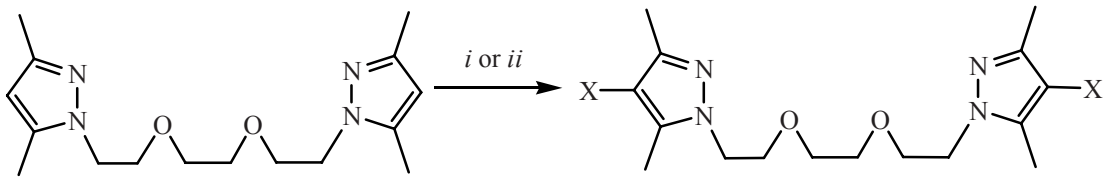
Compounds **Ia** and **Ib** were subjected to nitration with a mixture of nitric and sulfuric acids (Scheme 3), the yields of nitroproducts **IVa** and **IVb** were fairly high. This method was applied before to the nitration of di(pyrazol-1-yl)methanes [10], but the target dinitro derivatives always formed with an impurity of side products, mononitro derivatives. The NMR spectra of crude compounds **IVa** and **IVb** contained only the signals of dinitro compounds. This is understandable for in compounds **Ia** and **Ib** the pyrazole rings are remote as compared with di(pyrazol-1-yl)methanes, and therefore the first introduced nitro group does not hamper the nitration of the second pyrazole ring.

Under similar comditions we obtained from a ligand with one oxygen atom in the linker, 1,5-bis(3,5-dimethylpyrazol-1-yl)-3-oxapentane (**V**), dinitro derivative **VI** also without the formation of a monosubstituted product.

We prepared diamino derivatives **VII** and **VIII** by reduction of compounds **IVb** and **VI** with hydrogen in statu nascendi (by zinc in hydrochloric acid) (Scheme 4). The attained yields were 60–80%.

Thus in this study we synthesized for the first time chelate-forming pyrazole-containing ligands with two additional oxygen atoms in the linker between the heterocycles, and also their functional derivatives. The compounds obtained may be promising for metal ions extraction from solutions and for preparation of macromolecular compounds.

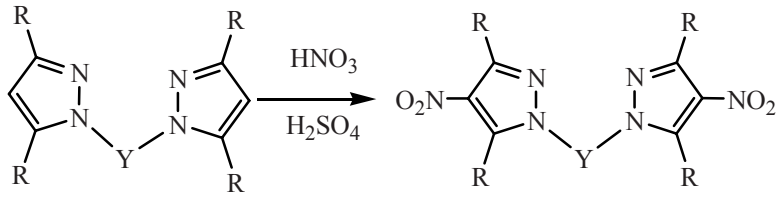
Scheme 2.



Ib **II, III**

i: I_2, HIO_3, H_2SO_4; X = I (**II**); *ii*: DMF, $POCl_3$; X = CHO (**III**).

Scheme 3.



Ia, Ib, V **IVa, IVb, VI**

R = H (**Ia, IVa**), Me (**Ib, IVb, V, VI**); Y = –$(CH_2)_2O(CH_2)_2O(CH_2)_2$– (**I, IV**), –$(CH_2)_2O(CH_2)_2$– (**V, VI**).

Conditions of the preparation of 1,8-di(pyrazol-1-yl)-3,6-dioxaoctanes **Ia** and **Ib**

Reaction product	Reagent	Temperature, °C	Reaction time, h	Yield, %
Ia	$Br[(CH_2)_2O]_2(CH_2)_2Br$	80	1	76
Ia	$Br[(CH_2)_2O]_2(CH_2)_2Br$	20	24	83
Ib	$Cl[(CH_2)_2O]_2(CH_2)_2Cl$	80	22	89
Ib	$Br[(CH_2)_2O]_2(CH_2)_2Br$	80	1	76
Ib	$Br[(CH_2)_2O]_2(CH_2)_2Br$	20	24	83

EXPERIMENTAL

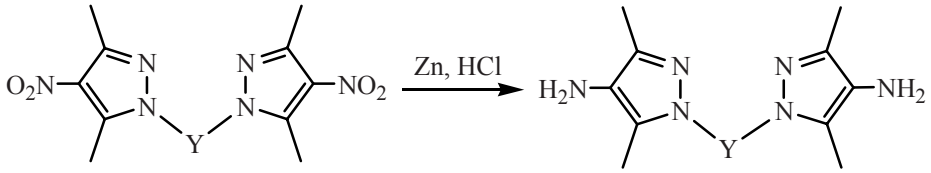
Monitoring of reaction progress and checking the purity of compounds was performed by TLC on Silufol plates, eluents hexane–acetone, 1:1, or benzene–ethanol, 1:2, visualizing of spots in iodine vapor. NMR spectra were registered on a spectrometer Bruker AV-300 from solutions in $CDCl_3$, IR spectra were recorded on a spectrophotometer Specord 71 IR from mulls in mineral oil. Elemental analyses were carried out on an instrument Carlo Erba.

1,8-Di(pyrazol-1-yl)-3,6-dioxaoctane (Ia). To 2 g (29.4 mmol) of pyrazole was added 3.3 g (58.9 mmol) of KOH powder and 20 ml of DMSO, the mixture was stirred for 30 min at 80°C, then dropwise was added 4.06 g (14.7 mmol) of 1,8-dibromo-3,6-dioxaoctane in 10 ml of DMSO, then the stirring was continued for another 1 h. The reaction mixture was diluted with water (200 ml) and extracted with chloroform (5 × 20 ml). The extract was washed with water (2 × 20 ml) and dried with calcium chloride. On removing the solvent the liquid residue was distilled in a vacuum. Yield 3.1 g (83%), color-less fluid, bp 195°C (6 mm Hg). IR spectrum, cm^{-1}: 1500, 1440, 1390, 1040 (Pz), 1100 (C–O). ^1H NMR spectrum, δ, ppm: 3.41 s (4H, OCH_2CH_2O), 3.70 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.19 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 6.13 t [2H, H^4 (Pz), *J* 2 Hz], 7.38 d [2H, H^3 (Pz), *J* 2 Hz], 7.42 d [2H, H^5(Pz), *J* 2 Hz]. ^{13}C NMR spectrum, δ, ppm: 51.9 (OCH_2CH_2O), 69.8 ($PzCH_2CH_2O$), 70.4 ($PzCH_2CH_2O$), 105.3 (C^4), 130.0 (C^5), 139.2 (C^3). Found, %: C 57.22; H 7.20; N 22.02. $C_{12}H_{18}N_4O_2$. Calculated, %: C 57.58; H 7.25; N 22.38.

1,8-Bis(3,5-dimethylpyrazol-1-yl)-3,6-dioxaoctane (Ib) was similarly obtained from 5 g (52 mmol) of 3,5-dimethylpyrazole, 5.88 g (105 mmol) of KOH, and 7.18 γ (26 mmol) of 1,8-dibromo-3,6-dioxaoctane. Yield 6.63 g (83%), colorless crystals, mp 61–62°C (hexane). IR spectrum, cm^{-1}: 1530, 1010 (Pz), 1100 (C–O). ^1H NMR spectrum, δ, ppm: 2.20 s (6H, 3-CH_3), 2.21 s (6H, 5-CH_3), 3.44 s (4H, OCH_2CH_2O), 3.74 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.09 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 5.74 s [2H, H^4 (Pz)]. ^{13}C NMR spectrum, δ, ppm: 10.9 (5-CH_3), 13.3 (3-CH_3), 48.4 (OCH_2CH_2O), 70.2 ($PzCH_2CH_2O$), 70.5 ($PzCH_2CH_2O$), 104.6 (C^4), 139.6 (C^5), 147.4 (C^3). Found, %: C 62.86; H 8.50; N 18.67. $C_{16}H_{26}N_4O_2$. Calculated, %: C 62.72; H 8.55; N 18.29.

1,8-Bis(4-iodo-3,5-dimethylpyrazol-1-yl)-3,6-dioxaoctane (II). To 0.2 g (0.65 mmol) of compound **Ib** was added 0.133 g (0.52 mmol) of finely ground iodine, 0.05 g (0.28 mmol) of iodic acid, 0.8 ml of 30% H_2SO_4, and 5 ml of AcOH. The reaction mixture was heated for 3 h on a water bath till complete discoloration. Then it was poured into 100 ml of water, the precipitate was filtered off, and dried. Yield 0.241 g (67%), colorless crystals, mp 76–77°C (EtOH–water, 1:1). IR spectrum, cm^{-1}: 1520, 1420, 1000 (Pz), 1120 (C–O). ^1H NMR spectrum, δ, ppm: 2.21 s (6H, 3-CH_3), 2.27 s (6H, 5-CH_3),

Scheme 4.



IVb, VI **VII, VIII**

Y = $–(CH_2)_2O(CH_2)_2O(CH_2)_2–$ (**IVb, VII**), $–(CH_2)_2O(CH_2)_2–$ (**VI, VIII**).

3.44 s (4H, OCH_2CH_2O), 3.72 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.18 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz). Found, %: C 34.25; H 4.30; N 10.08. $C_{16}H_{24}I_2N_4O_2$. Calculated, %: C 34.43; H 4.33; N 10.04.

1,8-Bis(3,5-dimethyl-4-formylpyrazol-1-yl)-3,6-dioxaoctane (III). To 0.5 g (1.36 mmol) of compound **Ib** was added 0.33 g (0.2 ml, 2.14 mmol) of $POCl_3$, 1 ml of DMF, and the mixture was heated for 24 h at 100°C. Then it was poured into 100 ml of water, neutralized with 10% NaOH solution, and extracted with chloroform (5× 20 ml). The extract was dried with calcium chloride, and the solvent was removed. Yield 0.39 g (65%), colorless crystals, mp 96–97°C (toluene). IR spectrum, cm^{-1}: 1660 (C=O), 1500, 1005 (Pz), 1110 (C–O). ^1H NMR spectrum, δ, ppm: 2.43 s (6H, 3-CH_3), 2.50 s (6H, 5-CH_3), 3.45 s (4H, OCH_2CH_2O), 3.76 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.12 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 9.98 (2H, CHO). ^{13}C NMR spectrum, δ, ppm: 10.1 (5-CH_3), 12.6 (3 CH_3), 48.6 (OCH_2CH_2O), 69.7 ($PzCH_2CH_2O$), 70.6 ($PzCH_2CH_2O$), 96.3 (C^4), 117.7 (C^5), 151.2 (C^3), 185.5 (C=O). Found, %: C 59.44; H 7.30; N 15.10. $C_{18}H_{26}N_4O_4$. Calculated, %: C 59.65; H 7.23; N 15.46.

1,8-Bis(4-nitropyrazol-1-yl)-3,6-dioxaoctane (IVa). To 0.2 g (0.8 mmol) of compound **Ia** was added 0.504 g (8 mmol) of HNO_3 (0.36 ml of 68% solution) and 1.8 ml of 96% H_2SO_4, the mixture was left standing for 24 h at room temperature, then 50 ml of water was added, the separated precipitate was filtered off, washed with water on the filter till neutral washings, and dried. Yield 0.19 g (70%), colorless crystals, mp 101–102°C (benzene). ^1H NMR spectrum, δ, ppm: 3.56 s (4H, OCH_2CH_2O), 3.84 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.34 t (4H, $PzCH_2CH_2O$, *J* 5.4Hz). ^{13}C NMR spectrum, δ, ppm: 11.7 (5-CH_3), 14.2 (3-CH_3), 53.1 (OCH_2CH_2O), 68.6 ($PzCH_2CH_2O$), 70.1 ($PzCH_2CH_2O$), 129.6 (C^4), 135.5 (C^5), 135.7 (C^3). Found, %: C 42.40; H 4.94; N 25.03. $C_{12}H_{16}N_6O_6$. Calculated, %: C 42.35; H 4.74; N 24.70.

Compounds **IVb** and **VI** were similarly obtained.

1,8-Bis(3,5-dimethyl-4-nitropyrazol-1-yl)-3,6-dioxaoctane (IVb) was prepared analogously from 0.5 g (1.6 mmol) of compound **Ib**, 1.01 g (16 mmol) of HNO_3 (0.7 ml of 68% solution), and 2.8 ml of 96% H_2SO_4. Yield 0.58 g (89%), colorless crystals, mp 141–142°C (benzene). IR spectrum, cm^{-1}: 1520, 990 (Pz), 1350 (N–O), 1100 (C–O). ^1H NMR spectrum, δ, ppm: 2.49 s (6H, 3-CH_3), 2.59 s (6H, 5-CH_3), 3.45 s (4H, OCH_2CH_2O), 3.75 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.15 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz). ^{13}C NMR spectrum, δ, ppm: 11.7 (5-CH_3), 14.2 (3-CH_3), 49.6 (OCH_2CH_2O), 69.4 ($PzCH_2CH_2O$), 70.5 ($PzCH_2CH_2O$), 130.9 (C^4), 141.5 (C^5), 146.3 (C^3). Found, %: C 48.10; H 5.90; N 21.00. $C_{16}H_{24}N_6O_6$. Calculated, %: C 48.48; H 6.10; N 21.20.

1,5-Bis(3,5-dimethyl-4-nitropyrazol-1-yl)-3-oxapentane (VI) was obtained from 0.5 g (1.9 mmol) of compound **V** [4], 1.2 g (19 mmol) of HNO_3, and 3.4 ml of 96% H_2SO_4. Yield 0.65 g (96%), colorless crystals, mp 130–131°C (toluene). IR spectrum, cm^{-1}: 1540, 1010 (Pz), 1350 (N–O), 1100 (C–O). ^1H NMR spectrum, δ, ppm: 2.47 s (6H, 3-CH_3), 2.54 s (6H, 5-CH_3), 3.76 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz), 4.11 t (4H, $PzCH_2CH_2O$, *J* 5.4 Hz). ^{13}C NMR spectrum, δ, ppm: 11.5 (5-CH_3), 14.1 (3-CH_3), 49.1 ($PzCH_2CH_2O$), 69.2 ($PzCH_2CH_2O$), 130.9 (C^4), 140.9 (C^5), 146.3 (C^3). Found, %: C 47.80; H 5.80; N 23.44. $C_{14}H_{20}N_6O_5$. Calculated, %: C 47.72; H 5.72; N 23.85.

1,8-Bis(4-amino-3,5-dimethylpyrazol-1-yl)-3,6-dioxaoctane (VII). To 0.17 g (0.5 mmol) of compound **IVb** was added zinc in excess and 3 ml of 35% HCl, and the mixture was heated at 80°C. After dissolution of all zinc a solution of NaOH was added to the reaction mixture till complete dissolution of the first precipitated zinc hydroxide. Then the product was extracted into chloroform (6×20 ml). The extract was washed with water (2×20 ml), dried with calcium chloride, and evaporated in a vacuum. Yield 0.112 g (80%), colorless crystals, mp 89–90°C (toluene). IR spectrum, cm^{-1}: 3350, 1620, 1580 (N–H), 1520, 1470, 1050 (Pz), 1305 (C–N), 1100 (C–O). ^1H NMR spectrum, δ, ppm: 2.10 s (6H, 3-CH_3), 2.11 s (6H, 5-CH_3), 2.54 (4H, NH_2), 3.42 s (4H, OCH_2CH_2O), 3.66 t (4H, $PzCH_2CH_2O$, *J* 5.7 Hz), 4.02 t (4H, $PzCH_2CH_2O$, *J* 5.7 Hz). ^{13}C NMR spectrum, δ, ppm: 8.7 (5-CH_3), 10.8 (3-CH_3), 48.8 (OCH_2CH_2O), 70.4 ($PzCH_2CH_2O$), 70.5 ($PzCH_2CH_2O$), 122.4 (C^4), 128.4 (C^5), 139.2(C^3). Found, %: C 57.17; H 8.48; N 25.30. $C_{16}H_{28}N_6O_2$. Calculated, %: C 57.12; H 8.39; N 24.98.

1,8-Bis(4-amino-3,5-dimethylpyrazol-1-yl)-3-oxapentane (VIII) was similarly obtained from 0.17 g (0.5 mmol) of compound **VI**, excess zinc, and 3 ml of 35% HCl. Yield 0.10 g (61%), colorless crystals, mp 92–93°C (toluene). IR spectrum, cm^{-1}: 3300, 1620, 1590 (N–H), 1500, 1010 (Pz), 1330 (C–N), 1090 (C–O). ^1H NMR spectrum, δ, ppm: 2.04 s (6H, 3-CH_3), 2.13 s (6H, 5-CH_3), 2.54 (4H, NH_2), 3.63 t (4H, $PzCH_2CH_2O$, *J* 5.7 Hz), 4.02 t (4H, $PzCH_2CH_2O$, *J* 5.7Hz). ^{13}C NMR spectrum, δ, ppm: 8.60 (5-CH_3), 10.7 (3-CH_3), 48.6 ($PzCH_2CH_2O$), 70.2 ($PzCH_2CH_2O$), 122.4 (C^4), 128.4 (C^5), 139.2 (C^3). Found, %: C 57.24; H 8.10;

N 28.98. $C_{14}H_{24}N_6O$. Calculated, %: C 57.51; H 8.27; N 28.74.

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