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SHORT COMMUNICATIONS

The potential of employing substituted bis[3-hydroxy-2-(pyrimidin-2-yl)-2*H*-pyrazol-4-yl]methane for the synthesis of symmetrical N,O-macroheterocycles with a dioxacycloalkane central fragment

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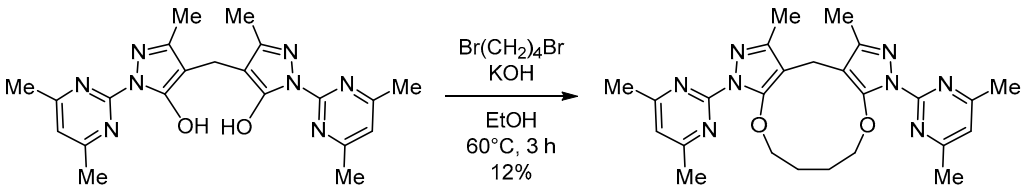


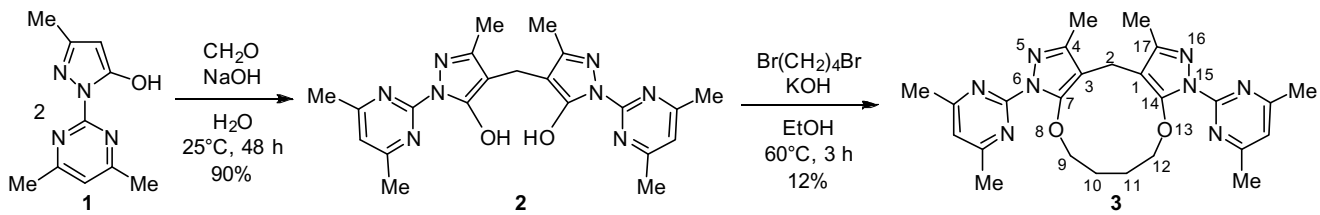
O-cyclialkylation of substituted bis[3-hydroxy-2-(pyrimidin-2-yl)-2*H*-pyrazol-4-yl]methane by α,ω-dibromoalkanes with a hydrocarbon chain length of up to three CH_2 groups has been carried out. A novel pyrazolophane, 1,6-dioxacycloundecane with symmetrically annulated fragments of 1-(pyrimidin-2-yl)-1*H*-pyrazole, was isolated and characterized as a result of this reaction. The precursor bridged heterocycle was obtained by condensation of the corresponding 2-(pyrimidin-2-yl)-2*H*-pyrazol-3-ol with formaldehyde in a 2:1 molar ratio.

Keywords: bis[3-hydroxy-2-(pyrimidin-2-yl)-2*H*-pyrazol-4-yl]methane, α,ω-dibromoalkanes, formaldehyde, pyrazolophane, 2-(pyrimidin-2-yl)-2*H*-pyrazol-3-ol, condensation, *O*-cyclialkylation.

Despite the fact that bis(3-hydroxy-2*H*-pyrazol-4-yl)-methane derivatives attract attention with the simplicity of preparation and a wide spectrum of biological activity,[1] methods of modifying their structure are very few, and *O*-cyclialkylation is not one of them. At the same time, this reaction is of particular interest from the point of view of expanding the number of known pyrazolophanes, which until now have been obtained by cyclocondensation of hydrazines with cycloalken-2-ones[2] and cycloaddition of nitrilimines to terminal multiple C–C bonds.[3] As representatives of macroheterocycles containing (poly)-ether fragments,[4,5] pyrazolophanes derived from bis-(3-hydroxy-2*H*-pyrazol-4-yl)methanes may be suitable compounds for the creation of new complexing agents, supramolecular assemblies, and molecular recognition elements.[6]

The objectives of this work were to carry out condensation of hydroxypyrazole **1** with formaldehyde in a molar ratio of 2:1 and to estimate the possibility of *O*-cyclialkylation of the product of this reaction (compound **2**) with α,ω-dibromoalkanes with a hydrocarbon chain length of up to three CH_2 groups.

Scheme 1



To obtain bispyrazolylmethane **2**, we carried out the condensation of compound **1** with formaldehyde in the indicated molar ratio in a 5% aqueous solution of NaOH at 25°C (Scheme 1). The presence of the base in the reaction mixture caused the ionization of substrate **1** and thereby increased its nucleophilicity.

It can be inferred from the IR spectrum that bispyrazolylmethane **2** exists as a monolactam, at least in the crystalline state. This is indicated by the proximity of the band in the 1655–1651 cm^{-1} region to the $\nu_{C=O}$ band of 1,5-dimethyl-2-(4,6-dimethylpyrimidin-2-yl)-1,2-dihydro-3*H*-pyrazol-3-one (1659 cm^{-1}).[7] In combination with a low intensity band at 2691 cm^{-1}, the observed band splitting in the 1655–1651 cm^{-1} region of the spectrum indicates the possibility of the participation of the C=O group in the formation of various[8] intramolecular hydrogen bonds.

Of the α,ω-dibromoalkanes used, only 1,4-dibromobutane gave the *O*-cyclialkylation product of compound **2**, pyrazolophane **3**, with a yield of 12% by heating the reagent mixture in EtOH in the presence of KOH at 60°C. The remaining α,ω-dibromoalkanes showed different reactivity under these conditions. 1,2-Dibromoethane did not react with compound **2**. After removal of the solvent, the crystalline residue (presumably the dipotassium salt of the substrate) was easily dissolved in water, and when neutralized with AcOH, the starting bispyrazolylmethane **2** was recovered out of this solution. The result of the reaction of 1,6-dibromohexane with compound **2** was the formation of a rubber-like mixture of substances (according to TLC), which could not be crystallized. The results of experiments employing α,ω-dibromoalkanes with $(CH_2)_4$ and $(CH_2)_6$ lead to the conclusion that the cyclization of the presumed intermediates of the reaction, mono-ω-bromoalkyl ethers of bispyrazolylmethane **2**, becomes possible only when the length of the alkyl chain is comparable to the distance between the oxygen atoms of the substrate. A similar conclusion was made by other researchers,[9] who investigated the *O*-cyclialkylation of 2,2'-(1,3,4-oxadiazole-2,5-diyl)diphenol with various α,ω-dihaloalkanes. It should also be noted that the yield of compound **3** turned out to be extremely dependent on the reaction temperature; when it was reduced to 50°C, the product yield decreased almost by half.

Attempts to increase the yield of pyrazolophane **3** by varying the conditions of *O*-cyclialkylation of compound **2** did not lead to the desired result. After heating the heterogeneous mixture of bispyrazolylmethane **2**, 1,4-dibromobutane, K_2CO_3, and MeCN under reflux for 5 h, an a very small amount of compound **3** (less than 5%) was isolated. It is noteworthy that previously[10] the K_2CO_3–MeCN system was considered as a two-phase system of the solid-liquid type and was employed for *O*-alkylation, including with α,ω-dihaloalkanes, of 2*H*-pyrazol-3-ols in the presence of a phase-transfer catalyst tetrabutylammonium bromide.

We achieved the indicated yield (12%) of pyrazolophane **3** by *O*-cyclialkylation of the previously obtained dipotassium salt of compound **2** in the cation-solvating DMF at 60°C. In this case, however, the target product, which was difficult to purify from colored impurities, was characterized by a lowered melting point (219–223°C (decomp.)), and its ^{1}H NMR spectrum contained unidentifiable upfield signals (1.90–2.40 ppm). *O*-Cyclialkylation of bispyrazolylmethane **2** by stirring in a two-phase system of 5% aqueous KOH–$CHCl_3$ in the presence of tetrabutylammonium bromide (3 mol %) at 25°C for 24 h did not yield the desired results, as well. At the end of the indicated time period, we recovered about 73% of unchanged compound **2** from the aqueous layer. Evaporation of $CHCl_3$ gave a small amount of dark oil, the R_f value of which (0.57, eluent *n*-BuOH–AcOH–H_2O, 1:1:1) differed from the same parameter of pyrazolophane **3**. The absence of the target compound in the organic layer is probably due to the fact that the expected ion pair was either not formed at all or its extraction into the organic layer did not occur.

The structure of pyrazolophane **3** was confirmed by the spectral data set. The ^{1}H NMR spectrum contains the characteristic signals of the protons of the CH_2 group (the singlet at 3.51 ppm) and the unsplit signals of the protons of the butane-1,4-diyl fragment, the singlets at 2.02 and 4.36 ppm. Due to the formal symmetry of compound **3**, its ^{13}C NMR spectrum contains 11 signals, of which those appearing at 27.58 and 75.94 ppm can be assigned to C-2 and C-9(12) atoms, respectively. The absence of the absorption bands at 3422 and 2691 cm^{-1} (OH and NH groups and the H-bonded OH group, respectively), as well as the $\nu_{C=O}$ bands in the 1655-1651 cm^{-1} region in the IR spectrum, characteristic of the starting bispyrazolylmethane **2**, is an evidence of *O*-cyclialkylation of the latter. The high-resolution mass spectrum of pyrazolophane **3** is characterized by the presence of the monoprotonated $[M+H]^+$ molecular peak.

For final confirmation of the structure of compound **3**, we carried X-ray structural analysis of single crystals isolated by slow evaporation of its solution in MeCN (Fig. 1). It was established that their structural unit is a crystallographically nonequivalent molecule of pyrazolophane **3** ($C_{25}H_{30}N_8O_2$, *M* 474.57); a multitude of these molecules are combined into zigzag chains. In the crystal lattice, these chains are oriented along one axis, located at a distance of ~3.3 Å from each other, and are maintained by π-electron and van der Waals interactions.

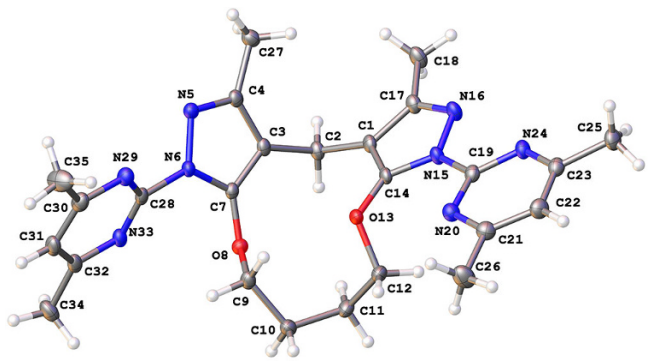


Figure 1. Molecular structure of compound **3** with atoms represented as thermal vibration ellipsoids of 50% probability.

Thus, *O*-cyclialkylation of substituted bis[3-hydroxy-2-(pyrimidin-2-yl)-2*H*-pyrazol-4-yl]methane with α,ω-dibromoalkanes with a hydrocarbon chain length of up to three CH_2 groups is not general; under the employed conditions, only a derivative of 1,6-dioxacycloundecane with symmetrically annulated fragments of 1-(pyrimidin-2-yl)-1*H*-pyrazole can be obtained using this reaction.

Experimental

IR spectra were registered on a Shimadzu FTIR-8400S spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance III spectrometer (400 and 100 MHz, respectively) in $CDCl_3$; chemical shifts were assigned relative to the signal of the solvent $CDCl_3$ (7.25 ppm of ^{1}H and 77.2 ppm for ^{13}C). High-resolution mass spectrum was recorded on a Bruker MaXis quadrupole time-of-flight mass spectrometer in the positive electrospray ionization mode (ionization chamber temperature 180°C, capillary voltage 4500 V). Elemental analysis was performed on a Leco CHNS-932 Elemental analyzer. Purity of synthesized compounds was controlled by TLC on Silufol UV-254 plates, eluent *n*-BuOH–AcOH–H_2O, 1:1:1, visualization under UV light at 254 nm.

The solvents (EtOH, MeCN, and DMF) were absolutized according to well-known routines.[11] Hydroxypyrazole **1** was obtained starting with 2-hydrazino-4,6-dimethylpyrimidine by cyclization of the intermediate ethyl 3-[(4,6-dimethylpyrimidin-2-yl)hydrazino]butanoate according to a literature method.[12]

Bis[3-hydroxy-2-(4,6-dimethylpyrimidin-2-yl)-5-methyl-2*H*-pyrazol-4-yl]methane (2). Formaldehyde (0.11 g, as 0.28 g of formalin, 3.7 mmol) was added in one batch to a solution of hydroxypyrazole **1** (1.5 g, 7.4 mmol) in aqueous NaOH (28 ml H_2O, 1.5 g NaOH). The mixture was stirred at room temperature until the smell of formaldehyde disappeared (about 48 h). Upon completion of stirring, the mixture was neutralized with AcOH. The formed suspension was diluted with H_2O (10 ml), and the residue was filtered. After washing with H_2O, this was recrystallized from EtOH and dried at 70°C to constant mass. Yield 1.40 g (90%), colorless wool-like crystals, mp 235–238°C, R_f 0.52. IR spectrum, ν, cm^{-1}: 3422 (O−H, N−H), 2691 (O−H), 1655 (C=O), 1651 (C=O), 1599 (C=N), 1555 (C=C). ^{1}H NMR spectrum, δ, ppm: 2.25 (6H, s, $2CH_3$); 2.54 (12H, s, $4CH_3$); 3.43 (2H, s, CH_2); 6.85 (2H, s, 2CH); 12.31 (2H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 13.3; 14.1; 24.0; 98.7; 116.2; 152.9; 153.2; 156.9; 168.5. Found, %: C 54.71; H 5.87; N 24.53. $C_{21}H_{24}N_8O_2 \cdot 2H_2O$. Calculated, %: C 55.26; H 6.14; N 24.56.

6,15-Di(4,6-dimethylpyrimidin-2-yl)-4,17-dimethyl-8,13-dioxa-5,6,15,16-tetraazatricyclo[12.3.0.0^{3,7}]heptadeca-1(14),3(7),4,16-tetraene (3). Bis(pyrazolyl)methane **2** (0.80 g, 1.9 mmol) and 1,4-dibromobutane (0.41 g, 1.9 mmol) were consecutively added to a solution of KOH (0.21 g, 3.8 mmol) in EtOH (20 ml). The mixture was heated to 60°C and kept at this temperature until the color of the mixture changed (about 3 h). After cooling, a suspension formed, which was filtered, and the filtrate was evaporated under reduced pressure to dryness. The residue was triturated with H_2O (10 ml), the precipitate was filtered off, and recrystallized from H_2O–EtOH, 2:1 mixture. The product was washed with water and dried at 70°C to constant mass. Yield 110 mg (12%), colorless powder, mp > 230°C (decomp.), R_f 0.65. IR spectrum, ν, cm^{-1}: 1606 (C=N), 1593 (C=C). ^{1}H NMR spectrum, δ, ppm: 2.02 (4H, s, 10,11-CH_2); 2.30 (6H, s, $2CH_3$); 2.53 (12H, s, $4CH_3$); 3.51 (2H, s, CH_2); 4.36 (4H, s, 9,12-CH_2); 6.88 (2H, s, 2CH). ^{13}C NMR spectrum, δ, ppm: 13.5; 15.7; 24.2; 27.6; 75.9; 107.2; 117.1; 149.9; 152.8; 156.0; 168.7. Found, *m*/*z*: 475.2582 $[M+H]^+$. $C_{25}H_{30}N_8O_2$. Calculated, *m*/*z*: 475.2564.

X-ray structural analysis of compound 3 was performed on a Rigaku Oxford Diffraction SuperNova XtaLAB diffractometer, equipped with a HyPix-3000 two-dimensional semiconductor detector. Measurements were done at 100 K using microfocused monochromatic CuKα radiation. Unit cell parameters (triclinic singony; spatial symmetry group *P*1; *a* 9.1002(2), *b* 11.3466(2), *c* 12.4224(3) Å; α 70.6779(19), β 86.4910(18), γ 83.3558(17)°; *V* 1201.96(5) Å^3; *Z* 2) were refined by the least-squares technique on the basis of 46830 reflections with 2θ within 7.54–140.00°. The data were integrated accounting for the Lorentz factor and polarization effects in the CrysAlisPro software package.[13] Absorption correction was introduced empirically in CrysAlisPro using spherical harmonics implemented in the SCALE3 ABSPACK scaling algorithm. The structure was solved with the direct method and refined to the final R_1 of 0.035 (wR_2 0.089) for 4256 independent reflections with $|F_o| \geq 4\sigma_F$ using the program SHELX[14,15] built into the OLEX2 complex.[16] The positions of hydrogen atoms were calculated by the algorithms incorporated in the SHELX software package, where U_{iso}(H) was set as $1.5U_{eq}$(C), and the length of C–H bond set at 0.96 Å for CH_3 groups; U_{iso}(H) was set as $1.2U_{eq}$(C), and the length of C–H bond set at 0.97 Å for CH_2 groups; U_{iso}(H) was set as $1.2U_{eq}$(C), and the length of C–H bond set at 0.93 Å for CH groups. The full set of X-ray structural data for compound **3** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1852466).

*X-ray structural analysis of single crystals of pyrazolophane **3** was performed at the resource center "X-ray diffraction research methods" of the Saint Petersburg State University.*

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