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Synthesis and structure of pyrimidinophanes with a sulfur atom in the spacer

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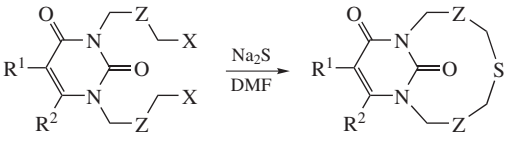
The cyclization of 1,3-bis(ω-bromoalkyl)uracils with sodium sulfide led to pyrimidinophanes, containing one uracil unit and an S atom in the spacer, macrocyclic structure was confirmed by X-ray data; the S atom in bridge can be oxidized into sulfoxide or sulfone or converted into sulfonium ion.

We consider pyrimidine-containing macrocycles – pyrimidinophanes – to be promising compounds, which are of interest as biologically active compounds,[1] as compounds capable of self-organization in solution,[2] and as ligands capable of forming complexes with both metal ions[3(a)–(d)] and organic substrates.[3(e)–(g)] Introduction of a heteroatom (such as the N atom) into the structure of a pyrimidinophane is an effective way to enhance complexation ability[3(d),(e)] and to enable further functionalization, *e.g.*, quaternization of N atoms in bridges with alkyl bromides. Thus, a series of amphiphilic pyrimidinophanes with onium groups in bridges was obtained, which possess antimicrobial[1(a)] and cholinolytic[1(d)] activity and are capable of forming aggregates used as nanoreactors,[2] in water solutions.

1,3-Bis(ω-bromoalkyl)uracils were used as starting compounds in the synthesis of pyrimidinophanes with N atoms in bridges, their reactions with amines led to pyrimidinophanes, containing one[4] or two uracil units.[1(a),2] One can expect the formation of macrocycles containing S atoms in bridges, if the cyclization is performed using Na_2S instead of amines. In our opinion, such pyrimidinophanes, as well as previously obtained pyrimidinophanes with N atoms, are promising ligands and biologically active compounds. This work deals with the synthesis and properties of pyrimidinophanes with S atoms in polymethylene chains.

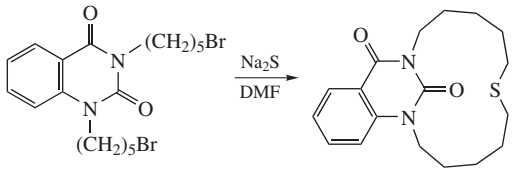
Initial 1,3-bis(ω-halogenoalkyl)-5,6-substituted uracils **1** were obtained according to established routines.[1(a),4] Reactions of dihalides **1** with Na_2S in DMF at 100–110 °C afforded a series of pyrimidinophanes **2**† containing various numbers of methylene groups or ethoxyethyl fragments (Scheme 1). This synthetic approach allows one to vary uracil derivatives, in particular, pyrimidine derivatives with the fused aromatic system can be used in the cyclization reactions. Thus, reaction of 1,3-bis(5-bromo-



1 **2**

a R^1 = H, R^2 = Me, Z = CH_2OCH_2, X = Cl (28%)
b R^1 = H, R^2 = Me, Z = $(CH_2)_4$, X = Br (24%)
c R^1 = $C_{10}H_{21}$, R^2 = Me, Z = $(CH_2)_4$, X = Br (19%)
d R^1 = NO_2, R^2 = H, Z = $(CH_2)_3$, X = Br (13%)

Scheme 1



3 **4** (38%)

Scheme 2

pentyl)quinazoline-2,4-dione **3** with Na_2S afforded the macrocycle **4** (Scheme 2). The yields of macrocycles in these reactions (up to 40%) are significantly higher than those of pyrimidinophanes obtained by the cyclization of 1,3-bis(ω-bromoalkyl)-uracils with amines.[4]

The structure and purity of the synthesized compounds were confirmed using a variety of methods (HRMS, IR and NMR spectroscopy), the structure of compound **4** was additionally confirmed by X-ray analysis‡ (Figure 1). Note that the torsion angles in the decamethylene bridge of pyrimidinophane **4** deviate significantly from 180°, and thus the polymethylene chain 'hangs over' the quinazoline unit. Such a shape of pyrimidinophane **4** is very much alike the 'bent' geometry of pyrimidinophanes with the $–(CH_2)_5N(CH_2)_5–$ bridge.[4(a)]

Reactions of compounds **1** with Na_2S lead to complex mixtures of products: besides the target pyrimidinophanes, which are only minor products, a large amount of oligomers is formed. Although these reactions can lead to macrocyclic products

† *Pyrimidinophanes with one uracil unit and a sulfur atom in spacer.* Catalytic amounts of $[NBu_4]HSO_4$ and a suspension of 8.5 mmol of Na_2S in DMF were added to a solution of 6.5 mmol of 1,3-bis(ω-bromoalkyl)-uracil or quinazoline-2,4-dione in DMF at 60 °C. Stirring was continued at 100–110 °C until the consumption of the starting materials (monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified using column chromatography (SiO_2, EtOAc–light petroleum, 1:1) to afford the product.

2a: mp 98–102 °C. HRMS (EI), *m/z*: 300.1141 [M+] ($C_{13}H_{20}N_2O_4S$ requires 300.11438).

2b: mp 85.5–86.5 °C. HRMS (EI), *m/z*: 324.1869 [M+] ($C_{17}H_{28}N_2O_2S$ requires 324.1872).

2c: mp 60–61 °C. HRMS (EI), *m/z*: 464.3432 [M+] ($C_{27}H_{48}N_2O_2S$ requires 464.34366).

2d: mp 118–121 °C. MS (MALDI-TOF), *m/z*: 327 [M+] ($C_{14}H_{21}N_3O_4S$ requires 327).

4: mp 106–107 °C. HRMS (EI), *m/z*: 332.1560 [M+] ($C_{18}H_{24}N_2O_2S$ requires 332.1558).

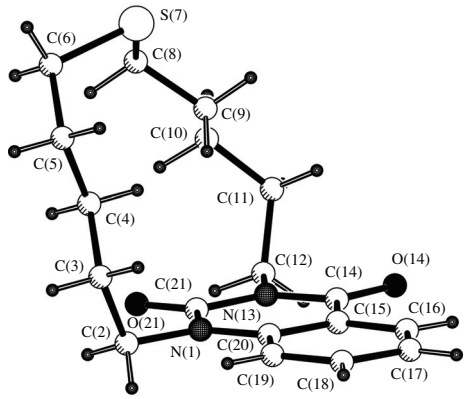
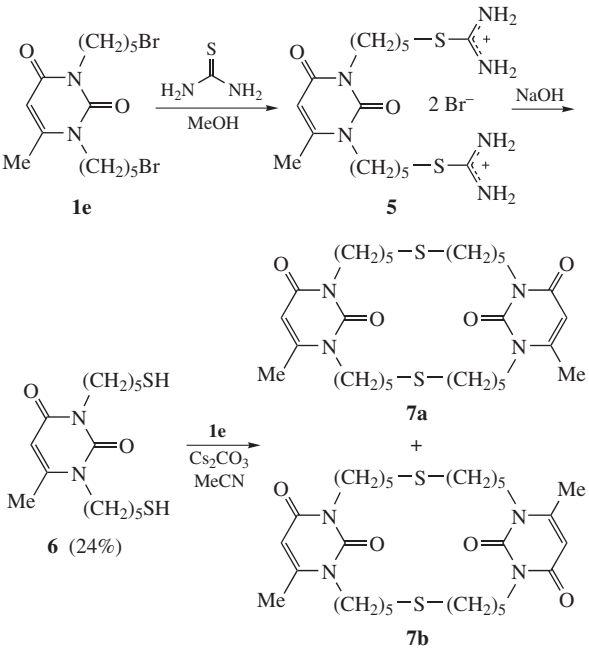


Figure 1 Molecular structure of independent molecule A of compound **4**. Selected torsion angles for molecule A (molecule B) (°): C(21)–N(1)–C(2)–C(3) 100.6(4) [–103.1(4)], N(1)–C(2)–C(3)–C(4) –59.6(4) [61.1(5)], C(2)–C(3)–C(4)–C(5) –179.4(4) [62.2(5)], C(3)–C(4)–C(5)–C(6) 179.8(4) [165.0(4)], C(4)–C(5)–C(6)–S(7) 65.7(5) [50.8(5)], C(5)–C(6)–S(7)–C(8) –96.0(3) [89.3(3)], C(6)–S(7)–C(8)–C(9) 119.5(4) [–81.6(4)], S(7)– C(8)–C(9)–C(10) 178.4(4) [–54.7(5)], C(8)–C(9)–C(10)–C(11) 177.2(4) [–164.4(4)], C(9)–C(10)–C(11)–C(12) –86.2(5) [–65.1(5)], C(10)–C(11)–C(12)–N(13) 71.9(5) [–64.1(5)], C(11)–C(12)–N(13)–C(14) 79.7(4) [–80.8(5)].

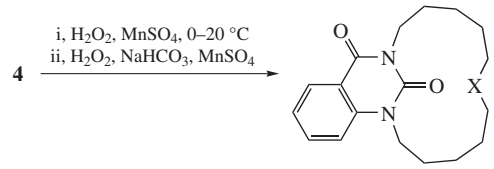
containing several uracil units, only pyrimidinophanes with one uracil moiety were detected in the mass spectra of the reaction mixtures. We applied another strategy for the synthesis of



Scheme 3

‡ *Crystallographic data for* **4** *at* 20 °C: $C_{18}H_{24}N_2O_2S$, triclinic, crystal size 0.5×0.2×0.1 mm, space group $P\bar{1}$, $a = 9.704(3)$, $b = 9.881(3)$ and $c = 20.023(8)$ Å, $\alpha = 87.26(3)°$, $\beta = 84.56(3)°$, $\gamma = 62.34(3)°$, $V = 1692.8(10)$ Å^3, $Z = 4$ (two independent molecules), $d_{calc} = 1.304$ g cm^{-3}, μ(CuKα) = 1.786 mm^{-1}, $F(000) = 712$. The intensities of 7243 reflections were measured on an Enraf-Nonius CAD-4 diffractometer at 20 °C (CuKα radiation, $\omega/2\theta$ scan, $4.44° < \theta < 74.22°$), and 6829 independent reflections were used in further calculations and refinement. The structure was solved by a direct method and refined using the full-matrix least-squares method against F^2 in the isotropic–anisotropic approximation. The refinement is converged to $wR_2 = 0.2030$ and GOF = 1.029 for all independent reflections [$R_1 = 0.0622$ is calculated against F for 4045 observed reflections with $I > 2\sigma(I)$]. The number of refined parameters is 415. All the calculations were performed using the SHELXS and SHELXL93 programs.

CCDC 694559 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2010.



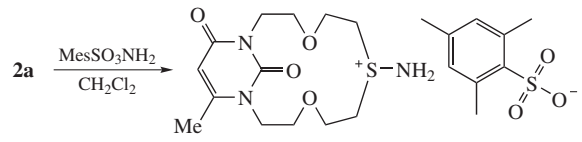
8a X = SO (i, 77%)
8b X = SO_2 (ii, 46%)

Scheme 4

pyrimidinophanes containing two uracil units. First, thiuronium salt **5** was obtained by the reaction of 1,3-bis(5-bromopentyl)-6-methyluracil **1e** with thiourea, which was subsequently decomposed with water alkali to give compound **6**. Then, dithiol **6** was reacted with initial dibromide **1e** in MeCN in the presence of Cs_2CO_3, this reaction afforded isomeric pyrimidinophanes **7a** and **7b** with different mutual arrangements of carbonyl groups C(4)=O at pyrimidine units (*cis* and *trans* arrangements, respectively)§ (Scheme 3). We did not succeed in isolating macrocycles **7a** and **7b**, and they were further used and characterized as a mixture of isomers.

Sulfur atoms in the bridges of the synthesized pyrimidinophanes can be modified in different ways; *e.g.*, they can be oxidized or converted into the sulfonium group. Thus, the oxidation of macrocycles with hydrogen peroxide affords sulfoxide **8a** or sulfone **8b** depending on the reaction conditions[5] (Scheme 4).¶ Amination of the S atom in pyrimidinophane **2a** utilizing *O*-mesitylenesulfonylhydroxylamine[6] in CH_2Cl_2 led to macrocyclic salt **9**, which decomposed to initial sulfide **2a** on attempt to convert it to sulfimine using DBU (Scheme 5).

Pyrimidinophanes with S atoms in bridges do not react with alkyl halides, though we obtained macrocycles **10** and **11** with the sulfonium group in the bridge†† by reaction of pyrimidinophanes **2b**,**c** and **4** with methyl and nonyl esters of *p*-toluene-



9 (79%)

Scheme 5

§ To the solution of dibromide **1e** (4.72 mmol) in 60 ml of methanol, thiourea (9.44 mmol) was added. Reaction mixture was refluxed for 25 h, the solvent was removed and diethyl ether was added. The precipitate of the thiuronium salt **5** was separated and the solution of 0.57 g of NaOH (14.16 mmol) in 50 ml of water was added. Reaction mixture was stirred for 2 h at 50 °C, acidified with HCl until pH < 7 and extracted with dichloromethane. The solvent was removed under reduced pressure, and the residue was purified using column chromatography (SiO_2, EtOAc–light petroleum, 2:1) to afford the product **6**. Cs_2CO_3 (3.39 mmol) and a catalytic amount of $[NBu_4]HSO_4$ were added to the solution of dibromide **1e** (1.13 mmol) and dithiol **6** (1.12 mmol) in MeCN. The reaction mixture was stirred at 70–75 °C for 14 h. After cooling to room temperature the solvent was removed under reduced pressure, and the residue was purified using column chromatography (SiO_2, EtOAc–methanol, 20:1) to yield the mixture of pyrimidinophanes **7a**,**b**.

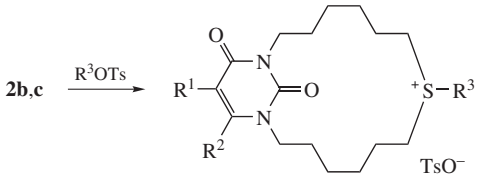
6: oil. Found (%): C, 54.33; H, 7.88; N, 8.61; S, 19.54. Calc. for $C_{15}H_{26}N_2O_2S_2$ (%): C, 54.51; H, 7.93; N, 8.48; S, 19.40.

7a,**b**: mp 60–90 °C. HRMS (EI), *m*/*z*: 592.3100 [M$^+$] ($C_{30}H_{48}N_4S_2O_4$ requires 592.3117).

¶ **8a**: mp 215 °C. HRMS (EI), *m*/*z*: 348.1500 [M$^+$] ($C_{18}H_{24}N_2O_3S$ requires 348.1508).

8b: mp 188–189 °C. HRMS (EI), *m*/*z*: 364.1441 [M$^+$] ($C_{18}H_{24}N_2O_4S$ requires 364.1452).

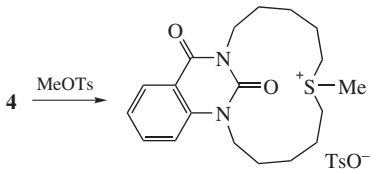
9: oil. Found (%): C, 51.06; H, 6.59; N, 7.93; S, 12.18. Calc. for $C_{22}H_{33}N_3O_7S_2$ (%): C, 51.24; H, 6.45; N, 8.15; S, 12.44.



10a $R^1 = H$, $R^2 = R^3 = Me$ (85%)
10b $R^1 = C_{10}H_{21}$, $R^2 = R^3 = Me$ (89%)
10c $R^1 = C_{10}H_{21}$, $R^2 = Me$, $R^3 = C_9H_{19}$ (46%)

Scheme 6

sulfonic acid (Schemes 6 and 7). The nonyl ester was prepared by analogy with a known protocol of *p*-toluenesulfonic esters synthesis.[7]



11 (64%)

Scheme 7

The bacteriostatic and fungistatic activities of macrocyclic sulfides were *in vitro* tested towards a series of bacteria and fungi. Compound **10b** appeared to be the most potent towards gram-positive bacteria – the minimal inhibitory concentration towards *Staphylococcus aureus* is less than 1 μg cm^{-3}.

In conclusion, we showed that 1,3-bis(ω-halogenoalkyl)-5,6-substituted uracils and their derivatives are excellent starting compounds for the synthesis of pyrimidinophanes with heteroatoms (N, S) in bridges. The macrocycles can be further functionalized by different means, and it opens up possibilities for the controllable synthesis of compounds with the desired properties, in particular, biologically active compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2010.01.002.

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†† *Reactions of pyrimidinophanes with the esters of* p-*toluenesulfonic acid*. Pyrimidinophane was added to 4 g of methyl or nonyl ester of *p*-toluenesulfonic acid and the reaction mixture was stirred for 6 h at 80 °C. After cooling diethyl ether was added, the formed precipitate was separated, washed thrice with diethyl ether and dried *in vacuo*.

10a: oil. Found (%): C, 58.58; H, 7.34; N, 5.55; S, 12.77. Calc. for $C_{25}H_{38}N_2O_5S_2$ (%): C, 58.79; H, 7.50; N, 5.49; S, 12.56.

10b: oil. Found (%): C, 64.44, H, 9.06; N, 4.19; S, 10.01. Calc. for $C_{35}H_{58}N_2O_5S_2$ (%): C, 64.58; H, 8.98; N, 4.30; S, 9.85.

10c: oil. Found (%): C, 67.89; H, 9.54; N, 3.43; S, 8.69. Calc. for $C_{43}H_{74}N_2O_5S_2$ (%): C, 67.67; H, 9.77; N, 3.67; S, 8.40.

11: mp 210 °C. Found (%): C, 60.08; H, 6.53; N, 5.29; S, 12.48. Calc. for $C_{26}H_{34}N_2O_5S_2$ (%): C, 60.21; H, 6.61; N, 5.40; S, 12.36.

12: oil. Found (%): C, 64.21; H, 8.81; S, 10.88. Calc. for $C_{16}H_{26}O_3S$ (%): C, 64.39; H, 8.78; S, 10.74.