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Macrocyclic 5-bromouracil derivatives: synthesis and transformation of a uracil ring

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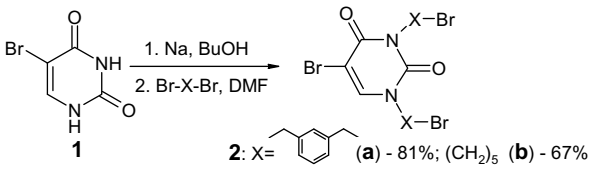
ABSTRACT

Cyclization of 1,3-bis(ω-bromoalkyl)-5-bromouracil with *p*-methoxybenzylamine or sodium sulfide led to a series of pyrimidinophanes containing heteroatoms in bridges. An unusual behaviour of the 5-bromouracil ring, namely its contraction into hydantoin units during the cyclization reactions with *p*-methoxybenzylamine was observed. Sodium sulfide does not affect the 5-bromouracil ring, and no transformation products were observed in the synthesis of pyrimidinophanes with sulfur bridges. A possible reaction mechanism is given.

There is a continuing interest in calixarenes as versatile hosts and candidates for synthetic receptors and enzymes.[1] Replacement of the carbon in the bridge with another element affects the conformational and complexation properties of calixarenes by changing the mode of the characteristic circular intramolecular hydrogen bonding. Besides, some of the heteroatoms can serve as additional coordination sites due to the presence of lone electron pairs and can undergo further modification easily. Different types of calixarene analogues with heteroatoms have been reported, such as homoazacalix[*n*]arenes with CH_2NRCH_2 bridges[2] homooxacalix[*n*]arenes with CH_2OCH_2 bridges,[3] and homothiacalix[*n*]arenes containing CH_2SCH_2 as linkages.[4] All these calixarene analogues have characteristics similar to those of calixarene. They also possess special properties due to the bridged substituents. Substitution of the phenol units with heterocyclic rings leads to the large group of heterocalixarenes,[5–7] which, depending on the nature of the heterocyclic moieties, encompass numerous new opportunities for π–π interactions with electron-rich and electron-deficient π-systems. Calixarene analogues, in which both structural elements (bridges and aromatic subunits) contain heteroatoms, have been reported.[7e]

Despite the significance of nucleotide bases, and in particular uracil and its derivatives towards complexation with H^+ and other biological cations,[8] investigations on uracil-based synthetic cyclic receptors are few.[9] However, some interesting results concerning cation extraction and transport properties of uracil-based calixarenes have been obtained.[6a,6b] We consider macrocycles with pyrimidine moieties, pyrimidinophanes, to be promising compounds, and recently we obtained data regarding biological activity[10] and structural features of pyrimidinophanes.[11] This work is a continuation of our interest in macrocyclic pyrimidine derivatives and deals mainly with our synthetic efforts towards uracil-based homocalixarene analogues, containing nitrogen and sulfur in bridges, and also closely related macrocycles with flexible $-(CH_2)_n$-chains which were synthesized to compare the properties of pyrimidinophanes with different bridges. As a result of our interest in further functionalization of the target compounds, we decided to use 5-bromouracil (**1**) as a uracil motif. It is known that the Br at C(5) of uracil can be easily substituted by nucleophiles and in particular amines.[12]

We consider 1,3-bis(ω-bromoalkyl)uracils to be excellent starting compounds for the synthesis of pyrimidinophanes with various structures.[13] Treatment of these compounds with amines leads to macrocycles with one uracil unit and a bridging N atom.[11a,11b] Using an established procedure, dibromides **2a** and **2b** were prepared in good yields by reaction of an 8-fold excess of (α,α′)-*m*-dibromoxylene or 1,5-dibromopentane with the disodium salt of **1** in DMF (Scheme 1).



Scheme 1.

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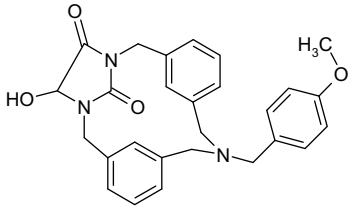
Cyclization of compound **2a** with *p*-methoxybenzylamine (**3**) in the presence of excess K_2CO_3 and catalytic amounts of NBu_4HSO_4 in BuOH afforded pyrimidinophane **4**, which was isolated by column chromatography in a yield of 4% (Scheme 2).

Further elution of the column gave a compound, the structure of which was assigned using a variety of methods (HRMS, NMR and IR spectroscopy). Surprisingly, the 5-bromouracil ring had contracted into the 5-hydroxyhydantoin moiety to form macrocycle **5** in a yield of 8%.

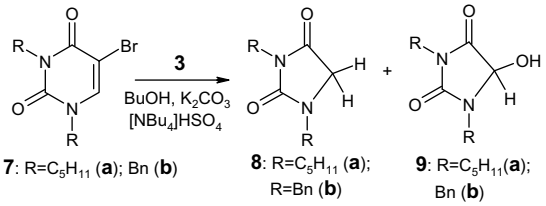


5

The macrocycles **4** and **5** can be considered as homocalix[3]arene analogues. Compound **2b** contains more flexible chains compared with **2a**. Cyclization of **2b** with amine **3** led to the expected pyrimidinophane 6 (Scheme 3) in a yield of 13%, and the mass spectrum of the reaction mixture showed the presence of trace amounts of the corresponding macrocycle with a 5-hydroxyhydantoin moiety.

Macrocycles **4**–**6** have the same spectral features as reported for pyrimidinophanes with similar structures prepared from 1,3-bis(5-bromopentyl)thymine or 1,3-bis(5-bromopentyl)-6-methyluracil and benzylamine.[11a,11b] In their ^{1}H NMR spectra, the geminal protons of the CH_2-groups at the N(1) and N(3) atoms of the heterocycle were observed as four doublets (macrocycles **4** and **5**) or four broadened multiplets (pyrimidinophane **6**) in δ 3.20–5.70 region. This results from the folded conformation and slow exchange on the NMR time-scale.

Does the flexibility of the chains in compounds **2a** and **2b** influence the transformation of the 5-bromouracil ring? Does the transformation of the 5-bromouracil moiety occur after the formation of macrocycle **4** or is it an acyclic hydantoin derivative that is formed first and then affords macrocycle **5**? To elucidate the factors responsible for the observed transformation, the reactions of amine **3** with model compounds 1,3-bis(pentyl- and benzyl)-5-bromouracils **7a** and **7b** were studied. The conditions were identical to those for the cyclization of **2a**,**b** with **3**. The products of the reactions were not isolated, and the mass spectra of the reaction mixtures indicated formation of hydantoin derivatives **8a**,**b** and **9a**,**b** (Scheme 4).



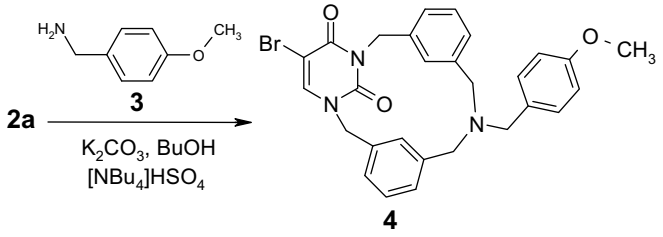
Scheme 4.

The molecular ions of hydantoins **8a** and **9a** (*m*/*z* 240, 256), and **8b** and **9b** (*m*/*z* 280, 296) were observed in the mass spectra of the reaction mixtures of **3** with **7a** or **7b**, respectively. However, the relative intensities of the ions were different. The peak for the molecular ion of **9a** was three times more intensive than that of **8a**, in contrast, the peaks of the molecular ions of **8b** and **9b** were of almost equal intensities. Thus, model alkyl derivatives of **1** were transformed into hydantoins in the reaction with amine **3**, and it seems that contraction of the 5-bromouracil moiety occurs in acyclic **2a**,**b** but not in pyrimidinophanes **4** and **6**. This conclusion was confirmed by reaction of pyrimidinophane **4** with amine **3** under the above conditions. The reaction afforded a series of products, and mass spectral analysis of the reaction mixture did not reveal any macrocyclic compounds except for traces of a pyrimidinophane which was formed by substitution of the Br in **4** with amine **3** (*m*/*z* = 588).

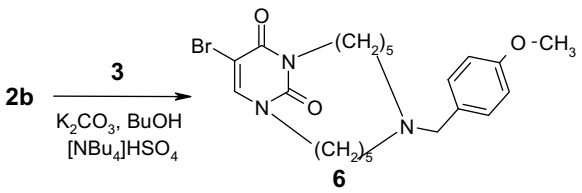
Cyclization of compounds **2a**,**b** with Na_2S led to pyrimidinophanes **10a**,**b** with bridging S atoms in yields of 8% and 29%, respectively (Scheme 5).

Similar to macrocycles **4** and **5**, pyrimidinophane 10a can also be considered as a homocalix[3]arene analogue. Homocalix[3]arenes are known to have a limited number of stable conformations,[14] and though the introduction of the uracil moiety makes conformational analysis more complicated, the calculated[15] possible conformation for pyrimidinophane **10a** appeared to be similar to homooxacalix[3]arenes. Contrary to the reactions with an amine, no traces of the 5-bromouracil transformation products were observed in the mass spectra of the reaction mixtures of **2a** or **2b** with Na_2S. The ^{1}H NMR spectra of homocalixarene analogues **4**, 5 and **10a** were almost the same, while broadening and coalescence of the resonances of the geminal protons of the CH_2-groups at N(1) and N(3) of the uracil ring was observed in the ^{1}H NMR spectrum of **10b** compared with **6**. Faster exchange in the solution of pyrimidinophane **10a** can be explained by the increasing flexibility of the bridge in **10a** due to the larger radius of the S atom compared with N.

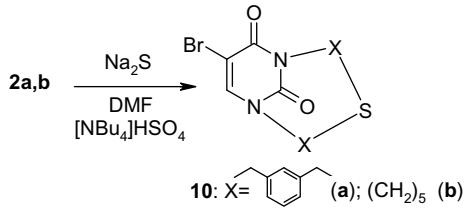
Several examples of similar transformations of 5-bromouracil derivatives have been reported.[16] In most cases, such transformations occur on exposure to strong oxidants (e.g., ozone[16b,16c]) or in alkaline solutions as a result of hydroxy anion attack.[16d–f] Assumed mechanisms are probably not realized herein, because



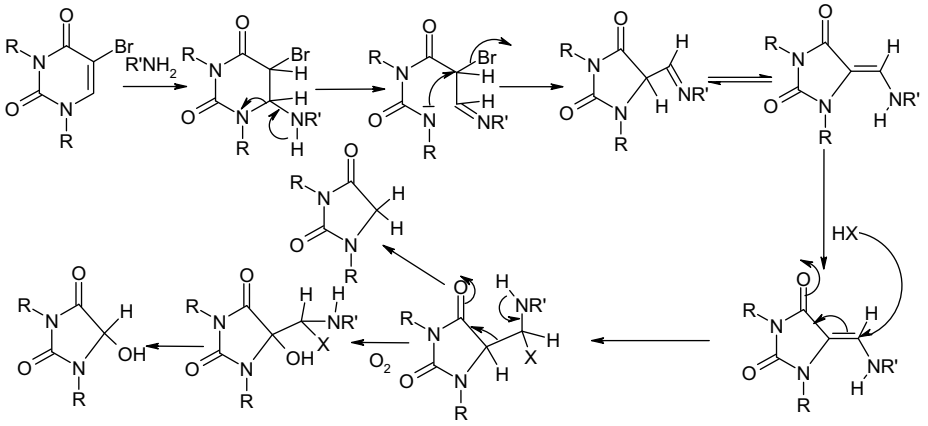
Scheme 2.



Scheme 3.



Scheme 5.



Scheme 6.

model compounds **7a**,**b** did not afford any transformation products in the absence of the amine. Thus, it is attack of the amine **3** that causes contraction of the 5-bromouracil moiety. It is possible that the reaction proceeds in the following way. First, addition of the amine **3** to the double bond of the uracil unit occurs with subsequent ring opening.[16a] Then, recyclization to the substituted hydantoin takes place and finally the substituent is removed. The proposed contraction mechanism is depicted in Scheme 6. In the case of benzyl substituents at N(1) and N(3), it seems that the ring contraction proceeds more easily. Oxidation of the anions proceeds smoothly involving oxygen, and 5-hydroxyhydantoin derivatives form with both benzyl and pentyl substituents. Neither compound **8a** nor compound **9a** was detected in the mass spectrum of the reaction mixture of model compound **7a** with amine **3** and K_2CO_3 after heating under an inert argon atmosphere (sealed tube, BuOH, 100 °C, 20 h).

In conclusion, a series of macrocycles containing a uracil moiety have been obtained by treatment of 1,3-bis(ω-bromoalkyl)-5-bromouracils with *p*-methoxybenzylamine or sodium sulfide. An unusual behaviour of the 5-bromouracil motif in these reactions was observed, namely its contraction into hydantoin five-membered ring, the macrocyclic structure is unaffected by these transformations. The transformation into hydantoin or hydroxyhydantoin units depends on the nature of the substituents on the uracil ring nitrogens.

General procedure for the synthesis of macrocycles with N bridges: To a solution of amine **3** (1.3 equiv) and K_2CO_3 (4 equiv) in *n*-BuOH, compounds 2a or **2b** and a catalytic amount of $[NBu_4]HSO_4$ were added at 90 °C, and the reaction mixture was stirred at 100–110 °C. The course of the reaction was followed by TLC and excess amine was added if necessary. The solvent was removed under reduced pressure and the residue was purified using chromatography (SiO_2) to afford the product.

General procedure for the synthesis of macrocycles with S bridges: A suspension of Na_2S (1.3 equiv) and a catalytic amount of $[NBu_4]HSO_4$ in DMF were added to a solution of compound **2a** or **2b** (1 equiv) in DMF at 60 °C. Stirring was continued at 90–100 °C until 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) to afford the product.

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Supplementary data

Synthetic routines, spectral and computational data are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.164.

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