Synthesis and structures of pyrimidinophanes containing a nitrogen atom in the bridge

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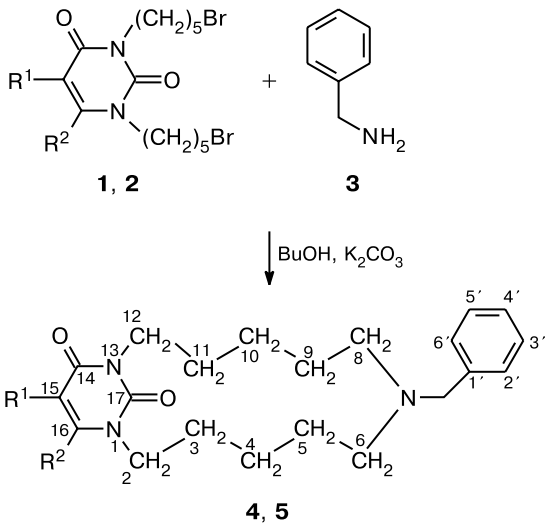
The reactions of 1,3-bis(5-bromopentyl)-5-methyl- or 1,3-bis(5-bromopentyl)-6-methyluracil with benzylamine afforded pyrimidinophanes containing the nitrogen atom in the polymethylene bridge. Single-crystal X-ray diffraction study and NMR and UV spectroscopic study in solution demonstrated that the phenyl and uracil fragments in the macrocycles are in spatial proximity. Unlike the known macrocycles containing the pyrimidine ring, the pyrimidinophanes under study are conformationally rigid.

Key words: macrocyclic compounds, pyrimidinophanes, conformation, X-ray diffraction study, NMR spectroscopy, hypochromic effect, dipole moment.

The chemistry of macrocyclic compounds containing pyrimidine rings, *viz.*, pyrimidinophanes, including their synthesis and investigations, is a rapidly developing field of chemistry of nucleotide bases.[1—4] Pyrimidinophanes are of interest as compounds simulating interactions between fragments involved in nucleic acids as well as interactions between nucleotide bases and proteins. In addition, macrocycles containing the pyrimidine ring hold promise as complex-forming agents and as compounds for studying various biological activities.

Earlier,[5] with the aim of investigating the complex-forming properties and biological activities of water-soluble pyrimidinophanes, we have synthesized macrocycles containing two 6-methyluracil fragments and nitrogen atoms in the bridges, *viz.*, 6,20-bis(ethylamino)[9,9](1,3)- and 7,23- bis(ethylamino)[11,11](1,3)-pyrimidinophanes, by the reactions of 1,3-bis(ethylaminoalkyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidines (1,3-bis(ethylaminoalkyl-6-methyluracils) with 1,3-bis(bromoalkyl)-6-methyluracils. We synthesized another type of macrocycles, *viz.*, 7-benzylamino[11](1,3)pyrimidinophanes **4** and **5**, by the reactions of 1,3-bis(bromopentyl)-6-methyluracil (**1**) or 1,3-bis(5-bromopentyl)-5-methyluracil (1,3-bis(5-bromopentyl)thymine) (**2**), respectively, with a two-to-three-fold excess of benzylamine (**3**) (Scheme 1). The yields of the macrocycles were at most 20%. We failed to prepare these pyrimidinophanes in higher yields by varying the reactions conditions (the use of different solvents, dilute solutions, or the addition of tetraalkylammonium salts or transition metal salts).

Scheme 1



R^1 = H (**1**, **4**), Me (**2**, **5**); R^2 = H (**2**, **5**), Me (**1**, **4**)

Macrocycles **4** and **5** are structural isomers, which differ in the arrangement of the methyl group at the uracil fragment, and are characterized by different mass spectra. In the mass spectrum of compound **4**, the intensity of the molecular ion is 42.8% of the maximum peak, whereas the intensity of the corresponding molecular ion in the mass spectrum of compound **5** is 94.1%. It is the arrangement of the CH_3 group that has the most destabilizing effect on the molecular ion $[M]^+$. In pyrimidinophane **4**, the intensity of the ion corresponding to the loss of the

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methyl group from the molecular ion is 80.7%; in compound **5**, only 4.8%. This result can be attributed to the influence of the $N(1)_{pyr}$ atom, which is responsible for the cleavage of the β-bond with respect to the N(1)—C(16) bond. In this case, the positive charge is localized on the nitrogen atom to form a conjugated bond system in the $[M - Me]^+$ ion.[6] The mass spectra of these compounds differ also in the intensity of the $[M - H]^+$ ion (5.4% for **4** and 41.5% for **5**). This difference could be expected from the above-considered data. A high probability of the loss of the Me group from $[M]^+$ in pyrimidinophane **4** leads to a sharp decrease in the probability of the competitive reaction of proton abstraction from $[M]^+$. The same situation was observed in the case of the loss of the Et group from $[M]^+$ as a result of the rearrangement in the pentamethylene bridges. It is the formation of a stable molecular ion that makes energetically less favorable processes (for example, the loss of the ethyl group from ions at m/z = 340 and 326 with an intensity of 8.7% for compound **4** and 33.1% for compound **5**) more probable, all other factors being the same. The ion at m/z 278 is formed as a result of the loss of the benzyl radical from $[M]^+$. This process is predictable,[7] and the high intensity of this ion in the mass spectrum of macrocycle **5** (94.9%) agrees well with the above-discussed features of the ion fragmentation for **4** and **5**. The formation of the most intense ion $[C_6H_5CH_2]^+$ (m/z 91) is accompanied by the cleavage of the β-bond with respect to the benzene ring (a weaker bond). The charge is delocalized with the involvement of the aromatic ring, which is followed by the rearrangement into the energetically more favorable tropylium ion.

Single crystals of pyrimidinophanes **4** and **5** were grown from DMSO. X-ray diffraction study demonstrated that the crystals contain no solvent molecules. There are two crystallographically independent molecules (A and B) in the crystal structure of pyrimidinophane **4**. The geometric parameters of these molecules are equal within experimental error, except for the signs of the corresponding torsion angles. (One of two independent molecules is shown in Fig. 1. The average geometric parameters are given in Table 1 and the further discussion.)

There is one molecule per asymmetric unit in the crystal structure of pyrimidinophane **5**. One of the atoms in the bridge, *viz.*, C(10), is disordered over two positions with approximately equal occupancies.

In the crystals, the molecules of pyrimidinophanes **4** and **5** (Figs 1 and 2; Table 1) adopt a folded C-shaped conformation with the phenyl and uracil fragments in close proximity. The conformations of pyrimidinophanes **4** and **5** can be quantitatively characterized by the mutual arrangement of the following three planes: the plane of the pyrimidine ring (1), the mean plane of the 14-membered heterocycle (2), and the plane of the benzene ring (3). The mutual arrangement of these fragments is shown in Fig. 3. The corresponding dihedral angles are

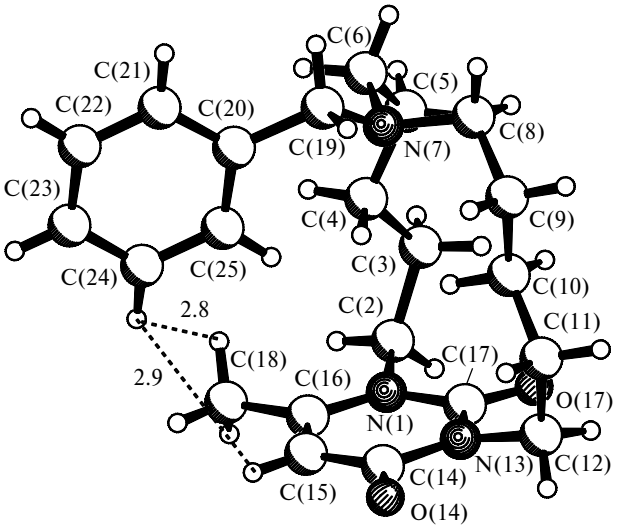

Fig. 1. Geometry of molecule B of pyrimidinophane **4** in the crystal. The shortest distances (Å) between the phenyl and uracil fragments are indicated by dashed lines.

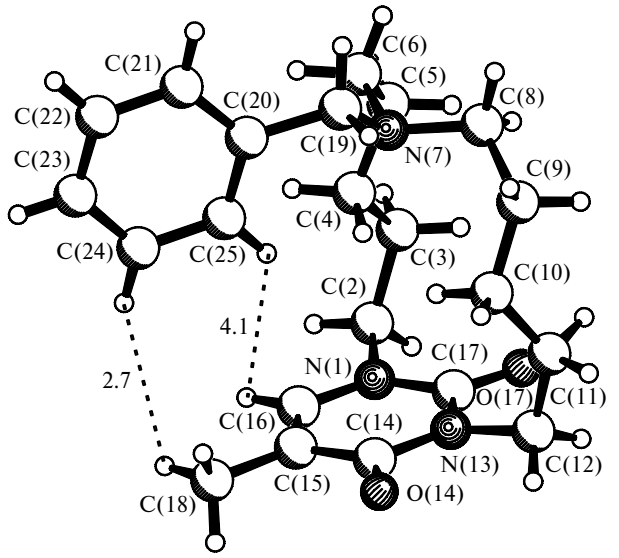

Fig. 2. Geometry of molecule **5** in the crystal. The disorder is omitted for simplicity. The shortest distances (Å) between the phenyl and uracil fragments are indicated by dashed lines.

listed in Table 2. It can be seen that the plane of the pyrimidine ring (1) is virtually orthogonal to both the plane of the benzene ring (3) and the mean plane of the 14-membered heterocycle (2). However, edge-to-face π—π interactions or C—H...π interactions cannot, apparently, occur between the pyrimidine and benzene rings, because these fragments are shifted with respect to each other. The distances between the centers of the rings are 5.8 and 6.0 Å in macrocycles **4** and **5**, respectively.[8,9]

The polymethylene bridge together with the nitrogen and carbon atoms of the pyrimidine ring and the nitrogen atom in the bridge form a 14-membered heterocycle. In

Table 1. Selected geometric parameters of pyrimidinophanes **4** and **5** (X-ray diffraction data)

Parameter	**4**	**5**
Bond length	*d*/Å	
O(14)—C(14)	1.220(5)	1.228(4)
O(17)—C(17)	1.222(5)	1.215(3)
N(1)—C(16)	1.384(5)	1.372(3)
N(1)—C(2)	1.473(5)	1.476(4)
N(1)—C(17)	1.395(5)	1.370(3)
N(7)—C(8)	1.465(5)	1.464(4)
N(7)—C(6)	1.465(6)	1.462(4)
N(7)—C(19)	1.451(6)	1.464(4)
N(13)—C(14)	1.402(5)	1.404(4)
N(13)—C(17)	1.375(5)	1.390(3)
N(13)—C(12)	1.464(5)	1.485(4)
C(2)—C(3)	1.515(6)	1.518(4)
C(3)—C(4)	1.520(5)	1.506(4)
C(4)—C(5)	1.527(5)	1.514(4)
C(5)—C(6)	1.520(6)	1.504(4)
C(8)—C(9)	1.528(6)	1.524(5)
C(11)—C(12)	1.509(5)	1.446(6)
C(14)—C(15)	1.428(6)	1.426(4)
C(15)—C(16)	1.344(5)	1.339(4)
C(16)—C(18)	1.493(6)	—
C(15)—C(18)	—	1.501(4)
C(19)—C(20)	1.503(6)	1.506(4)
Bond angle	ω/deg	
C(2)—N(1)—C(16)	123.6(3)	120.1(2)
C(2)—N(1)—C(17)	115.0(3)	117.2(2)
C(16)—N(1)—C(17)	121.0(3)	121.8(2)
C(6)—N(7)—C(8)	111.8(3)	112.6(2)
C(6)—N(7)—C(19)	111.6(3)	110.3(2)
C(8)—N(7)—C(19)	111.0(3)	110.3(2)
C(12)—N(13)—C(14)	118.5(3)	118.7(2)
C(12)—N(13)—C(17)	116.7(3)	116.3(2)
C(14)—N(13)—C(17)	124.3(3)	124.8(2)
O(14)—C(14)—N(13)	120.2(3)	119.5(3)
O(14)—C(14)—C(15)	125.3(4)	124.6(3)
N(13)—C(14)—C(15)	114.5(3)	115.9(2)
C(14)—C(15)—C(16)	122.5(4)	119.0(2)
N(1)—C(16)—C(15)	120.1(3)	123.0(2)
C(15)—C(16)—C(18)	121.0(4)	—
C(16)—C(15)—C(18)	—	122.0(3)
N(1)—C(16)—C(18)	118.9(3)	
C(14)—C(15)—C(18)	—	118.9(3)
O(17)—C1(7)—N(13)	122.5(3)	122.4(2)
O(17)—C1(7)—N(1)	120.3(4)	122.2(2)
N(7)—C(19)—C(20)	114.3(3)	113.3(3)
N(1)—C(2)—C(3)	113.6(3)	112.3(2)
C(2)—C(3)—C(4)	114.0(3)	114.5(3)
C(3)—C(4)—C(5)	113.3(4)	113.6(3)
C(4)—C(5)—C(6)	113.1(4)	114.2(2)
N(7)—C(6)—C(5)	112.4(3)	114.7(2)
N(7)—C(8)—C(9)	112.7(4)	113.8(3)
N(13)—C(12)—C(11)	112.1(3)	113.4(3)

the most developed projection, the conformation of the heterocycle has a figure-of-eight shape, and the shortest

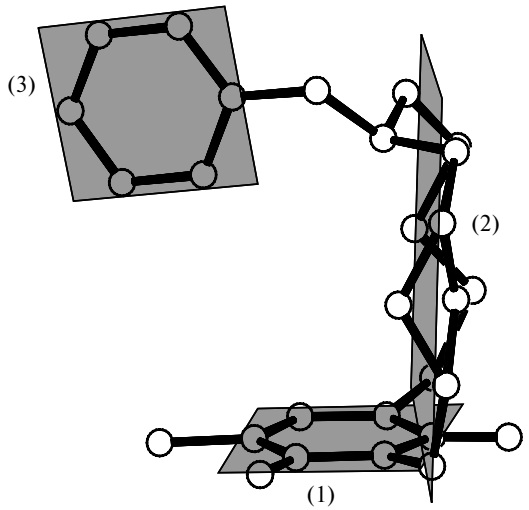

Fig. 3. Mutual arrangement of the fragments in pyrimidinophanes **4** and **5**.

Table 2. Interplanar angles in macrocycles **4** and **5** (X-ray diffraction data)

Planes	Dihedral angle/deg	
	4	**5**
(1), (2)	88.5	87.6
(1), (3)	86.7	88.7
(2), (3)	70.9	71.0

transannular C(4)...C(10) distance is 3.97 and 3.95 Å in pyrimidinophanes **4** and **5**, respectively (Fig. 4). This shape of the bridge is characterized by four C—H...N interactions between the intraannular hydrogen atoms at the C(4) and C(10) atoms, on the one hand, and the N(1) and N(13) atoms of the pyrimidine rings and the N(7) atom in the bridge, on the other hand. The parameters of the C—H...N interactions are given in Table 3.

It is of interest to analyze intermolecular interactions in the crystals of pyrimidinophanes **4** and **5**. The independent molecules A and B in macrocycle **4** are involved in different interactions with the adjacent molecules. The pyrimidine rings of molecules A related by the symmetry operation $[-x, 1-y, -z]$ are involved in rather strong[9,10]

Table 3. Parameters of intramolecular C—H...N interactions in pyrimidinophanes **4** and **5**

Fragment	*d*(H...N)/Å		∠C—H...N/deg	
	4	**5**	**4**	**5**
C(4)—H...N(1)	2.58	2.51	105	104
C(10)—H...N(7)	2.64	2.48	102	108
C(4)—H...N(7)	2.67	2.67	105	105
C(10)—H...N(13)	2.52	2.61	101	105

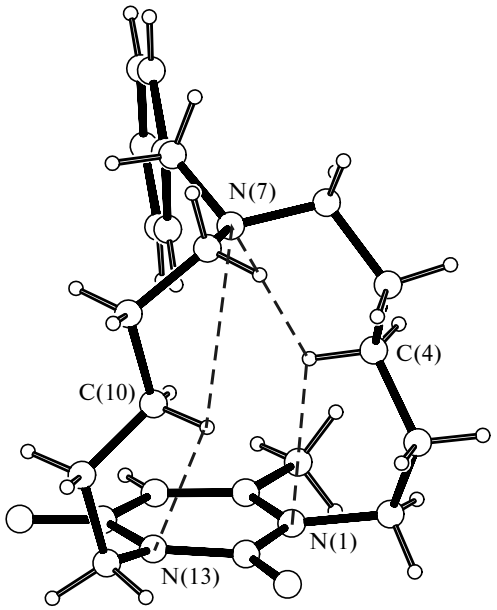

Fig. 4. Intramolecular C—H...N interactions in pyrimidinophanes **4** and **5**.

π—π interactions (the distance between the centers of the rings is 3.8 Å, the dihedral angle between the rings is 0°, and the distance between the planes of the rings is 3.39 Å). In the adjacent molecules B related by the symmetry operation $[1 - x, -y, -z]$, the pyrimidine rings are shifted with respect to each other, and the distance between their centers is 5.06 Å. There are C—H...O interactions between these rings involving the proton of the $C(18)H_3$ group and the O(17) atom (H(18B)...O(17B), 2.56 Å; C(18)—H(18B)...O(17B), 145.8°; Fig. 5). In the crystal structure, the aromatic systems of the thymine fragments of two adjacent molecules of pyrimidinophane **5** overlap to a greater degree than the aromatic systems of the 6-methyluracil fragments of molecules A in the crystal structure of pyrimidinophane **4**. The parameters of the π—π interactions of two molecules of macrocycle **5** related by a center of symmetry (the symmetry transformation $[1 - x, -y, 1 - z]$) are as follows: the distances between the centers of the rings are 3.4 Å, the dihedral angle between the rings is 0°, and the distance between the planes of the rings is 3.34 Å. On the whole, the molecules in the crystals of pyrimidinophanes **4** and **5** are packed in layers. The layers are linked to each other by π—π and C—H...O interactions.

The structures of the pyrimidinophanes in solution was studied by NMR spectroscopy. The full assignment of the signals in the ^1H and ^{13}C NMR spectra of compounds **4** and **5** in $CDCl_3$ was made based on the 2D COSY, 2D TOCSY, 2D HSQC, 2D HMBC,[11,12] and 1D ROESY experiments[13] at 303 and 263 K. The low temperature was used to increase the intensities of cross-peaks in the 2D HMBC spectra.

Let us consider the assignment of the signals in the ^1H and ^{13}C NMR spectra in detail using pyrimidinophane **4** as an example (Fig. 6). In the first step, the structures of the fragments starting from C(5)H for the 6-methyluracil fragment, from H(2) and H(12) for the aliphatic bridges, and from the CH_2 group for the benzyl fragment were determined using both 1D and 2D NMR experiments aimed at revealing correlations due to homo- and heteronuclear spin-spin coupling constants. In the next step, the fragments are combined based on 2D HMBC correlations.

Information on the presence of through two- or more-bond spin-spin coupling constants between the protons of

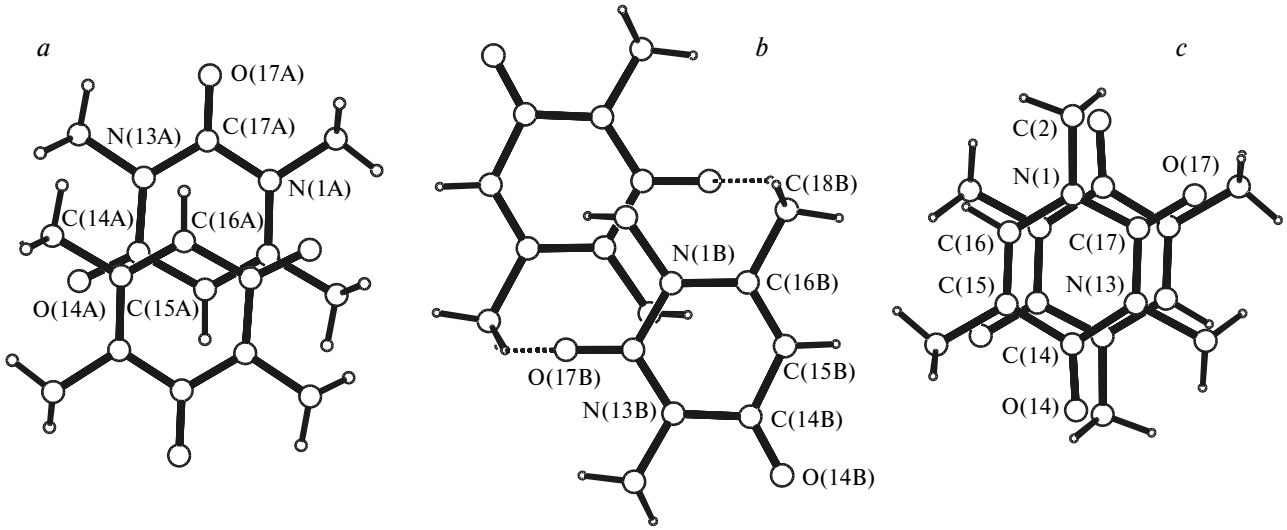

Fig. 5. Diagram of overlap of the pyrimidine rings in the adjacent independent molecules A of macrocycle **4** (*a*), independent molecules B of macrocycle **4** (*b*), and molecules of macrocycle **5** (*c*).

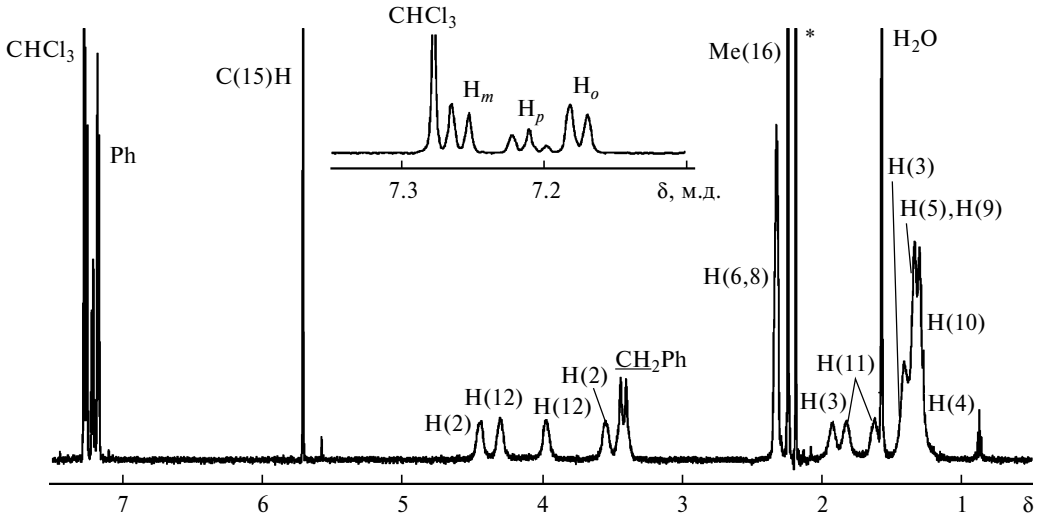

Fig. 6. ^{1}H NMR spectrum of macrocycle **4** in $CDCl_3$ at $T = 303$ K (the signals of an unidentified impurity in the solvent are marked with asterisks).

the macrocycle can be obtained from 2D TOCSY spectra. The proton-proton correlations found in the 2D COSY and 2D TOCSY spectra are shown in Fig. 7, *a*. The 2D HMBC correlations and the observed nuclear Overhauser effects (NOE) for macrocycle **4** are presented in Fig. 7, *b*.

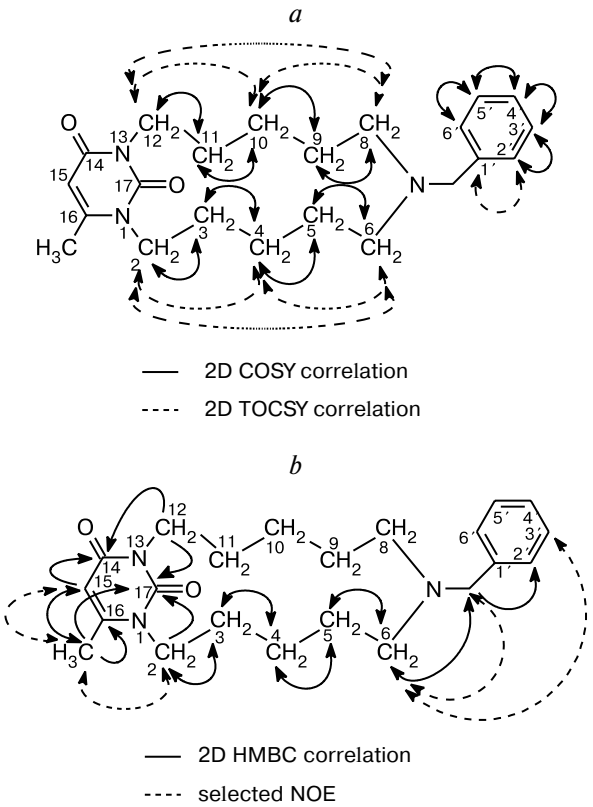

Fig. 7. Observed correlations based on the spin-spin coupling constants (*a*) and 2D HMBC and 1D ROESY experiments (*b*).

The resonances for the geminal protons at the C(2) atom in the bridge appear as two broadened multiplets at δ 4.43 and 3.53. The presence of cross-peaks between the signals for these protons and resonances for other protons of the bridge in the 2D TOCSY spectrum allows the determination of the resonances for all protons of the C(2)—C(6) chain. Cross-peaks between the signals for the vicinal CH_2 groups were distinguished among the signals observed in the 2D TOCSY spectrum based on the analysis of the cross-peaks in the 2D COSY spectrum, thus making possible the assignment of all signals. For example, based on the presence of cross-peaks between the signals for the C(2)H protons and broadened multiplets at δ 1.91 and 1.42 in the 2D COSY spectrum, these signals were assigned to the resonance of the protons at the C(3) atom of the bridge. The positions of the resonances for other protons of the C(2)—C(6) chain were determined analogously (δ 1.30 for C(4)H, 1.40 for C(5)H, and 2.33 for C(6)H). The cross-peaks between the signals for the protons at δ 4.43 and 3.53 and the ^{13}C signal at δ 152.6 (C(17)) and the correlations between C(15), C(2)H, and the CH_3 group and the signal at δ 151.7 in the 2D HMBC spectrum of pyrimidinophane **4** additionally confirmed the assignment of the signals for the C(2)H group and made it possible to assign the signal at δ 151.7 to the C(16) atom.

In the ^{1}H NMR spectrum of macrocycle **4**, the assignment of the signals for the C(12)—C(8) chain, in which two broadened multiplets at δ 4.28 and 3.96 belong to the protons at C(12), was made analogously. This assignment was confirmed by the presence of cross-peaks between the signals at δ 4.28 and 3.96 and the resonance for C(14) of the 6-methyluracil fragment in the 2D HMBC spectrum of pyrimidinophane **4**. In addition, the 1D ROESY spectrum (Fig. 8, *b*) shows NOE between the signals

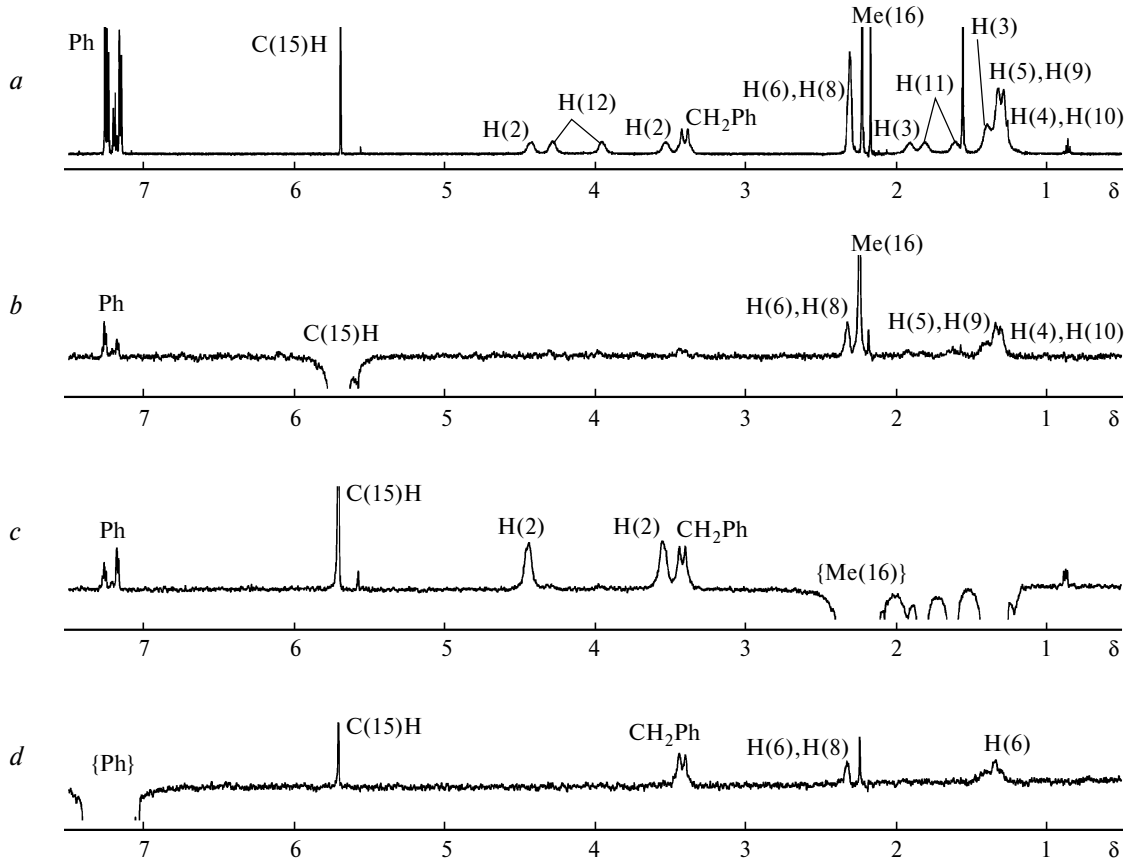

Fig. 8. ^{1}H NMR (a) and 1D ROESY (*b*—*d*) spectra of pyrimidinophane **4**.

for the protons at the C(2) atom and the methyl group at C(16) of the 6-methyluracil fragment, which additionally confirms the validity of the differentiation and assignment of the signals for the C(2)H and C(12)H protons.

The chemical shifts of the carbon atoms of the C(2)—C(6) and C(12)—C(8) chains were determined based on the 2D HSQC spectrum taking into account the known positions of the resonances for the protons in the bridge.

The signals for the geminal protons of the methylene group of the benzyl fragment at 263 K appear as an AB system. The resonances for the phenyl protons, which appear as two triplets and one doublet, were identified from the cross-peaks between the signals for these protons and the low-field signal in the 2D TOCSY spectrum. In addition, the 2D COSY spectrum shows cross-peaks between the signals for the H_m and H_o protons and between the H_m and H_p protons. Based on the cross-peak between the signals for the CH_2Ph and H_o protons and the signal at δ 140.5 in the 2D HMBC spectrum, the latter was assigned to the C(1′) atom. The chemical shifts of other carbon atoms involved in the benzyl fragment were determined based on the corresponding cross-peaks in the 2D HSQC spectrum.

The ^{1}H NMR spectrum of pyrimidinophane **5** is similar to that described above. Analysis for the macrocycle was performed analogously. The 2D HMBC spectrum of **5**, unlike the spectrum of pyrimidinophane **4**, shows additional cross-peaks between the CH_3 group and C(14), C(16), and C(2)H and NOE between C(2)H and C(16)H.

Therefore, the geminal protons of the CH_2 groups at N(13) and N(1) of pyrimidinophanes **4** and **5** are essentially nonequivalent. The magnetic nonequivalence of these protons is a consequence of conformational rigidity of the pyrimidinophane molecules, on the one hand, and the anisotropy of the pyrimidine ring, on the other hand. In this case, the conformational rigidity implies that the inversion of the macrocycle between two or several symmetrical forms (intramolecular transitions) is slow on the NMR time scale, resulting in the spectrum nonaveraged due to exchange.

Due to larger conformational flexibility of pyrimidinophanes containing two or more pyrimidine fragments, the ^{1}H NMR spectra measured under fast exchange conditions are virtually first-order spectra of an AX system.[14—17] The flexibility (the inversion rate) of pyrimidinophanes increases with increasing length of the bridge. In the ^{1}H NMR spectra of [n](1,3)pyrimidinophanes described earlier,[14] the signals for the geminal protons first become

broader and then become narrower as the length of the bridge increases in going from macrocycles containing 10 methylene groups in the bridge to macrocycles containing 11 or more methylene groups, and finally the spectral pattern becomes similar to a first-order spectrum. The flexibility of the bridge in macrocycles containing a larger number of CH_2 groups in the bridge between the N(1) and N(13) atoms is also higher than that in pyrimidinophanes **4** and **5**, which is accompanied by the corresponding changes in the ^{1}H NMR spectra. These data will be discussed elsewhere.

The three-dimensional structures of pyrimidinophanes **4** and **5** in solutions in $CDCl_3$ were determined based on one-dimensional NOE experiments using gradients to refocus the signals, which made it possible to substantially increase the sensitivity threshold of the method for these effects. The spectrum of macrocycle **4** shows nontrivial cross-peaks between C(16)Me and C(15)H and the signals for the phenyl protons (Figs 8 and 9). The spectrum of macrocycle **5** shows nontrivial cross-peaks between C(15)Me, C(16)H, and ArH. These data indicate that the protons of the uracil and phenyl fragments are in close proximity in $CDCl_3$, *i.e.*, the molecule adopts a folded conformation analogous to that shown in Figs 1, 2, and 9. These three-dimensional structures of the macrocycles are, apparently, responsible for the deshielding effect of the benzene ring on C(15)H in pyrimidinophane **4** and on C(15)Me in pyrimidinophane **5**. In the spectra of compounds **1** and **2**, the signals for these protons are observed at higher field.

The fact that the uracil and phenyl fragments are in close proximity (the molecules adopt a folded conformation in $CHCl_3$) was confirmed by comparing the UV spectra of pyrimidinophanes **4** and **5** with those of acyclic 1,3-bisalkyl-substituted 6-methyluracil and thymine. The

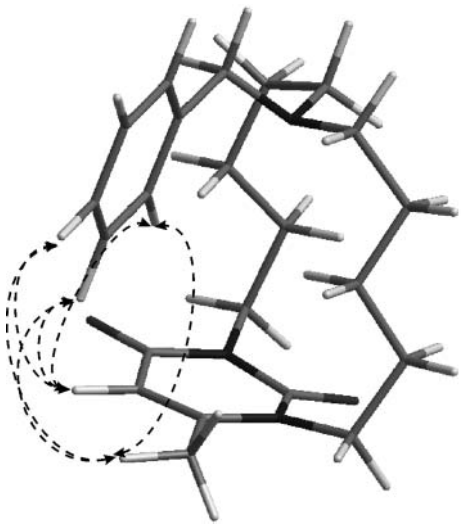

Fig. 9. Assumed three-dimensional structure of pyrimidinophanes **4** in $CDCl_3$ and observed nontrivial NOE.

UV spectra of pyrimidinophanes are determined by absorption of the uracil fragment at 272 nm and are characterized by the molar extinction coefficients ε = 8056 and 7735 for macrocycles **4** and **5**, respectively. We used acyclic 1,3-bis(bromobutyl)-6-methyluracil (**6**) and 1,3-bis(butyl)thymine (**7**) with ε = 10157 (267 nm) and ε = 8507 (272 nm), respectively, as the reference compounds. As can be seen from the above data, the intensity of absorption of the uracil fragment in cyclic structures is lower than that in acyclic structures, and this decrease can be numerically expressed by the hypochromic effect (in percent).[18] This effect is $(1 - 8056/10157) \cdot 100 = 20.7\%$ and $(1 - 7735/8507) \cdot 100 = 9.1\%$ for pyrimidinophanes **4** and **5**, respectively. Therefore, macrocycles **4** and **5** exhibit the hypochromic effect with respect to the corresponding 1,3-bisalkyl-substituted uracils. According to the theory of the hypochromic effect,[19,20] a decrease in the intensity of light absorbed by a nucleotide base can be attributed to the involvement of the latter in stacking interactins with other aromatic systems. Apparently, the pyrimidinophanes adopt conformations, in which the plane of the benzene ring is parallel to the plane of the pyrimidine ring, in a $CHCl_3$ solution on the UV time scale. According to the theory of π—π interactions,[21] the distance between the rings should be no larger than 3.4 Å, which is consistent with the NMR spectroscopic data, in particular, with the presence of NOE between the protons of the uracil and phenyl fragments.

The uracil fragments have large dipole moments (for example, the dipole moment for 1,3,6-trimethyluracil is 4.69 D).[22] Hence, the dipole moment method[23] can be used as an independent method for the analysis of the structures of pyrimidinophanes **4** and **5** in solution. The experimental dipole moments for macrocycles **4** and **5** in benzene are 4.85±0.05 and 3.90±0.04 D, respectively. In subsequent calculations of the theoretical molecular dipole moments of compounds **4** and **5**, the polarity of the pyrimidine fragments was described as follows. Using the approach to estimations of the polarities of pyrimidines proposed earlier,[22] we represented the dipole moment of 1,3,6-trimethyluracil (4.69 D)[22] as the following three vectors: C(17)→O (1.13 D), N(1)→C(2) (2.63 D), and C(14)→O (2.63 D). In turn, the dipole moment of 1,3,5-trimethyluracil (3.98 D)[22] was represented as the following three vectors: C(17)→O (1.33 D), N(1)→C(2) (2.30 D), and C(14)→O (2.30 D). The dipole moments of other polar bonds of pyrimidinophanes were estimated based on the published data:[23,24] 0.53 D for C—N, 0.28 D for H—C_{sp^3}, and 0.36 D for CH_2—Ph. The theoretical molecular dipole moments of compounds **4** and **5**, which were calculated according to the vector-additive scheme[24] with the use of the above-mentioned dipole moments of the bonds and the atomic coordinates determined by X-ray diffraction, are 4.85 and 3.98 D, respectively. A good agreement between the experimental and theoretical mo-

lecular dipole moments indicates that macrocycles **4** and **5** in benzene solutions adopt conformations very similar to those observed in the crystals (see Figs 1 and 2).

To summarize, we synthesized pyrimidinophanes, in which the N(1) and N(3) atoms of the 6-methyluracil or thymine fragments are linked to each other by a bridge containing 10 methylene groups and the N atom bearing the benzyl substituent. Compared to macrocycles containing two or more pyrimidine rings, the pyrimidinophanes under consideration are more rigid, which is reflected, in particular, in the spectroscopic features of pyrimidinophanes. In the crystals, the geometry of the pyrimidinophane molecules is characterized by the mutually orthogonal arrangement of the benzene and pyrimidine rings with the shortest distances between the protons of these aromatic fragments varying from 2.7 to 4.1 Å. In solution, the uracil and phenyl fragments are in close proximity (NMR and UV spectroscopic data and the results obtained by the dipole moment method), although it is difficult to unambiguously determine their mutual arrangement. The factors responsible for the close arrangement of the components involved in macrocycles **4** and **5** remain unclear. Nevertheless, interactions responsible for the above-described structural features can be determined by varying the distances between the uracil fragment and the substituent at the N atom in the bridge.

Experimental

The ^{1}H, ^{13}C, and 2D NMR spectra, including COSY, HSQC, HMBC, and ROESY experiments, for compounds **4** and **5** were recorded on a Bruker AVANCE-600 Fourier-transform spectrometer operating at 600.000 (^{1}H) and 150.864 (^{13}C) MHz in $CDCl_3$ at 30 °C with the use of the residual signal of $CDCl_3$ (δ_H 7.26 and δ_C 77.0) as the internal standard. The electron impact mass spectra were obtained on a MAT-212 Finnigan mass spectrometer at 1000 resolution with the use of the MSS MASPEC II data system. The experimental conditions: a direct inlet system, the ion source temperature was varied from 20 to 300 °C, the ionizing electron energy was 70 eV, and the electron emission current was 1.0 mA. The IR spectra were measured on a Bruker Vector-22 Fourier-transform spectrometer under standard conditions in KBr pellets. The UV spectra were recorded on a Specord UV-Vis spectrophotometer (Carl Zeiss Jena). The experimental dipole moments were determined in dilute benzene solutions at 20 °C using the second Debye method.[23,24]

X-ray diffraction data sets for compounds **4** and **5** were collected on automated four-circle Enraf-Nonius CAD-4 diffractometers at room temperature (20 °C). Crystals of compounds **4** and **5** were grown from DMSO. The crystallographic parameters and details of X-ray data study are given in Table 4. The calculations were carried out with the use of the MoIEN program[25] on an Alpha Station 200. The structures were solved by direct methods using the SIR program[26] and refined using the SHELXL97[27] and WinGX programs.[28]

The figures were drawn and the intermolecular contacts were analyzed using the PLATON program.[29]

Table 4. Crystallographic parameters of compounds **4** and **5** and details of X-ray diffraction study

Parameter	**4**	**5**
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/a$
a/Å	9.544(5)	12.426(7)
b/Å	12.358(8)	10.098(8)
c/Å	34.99(3)	16.61(1)
β/deg	91.52(6)	92.27(7)
V/Å^3	4125(5)	2083(3)
Z	8	4
M	369.50	369.50
d_{calc}/g cm^{-3}	1.19	1.18
Absorption coefficient, μ/cm^{-1}	6.1	6.0
Radiation (λ/Å)	CuK_α, 1.54184	
θ-Scan range/deg	$4.63 \le \theta \le 70.02$	$5.13 \le \theta \le 69.95$
Scanning technique	ω	ω
Number of measured reflections	7705	3989
Number of observed reflections with $I > 2\sigma(I)$	3618	2167
Final R factors:		
R	0.078	0.061
R_w	0.204	0.173
Fitting parameter	0.999	1.003
Number of reflections used in the refinement	7231	3804
Number of parameters in the refinement	490	249
Number of independent reflections (R_{int})	7622(0.053)	3950(0.015)

Note. Check reflections: two check reflections distributed in orientation and three check reflections distributed in intensity after every 200 reflections. The positions of the hydrogen atoms were revealed from difference Fourier maps and refined with fixed positional and thermal displacement parameters in the final steps.

The melting points were measured on a Boetius hot-stage apparatus and are uncorrected. Thin-layer chromatography was performed on Silufol-254 plates. The spots in plates were visualized with UV light.

All solvents and reagents were dried.

1,3-Bis(5-bromopentyl)-6-methyluracil[30] (1), 1,3-bis(bromobutyl)-6-methyluracil[30] (6), and 1,3-bis(4-bromobutyl)thymine[16] (7) were prepared according to known procedures.

1,3-Bis(5-bromopentyl)thymine (2). A solution of 1,5-dibromopentane (155.9 g, 677.8 mmol) in DMF (90 mL) was added dropwise with stirring to a solution of the disodium salt of thymine (14.4 g, 84.7 mmol) in DMF (150 mL). The reaction mixture was stirred at 50—60 °C for 5 h. The solvent was removed *in vacuo*, benzene (100 mL) was added, and the mixture was filtered. The filtrate was concentrated to 10—15 mL and chromatographed through an alumina column. The column was successively washed with petroleum ether and a 2 : 1 diethyl ether—petroleum ether mixture. Compound **2** was obtained as an oil from the first fractions in a yield of 15.9 g (45%), R_f 0.74

(diethyl ether as the eluent). Found (%): C, 42.38; H, 5.71; N, 6.53; Br, 37.77. $C_{15}H_{24}Br_2N_2O_2$. Calculated (%): C, 42.47; H, 5.70; N, 6.60; Br, 37.67. ^{1}H NMR ($CDCl_3$), δ: 7.01 (s, 1 H, C(16)H); 3.95 (t, 2 H, $N_{pyr}CH_2$, J = 7.2 Hz); 3.73 (t, 2 H, $N_{pyr}CH_2$, J = 7.2 Hz); 3.42 (m, 4 H, 2 CH_2Br); 1.93 (s, 3 H, C(15)CH_3); 1.89 (m, 4 H, 2 $N_{pyr}C\underline{CH_2}$); 1.76—1.58 (m, 4 H, 2 $\underline{CH_2}$CBr); 1.50 (m, 4 H, 2 CC$\underline{CH_2}$CC). MS (EI, 70 eV), *m/z*: 426 (9), 424 (22), 422 (10), 346 (28), 345 (88), 344 (28), 343 (88), 275 (75), 195 (86), 140 (100).

7-Benzyl-16-methyl-1,7,13-triazabicyclo[11.3.1]heptadeca-15-ene-14,17-dione (4). Potassium carbonate (4.90 g, 35.5 mmol) was added to a solution of benzylamine **3** (1.90 g, 17.8 mmol) in *n*-butanol (250 mL), and then a solution of compound **1** (2.5 g, 5.9 mmol) in *n*-butanol (100 mL) was added with stirring at 90 °C. The reaction mixture was stirred at 100—110 °C for 7 h and then cooled. The solvent was distilled off, chloroform (150 mL) was added to the residue, the mixture was filtered, and the filtrate was concentrated to 10—20 mL and chromatographed through an alumina column. The column was washed with a 1 : 3 petroleum ether—diethyl ether mixture to prepare pyrimidinophane **4** in a yield of 0.35 g (16%), R_f 0.29 (diethyl ether—hexane, 5 : 1, as the eluent), m.p. 114 °C. Found (%): C, 71.40; H, 8.57; N, 11.39. $C_{22}H_{31}N_3O_2$. Calculated (%): C, 71.51; H, 8.46; N, 11.37. Found: *m/z* 369.242 $[M]^+$. $C_{22}H_{31}N_3O_2$. Calculated: M = 369.2416. UV ($CHCl_3$), λ_{max}/nm (logε): 271 (3.91). IR (KBr), ν/cm^{-1}: 3085, 3021, 1614, 1493, 765, 718/699 (C(16)H, C_{arom}H, benzene ring), 2954, 2929, 2862, 1469, 1429, 1378, 1341, 744 (CH_3, CH_2), 2794 (CH_2(N)), 1687, 1652 (C=O, uracil fragment). ^{1}H NMR ($CDCl_3$), δ: 7.25 (t, 2 H, H_m, J = 7.3 Hz); 7.19 (t, 1 H, H_p, J = 7.3 Hz); 7.16 (d, 2 H, H_o, J = 7.3 Hz); 5.69 (s, 1 H, C(15)H); 4.42 (m, 1 H, C(2)H); 4.28 (m, 1 H, C(12)H); 3.95 (m, 1 H, C(12)H); 3.53 (m, 1 H, C(2)H); 3.43 (d, 1 H, CHPh, J = 12.2 Hz); 3.37 (d, 1 H, CHPh, J = 12.2 Hz); 2.33 (m, 2 H, C(8)H_2); 2.32 (m, 2 H, C(6)H_2); 2.22 (s, 3 H, C(16)CH_3); 1.91 (m, 1 H, C(3)H); 1.81 (m, 1 H, C(11)H); 1.61 (m, 1 H, C(11)H); 1.42 (m, 1 H, C(3)H), 1.35 (m, 2 H, C(4)H_2); 1.40 (m, 4 H, C(5)H_2, C(9)H_2); 1.30 (m, 2 H, C(10)H_2). ^{13}C NMR ($CDCl_3$), δ: 162.6 (C(14)), 152.6 (C(17)), 151.7 (C(16)), 101.7 (C(15)), 140.5 (C(1′)), 128.7 (C(2′)), 127.9 (C(3′), 126.5 ((C(4′)), 58.6 ($\underline{C}$(C(1′)), 53.9 (C(8)), 53.5 (C(6)), 44.3 (C(12)), 40.3 (C(2)), 28.2 (C(11)), 27.6 (C(10)), 27.5 (C(4)), 26.6 (C(3)), 22.8 (C(5), C(9)), 20.1 (C(16)$\underline{C}$). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 371 (1.7), 370 (10.2), 369 $[M]^+$ (42.8), 368 $[M - 1]^+$ (5.4), 354 $[M - 15]^+$ (80.7), 340 $[M - 29]^+$ (8.7), 327 (7.4), 314 (7.3), 313 (31.4), 292 (27.6), 279 (10.1), 278 $[M - 91]^+$ (46.6), 134 (13.0), 127 (7.8), 120 (7.3), 91 (100.0), 42 (15.5), 41 (21.4).

7-Benzyl-15-methyl-1,7,13-triazabicyclo[11.3.1]heptadeca-15-ene-14, 17-dione (5) was prepared under conditions of the synthesis of macrocycle **4** from compound **3** (2.14 g, 20 mmol), K_2CO_3 (2.95 g, 21 mmol), and compound **2** (4.1 g, 9.7 mmol). An alumina column was washed with diethyl ether, and pyrimidinophane **5** was isolated from the fractions in a yield of 0.6 g (17%), R_f 0.50 (diethyl ether—hexane, 5 : 1, as the eluent), m.p. 130—131 °C. Found (%): C, 71.49; H, 8.41; N, 11.40. $C_{22}H_{31}N_3O_2$. Calculated (%): C, 71.51; H, 8.46; N, 11.37. Found: *m/z* 369.242 $[M]^+$. $C_{22}H_{31}N_3O_2$. Calculated: M = 369.2416. UV ($CHCl_3$), λ_{max}/nm (logε): 272 (3.89). IR (KBr), ν/cm^{-1}: 3064, 3027, 3003, 1600, 1492, 765/758, 718/699 (C(16)H, C_{arom}H, benzene ring), 2950, 2927, 2863, 1467, 1443, 1379, 1345, 738 (CH_3, CH_2), 2808, 2789 (CH_2(N)), 1697, 1663, 1635 (C=O, uracil fragment). ^{1}H NMR ($CDCl_3$), δ: 7.27 (t, 2 H, H_m, J = 7.3 Hz); 7.25 (t, 1 H, H_p, J = 7.3); 7.15 (d, 2 H, H_o, J = 7.3 Hz); 6.97 (s, 1 H, C(16)H); 4.48 (m, 1 H, C(2)H); 4.28 (m, 1 H, C(12)H); 4.03 (m, 1 H, C(12)H); 3.44 (d, 1 H, CHPh, J = 12.2 Hz); 3.35 (d, 1 H, CHPh, J = 12.2 Hz); 3.18 (m, 1 H, C(2)H); 2.32 (m, 4 H, C(6)H_2, C(8)H(2)); 2.04 (s, 3 H, C(15)CH_3); 1.90 (m, 1 H, C(3)H); 1.80 (m, 1 H, C(11)H); 1.64 (m, 1 H, C(11)H); 1.48 (m, 1 H, C(3)H); 1.31 (m, 4 H, C(5)H_2, C(9)H_2); 1.25 (m, 2 H, C(4)H_2); 1.21 (m, 2 H, C(10)H_2). ^{13}C NMR ($CDCl_3$), δ: 163.9 (C(14)), 152.0 (C(17)), 138.6 (C(16)), 109.4 (C(15)), 140.2 (C(1′)), 128.7 (C(2′)), 127.9 ((C(3′)), 126.7 (C(4′)), 59.0 ((C(1′)), 53.5 (C(6), C(8)), 49.0 (C(12)), 40.5 (C(2)), 27.9 (C(11)), 27.1 (C(9)), 26.3 (C(3)), 22.9 (C(5)), 22.6 (C(4), C(10)), 13.2 (C(15)$\underline{C}$). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 371 (3.4), 370 (26.4), 369 $[M]^+$ (94.1), 368 $[M - 1]^+$ (41.5), 354 $[M - 15]^+$ (4.8), 340 $[M - 29]^+$ (33.1), 327 (4.8), 314 (6.2), 313 (19.0), 292 (7.1), 279 (24.0), 278 $[M - 91]^+$ (94.9), 250 (29.3), 134 (29.9), 127 (5.3), 120 (16.6), 91 (100.0), 42 (17.8), 41 (18.4).

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