

New type of pyrimidinophanes with α,ω -bis(uracil-1-yl)alkane and bis(uracil-5-yl)methane units

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New pyrimidinophanes containing four uracil units connected with methylene bridges through the N(1) and C(5) atoms of pyrimidine rings were obtained by treatment of 1,4-bis(3,6-dimethyluracil-1-yl)butane with paraform.

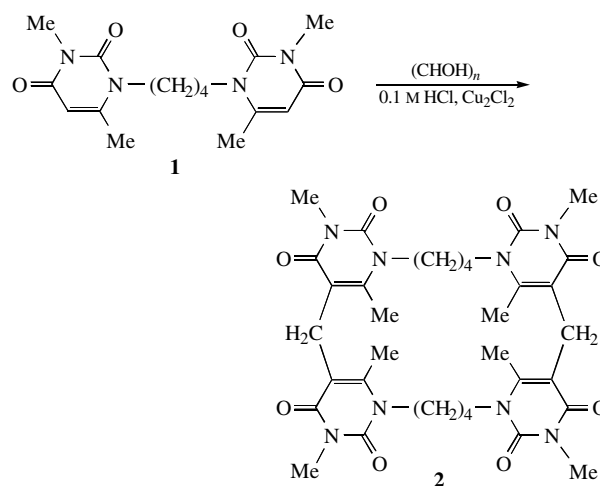
Macrocyclic compounds consisting of purine and pyrimidine bases are interesting model objects for the study of stacking structures in nucleic acids and can serve as precursors for host-guest molecules. While purinophanes of different types have been synthesised and well studied, pyrimidinophanes have been reported only recently.^{2–6} In the course of an investigation aimed at the creation of effective macrocyclic complexing agents, T. Itahara^{2,5} elaborated a direct method of pyrimidinophane preparation. These pyrimidinophanes, which were synthesised for the first time previously,^{7–10} consisted of two uracil or 2,4-dithiouracil units linking each other with polymethylene bridges through the N(1) and N(3) atoms of pyrimidine rings. They were obtained by the treatment of uracils and 2,4-dithiouracils, respectively, with dihaloalkanes in DMF as a solvent in the presence of NaH. Almost all of the pyrimidinophanes reported before are structurally similar to the above compounds, and they were synthesised by either the interaction of salts with dihaloalkanes and 1,3-bis(bromoalkyl)uracils⁶ or the oxydation of substituents at the N(1) atom of the pyrimidine ring in α,ω -bis(uracil-3-yl)alkanes.^{3,11}

A pyrimidinophane consisting of two uracil units was obtained by the reaction of 1-(hydroxyethyl)-3,6-dimethyluracil and paraform to afford 5,5'-bis[(2-hydroxyethyl)-3,6-dimethyluracil]-methane followed by sequential replacement of hydroxyls with thiol groups and oxidation to disulfide bridges.¹²

Note that uracils have a property to afford 5,5'-methylene bis-derivatives with paraform in water.^{13,14} We applied the reaction to the direct preparation of the polycyclic pyrimidinophanes.

We examined the interaction of bis(3,6-dimethyluracil-1-yl)-butane¹⁵ **1** with paraform in aqueous 0.1 M HCl at different 1:paraform ratios (1:1–1:10) and temperatures (50–100 °C). In no cases macrocyclic compounds were detected among the final products of the reactions by electron-ionization mass spectrometry, and only compounds with linear structures were found. When the reaction between **1** and paraform at the 1:paraform ratio 1:1.1 and at 95–98 °C was performed in aqueous 0.1 M HCl containing an equimolar amount of copper(I) ions 8,14,23,29,31,32,33,34-octamethyloctaazapentacyclo[25,3,1,1⁶,10,1¹²,16,1²¹,25]tetraatriaconta-10(34),12(33),25(32),27(31)-tetraene-7,9,13,15,22,24,28,30-octaone **2** was obtained in 10% yield.[†] The participation of monovalent copper in this reaction is unclear. However, because copper(I) complexes with pyrimidine derivatives were reported elsewhere,¹⁶ we suppose that **1** can be associated with copper(I) ions to promote ring-closure reactions at the 5-positions of the pyrimidine rings.

The structure of compound **2** was confirmed by mass spectrometry and NMR spectroscopy. The high-resolution mass spectrum exhibits the most intense peak of the molecular ion M^+ with m/z 692.328. The found mass of the molecular ion is in a very good agreement with the calculated value 692.3282 for $C_{34}H_{44}N_8O_8$. Moreover, the formation of the doubly charged ion ($z = 2$) with m/z 346.166 (calculated 346.1641 for $C_{34}H_{44}N_8O_8$) additionally confirms the suggested structure. The only fragment in the region of heavy masses is $[M - Me]^+$.



The ¹H NMR spectra exhibit five peaks with the integral intensity ratio 2:3:3:1:2, and the signal assigned to C(5)–H of the pyrimidine ring (5.65 ppm¹⁵) is absent, whereas a signal appears at 3.69 ppm, which is typical of a methylene group bridging the C(5) atoms of two uracils.¹⁴ In the ¹³C NMR spectra, the peak of C(5) of pyrimidine rings is observed with the multiplicity corresponding to only far C–H interactions (ⁿJ_{CH} ≤ 5 Hz) unlike the doublet structure of the signal with ¹J_{CH} 178 Hz for initial compound **1**.

Thus, this approach can be promising for the preparation of pyrimidinophanes with the structure like **2**; moreover, the initial units can carry functional substituents.

References

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[†] *Pyrimidinophane 2*. A mixture of **1** (3 g, 9 mmol), paraform (0.3 g, 10 mmol) and Cu₂Cl₂ (0.9 g, 4.5 mmol) was stirred for 30 h in 150 ml of an aqueous 0.1 M HCl solution at 95–98 °C. The precipitate was filtered off, dried and refluxed in 50 ml of chloroform. The undissolved residue was filtered off, and the rest solution was concentrated and chromatographed on Al₂O₃ with activity II. A dichloromethane–methanol (60:1) eluent was used, and the fraction with *R*_f 0.30 (Silufol; CH₂Cl₂–MeOH, 20:1) was separated. After evaporation of the solvent, 25 ml of diethyl ether were added to the residue and filtered to give 0.3 g (10%) of **2**. Small white crystals soluble in CH₂Cl₂ and CHCl₃, mp > 320 °C. ¹H NMR (250 MHz, CDCl₃) δ: 1.65 (br. m, 8H, CCH₂C), 2.19 (s, 12H, C_{pyr}Me), 3.31 (s, 12H, NMe), 3.69 (s, 4H, C_{pyr}CH₂C_{pyr}), 3.89 (br. m, 8H, NCH₂C). ¹³C NMR (250 MHz, CDCl₃) δ: 16.59 [MeC(6)_{pyr}], 22.33 [CH₂C(5)_{pyr}], 25.52 (CCH₂C), 28.43 (MeN), 44.81 (CH₂N), 110.36 [C(5)_{pyr}], 149.26 [C(6)_{pyr}], 151.61 [C(2)_{pyr}], 162.77 [C(4)_{pyr}]. MS, *m/z* (%): 693 (40), 692 (100) [M⁺], 677 (24), 347 (17), 346 (23) [M²⁺], 195 (36), 153 (31). Mass spectra were recorded on an MX-1310 instrument, the ionization energy was 60 eV, the emission current was 60 μA, the direct evaporation system was kept at 306 °C.

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