DOI 10.1007/s10593-015-1737-y

Chemistry of Heterocyclic Compounds **2015**, *51*(6), 568–572

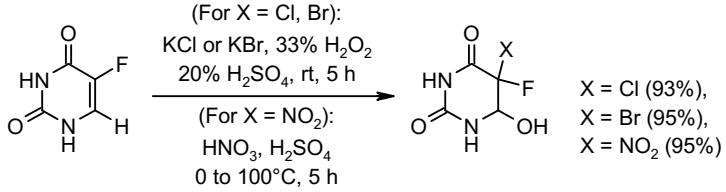
5-Fluoro-5-halo- and 5-fluoro-5-nitro-substituted uracil derivatives. Synthesis and structure

Inna B. Chernikova[1]*, Sergey L. Khursan[1], Leonid V. Spirikhin[1], Marat S. Yunusov[1]

[1] *Ufa Institute of Chemistry, Russian Academy of Sciences, 71 Oktyabrya Ave., Ufa 450054, Russia; e-mail: leben_87@mail.ru*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2015, *51*(6), 568–572

Submitted 5.05.2015
Accepted after revision 23.06.2015



5-Bromo-5-fluoro- and 5-chloro-5-fluoro-6-hydroxy-5,6-dihydrouracils were obtained in high yields by oxidative halogenation of 5-fluorouracil. Nitration of 5-fluorouracil gave 5-fluoro-6-hydroxy-5-nitro-5,6-dihydrouracil. Theoretical calculations in B3LYP/6-311+G(d,p) // B3LYP/6-311G(d,p) + IEFPCM approximation and GIAO simulation of ^{13}C NMR spectra and spin-spin coupling constants agree with the structure of the compounds obtained, which manifest an equatorial orientation of the fluorine atom and an axial orientation of the hydroxy group at position 6 of the dihydrouracil ring. The principal possibility of oxidative iodination of 5-halouracils was studied in B3LYP/CEP-121G approximation. It was found that reversible elimination of iodine by a nucleophilic agent to give the original compounds is the main transformation pathway of the intermediate in this process.

Keywords: 5-fluorouracil, 5-fluoro-5-halouracils, 5-fluoro-5-nitrouracil.

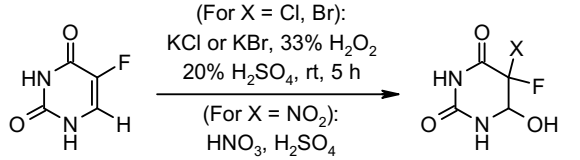
As a result of the similarity of the steric volumes of F and H atoms and the difference in their behavior due to different electronegativity, many fluorine-containing compounds act as antimetabolites with respect to a corresponding substrate containing no halogen.

Uracil and its derivatives play an important role in processes occurring in living organisms and are used in practical medicine as pharmaceuticals.[1,2] Certain 5-fluorouracil-containing pharmaceutical compounds are converted to 5-fluorouracil in the organism.[3,4] In some cases, the formation of 5-fluorouracil from these compounds occurs in a tumor tissue, thus minimizing a systemic action of 5-fluorouracil on healthy tissues. Thus, these compounds are prodrugs; activities aimed at synthesis of this kind of compounds are being undertaken continually.

This paper presents results on a synthesis of 5-substituted derivatives of 5-fluorouracil and a study of their structures, including stereochemistry. Methods to synthesize 5-fluoro-5-halo- and 5-fluoro-6-hydroxy-5-nitro-5,6-dihydrouracils by fluorination of 5-halouracils or 5-nitrouracil with a F_2/N_2 gas mixture were reported in literature. The yields of the products obtained by this method were 82–92%.[5]

We proposed a synthesis of 5-substituted fluorouracil derivatives using 5-fluorouracil (**1**) as the substrate. Oxidative halogenation of compound **1** was carried out using KHal–H_2O_2 mixture in 20% H_2SO_4.[6] This method gave 5-chloro-5-fluoro-6-hydroxy-5,6-dihydrouracil (**2**) and 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil (**3**) in 93 and 95% yields, respectively (Scheme 1). The structures of the compounds were determined by ^1H and ^{13}C NMR spectroscopy. The ^{13}C NMR spectra of compounds **2**, **3** show doubling of signals for the C-4,5,6 atoms due to spin-spin coupling with the nucleus of the fluorine atom.[7]

Scheme 1



1

2 X = Cl (93%),
3 X = Br (95%),
4 X = NO_2 (95%)

The synthesis of 5-fluoro-6-hydroxy-5-nitro-5,6-dihydrouracil (**4**) was carried out by nitration of compound **1** with a mixture of nitric and sulfuric acids. The yield of compound **4** was 95% (Scheme 1). Like in the case of 5,5-dihalogenated uracil derivatives **2**, **3**, the ^{13}C NMR spectrum of compound **4** shows doubling of signals for the C-4,5,6 atoms.

Spectral data do not allow us to identify the spatial structure of the compounds obtained unambiguously, therefore we performed theoretical calculations of equilibrium geometry parameters of compounds **2**–**4** in B3LYP/6-311+G(d,p) // B3LYP/6-311G(d,p) + IEFPCM approximation. Previously, we successfully used this level of theory to study the structure of 5-halo-6-methyluracils and the regularities of *ipso* substitution in these compounds.[8] When designing the structures of compounds **2**–**4**, we took into consideration that the hydroxy substituent at position 6 of the dihydropyrimidinedione ring is oriented axially because of anomeric stabilization due to coupling of an unshared electron pair on the N-1 atom with the σ*-antibonding orbital of the C(6)–O bond.[9] Furthermore, it was believed that in the polar solvent (DMSO used in the spectral measurements), the hydroxy group in compounds **2**–**4** is bound by an intermolecular hydrogen bond with a solvent molecule: $Me_2S{=}O\cdots H{-}O{-}C(6)$. Under these model restrictions, the possible isomers of compounds **2**–**4** will differ only in the mutual orientation of substituents at position 5 of the dihydrouracil ring, namely, the F atom and the X moiety (X = Cl, Br, NO_2). The equilibrium structures of isomers **2**–**4 a**,**b** were found by full optimization of their geometry parameters (Fig. 1). The Gibbs free energies of 1:1 complexes (**2**–**4**)–DMSO were calculated with the thermal correction, taking into account the solvation effect, and the most probable conformations of the studied compounds were determined (Table 1). The data presented in Table 1 indicate that the isomer with an equatorially oriented fluorine atom is the most thermodynamically stable isomer of all the compounds studied. The population values of isomers **2**–**4 b** are 92, 98, and 86%, respectively.

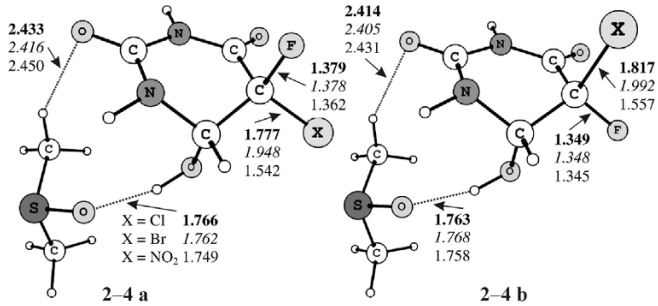


Figure 1. Spatial structure of compounds **2** (X = Cl), **3** (X = Br), and **4** (X = NO_2) based on B3LYP/6-311G(d,p) optimization of geometry parameters of the molecules.

To support our conclusions additionally, we calculated the theoretical ^{13}C NMR chemical shifts by the GIAO B3LYP/6-311+G(d,p) method, as well as spin-spin coupling constants $^1J_{CF}$ and $^2J_{CF}$ responsible for the observed splitting of signals for the C(4)–C(6) atoms (see above). The calculation results presented in Table 2 confirm the conclusion that compounds **2**–**4 b** are formed under conditions of our experiments. First, the regressional relationship between the experimental values of the ^{13}C NMR chemical shifts and the theoretical isotropic screening constants for compounds **2**–**4 b** is observed with a larger correlation coefficient than for compounds **2**–**4 a**. The same is observed in a study of the relationship between the theoretical and experimental $^1J_{CF}$ values for the C-5 atom in the series of compounds **2**–**4 b**. Finally, the theory predicts a correct order of spin-spin coupling constants ($^2J_{C(4)F} > {}^2J_{C(6)F}$) for compounds **2**–**4 b** and an inverse one for compounds **2**–**4 a** (Table 2).

The issue of preferential equatorial orientation of the fluorine atom and axial orientation of electronegative

Table 1. Full energies (E_{total}), thermal corrections (*TC*), absolute Gibbs free energies ($G°_{298}$), solvation energies in DMSO (G_{solv}), relative Gibbs energies ($\Delta G°_{298}$), and isomer population (*g*) of isomers of compounds **2**–**4**

Compound	Orientation of fluorine atom	E_{total}, Hartree	*TC*, Hartree	G_{solv}, kcal/mol	$G°_{298}$, Hartree	$\Delta G°_{298}$, kcal/mol	*g*, %
2a	Axial	–1603.570744	0.131377	–14.50	–1603.462474	**0.00**	**8**
2b	Equatorial	–1603.573096	0.131924	–14.84	–1603.464821	**–1.47**	**92**
3a	Axial	–3717.489195	0.129761	–14.52	–3717.382573	**0.00**	**2**
3b	Equatorial	–3717.492571	0.130173	–14.89	–3717.386126	**–2.23**	**98**
4a	Axial	–1348.501450	0.141424	–16.10	–1348.385683	**0.00**	**14**
4b	Equatorial	–1348.503602	0.141134	–15.66	–1348.387424	**–1.09**	**86**

Table 2. Calculated and experimental ^{13}C NMR spectral characteristics of compounds **2**–**4 a**,**b**

Compound	Chemical shift, δ, ppm				Spin-spin coupling constants, Hz			
	C-2	C-4	C-5	C-6	C-2 ($^4J_{CF}$)	C-4 ($^2J_{CF}$)	C-5 ($^1J_{CF}$)	C-6 ($^2J_{CF}$)
2a (Theoretical)	152.7	160.6	110.4	76.6	0.7	22.4	317.0	27.3
2b (Theoretical)	151.5	162.1	102.7	76.6	0.6	27.0	342.2	22.6
2 (Experimental)	151.0	163.0	97.1	77.0	0.0	27.1	255.5	26.6
3a (Theoretical)	152.8	160.8	117.2	77.2	0.7	20.7	326.7	25.6
3b (Theoretical)	151.5	163.0	105.9	77.1	0.7	24.8	353.2	21.3
3 (Experimental)	150.8	163.6	91.0	77.6	0.0	25.2	264.4	24.9
4a (Theoretical)	152.3	159.2	106.7	74.0	0.5	23.1	312.9	29.8
4b (Theoretical)	151.7	157.7	108.2	73.5	0.8	25.6	328.0	21.5
4 (Experimental)	150.9	158.4	107.1	73.6	0.0	26.1	245.7	24.7

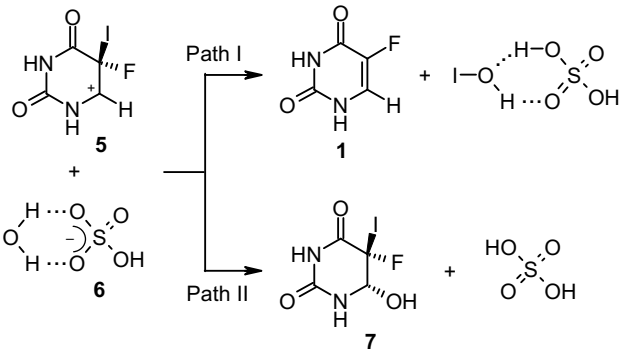
moiety X in the compounds studied is seemed an interplay of stabilization/destabilization effects and deserves a more detailed examination. It can be assumed as a working hypothesis that the axial orientation of X moiety is stabilized by partial population of the σ*(C(5)–X) orbital due to π(C(4)=O) → σ*(C(5)–X) coupling. The possibility of this stabilization is confirmed by the results of NBO analysis of electron density in molecules of compounds **2**–**4**. Thus, it was found at the B3LYP/6-311+G(d,p) level of theory that the population of the σ*(C(5)–X) orbital increases in a row 0.0745 (compound **2b**) – 0.0831 (compound **3b**) – 0.1680 (compound **4b**), and the energy of the orbital coupling is about 3 kcal/mol. Another stabilization interaction, namely, effect of the axial oxygen atom is worth to be mentioned. According to NBO analysis, the σ(C(6)–X) → σ*(C(5)–X) coupling may be an important factor for the conformation behavior of compounds **2**–**4**: the stabilization energy in the series of compounds **2b** – **3b** – **4b** (2.34, 2.64, and 1.84 kcal/mol, correspondingly) is somewhat higher than that in the row of compounds **2**–**4 a**. Finally, one cannot rule out, at least for compound **4**, a stereo-controlling repulsive interaction of polar group dipoles, the minimum value of which is apparently reached at a mutually perpendicular orientation of the groups with large dipole moments, namely C(4)=O (μ(H_2C=O) = 2.33 D) and C(5)–NO_2 (μ(H_3C–NO_2) = 3.46 D). For comparison, μ(H_3C–F) = 1.85 D (the dipole moments were taken from a database).[10]

It has been shown previously[8] that in acid medium or in the presence of nucleophilic agents, 5,5-dihalo-substituted uracils, where one of the halogen atoms is bromine, are converted to 5-monohalo derivatives. This fact allows one to assume that 5-fluoro-5-halouracil derivatives can, under appropriate conditions, play the role of 5-fluorouracil prodrugs. In view of this, we studied the behavior of compounds **2** and **3** in an acidic medium. Heating of compound **3** in 50% H_2SO_4 at 80°C gives 5-fluorouracil (**1**) in 93% yield. The reaction of compound **2** under the specified conditions did not give the expected 5-fluorouracil. A similar behavior, *viz.*, inertness of the chlorine atom in C(5)–Cl bond cleavage, was observed by us previously.[8]

We did not find data on 5-fluoro-6-hydroxy-5-iodo-5,6-dihydrouracil in literature. Therefore, we made an attempt to synthesize it. However, 5-fluorouracil did not react under conditions of oxidative iodination with KI–H_2O_2 in 20% H_2SO_4. We believe that the most natural explanation of this fact is that the intermediate cation of 5-fluoro-5-iodo-5,6-dihydrouracil (**5**) (Scheme 2) is unstable under oxidative iodination conditions and serves as a precursor of the final molecular product, namely, 5-fluoro-6-hydroxy-5-iodo-5,6-dihydrouracil (**7**).

Two circumstances make it difficult to check this assumption theoretically. First, simulation of iodine-containing compounds requires the use of basis sets with effective core potential. To compare the results, all the molecular systems were calculated in the B3LYP/CEP-121G approximation. We used this theory level previously[8] to simulate *ipso* substitution in a series of 5-halo-6-methyl-

Scheme 2



uracils. Second, objective difficulties exist in selection of a theoretical model for the process studied, since the reaction medium (20% aqueous solution of sulfuric acid) is directly involved in the reaction to give strong solvate complexes with ionic intermediates. We believe that a reasonable compromise in this situation is provided by the theoretical model where carbocation **5** reacts with nucleophilic particle **6**, which is a 1:1 complex of a water molecule and a hydrosulfate anion (Fig. 2). In the first place, we studied the effect of a halogen atom at position 5 and examined the changes in the series F – Cl – Br – I on semiquantitative level.

Efficient oxidative halogenation requires that competition of the two paths (I and II) of carbocation **5** transformation be in favor of reaction II (Scheme 2). We performed DFT calculations for these two paths (Table 3). In the series of halogens from fluorine to iodine, a distinct trend is observed: the Gibbs free energy of reaction I decreases, whereas $\Delta G°_{298}$(II) increases. The considerable negative $\Delta\Delta G°_{298}$ value (Table 3) for X = Cl or Br indicates that reaction II occurs preferentially in comparison with the reverse reaction I. This result agrees with the experiment according to which compounds **2** and **3** are formed smoothly and in high yields. In the case of X = I, $\Delta\Delta G°_{298}$ is close to zero under our model conditions, i.e., decomposition of carbocation **5** to give the starting 5-fluorouracil (**1**) begins to predominate. Considering the model restrictions and the imperfection of the basis set used, it can be concluded that the hypothesis on the easy reversible I^+ ion elimination as the main factor of the thermodynamic instability of the carbocation formed in oxidative halogenation of 5-fluorouracil (**1**) is quite reasonable, though it cannot be considered as completely proven.

The study of the structure of carbocation **5** does not contradict this hypothesis, either. A regular variation of the

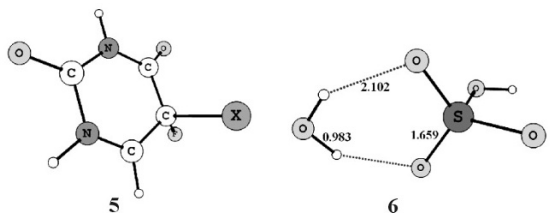


Figure 2. Ionic intermediates as the reagents in the reaction studied; X = F, Cl, Br, I. Calculation in the B3LYP/CEP-121G approximation.

Table 3. Energy characteristics of the interaction of carbocation **5** with anion **6**, the geometry and electron parameters of carbocation **5**. Calculation in B3LYP/CEP-121G + IEFPCM approximation

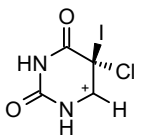
Characteristics	X			
	F	Cl	Br	I
$\Delta G°_{298}$(I), kcal/mol	35.3	4.4	–3.5	–13.8
$\Delta G°_{298}$(II), kcal/mol	–26.8	–23.9	–20.3*	–17.5*
$\Delta\Delta G°_{298}$,** kcal/mol	–62.1	–28.3	> –16.8	> –3.7
r(C(5)–X),*** Å	1.410	1.876	2.026	2.227
r(C(5)–C(6)),*** Å	1.533	1.514	1.506	1.313
r(C(6)–N(1)),*** Å	1.301	1.309	1.313	1.320
q(C(6)),*[4] a. u.	+0.376	+0.407	+0.363	+0.366
q(X),*[4] a. u.	–0.142	+0.239	+0.350	+0.485
Δq,*[5] a. u.	+0.518	+0.168	+0.013	–0.119

* The value is underestimated due to the formation of a C(6)–OH···F intramolecular hydrogen bond in the reaction product.
** $\Delta\Delta G°_{298} = \Delta G°_{298}$(II) – $\Delta G°_{298}$(I), the difference in the Gibbs free energies of reactions II and I.
*** The interatomic distances in molecule of carbocation **5**.
*[4] The effective charges on the atoms (for C-6 atom – the total charge including the hydrogen atom) in carbocation **5**.
*[5] The difference between the effective charges on the C-6 and halogen atoms.

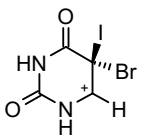
geometry parameters and electron density distribution features in compound **5** are observed upon step-by-step replacement of X in the series from fluorine to iodine (Table 3). It is noteworthy to compare the effective charges on the reaction centers of reactions I and II, i.e., the X and C-6 atoms, respectively. As it is seen from Table 3 data, only in the case of X = I the effective charge on the halogen atom exceeds the q value on the C-6 atom.

Hence, nucleophilic particle **6** will be preferentially oriented toward the halogen atom only in the case of the iodine-containing carbocation. In this case, reversible decomposition of the latter, i.e., reaction I, will occur preferentially only in the case of X = I, resulting in the experimentally noted inertness of 5-fluorouracil in oxidative iodination.

All previous attempts performed in our laboratory to obtain dihalo-substituted uracils, with iodine as one of the halogen atoms, failed. The results obtained in this study are in reasonable agreement with these observations. Furthermore, we examined the stability of carbocation **5**, in which the fluorine atom was replaced by a chlorine (cation **8**) or bromine atom (cation **9**), as well as the competition of the corresponding reactions I and II for these cations. It was found that the probability of reaction II for cations **8**, **9** decreased even more in comparison with I^+ ion elimination from carbocation **5** caused by attack of nucleophile **6** (Table 4). Thus, a theoretical simulation in the B3LYP/CEP-121G approximation indicates that it is impossible to obtain 5-halo-5-iodouracils by oxidative iodination, in agreement with the results of our previous studies in this field.[6]



8



9

Table 4. The Gibbs free energies for interaction of carbocations **5**, **8**, **9** with anion **6** and the effective charges on the C-6 and I atoms.* Calculation in the B3LYP/CEP-121G + IEFPCM approximation

Characteristics	**5**	**8**	**9**
$\Delta G°_{298}$(I), kcal/mol	–13.8	–14.6	–13.0
$\Delta G°_{298}$(II), kcal/mol	–17.5	–14.7	–12.1
$\Delta\Delta G°_{298}$,** kcal/mol	> –3.7	–0.1	+0.9
q(C(6)), a. u.	+0.366	+0.329	+0.311
q(I), a. u.	+0.485	+0.537	+0.513
Δq, a. u.	–0.119	–0.208	–0.202

* For designations, see the notes to Table 3.

Thus, we have developed an efficient alternative method to obtain 5-substituted 5-fluorouracil derivatives and suggested their spatial structure based on quantum-chemical calculations. Furthermore, we made an assumption about the reasons that make it impossible to synthesize 5-substituted 5-iodouracil derivatives.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) in DMSO-d_6, using the solvent signal as internal standard (2.50 ppm for ^{1}H nuclei, 39.5 ppm for ^{13}C nuclei). Melting points were determined in glass capillaries.

Quantum-chemical calculations were carried out using the Gaussian-09 program, Revision C.1.[11] Primary processing and visualization of the results were performed using the ChemCraft program.[12] Complete optimization of the geometry parameters of the compounds being studied and calculations of the force constants were carried out using the B3LYP hybrid electron density functional[13,14] and the 6-311G(d,p) basis set.[15] The total energies were determined by single point calculation for optimized states, using the 6-311+G(d,p) diffusion basis set. Since the specified basis sets are not applicable for compounds containing iodine atoms, the stability of 5-fluoro-5-halo-5,6-dihydrouracil carbocations was additionally analyzed with full optimization of the structures of all compounds and calculation of total energies and force constants in the B3LYP/CEP-121G approximation. Here CEP-121G is the basis set of triple valent splitting with the use of effective potential for the core (nonvalent) electrons.[16,17] The conformity of the structures found to the minima on the potential energy surface was ascertained by the absence of negative elements in the diagonalized Hessian matrix. Identification of the PES saddle points relied on the existence of a single negative (imaginary) frequency. The Gibbs free energies $G°$ of the compounds were calculated as $G° = E_{total} + + ZPE + TC$ (where E_{total} is the total energy of the compound, ZPE is the zero point energy, and TC is the thermal correction to the Gibbs energy calculated for the temperature of the experiments T = 298 K). The effect of the solvent (dimethyl sulfoxide or water) was taken into account using the IEFPCM continuum model.[18,19] The chemical shifts of atoms and the spin-spin coupling constants were calculated by the GIAO method[20,21] in the B3LYP/6-311+G(d,p) approximation.

Synthesis of 5-fluoro-5-halo-6-hydroxy-5,6-dihydrouracils 2, 3 (General method). A portion of 33% H_2O_2 (0.6 ml, 6.0 mmol) was added dropwise to a mixture of 5-fluorouracil (**1**) (0.20 g, 1.5 mmol) and KCl or KBr (3.0 mmol) in 20% H_2SO_4 (2.0 ml). The mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with H_2O and extracted with Et_2O (3×25 ml). The combined extracts were washed with H_2O, dried over Na_2SO_4, concentrated, and recrystallized from acetone.

5-Chloro-5-fluoro-6-hydroxy-5,6-dihydrouracil (2). Yield 0.26 g (93%), white crystals, mp 143–145°C (mp 149–152°C (H_2O).[5] ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.45 (1H, s, OH); 5.02 (1H, d, *J* = 3.8, 6-CH); 8.90 (1H, s, 1-NH); 11.05 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 77.0 (d, *J* = 26.6, C-6); 97.1 (d, *J* = 255.5, C-5); 151.0 (C-2); 163.0 (d, *J* = 27.1, C-4).

5-Bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil (3). Yield 0.33 g (95%), white crystals, mp 174–176°C (mp 181°C (H_2O).[5] ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.68 (1H, s, OH); 5.07 (1H, d, *J* = 5.1, 6-CH); 8.85 (1H, s, 1-NH); 11.00 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 77.6 (d, *J* = 24.9, C-6); 91.0 (d, *J* = 264.4, C-5); 150.8 (C-2); 163.6 (d, *J* = 25.2, C-4).

5-Fluoro-6-hydroxy-5-nitro-5,6-dihydrouracil (4). 5-Fluorouracil (**1**) (0.30 g, 2.3 mmol) was gradually added to conc. H_2SO_4 (0.6 ml). After the starting compound dissolved completely, the mixture was cooled to 0°C, HNO_3 (*d* 1.4 g/ml, 0.6 ml) and conc. H_2SO_4 (0.3 ml) were successively added dropwise, and the mixture was kept at 0–10°C for 4 h. The reaction mixture was diluted with H_2O and extracted with Et_2O (3×25 ml). The combined extracts were washed with H_2O, dried over Na_2SO_4, concentrated, and recrystallized from acetone. Yield 0.42 g (95%), white crystals, mp 171–173°C (mp 179–182°C (H_2O)[5]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.67 (1H, s, OH); 5.22 (1H, d, *J* = 4.7, 6-CH); 9.00 (1H, s, 1-NH); 11.70 (1H, s, 3-NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 73.6 (d, *J* = 24.7, C-6); 107.1 (d, *J* = 245.7, C-5); 150.9 (C-2); 158.4 (d, *J* = 26.1, C-4).

Reaction of 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil (3) with 50% H_2SO_4. Conc. H_2SO_4 (0.6 ml, 11.10 mmol) was added dropwise at 80°C to a suspension of compound **3** (0.15 g, 0.66 mmol) in H_2O (0.6 ml), and the mixture was stirred at the same temperature for 7 h. The resulting precipitate of compound **1** was filtered off, washed with H_2O to a neutral pH, and dried. Yield 0.08 g (93%). The physicochemical properties of the obtained compound **1** matched those reported previously.[22] The starting compound **3** (0.01 g, 7%) was isolated from the filtrate.

This study was financially supported by a Grant of the 2014 Contest on Russian Science Foundation activity "Fundamental scientific studies and research performed by separate scientific groups" (application number 14-13-01307). Information support: grant no. 13-00-14056 of the Russian Foundation for Basic Research. Spectroscopic studies and theoretical calculations were carried out using equipment available at the "Chemistry" User Facilities Center, Ufa Institute of Chemistry of the Russian Academy of Sciences.

References

1. Rideout, J. L.; Henry, D. W.; Beachen, L. M. In *Nucleosides, Nucleotides and their Biological Application*; Academic Press: New York, 1983, p. 1.
2. Blackburn, G. M.; Gait, M. J.; Loakes, D.; Williams, D. M. *Nucleic Acids in Chemistry and Biology*; 3rd ed.; RSC Publishing: Cambridge, 2006, p. 93, 127.
3. González-Barón, M.; Feliu, J.; de la Gándara, I.; Espinosa, E.; Colmenarejo, A.; Martínez-Martínez, B.; Blanco, E.; García-Girón, C.; Juárez, F.; Garrido, P.; Ordóñez, A.; Zamora, P. *Eur. J. Cancer* **1995**, *31*, 2215.
4. Mayer, R. J. *J. Clin. Oncol*. **2001**, *19*, 4093.
5. Cech, D.; Hein, L.; Wuttke, R.; von Janta-Lipinski, M.; Otto, A.; Langen, P. *Nucleic Acids Res*. **1975**, *2*, 2177.
6. Kasradze, V. G.; Ignatyeva, I. B.; Khusnutdinov, R. A.; Suponitskii, K. Yu.; Antipin, M. Yu.; Yunusov, M. S. *Chem. Heterocycl. Compd*. **2012**, *48*, 1018. [*Khim. Geterotsikl. Soedin.* **2012**, 1095.]
7. Günther, H. *NMR Spectroscopy. An Introduction*; John Wiley and Sons: Chichester, 1980, p. 379.
8. Chernikova, I. B.; Khursan, S. L.; Spirikhin, L. V.; Yunusov, M. S. *Russ. Chem. Bull*. **2013**, *62*, 2445. [*Izv. Akad. Nauk*, *Ser. Khim.* **2013**, 2445.]
9. Chernikova, I. B.; Khursan, S. L.; Yunusov, M. S.; Yumagulov, R. A. *Mendeleev Commun.* **2015**, *25*, 221.
10. *NIST Computational Chemistry Comparison and Benchmark Database, NIST Standard Reference Database Number 101*, Release 16a, August 2013; Johnson, R. D., III, Ed.; http://cccbdb.nist.gov/
11. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, *Revision C.1*; Gaussian, Inc.: Wallingford, 2009.
12. ChemCraft. http://www.chemcraftprog.com.
13. Becke, D. *J. Chem. Phys.* **1993**, *98*, 5648.
14. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.
15. Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650.
16. Stevens, W. J.; Basch, H.; Krauss, M. *J. Chem. Phys.* **1984**, *81*, 6026.
17. Stevens, W. J.; Krauss, M.; Basch, H.; Jasien, P. G. *Can. J. Chem.* **1992**, *70*, 612.
18. Mennucci, B.; Cancès, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506.
19. Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.
20. Ditchfield, R. *Mol. Phys.* **1974**, *27*, 789.
21. Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.
22. Duschinsky, R.; Pleven, E.; Heidelberger, C. *J. Am. Chem. Soc*. **1957**, *79*, 4559.