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Chemical Properties of 6-Methyluracil-5-carbaldehyde Oxime

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Abstract—Oxidative chlorination of 6-methyluracil-5-carbaldehyde oxime in a two-phase system gave *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride, and its bromination afforded *ipso*-substitution products, 5-bromo-6-methyluracil and 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil. The reaction of the title compound with acetic anhydride led to the formation of 6-methyluracil-5-carbonitrile or *O*-acetyl derivative, depending on the temperature. *N*-Hydroxy-6-methyluracyl-5-carboximidoyl chloride reacted with acetic acid at 100°C or with potassium iodide in boiling acetone to produce uracil-5-hydroxamic acid which was converted with high yields into the corresponding methyl ester and hydroximic acid amide. Quaternary ammonium salts were obtained by reactions of *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride with pyridine and 1-methyl-1*H*-imidazole.

Keywords: 6-methyluracil, 6-methyluracil-5-carbaldehyde oxime, halogenation, nucleophilic substitution, cycloaddition.

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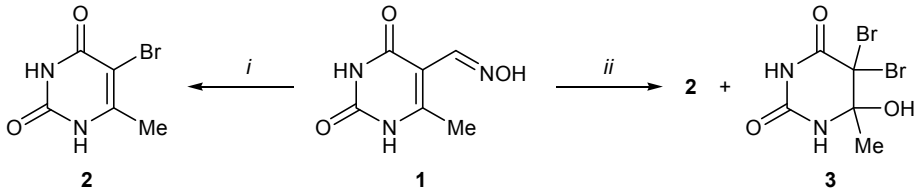
Chemical modifications of pyrimidine bases are important for the synthesis of biologically active compounds. Synthetic transformations of pyrimidines gave rise to new promising medicines. In recent years, the chemistry of 5-substituted pyrimidines has developed especially extensively. These compounds not only exhibit physiological activity but also can be used as starting materials for the synthesis of various pyrimidine derivatives. Therefore, development of methods of functionalization of uracil with the goal of obtaining potentially biologically active compounds and study of their chemical properties are important problems.

6-Methyluracil is a component of a number of drugs, which possesses a broad spectrum of physiological activity [1–4]. In continuation of our studies on halogenation of 6-methyluracil and its derivatives [5–9], herein we report the halogenation of 6-methyluracil-5-carbaldehyde oxime **1** [10] and chemical transformations of the halogenation product with a view to obtaining potential biologically active compounds.

Compound **1** remained unchanged in the system KCl/H_2O_2–20% H_2SO_4 at room temperature [5]. The bromination of **1** with potassium bromide under similar conditions gave *ipso*-substitution product, 5-bromo-6-methyluracil (**2**), in 85% yield. Compound **2** was also obtained by us previously in the bromination of 5-formyl- and 5-hydroxymethyl-6-methyluracils [6]. In order to rule out the possibility of initial formation of 6-methyl-5-formyluracil from compound **1**, the reaction was carried out under similar conditions in the absence of KBr. In this case, initial oxime **1** was recovered from the reaction mixture. It is known that oximes react with molecular halogens (Cl_2, Br_2) to

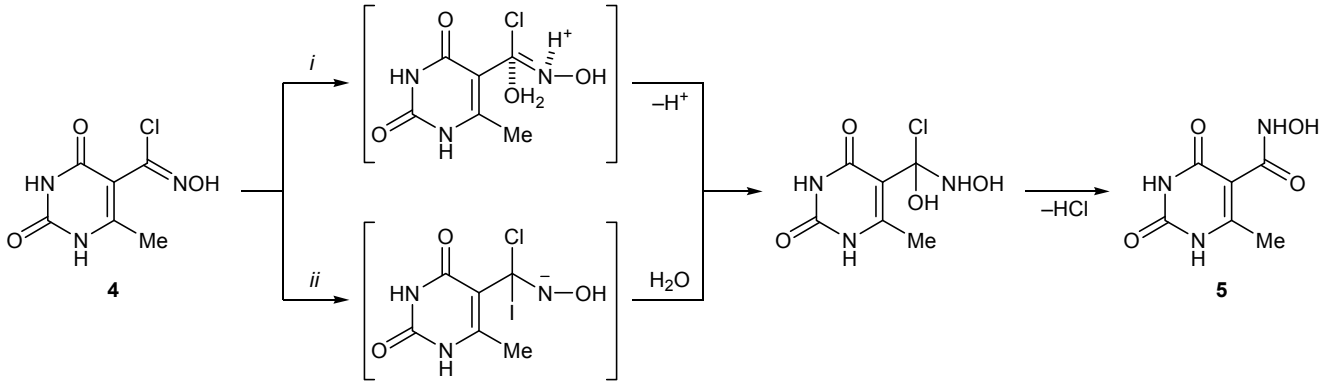
Scheme 1.



2 **1** **3**

Reagents and conditions: *i*: KBr (2 equiv), 33% H_2O_2 (3 equiv), 20% H_2SO_4, room temperature, 5 h, (yield 85%); *ii*: 10 or 38% HBr (3 equiv), 33% H_2O_2 (4 equiv), CH_2Cl_2, room temperature, 3 h; **2** (40–43%), **3** (38–51%).

Scheme 2.



Reagents and conditions: *i*: AcOH/H_2O 100°C, 1 h; *ii*: KI (3 equiv), Me_2CO/H_2O, reflux, 3 h.

give the corresponding hydroximoyl halides [11]; however, oxime **1** failed to react under these conditions. For comparison, benzaldehyde oxime was reacted with molecular chlorine at room temperature; as a result, 76% of benzoic acid was obtained. According to published data [12], the chlorination at 0°C gives benzohydroximoyl chloride (70%). The chlorination of the latter with Cl_2 at room temperature produced benzoic acid (83%).

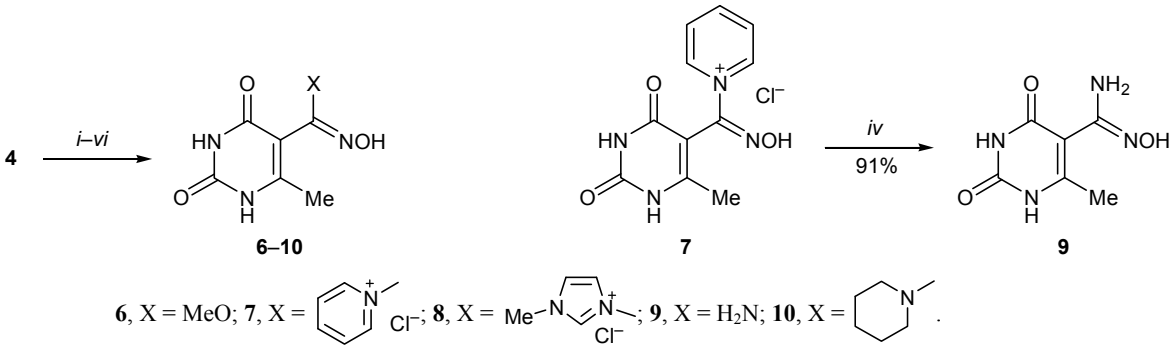
As we showed previously, the halogenation of **1** with $HCl–H_2O_2$ in methylene chloride at room temperature in 3 h afforded 90% of *N*-hydroxy-6-methyluracil-5-carboximidoyl chloride (**4**) [10]. However, the bromination of **1** with 38 or 10% HBr in the presence of 33% H_2O_2 in a two-phase system led to the formation of *ipso*-substitution products, 5-bromo-6-methyluracil (**2**) and 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil (**3**), in low yields (Scheme 1).

By treatment of chloride **4** with acetic acid at 100°C (1 h) we obtained hydroxamic acid **5** in a good yield (Scheme 2). In contrast to published data for hydroximoyl chlorides [13], compound **4** failed to react on heating in water in the absence of acetic acid. Interestingly, hydroxamic acid **5** was also formed in 70% yield when compound **4** was heated with excess potassium iodide in boiling acetone. A probable mechanism of formation of **5** is shown in Scheme 2.

In order to obtain 6-methyluracil-5-carbonitrile oxide and convert it to furoxan, compound **4** was treated with a mixture of triethylamine and methanol at room temperature. However, the product was hydroximic acid methyl ester **6** (yield 80%; Scheme 3). When the reaction was carried out in methanol containing no triethylamine, the initial chloride was recovered from the reaction mixture. Syntheses of hydroximic acid methyl esters by reactions with sodium alkoxides [14–15] or $CaCO_3$ [16] or in a MeOH–H_2O–dioxane mixture at 160°C [17] have been reported; however, these reactions are likely to follow different mechanisms.

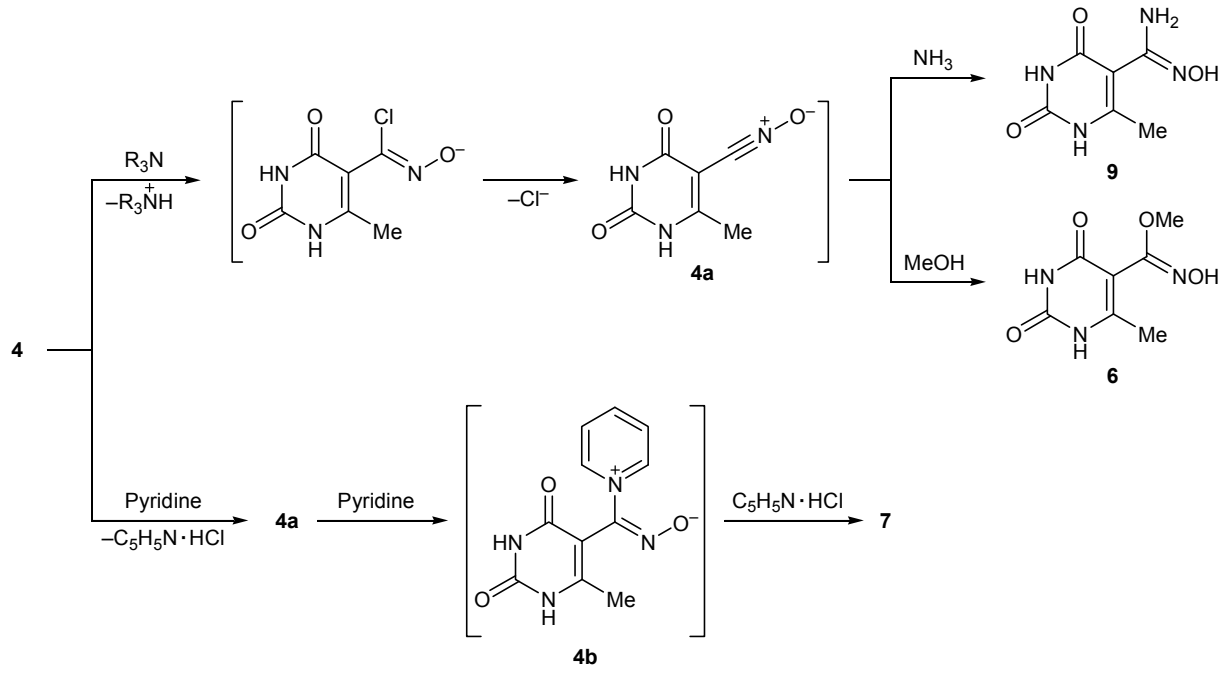
The reaction of **4** with pyridine gave quaternary pyridinium salt **7**. Analogous benzimidazolium salt

Scheme 3.



Reagents and conditions: *i*: Et_3N (2 equiv), MeOH, room temperature, 6 h (**6**, yield 80%); *ii*: pyridine, room temperature, 6 h (**7**, 82%); *iii*: *N*-methylimidazole, room temperature, 6 h (**8**, 77%); *iv*: 29% aq. NH_3, room temperature, 2 h (**9**, 70%); *v*: piperidine, room temperature, 6 h (**10**, 70%); *vi*: pyridine (2 equiv), MeOH, room temperature, 6 h (**7**, 83%).

Scheme 4.



8 was formed in a solution of **4** in 1-methyl-1*H*-imidazole. Treatment of **4** or **7** with aqueous ammonia for 2 h afforded amide oxime **9**, and amide oxime **10** was obtained in the reaction of **4** with piperidine (Scheme 3).

It should be noted that, unlike the reaction of **4** with triethylamine and methanol leading to methyl ester **6**, compound **4** reacted with 2 equiv of pyridine in methanol at room temperature to produce ammonium salt **7**. The structure of all isolated compounds was determined by NMR spectroscopy, including $^{1}H–^{1}H$ COSY, $^{13}C–^{1}H$ HSQC and HMBC, and $^{15}N–^{1}H$ HSQC and HMBC experiments. The experimental data were also confirmed by theoretical calculations.

Obviously, compounds **6**–**10** are formed through intermediate nitrile oxide **4a**, which is typical of hydroximoyl chlorides in alkaline medium [18]. The described reactions are likely to follow the mechanism outlined in Scheme 4. Nitrile oxide **4a** is capable of undergoing dimerization to furoxan (this process generally accompanies to a greater or lesser extent the formation of nitrile oxides [19] or reacting with a nucleophile present in the reaction mixture (methanol, pyridine, *N*-methylimidazole, ammonia, piperidine). However, our results suggest that under the given conditions dimerization of **4a** to furoxan does not occur.

The most widely known reaction of nitrile oxides is [3+2]-cycloaddition. Much less data are available for their reactions with nucleophiles. In particular, reactions with primary and secondary amines were reported to produce amide oximes [18]. Presumably, the only known example of reactions with nitrogen-containing aromatic compounds is the reaction of aminopyridine with carboxyethylhydroxamoyl chloride, which gave a bicyclic compound [20]. Although the path of product formation was not discussed, the reaction obviously involves intermediate nitrile oxide.

Our mechanistic views were confirmed by theoretical modeling of the observed transformations. The most favorable structures and energies of the initial reactants, transition states, and final products of reactions *i* and *vi* in Scheme 3 were calculated in the TPSSTPSS/6-311+G(*d*,*p*) approximation including solvent effect (MeOH) in terms of the IEFPCM-SMD polarized continuum model. The energy profile of these transformations is shown in Fig. 1. The rate constants of the elementary steps outlined in Fig. 1 were estimated using the Eyring equation, and the competing reaction rate ratios (Py vs. MeOH, Et_3N vs. MeOH) were calculated. Under the *v* conditions, nitrile oxide **4a** reacts exclusively with pyridine, $w_{Py}/w_{MeOH} = 3.1\times10^{5}$. Zwitterion **ZW1** thus formed (Fig. 1) is fairly stable: the change of the Gibbs free energy in the reversible decomposition of **ZW1** into pyridine and uracil **4a** is 54.3 kJ/mol, which is sufficiently high for the reversible reaction to be incapable of competing with the fast, obviously diffusion-controlled, protonation of **ZW1** leading to compound **7** (Scheme 4).

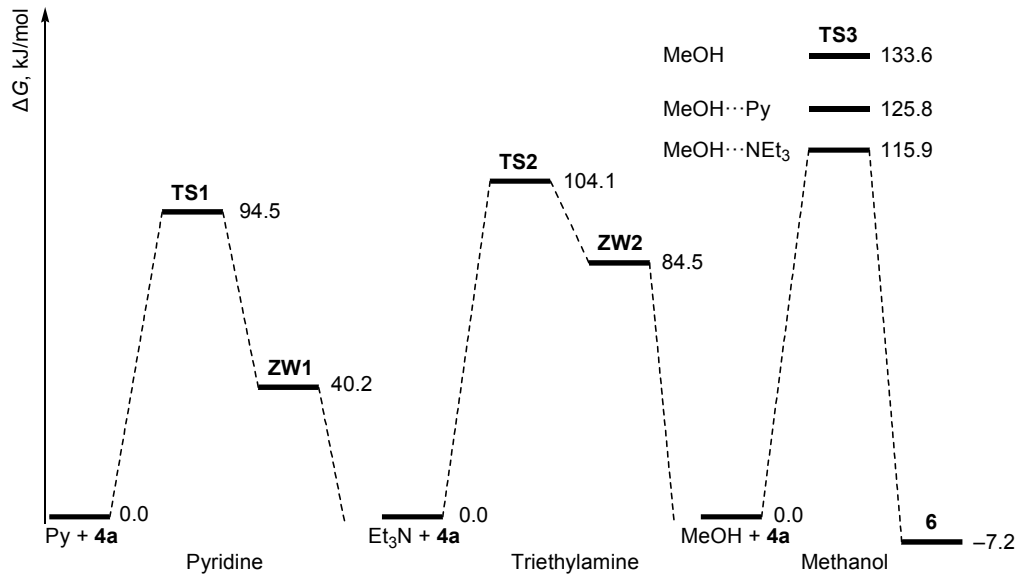


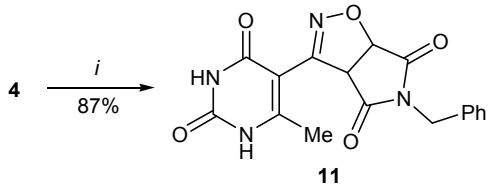
Fig. 1. Gibbs free energy profiles for the reactions of nitrile oxide **4a** with nucleophiles according to TPSSTPSS/6-311+G(*d*,*p*)/IEFPCM-SMD calculations. For the reaction with methanol, energies of transition states are given with account taken of association of methanol with pyridine and triethylamine, as well as for unassociated methanol; **ZW1** is a zwitterion derived from pyridine and **4a** (**4b**), **ZW2** is a zwitterion derived from triethylamine and **4a** (like **4b**), and **TS** is a transition state.

A different situation is observed under the *i* conditions. Though the ratio of the reaction rates of **4a** with Et_3N and MeOH favors the reaction with the former, w_{Et3N}/w_{MeOH} = 120, zwitterion **ZW2** thus formed is thermodynamically unstable. The reverse decomposition of **ZW2** is characterized by a low ΔG value, 19.6 kJ/mol (Fig.1), and hence by a high rate constant, $k = 2.3\times10^9$ s^{-1} (estimated by the Eyring equation). Obviously, the rate of diffusion-controlled stabilization of **ZW2** should be considerably lower that the rate of its reversible decomposition, and the main direction of the irreversible transformation of **4a** should be its reaction with methanol to produce ester **6**, which is observed experimentally.

The reaction of **4** with *N*-benzylmaleimide in the presence of triethylamine gave [3+2]-cycloaddition product **11** (Scheme 5). The results suggest that nitrile oxide **4a** is a weak dienophile. Theoretical DFT analysis of competing processes in the reaction of **4a** with *N*-benzylmaleimide was much simpler. This reaction, as well as the reaction of **4a** with methanol, is exothermic and hence virtually irreversible, ΔG^1 = 91.7 kJ/mol, $\Delta_r G$ = –60.3 kJ/mol; the calculated structures and energies of all species involved in the reaction are available from the authors. The ratio of the rates of the competing reactions, $w_{[3+2]}/w_{MeOH} = 10^4$, indicates that the [3+2]-cycloaddition predominates over the reaction of **4a** with the solvent, which is consistent with the experimental data.

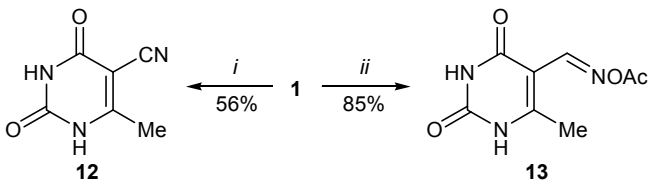
According to [21], oxime **1** in boiling acetic anhydride was converted to 5-cyano-6-methyluracil (**12**). However, by heating compound **1** in acetic anhydride at 70–80°C we obtained *O*-acetyl derivative **13** (Scheme 6). As we showed previously, oxime **1** readily undergoes acylation [10], which is typical of the *syn* isomer. The fact that the reaction of **1** with acetic anhydride at 70–80°C afforded *O*-acetyl oxime **13** in a good yield is likely to be related to its *syn* configuration.

Scheme 5.



Reagents and conditions: *i*: Et_3N (2 equiv), *N*-benzylmaleimide (2 equiv), MeOH, room temperature, 5 h.

Scheme 6.



Reagents and conditions: *i*: Ac_2O, reflux, 0.5 h; *ii*: Ac_2O, 70–80°C, 1 h.

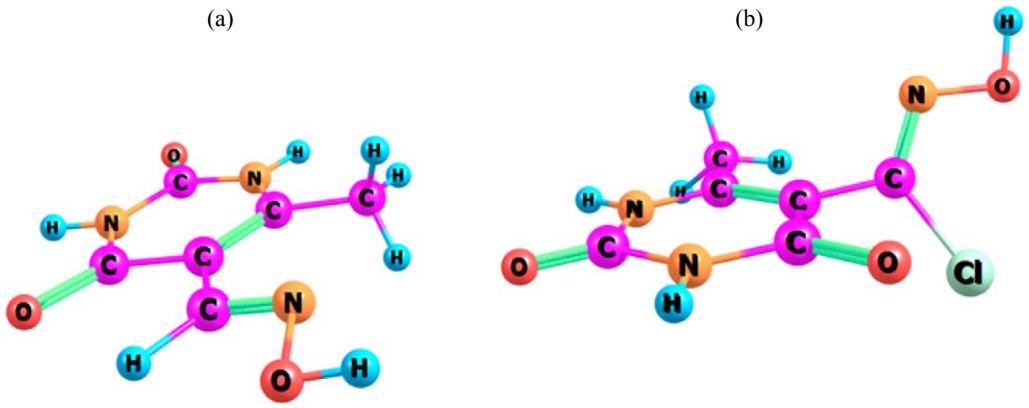


Fig. 2. Most stable isomers of compounds (a) **1** and (b) **4** (b) according to TPSSTPSS/6-311+G(*d*,*p*)/IEFPCM-SMD calculations with methanol as solvent.

This assumption was verified by TPSSTPSS/6-311+G(*d*,*p*)/IEFPCM-SMD calculations of the Gibbs free energies of all possible isomers of **1** and **4** in three solvents with different polarities (pyridine, methanol, water). In fact, the overall population of the *syn* isomers was 0.96 (H_2O), 0.98 (MeOH), and ~1 (Py); the structures of the most stable isomers with a population higher than 0.93 (**1**) and 0.88 (**4**) are shown in Fig. 2. The oxime group in compound **1** is coplanar to the pyrimidine ring, whereas the NOH group of **4** is turned through an angle of 68° with respect to the pyrimidine ring plane. These findings rationalize the high yield of **13** in the acetylation of 6-methyluracil-5-carbaldehyde oxime.

Thus, the oxidative bromination of oxime **1** gives *ipso*-substitution products, 5-bromo-6-methyluracil (**2**) and 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil (**3**). The reaction of hydroximoyl chloride **4** with methanol in the presence of triethylamine yields methyl ester **6**, quaternary salts **7** and **8** are readily formed in the reactions of **4** with pyridine and *N*-methylimidazole, and amide oximes **9** and **10** are products of the reactions of **4** with aqueous ammonia and piperidine, respectively. Amide **9** is also formed in the reaction of **7** with aqueous ammonia. The reaction of oxime **1** with acetic anhydride leads to the formation of nitrile **12** or *O*-acetyl derivative **13**, depending on the temperature.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded at 298 K from solutions in DMSO-d_6 on a Bruker Avance-III 500 spectrometer operating at 500.13 (^1H), 125.76 (^{13}C), or 50.68 MHz (^{15}N) using a PABBO 5-mm *Z*-gradient probe. The ^{15}N chemical shifts were determined from the F_1 projection of the ^1H–^{15}N HMBC spectra and are given relative to ammonia. The mass spectra were obtained on a Shimadzu LCMS-2010 EV quadrupole spectrometer [samples were dissolved in acetonitrile–chloroform and introduced with a syringe pump; eluent acetonitrile–water (95:5), flow rate 0.1 mL/min); positive and negative ion detection at a capillary voltage of 4.5 and –3.5 kV, respectively]; atmospheric pressure chemical ionization mass spectra were recorded at an interface capillary voltage of 25 to –25 V; interface temperature 250°C, heater temperature 200°C, vaporizer temperature 230°C; nebulizer gas nitrogen, flow rate 2.5 L/min. Elemental analyses were performed with a Euro 3000 analyzer. The melting points were measured in glass capillaries. Analytical TLC was performed using Sorbfil plates (Russia); eluent chloroform–methanol (9:1); spots were detected by treatment with a solution of 4-methoxybenzaldehyde.

Bromination of oxime 1. Oxime **1**, 0.20 g (1.2 mmol), was dissolved in 2.00 mL of methylene chloride, 0.56 mL of 38% HBr (3.6 mmol) or 2.70 mL of 10% HBr (3.6 mmol) was added with stirring at room temperature, and 0.48 mL of 33% H_2O_2 (4.8 mmol) was then added dropwise. The mixture was stirred for 3 h at room temperature, and the precipitate was filtered off, washed with distilled water, and dried. We thus isolated 0.10 g (43%) or 0.09 g (40%) of 5-bromo-6-methyluracil (**2**) whose physicochemical characteristics were consistent with those given in [5]. The filtrate was evaporated to obtain 0.14 g (40%) or 0.13 g (38%) of 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil (**3**) [5].

***N*-Hydroxy-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (5).** A suspension of 0.20 g (1.0 mmol) of hydroximoyl chloride **4** in

2.00 mL of acetic acid was stirred for 1 h at 100°C. Alternatively, a suspension of 0.20 g (1.0 mmol) of **4** in 2.00 mL of acetone containing 0.50 g (3.0 mmol) of potassium iodide was refluxed for 5 h. The mixture was evaporated, and the residue was repeatedly washed with chloroform, dried, and recrystallized from methanol. Yield 0.15 g (83%) or 0.13 g (70%), white crystals, mp >290°C (decomp., MeOH). ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 9.73 s (1H, NOH), 11.19 s (1H, 1-H), 11.29 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 17.83 (CH_3), 105.58 (C^5), 150.51 (C^4), 155.53 (C^7), 161.61 (C^2), 163.21 (C^6). Mass spectrum, *m*/*z* (I_{rel}, %): 184 (87) $[M - H]^-$, 166 (100) $[M - H - H_2O]^-$. Found, %: C 38.79; H 3.75; N 22.79. $C_6H_7N_3O_4$. Calculated, %: C 38.92; H 3.81; N 22.70; *M* 185.14.

Methyl *N*-hydroxy-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboximidate (6). Triethylamine, 0.28 mL (2.0 mmol), was added in one portion to a mixture of 0.20 g (1.0 mmol) of **4** and 2.00 mL of methanol, and the mixture was stirred for 6 h at room temperature. The mixture was evaporated, the viscous residue was ground with chloroform, and the precipitate was filtered off, repeatedly washed with chloroform, dried, and recrystallized from methanol. Yield 0.16 g (80%), white crystals, mp 195–197°C (decomp.; from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 3.50 s (3H, OCH_3), 9.75 s (1H, NOH), 11.10 s (1H, 1-H), 11.40 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 17.40 (CH_3), 55.37 (OCH_3), 102.55 (C^5), 150.33 (C^6), 150.98 (C^2), 155.04 (C^7), 163.36 (C^4). Mass spectrum, *m*/*z* (I_{rel}, %): 198 (100) $[M - H]^-$, 166 (25) $[M - H - CH_3OH]^-$. Found, %: C 42.09; H 4.35; N 21.20. $C_7H_9N_3O_4$. Calculated, %: C 42.21; H 4.55; N 21.10. *M* 199.16.

1-[(Hydroxyimino)(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]pyridin-1-ium chloride (7). A suspension of 0.20 g (1.0 mmol) of **4** in 2.00 mL of pyridine or in 2.00 mL of methanol containing 0.16 mL (2.0 mmol) of pyridine was stirred for 6 h at room temperature. The precipitate was filtered off, washed with a 1% aqueous solution of potassium carbonate (pH 8), distilled water, and acetone, dried, and recrystallized from methanol. Yield 0.24 g (82%) or 0.25 g (83%), white crystals, mp 185–187°C (decomp.; from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 8.28 t (2H, 3′-H, 5′-H, *J* = 7.2 Hz), 8.79 t (1H, 4′-H, *J* = 7.2 Hz), 9.20 d (2H, 2′-H, 6′-H, *J* = 7.2 Hz), 11.50 s (1H, 1-H), 11.90 s (1H, 3-H), 13.31 s (1H, NOH). ^{13}C NMR spectrum, δ_C, ppm: 17.55 (CH_3), 100.53 (C^5), 127.24 ($C^{3'}$, $C^{5'}$), 139.76 (C^7), 144.54 ($C^{2'}$, $C^{6'}$), 148.23 ($C^{4'}$), 149.99 (C^2), 158.65 (C^6), 162.46 (C^4). ^{15}N NMR spectrum, δ_N, ppm: 146.27 (N^1), 156.90 (N^3), 209.60 (NOH), 354.90 ($N^{1'}$). Found, %: C 43.81; H 4.02; Cl 11.85; N 18.79. $C_{11}H_{11}ClN_4O_3 \cdot H_2O$. Calculated, %: C 43.94; H 4.36; Cl 11.79; N 18.63. *M* 300.70.

3-[(Hydroxyimino)(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)methyl]-1-methyl-1*H*-imidazol-3-ium chloride (8). A suspension of 0.2 g (1.0 mmol) of **4** in 2.0 mL of *N*-methylimidazole was stirred for 6 h at room temperature. The precipitate was filtered off, washed with a 1% aqueous solution of potassium carbonate (pH 8), distilled water, and acetone, dried, and recrystallized from methanol. Yield 0.23 g (77%), white crystals, mp 224–226°C (decomp.; from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, CH_3), 3.88 s (3H, NCH_3), 7.70 d (1H, 5′-H, *J* = 7.8 Hz), 7.99 d (1H, 4′-H, *J* = 7.8 Hz), 9.70 s (1H, 2′-H), 11.44 s (2H, 1-H, 3-H), 13.05 s (1H, NOH). ^{13}C NMR spectrum, δ_C, ppm: 17.65 (CH_3), 36.90 (NCH_3), 102.00 (C^5), 122.66 ($C^{5'}$), 123.44 ($C^{4'}$), 134.27 ($C^{2'}$), 138.58 (C^7), 151.14 (C^2), 158.36 (C^6), 163.52 (C^4). ^{15}N NMR spectrum, δ_N, ppm: 143.10 (N^1), 166.90 (N^3), 173.90 ($N^{3'}$), 183.90 (NOH), 349.00 ($N^{1'}$). Found, %: C 39.37; H 4.36; Cl 11.75; N 23.17. $C_{10}H_{12}ClN_5O_3 \cdot H_2O$. Calculated, %: C 39.55; H 4.65; Cl 11.67; N 23.06; *M* 303.70.

***N*-Hydroxy-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboximidamide (9).** A suspension of 0.20 g (1.0 mmol) of **4** or of 0.20 g (0.7 mmol) of **7** in 2.00 mL of 29% aqueous ammonia was stirred for 2 h at room temperature. The precipitate was filtered off, washed with distilled water and acetone, dried, and recrystallized from methanol. Yield 0.13 g (70%) or 0.11 g (91%), white crystals, mp > 220°C (decomp.; from MeOH). ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 9.15 s (3H, NOH, NH_2), 10.99 s (2H, 1-H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 17.27 (CH_3), 106.08 (C^5), 147.19 (C^7), 151.07 (C^2), 152.55 (C^6), 163.33 (C^4). Mass spectrum, *m*/*z* (I_{rel}, %): 183 (100) $[M - H]^-$, 165 (12) $[M - H - H_2O]^-$, 166 (9) $[M - H - NH_3]^-$. Found, %: C 39.02; H 4.26; N 30.51; $C_6H_8N_4O_3$. Calculated, %: C 39.13; H 4.38; N 30.42. *M* 184.15.

5-[(Hydroxyimino)(piperidin-1-yl)methyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (10). A suspension of 0.20 g (1.0 mmol) of **4** in 2.00 mL of piperidine was stirred for 6 h at room temperature. The precipitate was filtered off, washed with a 1% aqueous solution of potassium carbonate (pH 8), distilled water, and acetone, dried, and recrystallized from methanol. Yield 0.17 g (70%), white crystals, mp 176–178°C (decomp.;

from MeOH). ^{1}H NMR spectrum, δ, ppm: 1.44 s (4H, 3′-H, 5′-H), 1.47 s (2H, 4′-H), 1.90 s (3H, CH_3), 2.96 d.d (2H, 2′-H, 6′-H, ^2J = 12.8, ^3J = 4.3 Hz), 3.03 d.d (2H, 2′-H, 6′-H, ^2J = 12.8, ^3J = 5.2 Hz), 9.02 s (1H, NOH), 11.02 s (2H, 1-H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 17.00 (CH_3), 24.70 ($C^{4'}$), 25.50 ($C^{3'}$, $C^{5'}$), 46.88 ($C^{2'}$, $C^{6'}$), 104.08 (C^5), 150.52 (C^6), 151.40 (C^7), 153.22 (C^2), 161.91 (C^4). Found, %: C 52.28; H 6.11; N 22.38. $C_{11}H_{16}N_4O_3$. Calculated, %: C 52.37; H 6.39; N 22.21. *M* 252.27.

5-Benzyl-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3a*H*-cyclopenta[*d*][1,2]oxazole-4,6(5*H*,6a*H*)-dione (11). Triethylamine, 0.24 mL (1.7 mmol), was added in one portion to a mixture of 0.17 g (0.8 mmol) of **4** and 0.30 g (1.6 mmol) of *N*-benzylmaleimide in 4.00 mL of methanol. The mixture was stirred for 5 h at room temperature, and the precipitate was filtered off, washed with distilled water, dried, and recrystallized from water. Yield 0.27 g (87%), white crystals, mp > 300°C (from Me_2CO–H_2O). ^{1}H NMR spectrum, δ, ppm: 1.82 s (3H, CH_3), 4.53 d and 4.58 d (1H each, C**H**$_2$Ph, *J* = 14.9 Hz), 5.15 d and 5.63 d (1H, each, 4′-H, *J* = 9.4 Hz), 7.17 d (2H, *o*-H, *J* = 7.0 Hz), 7.27 t (1H, *p*-H, *J* = 7.0 Hz), 7.30 t (2H, *m*-H, *J* = 7.0 Hz), 11.50 s (2H, 1-H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 17.30 (CH_3), 41.90 (**C**H_2Ph), 56.50 ($C^{3'}$), 79.90 ($C^{4'}$), 98.10 (C^5), 127.63 (C^o), 127.84 (C^p), 128.66 (C^m), 135.60 (C^i), 149.80 (C^7), 150.28 (C^2), 154.30 (C^6), 162.40 (C^4), 171.30 ($C^{5'}$), 173.20 ($C^{2'}$). ^{15}N NMR spectrum, δ_N, ppm: 142.30 (N^1), 156.39 (N^3), 178.70 ($N^{1'}$), 373.60 ($N^{7'}$). Mass spectrum: *m*/*z* 353 (I_{rel} 100%) $[M - H]^-$. Found, %: C 57.51; H 3.79; N 15.94. $C_{17}H_{14}N_4O_5$. Calculated, %: C 57.63; H 3.98; N 15.81. *M* 354.32.

6-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (12) was synthesized as described in [21]. ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 11.65 s (1H, 1-H), 11.95 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 18.41 (CH_3), 86.52 (C^7), 114.83 (C^5), 149.73 (C^2), 161.17 (C^4), 163.73 (C^6). Found, %: C 47.52: H 3.25; N 27.89. $C_6H_5N_3O_2$. Calculated, %: C 47.69; H 3.33; N 27.81. *M* 151.12.

6-Methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde *O*-acetyloxime (13). A suspension of 0.20 g (1.2 mmol) of oxime **1** in 2.00 mL of acetic anhydride was stirred for 1 h at 70–80°C. The mixture was cooled, and the precipitate was filtered off, washed with acetone, dried, and recrystallized from methanol. Yield 0.21 g (85%), white crystals, mp > 300°C (decomp.; from MeOH). ^{1}H NMR spectrum, δ, ppm: 2.10 s [3H, C(O)CH_3], 2.35 s (3H, CH_3), 8.33 s (1H, 7-H), 11.41 s (1H, 1-H), 11.53 s (1H, 3-H). ^{13}C NMR spectrum, δ_C, ppm: 19.65 (C^{10}), 19.85 (C^9), 100.31 (C^5), 150.48 (C^6), 152.22 (C^7), 156.98 (C^2), 163.22 (C^4), 168.79 (C^8). Found, %: C 45.41; H 4.15; N 19.99. $C_8H_9N_3O_4$. Calculated, %: C 45.50; H 4.30; N 19.90. *M* 211.17.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

SUPPLEMENTARY INFORMATION

Supplementary information to this article is available from the authors.

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