Halogenation and nitration of 1-carboxymethyl-5-methyluracil. Halophilic reaction involving acetic anhydride

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1-Carboxymethyl-5-halo-6-hydroxy-5-methyl-5,6-dihydrouracils and 1-carboxymethyl-6-hydroxy-5-methyl-5-nitro-5,6-dihydrouracils were synthesized for the first time by oxidative halogenation and nitration of 1-carboxymethyl-5-methyluracil. Dihydrouracil derivatives bearing a Br atom at position C(5) and a hydroxy group at position C(6) treated with Ac_2O undergo deoxyhalogenation.

Keywords: thymine, halogenation, nitration, halophilic reaction.

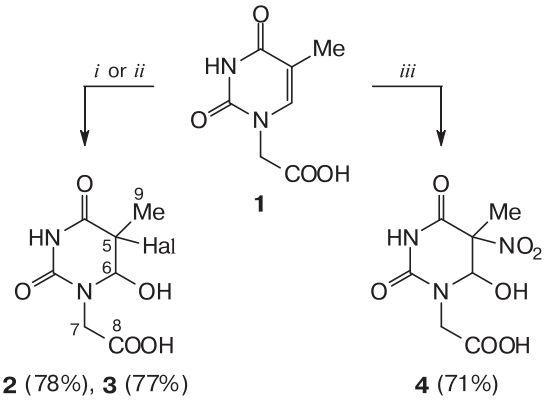
Pyrimidine derivatives are essential components of modern medicines. The high pharmacological activity of pyrimidines is determined by their structural similarity with endogenous biologically active compounds. Antiviral,[1,2] antitumor,[3] antiinflammatory,[4] antibacterial,[5] and antioxidant[6] properties of uracil derivatives have been widely studied.

In order to expand the range of potential biologically active compounds among uracil derivatives, in the present work we synthesized 1-carboxymethyl-5-methyluracil derivatives using oxidative halogenation and electrophilic nitration.

The starting compound, 1-carboxymethyl-5-methyluracil (**1**), was obtained by alkylation of thymine with chloroacetic acid.[7] Derivatives **2—4** were synthesized for the first time by halogenation or nitration of compound **1** according to procedures developed earlier[8] (Scheme 1). Bromination of compound **1** with KBr in 20% aqueous H_2SO_4 gave bromohydrin **2** in 78% yield. The use of a mixture of HCl—H_2O_2 in CH_2Cl_2 was found to be the best method for the synthesis of chlorohydrin **3**. Treatment of compound **1** with a nitrating mixture H_2SO_4—HNO_3 gave product **4**. Geometry of compounds **2—4** probably corresponds to the structure of analogous 5-substituted derivatives of 5-fluorouracil, in which the OH group at the C(6) atom occupies an axial position due to the anomeric effect, while the fluorine atom is equatorial.[9] The suggested stereochemistry is consistent with the anomeric effect for α-substituted saturated *N(O,S)*-heterocycles, which, as shown in many examples, predominantly leads to the axial orientation of the OH group at α-position to the heteroatom in the heterocycle.[10]

In order to study the possibility of intramolecular lactonization involving the C(6)OH and N(1)CH_2COOH groups of compound **2**, which will lead to the corresponding bicyclic product, compound **2** was treated with 10% aq. H_2SO_4 at 70 °C; however, the cyclization did not take place under these conditions (Table 1, entry *1*). Heating compound **2** in 50% aq. H_2SO_4 at 80 °C led to 1-carboxymethyl-5-methyluracil (**1**) in 40% yield (entry *2*). Earlier,[9,11,12] we observed deoxybromination of various pyrimidine substrates following a halophilic mechanism. The term "halophilic ("X-philic") reaction" was introduced by N. S. Zefirov and implies the substitution of a halogen atom by a direct attack of a nucleophilic agent on the halogen atom.[13—15] The halophilic mechanism of the reaction of compound **2** with sulfuric acid was confirmed by the isolation of the expected product **1** in 60% yield

Scheme 1



Hal = Br (**2**), Cl (**3**)

Reagents and conditions: *i*. (for **2**) KBr (2 equiv.), 20% aq. H_2SO_4, 33% aq. H_2O_2 (3 equiv.), ~20 °C, 10 h; *ii*. (for **3**) 34% aq. HCl (3 equiv.), 33% aq. H_2O_2 (4 equiv.), CH_2Cl_2, ~20 °C, 5 h; *iii*. 98% H_2SO_4, 67% aq. HNO_3, 0—20 °C, 5 h.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2159—2162, November, 2020.

Table 1. Reaction of compound **2** with sulfuric acid

Entry	Conditions*	Product	Yield (%) (ratio of **2** : **1**)
1	10% aq. H_2SO_4, 70 °C	**2****	—
2	50% aq. H_2SO_4, 80 °C	**1**	40
3	10% aq. H_2SO_4, KI (5 equiv.), 80 °C	**1**	60
4	Ac_2O, 60 °C	**2****	—
5	Ac_2O, 80 °C	**2** + **1**	(1 : 1)
6	Ac_2O, 100 °C	**2** + **1**	(1 : 1.8)
7	Ac_2O, 140 °C	**1**	62

* The reaction time was 5 h.

** The reaction did not occur, the starting compound **2** was recovered.

after treatment of compound **2** with 10% aq. H_2SO_4 in the presence of an excess of KI at 80 °C according to the procedure we developed earlier[12] (entry *3*).

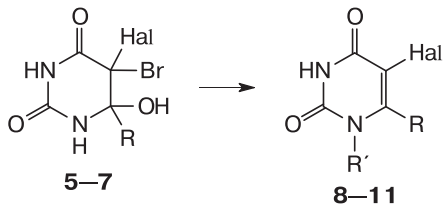
In further research, we attempted to use Ac_2O as a dehydrating agent in the lactonization reaction (see Table 1, entries *4*—*7*). The reaction did not take place when compound **2** was heated in Ac_2O at 60 °C, the starting compound remained unchanged and was recovered (entry *4*). Raising the temperature to 80 °C resulted in a mixture of starting compound **2** and product **1** in a 1 : 1 ratio, and a mixture of **2** : **1** = 1 : 1.8 was obtained at 100 °C (entries *5* and *6*). Reflux of bromide **2** in Ac_2O for 5 h was accompanied by partial resinification of the reaction mixture and the formation of compound **1** in 62% yield (entry *7*). Thus, heating 5-bromo derivative **2** with Ac_2O can lead to deoxyhalogenation products.

We studied the possibility of using Ac_2O for the dehalogenation of uracil derivatives **5**—**9** (Scheme 2). Reflux of 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil (**5**) in Ac_2O for 5 h gave 5-fluorouracil (**8**) in 40% yield, with the reaction being accompanied by resinification. In order to avoid resinification, we tried to shorten the reaction time to 2 h, but in this case we only recovered the starting compound **5**. Reflux of dibromohydrin **6** with Ac_2O resulted in a mixture of 5-bromo-6-methyluracil (**9**) and *N*-bromo-5-bromo-6-hydroxymethyluracil (**10**)[11] in the ratio of 5 : 1. 5-Chloro-6-methyluracil (**11**) was formed in 65% yield upon reflux of bromochlorohydrin **10** in Ac_2O (see Scheme 2).

The use of 5-iodo- and 5-bromo-1,3,6-trimethyluracils as substrates did not lead to 1,3,6-trimethyluracil, the starting compounds were recovered. Apparently, the halophilic debromination of 5-bromouracil derivatives under the action of Ac_2O is possible only if an OH group is present at position 6 of the pyrimidine ring. The plausible mechanism of the halophilic reaction of 5-bromo dihydrouracil derivatives involving Ac_2O is shown in Scheme 3. The reaction can follow the monomolecular (path ***A***) or the bimolecular (path ***B***) mechanism.

In conclusion, in this work we showed for the first time that oxidative halogenation and nitration of 1-carboxymethyl-5-methyluracil results in its 5-substituted (Br, Cl, NO_2) derivatives. It was also shown that Ac_2O promotes the deoxybromination reaction in the series of 5-bromo

Scheme 2

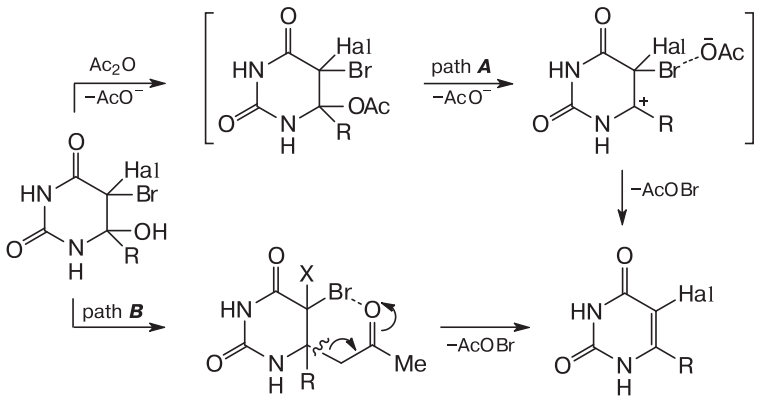


5—7: R = H, Hal = F (**5**); R = Me, Hal = Br (**6**), Cl (**7**)

Compound	R	R′	Hal
8	H	H	F
9	Me	H	Br
10	CH_2OH	Br	Br
11	Me	H	Cl

Reagents and conditions: Ac_2O, 140 °C, 5 h.

Scheme 3



dihydrouracil derivatives containing a hydroxy group at the C(6) atom. This reaction is likely to follow a halophilic mechanism.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 pulsed spectrometer (500.13 (^{1}H) and 125.76 MHz (^{13}C), respectively), using a 5-mm PABBO sensor with a *Z*-gradient at a constant sample temperature of 298 K. Residual signals of solvents were used as references. The ^{13}C NMR spectra were edited based on DEPT-90 and DEPT-135 experiments. Mass spectra were obtained on a LCMS-2010 EV (Shimadzu) quadrupole liquid chromato-mass spectrometer (syringe injection, solvent acetonitrile, eluent acetonitrile—water (95 : 5), flow rate 0.1 mL min^{-1}) in positive and negative ion mode at a capillary potential of 4.5 and −3.5 kV, respectively, under conditions of atmospheric pressure chemical ionization (APCI). The temperature of the APCI interface was 250 °C, the heater temperature was 200 °C, the evaporator temperature was 230 °C, the voltage at the interface capillary was 25÷(−25) V. The flow rate of the drying gas (nitrogen) was 2.5 L min^{-1}. Elemental analysis was performed on a EURO-3000 analyzer. Melting points were determined in a glass capillary. The product ratios in the mixtures was determined from the signal integral intensities in the ^{1}H NMR spectra.

5-Bromo-1-carboxymethyl-6-hydroxy-5-methyl-5,6-dihydrouracil (2). A 33% solution of H_2O_2 (0.33 mL, 3.30 mmol) was added dropwise to a mixture of compound **1** (0.20 g, 1.10 mmol) and KBr (0.26 g, 2.20 mmol) in 20% aq. H_2SO_4 (2.30 mL). The reaction mixture was stirred for 5 h at room temperature, diluted with water, and extracted with diethyl ether. The combined extracts were washed with water, dried with Na_2SO_4, and concentrated. The yield was 0.24 g (78%), white needles, m.p. 141—143 °C (from acetone). ^{1}H NMR (DMSO-d_6), δ: 1.75 (s, 3 H, H(9)); 3.95 (d, 1 H, H_a(7), J = 17.4 Hz); 4.15 (d, 1 H, H_b(7), J = 17.4 Hz); 5.00 (s, 1 H, H(6)); 6.95 (br.s, 1 H, OH); 10.80 (s, 1 H, H(3)). ^{13}C NMR (DMSO-d_6), δ: 23.42 (s, C(9)); 48.08 (s, C(7)); 55.16 (s, C(5)); 85.45 (s, C(6)H); 151.65 (s, C(2)); 168.51 (s, C(4)); 170.57 (s, C(8)). MS, m/z (I_{rel} (%)): 199 [M − HBr]$^-$ (25); 279 [M − H]$^-$ (22), 281 (22); 359 [M + Br]$^-$ (13), 361 (31), 363 (12); 559 [2 M − H]$^-$ (39), 561 (100), 563 (46). Found (%): C, 29.87; H, 3.18; Br, 28.50; N, 9.99. $C_7H_9BrN_2O_5$. Calculated (%): C, 29.91; H, 3.23; Br, 28.43; N, 9.97.

1-Carboxymethyl-5-chloro-6-hydroxy-5-methyl-5,6-dihydrouracil (3). A 34% aq. HCl (0.30 mL, 3.30 mmol) was added to a solution of compound **1** (0.20 g, 1.10 mmol) in CH_2Cl_2 (2.00 mL) with stirring at room temperature, followed by a dropwise addition of 33% aq. H_2O_2 (0.44 mL, 4.40 mmol). The reaction mixture was stirred at room temperature for 5 h, diluted with water, and extracted with diethyl ether. The combined extracts were washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The yield was 0.20 g (77%), colorless needles, m.p. 100—102 °C (from acetone). ^{1}H NMR (DMSO-d_6), δ: 1.65 (s, 3 H, H(9)); 3.97 (d, 1 H, H_a(7), J = 17.4 Hz); 4.17 (d, 1 H, H_b(7), J = 17.4 Hz); 4.95 (s, 1 H, H(6)); 7.25 (br.s, 1 H, OH); 10.88 (s, 1 H, H(3)). ^{13}C NMR (DMSO-d_6), δ: 22.56 (s, C(9)); 48.27 (s, C(7)); 63.02 (s, C(5)); 85.56 (s, C(6)H); 151.99 (s, C(2)); 168.37 (s, C(4)); 171.01 (s, C(8)). MS, m/z (I_{rel} (%)): 235 [M − H]$^-$ (100), 237 (28); 471 [2 M − H]$^-$ (56), 473 (36), 475 (5). Found (%): C, 35.49; H, 3.78; Cl, 15.01; N, 11.87. $C_7H_9ClN_2O_5$. Calculated (%): C, 35.53; H, 3.83; Cl, 14.98; N, 11.84.

1-Carboxymethyl-6-hydroxy-5-methyl-5-nitro-5,6-dihydrouracil (4). Compound **1** (0.20 g, 1.10 mmol) was gradually dissolved with stirring in concentrated H_2SO_4 (d = 1.8356 g mL^{-1}, 0.33 mL). A 67% aq. HNO_3 (d = 1.399 g mL^{-1}, 0.20 mL) was added dropwise to the resulting solution of compound **1** cooled to 0 °C. The reaction mixture was allowed to stand for 5 h at 0—10 °C, diluted with water, neutralized with $NaHCO_3$ to pH 3, and extracted with diethyl ether. The combined extracts were washed with water, dried with Na_2SO_4, and concentrated *in vacuo*. The yield was 0.19 g (71%), white needles, m.p. 168—170 °C (from acetone). ^{1}H NMR (DMSO-d_6), δ: 1.70 (s, 3 H, H(9)); 3.89 (d, 1 H, H_a(7)), J = 17.4 Hz); 4.18 (d, 1 H, H_b(7), J = 17.4 Hz); 5.35 (s, 1 H, H(6)); 7.00 (br.s, 1 H, OH); 11.32 (s, 1 H, H(3)). ^{13}C NMR (DMSO-d_6), δ: 17.91 (s, C(9)); 46.40 (s, C(7)); 82.05 (s, C(5)); 90.47 (s, C(6)H); 151.42 (s, C(2)); 163.56 (s, C(4)); 170.27 (s, C(8)). MS, m/z (I_{rel} (%)): 246 [M − H]$^-$ (100); 493 [2 M − H]$^-$ (55). Found (%): C, 33.97; H, 3.63; N, 17.05. $C_7H_9N_3O_7$. Calculated (%): C, 34.02; H, 3.67; N, 17.00.

Reaction of 5-bromo-1-carboxymethyl-6-hydroxy-5-methyl-5,6-dihydrouracil (2) with 50% aq. H_2SO_4. A 98% H_2SO_4 (0.66 mL, 12.00 mmol) was slowly added dropwise to a mixture of compound **2** (0.20 g, 0.70 mmol) in H_2O (0.70 mL) at 80 °C and the mixture was stirred for 5 h at the same temperature. After cooling, the precipitate formed was collected by filtration, washed with distilled water, and dried to obtain compound **1** (0.05 g, 40%).

Reaction of 5-bromo-1-carboxymethyl-6-hydroxy-5-methyl-5,6-dihydrouracil (2) with 10% aq. H_2SO_4 in the presence of KI. Potassium iodide (0.58 g, 3.50 mmol) was added to a mixture of compound **2** (0.20 g, 0.70 mmol) in 10% aq. H_2SO_4 (2.00 mL) and the mixture was stirred for 5 h at 80 °C. After cooling, the reaction mixture was diluted with distilled water (5 mL) and extracted with $CHCl_3$ (3×10 mL). The combined extracts were washed with water, dried with Na_2SO_4, and concentrated *in vacuo* to obtain compound **1** (0.08 g, 60%).

Dehydroxyhalogenation of compounds 2 and 5—7 with Ac_2O (general procedure). Compound **2** or **5—7** (0.20 g) was heated with stirring with Ac_2O (2 mL) for 5 h. The reaction mixture was concentrated, the residue was sequentially treated with $CHCl_3$ and water and dried.

Compound **2** (0.19 g) was recovered after heating of compound **2** (0.20 g, 0.70 mmol) at 60 °C and the work-up of the reaction mixture. A 1 : 1 mixture of compounds **2** and **1** (0.12 g) was isolated after heating of compound **2** (0.20 g, 0.70 mmol) at 80 °C and the work-up process. A 1 : 1.8 mixture of compounds **2** and **1** (0.10 g) was isolated after heating of compound **2** (0.20 g, 0.70 mmol) at 100 °C and the work-up process. Product **1** (0.08 g, 62%) was isolated after reflux of compound **2** (0.20 g, 0.70 mmol) and the work-up process.

5-Fluorouracil (**8**) (0.05 g, 40%) was isolated after reflux of compound **5** (0.20 g, 0.88 mmol) and subsequent work-up of the reaction mixture, the physicochemical characteristics of which corresponded to those of the known sample.[16]

A 5 : 1 mixture of compounds **9** and **10** (0.09 g) was isolated after reflux of compound **6** (0.20 g, 0.66 mmol) and subsequent work-up of the reaction mixture. The physicochemical characteristics of products **9** and **10** corresponded to those of the known samples.[9,17]

5-Chloro-6-methyluracil (**11**) (0.08 g, 65%) was isolated after reflux of compound **7** (0.20 g, 0.78 mmol), the physicochemical characteristics of the product corresponded to those of the known sample.[17]

The spectral part of the study was carried out on the equipment of the "Khimiya" User Service Center of the Ufa Institute of Chemistry, Ufa Federal Research Center of the Russian Academy of Sciences.

This work was financially supported by the Ministry of Higher Education and Science of the Russian Federation (Topic No. AAAA-A20-120012090026-9).

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Received February 28, 2020;
in revised form March 26, 2020;
accepted June 17, 2020