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REACTION OF HALOGENATED URACILS WITH KI

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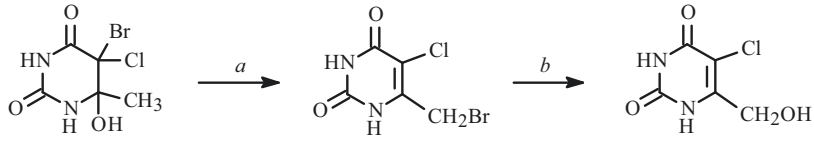
Treatment of 5-iodo-1,3,6-trimethyluracil or 5-bromo-1,3,6-trimethyluracil with H_2SO_4 (5%) in the presence of an excess of KI at 80°C for 5 h produced 1,3,6-trimethyluracil as the only product. Analogous treatment of N*-bromo-6-iodomethyluracil gave a mixture with 5-bromo-6-iodomethyluracil as the main constituent. The reaction with an excess of KI in MeOH at 50°C formed 5-bromo-6-hydroxymethyluracil,* N*(1)-iodo-5-bromo-6-hydroxymethyluracil,* N*(3)-iodo-5-bromo-6-iodomethyluracil, and 5-bromo-6-iodomethyluracil depending on the reaction time.*

Keywords: bromo- and iodo-derivatives of methyluracils.

Halogenated uracils are important components in drug design [1–4]. They are formed in the human body in various inflammations [5, 6]. Therefore, the development of synthetic methods for halogenated uracils, their conversions under various conditions, and the study of the mechanisms of these conversions are highly critical problems.

Previously, oxidative halogenation of 6-methyluracil derivatives was shown to be effective and several of their conversions were studied [7]. Thus, treatment of 5-iodo-1,3,6-trimethyluracil with H_2SO_4 (50%) at 80°C gave 1,3,6-trimethyluracil although 5-bromo-1,3,6-trimethyluracil formed a mixture of 1,3,6-trimethyluracil and 6-bromomethyl-1,3-dimethyluracil. However, 5-chloro-1,3,6-trimethyluracil did not react. The reaction with 5,5-dibromo-6-hydroxy-6-methyl-5,6-dihydrouracil under analogous conditions gave *N*-bromo-5-bromo-6-hydroxymethyluracil [8]. Herein, it is demonstrated that treatment of 5-bromo-5-chloro-6-hydroxy-6-methyl-5,6-dihydrouracil (**1**) with H_2SO_4 (50%) at 80°C formed 5-chloro-6-bromomethyluracil (**2**). Refluxing **2** in aqueous MeCN for 2 h produced **3** with a 6-hydroxymethyl group (Scheme 1). Under the same conditions, 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil converted in good yield into 5-fluorouracil whereas 5-chloro-5-fluoro-6-hydroxy-5,6-dihydrouracil turned out to be inert [9].

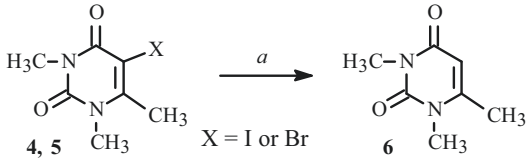


1 **2** **3**

a. 50% H_2SO_4, 80°C, 5 h; *b*. MeCN–H_2O 1:1, reflux, 2 h

Scheme 1

It was also demonstrated that 1,3,6-trimethyluracil (**6**) was formed as the only product from treatment of 5-iodo- (**4**) or 5-bromo-1,3,6-trimethyluracil (**5**) with H_2SO_4 (5%) in the presence of an excess of KI at 80°C for 5 h (Scheme 2). These reactions without KI returned starting **4** and **5**. The corresponding 5-chloro-derivative was unreactive.



4, 5 X = I or Br **6**

a. KI (5 equiv.), 5% H_2SO_4, 80°C, 5 h

Scheme 2

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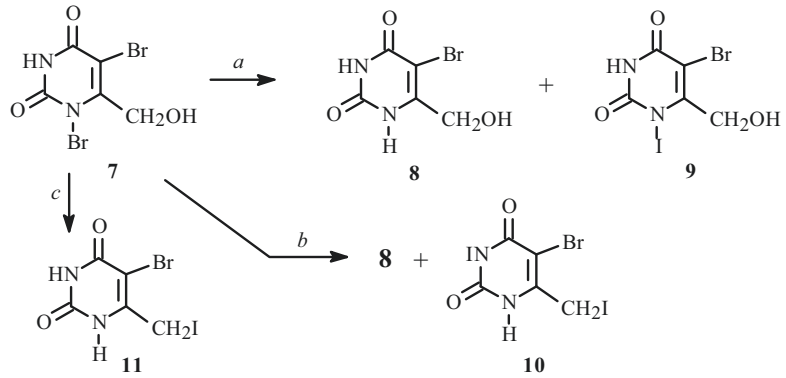
The reaction mechanism probably involved initial protonation of C-5 and formation of a carbonium ion on C-6 followed by cleavage of a halo cation X by I^- to release I_2 (X = I) or IBr (X = Br).

The reactions of previously reported [8] *N*-bromo-5-bromo-6-hydroxymethyluracil (**7**) with KI under various conditions seemed interesting. Treatment of **7** with a two-fold excess of KI in MeOH at 50°C for 4 h (Scheme 3) formed two products in a 3:1 ratio (determined from integrated intensities in PMR spectra).



a. KI (2 equiv.), MeOH, 50°C, 4 h; *b*. KI (2 equiv.), MeOH, 50°C, 1-2 h; *c*. KI (5 equiv.), 5% H_2SO_4, 80°C, 5 h

Scheme 3

The PMR spectrum of the main product had H-1:H-3:H-7 resonances with integrated intensities of 1:1:2. The ^1H–^{13}C HMBC NMR spectrum indicated all these protons gave cross peaks with the C-5 resonance (92.25 ppm); proton H-1, with the resonance of C-7 (59.67 ppm). Resonances of the N-1 and N-3 protons were located at 10.53 and 11.50 ppm, respectively. ^{15}N–^1H correlation spectra showed that these two protons correlated to resonances for N-1 at 134.80 and N-3 at 156.13 ppm. The ^{13}C NMR spectrum had resonances that coincided accurately up to 0.4–0.5 ppm with the resonances of starting **7** [8]. Thus, the main reaction product had the structure 5-bromo-6-hydroxymethyluracil (**8**).

A second minor product gave ^{13}C NMR resonances that were significantly different from those of **7**, i.e., C-7 $\Delta\delta = 17$; C-6 $\Delta\delta = 10$, and C-5 $\Delta\delta = 8$ ppm. The ^{15}N NMR spectrum with full proton suppression gave two weak resonances at δ 137.68 and 156.87 ppm for N-1 and N-3. The ^{15}N NMR spectrum recorded in *inept* mode was missing the resonance at 137.68 ppm. This suggested that the proton on this atom was replaced. The ^1H–^{13}C HMBC spectrum showed that H-3 coupled with C-5 (100.29 ppm) and C-4 (159.80 ppm).

The electrospray ionization (ESI) mass spectrum in negative-ion mode of the reaction product had two strong peaks with *m*/*z* 329/331 of approximately equal intensity that corresponded to the ion $[M - 17]^-$ that formed by loss of hydroxyl radical from the parent ion. The peak was doubled because of the Br atom. The mass showed that the N(1) substituent was an I atom, as shown above. This confirmed the ^{15}N NMR spectral data recorded in *inept* mode. Therefore, the second product had the structure *N*(1)-iodo-5-bromo-6-hydroxymethyluracil (**9**). The mass spectrum of the product had a triplet of peaks for $[M - OH]^-$ for an impurity of starting **7** with *m*/*z* 281:283:285 in a 0.5:1:0.4 ratio that corresponded to a compound with two Br atoms.

Shortening the reaction time to 1 and 2 h produced **10** in addition to **8** (main product from the reaction for 2 h). Compound **10** had a C-7 I atom (main product of the reaction for 1 h). This was confirmed by a characteristic resonance for the $–CH_2I$ group in the ^{13}C NMR spectrum at –1.52 ppm (Scheme 3b).

Compound **10** was assumed to have an I atom on N-3 because of the appearance in negative-ion ESI mass spectra of **10** of a doublet of peaks with *m*/*z* 329/331. Its loss from the molecular ion was responsible for the formation of this ion $[M - I]^-$ with *m*/*z* 329/331. An analysis of ^{13}C NMR spectra of all synthesized compounds suggested that the N-3 I atom had little effect on the chemical shifts of the uracil core, in contrast to an N-1 I atom.

The dominant product from the reaction of **7** with a five-fold excess of KI in H_2SO_4 (5%) at 80°C for 5 h was 5-bromo-6-iodomethyluracil (**11**) (Scheme 3c). Its structure was confirmed by PMR and ^{13}C NMR spectral data. The negative-ion ESI mass spectrum of **11** showed a doublet of peaks with *m*/*z* 329/331 that were apparently due to the $[M - H]^-$ ion. Minor products were obviously compounds with a C-6 hydroxymethyl, a C-5 Br atom, and an N-1 or N-3 I atom.

An analysis of negative-ion mass spectra of the uracil derivatives indicated that the C-7 substituent (OH, Br, I) (**2**, **3**, **7**, **9**–**11**) and a halogen on one of the N atoms (Br or I; **7**, **9**–**11**) led under ESI conditions to the loss of the C-7 substituent. H atom was lost if the N atom did not have a halogen (**2**, **3**, **11**).

EXPERIMENTAL

PMR, ^{13}C NMR, and ^{15}N NMR spectra were recorded on a pulsed Bruker Avance-III 500 MHz spectrometer at operating frequency 500.13 MHz for ^{1}H and 125.47 MHz for ^{13}C. Chemical shifts in PMR and ^{13}C NMR spectra were given in ppm with solvent resonances as standards. Chemical shifts in ^{15}N NMR were obtained in F_1-projection of ^{1}H–^{15}N HMBC spectra and were adjusted to the ammonia scale. 2D spectra were recorded using standard multi-pulse sequences in standard modes of the instrument software. Mass spectra were obtained on an LCMS-2010 EV quadrupole liquid chromatograph–mass-spectrometer (Shimadzu) in negative-ion mode with ESI. Melting points were determined in glass capillaries.

Starting compounds **1** [7], **4** [8], **5** [8], and **7** [8] were synthesized by the previously published methods. Physicochemical characteristics agreed with known data.

5-Chloro-6-bromomethyluracil (2). A suspension of **1** (0.27 g, 1 mmol) in H_2O (1.40 mL) at 80°C was treated dropwise with H_2SO_4 (98%, 1.30 mL, 25.5 mmol) and stirred at this temperature for 5 h. The resulting precipitate was filtered off, rinsed with distilled H_2O until neutral, and dried at 60°C to afford white crystals of **2** (0.13 g, 52%), mp 250–252°C (EtOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 3.35 (2H, s, H-7), 10.80 (1H, s, H-1), 11.50 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 24.82 (t, C-7), 105.50 (s, C-5), 147.97 (s, C-2), 149.95 (s, C-6), 160.12 (s, C-4). Mass spectrum, ESI, *m/z* (I_{rel}, %): $[M - H]^-$ 237 (71), 239 (100), 241 (29).

5-Chloro-6-hydroxymethyluracil (3). A suspension of **2** (0.24 g, 1 mmol) in aqueous MeCN (4 mL, MeCN–H_2O, 1:1) was stirred and refluxed for 2 h. The resulting precipitate was filtered off, rinsed with distilled H_2O, and dried at 60°C to afford white crystals of **3** (0.21 g, 95%), mp 237–239°C (EtOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm, J/Hz): 4.05 (2H, d, J = 3.5, H-7), 4.35 (1H, br.s, OH), 10.70 (1H, s, H-1), 11.50 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 57.58 (t, C-7), 102.70 (s, C-5), 149.25 (C-2), 151.25 (C-6), 160.66 (C-4). $C_5H_5ClN_2O_3$. Mass spectrum, ESI, *m/z* (I_{rel}, %): $[M - H]^-$ 175 (76), 177 (24).

Reaction of 5-Iodo-1,3,6-trimethyluracil (4), 5-Bromo-1,3,6-trimethyluracil (5), or *N*-Bromo-5-bromo-6-hydroxymethyluracil (7) with KI in H_2SO_4 (5%) (General Method). A suspension of **4**, **5**, or **7** (1 mmol) and KI (0.83 g, 5 mmol) in H_2O (1.88 mL) at 80°C was treated dropwise with H_2SO_4 (98%, 0.05 mL, 1 mmol), stirred for 5 h at that temperature, cooled, treated with $Na_2S_2O_3 \cdot 5H_2O$ solution (10%), and extracted with $CHCl_3$. The combined extracts were washed with distilled H_2O, dried over Na_2SO_4, and evaporated to produce **6** (0.10 g, 68% yield from **4** and 0.10 g, 65% from **5**). The physicochemical characteristics agreed with known data [8]. Compound **7** (0.27 g) was obtained as a mixture and a yellow amorphous powder, the main component of which was 5-bromo-6-iodomethyluracil (**11**).

5-Bromo-6-iodimethyluracil (11). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 4.09 (2H, s, H-7), 11.44 (1H, s, H-1), 11.52 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): –1.44 (t, C-7), 95.57 (s, C-5), 150.14 (s, C-2), 152.11 (s, C-6), 160.54 (s, C-4). Mass spectrum, ESI, *m/z* (I_{rel}, %): $[M - H]^-$ 329 (99), 331 (100).

Reaction of *N*-Bromo-5-bromo-6-hydroxymethyluracil (7) with KI for 1, 2, and 4 h (General Method). A mixture of **7** (0.3 g, 1 mmol) and KI (0.33 g, 2 mmol) in MeOH (2 mL) was stirred at 50°C for 1, 2, and 4 h and cooled. The precipitate was filtered off, rinsed with distilled H_2O and Me_2CO, and dried at 60°C to afford a mixture of **8** and **9** as a yellow amorphous powder (0.23 g, 3:1 ratio) if the reaction was carried out for 4 h; a mixture of **8** and **10** (0.33 g, 1:2 ratio), for 1 h; and a mixture of **8** and **10** (0.36 g, 3:1 ratio), for 2 h.

5-Bromo-6-hydroxymethyluracil (8). ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 4.00 (1H, br.s, OH), 4.30 (2H, s, H-7), 10.54 (1H, s, H-1), 11.50 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 59.67 (t, C-7), 92.25 (s, C-5), 150.12 (s, C-2), 152.83 (s, C-6), 159.94 (s, C-4). ^{15}N NMR spectrum (50.58 MHz, DMSO-d_6, δ, ppm): 134.80 (N-1), 156.13 (N-3).

***N*(1)-Iodo-5-bromo-6-hydroxymethyluracil (9).** ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 4.00 (1H, br.s, OH), 4.50 (2H, s, H-7), 11.72 (1H, s, H-3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): 42.89 (t, C-7), 100.29 (s, C-5), 149.90 (s, C-2), 142.00 (s, C-6), 159.80 (s, C-4). ^{15}N NMR spectrum (50.58 MHz, DMSO-d_6, δ, ppm): 137.68 (N-1), 156.87 (N-3). Mass spectrum, ESI, *m/z* (I_{rel}, %): $[M - OH]^-$ 329 (99), 331 (100).

***N*(3)-Iodo-5-bromo-6-iodomethyluracil (10).** ^{1}H NMR spectrum (500 MHz, DMSO-d_6, δ, ppm): 4.17 (2H, s, H-7), 10.50 (1H, s, H-1). ^{13}C NMR spectrum (125 MHz, DMSO-d_6, δ, ppm): –1.52 (t, C-7), 94.88 (s, C-5), 150.00 (s, C-2), 151.73 (s, C-6), 159.88 (s, C-4). Mass spectrum, ESI, *m/z* (I_{rel}, %): $[M - I]^-$ 329 (99), 331 (100).

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