# Inhibiting effect of 6-methyluracil derivatives on the free-radical oxidation of 1,4-dioxane

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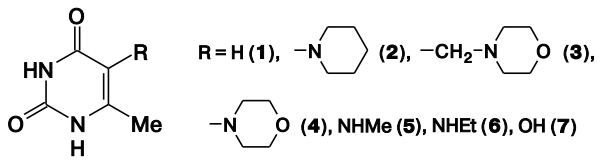
The antioxidation activity of 5-substituted 6-methyluracils was quantitatively estimated in the model system of initiated radical-chain oxidation of 1,4-dioxane. The rate constants of the reactions of 1,4-dioxane peroxide radicals with 6-methyluracil (**1**), 6-methyl-5-piperidinouracil (**2**), 6-methyl-5-morpholinomethyluracil (**3**), 6-methyl-5-morpholinouracil (**4**), 6-methyl-5-methylaminouracil (**5**), 5-ethylamino-6-methyluracil (**6**), and 5-hydroxy-6-methyluracil (**7**) were measured. Among compounds **1**—**7**, derivative **7** is most efficient with an inhibition rate constant of $(5.2\pm0.1)\cdot10^4$ L mol$^{-1}$ s$^{-1}$ (60 °C).

**Key words:** radical chain oxidation, inhibition rate constant, 5-hydroxy-6-methyluracil.

Uracil derivatives are used in medicines as drugs with a wide range of pharmacological activity associated, in particular, with the antiradical properties of these compounds. The inhibiting effect of 6-methyluracil (**1**) and its 5-substituted derivatives **2**—**7** on the oxidation process was quantitatively estimated in the present work. The initiated radical-chain oxidation of 1,4-dioxane was chosen as a model system to solve this problem.[1] The inhibition rate constants were measured. The influence of substituents in position 5 of the 6-methyluracil cycle on the antioxidation activity was analyzed.




**1—7**

## Experimental

1,4-Dioxane was purified by multiple fractional distillation over potassium hydroxide. Azobis(isobutyronitrile) (AIBN) was twice recrystallized from freshly distilled ethanol and then dried *in vacuo*.

6-Methyluracil (**1**) (Joint-Stock Company "Farmakon") was used as received. 5-Hydroxy-6-methyluracil (**7**) was synthesized and purified according to the known procedure.[2]

6-Methyl-5-piperidinouracil (**2**) and 6-methyl-5-morpholinouracil (**4**) were synthesized by the reflux of 5-bromo-6-methyluracil (0.01 mol) in morpholine or piperidine excess (0.5 mol), respectively, followed by the removal of the solvent under reduced pressure and by the precipitation of the product with ethanol. 6-Methyl-5-methylaminouracil (**5**) and 5-ethylamino-6-methyluracil (**6**) were synthesized by heating of a mixture of 5-bromo-6-methyluracil (0.05 mol) and the corresponding amine hydrochloride in an aqueous solution of potassium hydroxide in an autoclave for 7 h at 160 °C followed by cooling of the reaction mixture and separation of the precipitate formed. 6-Methyl-5-morpholinomethyluracil (**3**) was synthesized by the reflux of a mixture of 6-methyluracil (0.05 mol), morpholine (0.05 mol), and 31% formalin (6.7 mL) in ethanol (150 mL) for 6 h with the separation of the precipitate formed from the cooled reaction mixture. The yields of compounds **2**—**6** after recrystallization from ethanol were 75, 86, 54, 69, and 64%, respectively.

$^1$H and $^{13}$C NMR spectra of compounds **2**—**6** were recorded on a Bruker AM-300 instrument in DMSO-$d_6$ using $Me_4Si$ as an internal standard. IR spectra of suspensions of the substances in Nujol were obtained on a Specord UR-20 spectrometer (Carl Zeiss Jena) equipped with NaCl and LiF prisms. The UV spectra of 0.00001% solutions were recorded on a Specord M-400 instrument in the range of 200—350 nm in a 10-mm optical cell. Melting points were determined on a Boetius heating stage. The physicochemical and spectral characteristics of compounds **2**—**6** are given in Table 1.

The initiator was AIBN. The initiation rate was calculated by the equation

$$w_i = 2ek_d[\text{AIBN}]$$

using the rate constant for AIBN decomposition ($k_d$) in cyclohexanol ($\log k_d = 17.70 - 35/(4.575T\cdot10^{-3})$, $e = 0.5$). The chosen $k_d$ value is satisfactorily consistent with the rate constants for AIBN decomposition in 1,4-dioxane measured from the rate of nitrogen evolution.[3]

1,4-Dioxane was oxidized with air oxygen at 60 °C in a glass reactor. The reactor was loaded with a solution of the initiator in

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**Table 1.** Physicochemical and spectral characteristics of compounds **2—6**

| Compound | M.p. /°C | Found / Calculated (%) C | H | N | Empirical formula | UV*, $\lambda_{min}/\lambda_{max}$ /nm | IR, $\nu/cm^{-1}$ | NMR, δ $^1$H | NMR, δ $^{13}$C |
|---|---|---|---|---|---|---|---|---|---|
| **2** | 215—217 | 57.78 / 57.40 | 7.95 / 7.23 | 20.42 / 20.08 | $C_{10}H_{15}N_3O_2$ | 234/262 | 1116—1263 (=N—), 1377 ($CH_3$), 1456 ($CH_2$), 1647 (C=C), 1662, 1762 (C=O), 2852, 2920 (CH), 3109, 3159 (NH), 3213 (=N—) | 1.65 (t, 2 H, C(11)$H_2$, $J$ = 5.8); 1.82 (q, 4 H, C(8)$H_2$, C(10)$H_2$, $J$ = 5.8); 2.20 (s, 3 H, C(6)$CH_3$); 3.20 (t, 4 H, C(7)$H_2$, C(11)$H_2$, $J$ = 5.5); 10.10 (br.s, 2 H, N(1)H, N(3)H) | 14.78 (C(6)<u>C</u>$H_3$); 24.62 (C(9)); 27.62 (C(8), C(10)); 51.80 (C(7), C(11)); 123.02 (C(5)); 150.40 (C(6)); 151.33 (C(2)=O); 163.40 (C(4)=O) |
| **3** | 269—271 | 53.83 / 53.32 | 6.95 / 6.71 | 18.58 / 18.66 | $C_{10}H_{15}N_3O_3$ | 234/266 | 1002—1244 (=N—), 1377 ($CH_3$), 1113 (C—O—C), 1448, 1460 ($CH_2$), 1645 (C=C), 1660, 1726 (C=O), 2852, 2920 (CH), 3136, 3199 (NH), 3267 (=N—) | 2.26 (s, 3 H, C(6)$CH_3$); 2.36 (t, 4 H, C(8)$H_2$, C(10)$H_2$, $J$ = 4.4); 3.22 (s, 2 H, C(7)$H_2$); 3.55 (t, 4 H, C(9)$H_2$, C(11)$H_2$, $J$ = 5.6); 10.90 (br.s, 2 H, N(1)H, N(3)H) | — |
| **4** | 205—207 | 51.78 / 51.18 | 5.95 / 6.20 | 20.02 / 19.89 | $C_9H_{13}N_3O_3$ | 246/267 | 1093—1228 (=N—), 1111 (C—O—C), 1379 ($CH_3$), 1455 ($CH_2$), 1651 (C=C), 1664, 1732 (C=O), 2852, 2921 (CH), 3109, 3157 (NH), 3209 (=N—) | 2.10 (s, 3 H, C(6)$CH_3$); 3.07 (t, 4 H, C(9)$H_2$, C(10)$H_2$, $J$ = 4.7); 3.75 (t, 4 H, C(7)$H_2$, C(8)$H_2$, $J$ = 4.7); 10.80 (br.s, 2 H, N(1)H, N(3)H) | 16.54 (C(6)<u>C</u>$H_3$); 53.91 (C(7), C(8)); 67.32 (C(9), C(10)); 105.97 (C(5)); 151.61 (C(6)); 151.59 (C(2)=O); 160.18 (C(4)=O) |
| **5** | 175—177 | 46.83 / 46.45 | 5.95 / 5.85 | 27.42 / 27.08 | $C_6H_9N_3O_2$ | 253/284 | 1037—1247 (=N—), 1377 ($CH_3$), 1458 ($CH_3$), 1649 (C=C), 1670, 1735 (C=O), 2852, 2924 (CH), 3034, 3196 (NH), 3321, 3344 (NH) | 2.05 (s, 3 H, C(6)$CH_3$); 2.45 (s, 3 H, $CH_3$); 3.40 (br.s, 1 H, NHC(5)); 10.40 (br.s, 1 H, N(1)H); 11.00 (br.s, 1 H, N(3)H) | — |
| **6** | 219—221 | 49.83 / 49.70 | 6.95 / 6.55 | 24.42 / 24.84 | $C_7H_{11}N_3O_2$ | 253/285 | 1012—1234 (=N—), 1377 ($CH_3$), 1446, 1460 ($CH_2$, $CH_3$), 1631 (C=C), 1654, 1734 (C=O), 2852, 2922 (CH), 3070 (NH), 3213, 3323 (NH) | 1.00 (t, 3 H, C<u>H</u>$_3$NH, $J$ = 7.1); 2.00 (s, 3 H, C(6)$CH_3$); 2.70 (q, 2 H, C(7)H, $J$ = 7.1); 3.10 (br.s, 1 H, NH); 10.40 (br.s, 1 H, N(1)H); 11.00 (br.s, 1 H, N(3)H) | — |

* In EtOH.

1,4-dioxane, and the temperature was maintained constant for several minutes. Then the inhibitor in a 1,4-dioxane solution was added, and the oxygen absorption in the gas phase was monitored using a universal manometric differential setup. The measurement part of the setup was a highly sensitive differential pressure gauge based on a silicon membrane cell. Two reactors were attached to the pressure gauge; one of them was the working reactor. The reactors were disconnected during measurements, the change in the gas pressure in the working reactor was detected using a microprocessor device, and the results were transmitted to a computer for processing. Oxygen absorption rate in the liquid phase was calculated as described earlier.[4] The rate of 1,4-dioxane oxidation ($w$) was determined from initial part of the kinetic curve for oxygen absorption.

## Results and Discussion

The liquid-phase oxidation of 1,4-dioxane (RH) under our experimental conditions (60 °C, $w_i$ = $= 5.3 \cdot 10^{-8}$ mol $L^{-1}$ $s^{-1}$) proceeds *via* the radical-chain mechanism with square chain termination.[1]

$$\text{AIBN} \xrightarrow{k_i} r^{\cdot} \xrightarrow{RH} R^{\cdot}$$

$$R^{\cdot} + O_2 \xrightarrow{k_1} RO_2^{\cdot}$$

$$RO_2^{\cdot} + RH \xrightarrow{k_2} ROOH + R^{\cdot}$$

$$RO_2^{\cdot} + RO_2^{\cdot} \xrightarrow{k_6} \text{Molecular products}$$

The introduction of 6-methyluracils (InH) into the oxidized substrate decreases the oxygen absorption rate due to the appearance of an additional channel of consumption of peroxide radicals

$$RO_2^{\cdot} + InH \xrightarrow{k_7} ROOH + In^{\cdot},$$

$$In^{\cdot} + RO_2^{\cdot} \longrightarrow \text{Inactive products.}$$

As can be seen from the experimental data, in the presence of 6-methyluracils in a medium of oxidized 1,4-dioxane, the chain length is at least five units and, hence, the chain regime is retained. In this case, the following equation is appropriate for the quantitative estimation of the inhibition efficiency[5]:

$$F = w_0 w^{-1} - w(w_0)^{-1} = fk_7[InH]_0(2k_6 w_i)^{-0.5}, \quad (1)$$

where $w_0$ and $w$ are the initial rates of oxygen absorption in the absence and in the presence of 6-methyluracils, respectively, mol $L^{-1}$ $s^{-1}$; $[InH]_0$ is the initial concentration of 6-methyluracils, mol $L^{-1}$; $2k_6$ and $fk_7$ are the rate constants for oxidation chain termination in the reaction of recombination of 1,4-dioxane peroxide radicals and on inhibitor molecules, respectively, mol $L^{-1}$ $s^{-1}$; $f$ is the stoichiometric inhibition factor.

The typical dependence of the initial rate for 1,4-dioxane oxidation on the 6-methyluracil concentration and the results of experimental data processing by Eq. (1) are shown in Fig. 1. The observed satisfactory linear dependence of the $F$ parameter on the concentration of compound **7** makes it possible to quantitatively estimate the efficiency of 6-methyluracil as an inhibitor of 1,4-dioxane oxidation. The rate constants ($fk_7$) obtained for compounds **1**—**7** studied as inhibitors are listed in Table 2 (it was accepted in the calculation that $2k_6 = 10^9$ mol $L^{-1}$ $s^{-1}$).[1]

If the inhibited oxidation rate $w$ is much lower than $w_0$, it can be assumed that almost all chains terminate on the inhibitor molecules and radicals. Then the inhibitor is consumed with a constant rate

$$w_{InH} = f^{-1} w_i.$$

In this case, at $w_i$ = const the inhibition time (induction period $\tau$) is as follows:

$$\tau = f[InH]_0(w_i)^{-1}. \quad (2)$$

In the case of long chains, the following equation is valid for the reaction rate:

$$w = -d[O_2](dt)^{-1} = w_i k_2[RH](fk_7[InH])^{-1}. \quad (3)$$

For a given time $t$, Eq. (2) can be written as

$$t = f([InH]_0 - [InH])(w_i)^{-1}. \quad (4)$$

After substituting [InH] from Eq. (4) to Eq. (3) and integrating, the following equation can be ob-

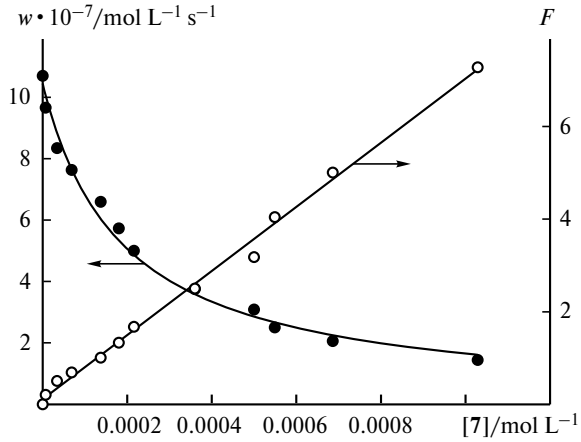


**Fig. 1.** Oxygen absorption rate ($w$) during 1,4-dioxane oxidation and inhibiting effect parameter ($F$) *vs* 5-hydroxy-6-methyluracil (**7**) concentration ($r = 0.98$, 60 °C, $w_i = 5.3 \cdot 10^{-8}$ mol $L^{-1}$ $s^{-1}$).

**Table 2.** Rate constants for the reactions of the peroxide radicals of 1,4-dioxane with 6-methyluracil (**1**) and its 5-substituted derivatives **2**—**7** (InH) (60 °C, $w_i = 5.3 \cdot 10^{-8}$ mol $L^{-1}$ $s^{-1}$)

| InH | [InH] /mol $L^{-1}$ | $fk_7$[a] | $fk_7$[b] | $k_7$[c] |
|---|---|---|---|---|
| | | L mol$^{-1}$ s$^{-1}$ | | |
| **1** | $(0.065—7.0) \cdot 10^{-3}$ | $(4.4 \pm 0.6) \cdot 10^2$ | — | — |
| **2** | $(0.065—2.9) \cdot 10^{-3}$ | $(5.3 \pm 0.3) \cdot 10^3$ | $4.7 \cdot 10^3$ | $1.9 \cdot 10^3$ |
| **3** | $(0.1—7.6) \cdot 10^{-4}$ | $(2.5 \pm 0.2) \cdot 10^3$ | — | — |
| **4** | $(0.19—8.5) \cdot 10^{-3}$ | $(2.4 \pm 0.2) \cdot 10^3$ | $(3.7 \pm 0.5) \cdot 10^3$ | $(1.8 \pm 0.2) \cdot 10^3$ |
| **5** | $(3.0 \pm 15.0) \cdot 10^{-3}$ | $(3.8 \pm 0.4) \cdot 10^3$ | $(3.8 \pm 0.4) \cdot 10^3$ | $(1.5 \pm 0.1) \cdot 10^3$ |
| **6** | $(1.7 \pm 7.0) \cdot 10^{-3}$ | $(4.6 \pm 0.1) \cdot 10^3$ | $(6.0 \pm 0.4) \cdot 10^3$ | $(2.8 \pm 0.2) \cdot 10^3$ |
| **7** | $(0.0068—10.3) \cdot 10^{-4}$ | $(5.2 \pm 0.1) \cdot 10^4$ | $(6.3 \pm 0.2) \cdot 10^4$ | $(3.4 \pm 0.3) \cdot 10^4$ |

[a] Calculated by Eq. (1).
[b] Calculated by Eq. (3).
[c] Calculated by Eq. (5).

tained for low hydrocarbon conversions ([RH] ≈ ≈ $[RH]_0$)[5]:

$$\Delta[O_2] = -k_2(k_7)^{-1}[RH]\ln(1 - t/\tau), \quad (5)$$

where $\Delta[O_2]$ is the change in the oxygen concentration during the reaction.

The length of the induction period for the initiated oxidation of 1,4-dioxane in the presence of 6-methyluracils was calculated by Eq. (2). At rather high concentrations of the inhibitor, the initial part of the kinetic curves of oxygen consumption are satisfactorily linearized in the coordinates of Eq. (5). The typical semilogarithmic transformation of the kinetic curve of oxygen absorption during 1,4-dioxane oxidation inhibited by compound **7** is shown in Fig. 2. The satisfactory linear dependence makes it possible to determine the $k_2(k_7)^{-1}$ ratio. To calculate $k_7$, the $k_2$ constant was accepted equal to 9.48 mol $L^{-1}$ $s^{-1}$. This value was calculated from the oxidizability parameter $k_2(2k_6)^{-0.5} = (3.0\pm0.5)\cdot10^{-4}$ $L^{0.5}$ $mol^{-0.5}$ $s^{-0.5}$ assuming that $2k_6 = 10^9$ mol $L^{-1}$ $s^{-1}$. The rate constants obtained for the inhibition of 1,4-dioxane oxidation by 6-methyluracils studied are listed in Table 2. As can be seen, the rate constants $fk_7$ calculated by Eqs (1) and (3) agree satisfactorily with the $k_7$ value found from Eq. (5) assuming that $f$ equals 2. To evaluate parameter $f$ for all compounds used in this work further studies are necessary.

The introduction of substituents into position 5 of the uracil cycle increases the inhibition activity of 6-methyluracils (see Table 2). The inhibition rate constant obtained for compound **7** is by two orders of magnitude higher than the $fk_7$ constant measured for unsubstituted 6-methyluracil and by an order of magnitude higher than this constant for other substituted uracils. Analogous results were obtained for 5-substituted 6-methyluracils in isopropyl alcohol[6] and ethylbenzene.[7] The rate constant for the reaction of ethylbenzene peroxide radicals with compound **7** measured by the chemiluminescence method ($k_7$ = $= 2.6\cdot10^4$ mol $L^{-1}$ $s^{-1}$ at 50 °C)[7] agrees satisfactorily with our results under assumption that $f$ equals 2 (Table 3). Most likely, the difference in the $fk_7$ values for compound **7** in 1,4-dioxane and in isopropyl alcohol (see Table 3) is due to the fact that the 1,4-dioxane peroxide radicals are less reactive in the reaction of hydrogen elimination than the hydroperoxide radicals, which lead the oxidation chains of isopropyl alcohol oxidation at the initial moments of the reaction.[8]

The quantum chemical analysis of 5-substituted 6-methyluracils has been performed earlier,[9] and the dissociation energies of the N—H bonds were calculated by the method of isodesmic reactions and by the G3MP2B3 procedure. It was established that the antioxidation activity of 6-methyluracils is determined by the N(1)—H bond strength ($D_{N(1)-H}$), because the N(3)—H bond is stronger by 40—90 kJ $mol^{-1}$. A comparison of the inhibition rate constants $fk_7$ and the N(1)—H bond strength in the 6-methyluracils studied shows (see Table 3) that the correlation between $\log fk_7$ and $D_{N(1)-H}$ is observed only for compounds **1**, **3**, and **7**. For 6-methyluracil unsubstituted in position 5, the N(1)—H bond strength is 422.5 kJ $mol^{-1}$ and the inhibition rate constant is $(4.4\pm0.6)\cdot10^2$ mol $L^{-1}$ $s^{-1}$. This value is by an order of magnitude lower than those for other 6-methyluracils in which the N(1)—H bond strength is lower than 400 kJ $mol^{-1}$. However, not all studied compounds can be described by this correlation. In particular, although the N(1)—H bond strength in compound **7** is by 20 kJ $mol^{-1}$ higher than those in compounds **5** and **6**, the rate constant $fk_7$ for the latter is by an order of magnitude lower. This possibly indicates that in compound **7** the N(1)—H bond is not the single site of attack by the peroxide radical.

Thus, 6-methyluracils are inhibitors of the radical-chain oxidation of 1,4-dioxane. Among compounds **1**—**7**,

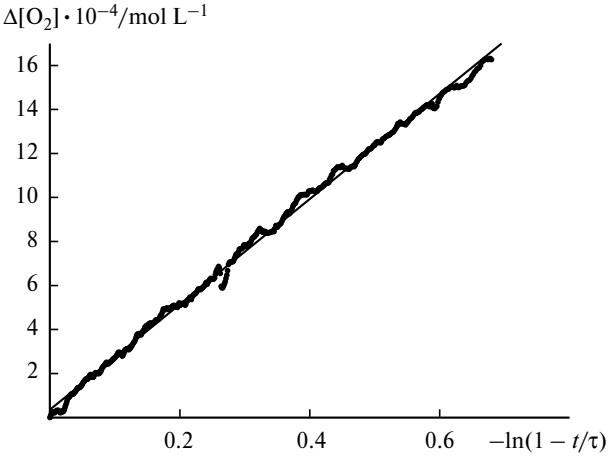


**Fig. 2.** Semilogarithmic transformation of the oxygen absorption kinetic curve ($\Delta O_2$) during 1,4-dioxane oxidation (60 °C, $w_i = 5.3\cdot10^{-8}$ mol $L^{-1}$ $s^{-1}$, [**7**] $= 1.4\cdot10^{-4}$ mol $L^{-1}$).

**Table 3.** Bond strengths $D_{N(1)-H}$ and the rate constants $fk_7$ for 6-methyluracil (**1**) and its 5-substituted derivatives **2**—**7**

| Compound | $D_{N(1)-H}$[8] /kJ $mol^{-1}$ | $fk_7$ /L $mol^{-1}$ $s^{-1}$ |
|---|---|---|
| **1** | 422.5 | $(4.4\pm0.6)\cdot10^2$ |
| **2** | — | $(5.3\pm0.3)\cdot10^3$ |
| **3** | 400.4 | $(2.5\pm0.2)\cdot10^3$ |
| **4** | — | $(2.40\pm0.15)\cdot10^3$ |
| **5** | 349.9 | $(3.8\pm0.4)\cdot10^3$ |
| **6** | 350.1 | $(4.6\pm0.1)\cdot10^3$ |
| **7** | 371.5 | $(5.2\pm0.1)\cdot10^4$ |
| **7** | 371.5 | $1.5\cdot10^5$ * |
| **7** | 371.5 | $5.2\cdot10^4$ ** |

* In isopropyl alcohol (see Ref. 6).
** In ethylbenzene (see Ref. 7).

5-hydroxy-6-methyluracil (**7**) has the highest efficiency and its inhibition constant $fk_7$ is $(5.2\pm0.11)\cdot10^4$ mol $L^{-1}$ $s^{-1}$ at 60 °C, which is twice as large as the constant measured for ionol in this model system.[1]

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