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LETTERS TO THE EDITOR

Synthesis of Pyrinidine-2,4(1*H*,3*H*)-dione Derivatives Containing N-Alkyl Substituents

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Abstract—6-Methyluracil derivatives containing a *gem*-dichlorocyclopropane and a 1,3-dioxolane fragments were synthesized for the first time. The condensation of 6-methyluracil with chloromethyl derivatives gives a mixture of N^1- and N^3-monosubstituted products, and the profound N-alkylation of this compound provides disubstituted uracils. The structure of the synthesized compounds was studied by H^1 and ^{13}C NMR spectroscopy and their relative antioxidant activity was evaluated by luminol-dependent chemiluminescence measurements.

Keywords: 6-methyluracil, N-alkylation, *gem*-dichlorocyclopropane, 4-(chloromethyl)-1,3-dioxolane, antioxidant properties

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6-Methyluracil [6-methylpyrimidine-2,4(1*H*,3*H*)-dione] and its derivatives exhibit broad-spectrum biological and pharmacological activities and are successfully used in medical chemistry [1, 2]. Substituted uracils are most commonly prepared by N-alkylation of 6-methyluracil by polyfunctional halomethyl derivatives [3, 4]. Among N^1- and N^3-substituted compounds of this series, efficient antioxidants and anti-inflammatory agents were found [5, 6].

In this connection we considered it of interest to prepare *gem*-dichloropropane and cycloacetal derivatives of 6-methyluracila **1** and estimate their biological activity. To this end, we performed condensation of 6-methyluracil **1** with accessible chloromethyl-*gem*-dichlorocyclopropane **2a** and 4-chloromethyl-1,3-dioxolane **2b** [7].

It was found that the reaction of 6-methyluracil **1** with chlorides **2a** and **2b** under the studied conditions (**1** : **2** = 1 : 1, K_2CO_3, DMF, triethylbenzylammonium chloride, 90°C, 4–8 h) gives a mixture of N^1- and N^3-monosubstituted products **3a**, **3b** and **4a**, **4b** (yield 25–30%) in the ratios **3a** : **4a** = 6 : 1 and **3b** : **4b** = 4 : 1 (Scheme 1).

With a double excess of chlorides **2a** and **2b** and after a long reaction time (10–12 h), the formation of disubstituted uracils **5** and **6** was observed (yields 30–40%).

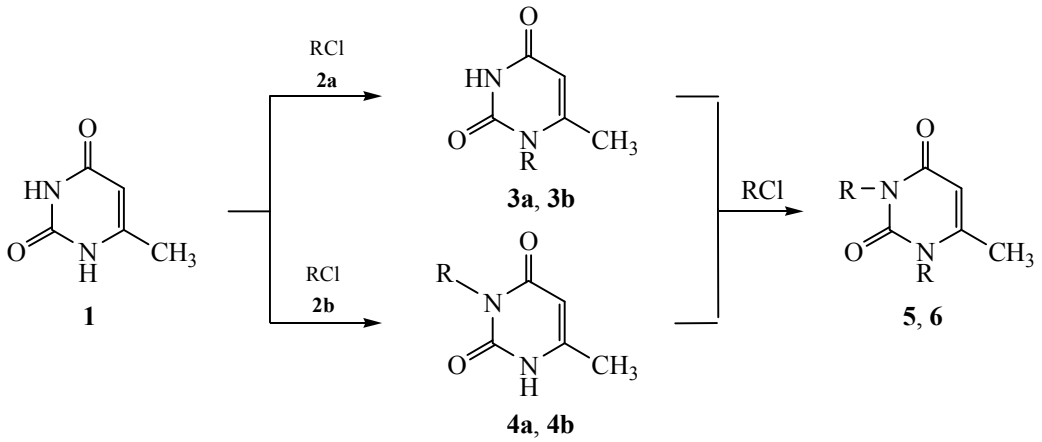
The structure of compounds **3–6** was established by ^1H and ^{13}C NMR spectroscopy. Complete assignment of the proton and carbon signals was performed using the COSY, HSQC, and HMBC spectra.

Krivonogov et al. [3] analyzed the ^1H NMR spectra of a series of substituted uracils to show that the N^1H proton signal of N^3-substituted derivatives appears at 8–9.5 ppm, whereas the N^3H proton signal of N^1-substituted derivatives appears at 10–11 ppm. The ^1H NMR spectrum of a mixture of compounds **3a** and **4a** shows NH proton signals at 10.2 and 9.7 ppm with the intensity ratio of 6 : 1, which implies the prevalence of the N^1-substituted isomer.

The same intensity ratios have the signals of the methyl groups at the uracil C^6 carbon at 2.17 (**3a**) and 2.35 ppm (**4a**), as well as the C^5H proton signals at 5.61 (**3a**) and 5.63 ppm (**4a**).

The *gem*-dichlorocyclopropane protons resonate in their characteristic region (2.06–2.14 ppm). The dia-

Scheme 1.



R = (2,2-dichloropropyl)methyl (**2a**, **3a**, **4a**, **5**), 1,3-dioxolan-4-ylmethyl (**2b**, **3b**, **4b**, **6**).

stereotopic protons of the methylene group at $C^{3'}$ appear as two doublets of doublets at 1.51 (^2J = 10.0, ^3J = 7.2 Hz) and 1.59 ppm (^2J = 10.0, ^3J = 4.7 Hz). The signals of the methyl protons at $C^{4'}$, too, are registered as doublets of doublets at 4.18 (^2J = 13.6, ^3J = 5.1 Hz) and 4.0 ppm (^2J = 13.6, ^3J = 9.7 Hz). The JMOD ^{13}C NMR spectrum provides unequivocal evidence for the structure of compound **3a**. The characteristic signals of the uracil fragment appear at 153.1 (C^2) and 162.4 ppm (C^4); the signals of the methine C^5 carbon are observed at 100.1 ppm. The quaternary C^6 carbon signal appears at 150.4 ppm.

The substitution of the N^1 and N^3 atoms was proved by the HMBC spectroscopy. The ^1H–^{13}C NMR spectrum of N^1-substituted compound **3a** shows cross-peaks between protons at $C^{4''}$ and the uracil C^2 (153.1 ppm) and C^6 atoms (150.4 ppm). The ^1H–^{13}C NMR spectrum of N^3-derivative **4a** shows cross peaks between protons at $C^{4''}$ and the uracil C^2 (151.4 ppm) and C^4 atoms (164.4 ppm).

The structure of disubstituted uracils **5** and **6** is confirmed by the lack in the ^1H NMR spectra of NH proton signals at 9–11 ppm and by the presence of alkyl signals in the ^1H and ^{13}C NMR spectra.

We estimated the influence of compounds **3–6** on in vitro free-radical oxidation processes in model systems generating reactive oxygen species (ROS) and in systems modulating lipid peroxidation (LPO). The antioxidant activity assay was performed in DMSO by measuring chemilumiscence by known procedures [5, 6]. Control measurements were performed in the absence of antioxidants. The reference was 5-hydroxy-6-methyluracil, a well-known free-radical oxidation inhibitor for biological systems. The main parameters that were estimated were the total chemiluminescence (S) and maximum flash amplitude (I_{max}).

As seen from the table, compounds **3–6** exhibit antioxidant activity of different degree. Compound **6** which contains two 1,3-dioxolane fragments ranks first in the ability to inhibit ROS generation and compares in activity with 5-hydroxy-6-methyluracil.

The mixture of isomers **3a** and **4a**, as well as compounds **5** and **6** only slightly decreased the luminescence light sum in the model LPO reaction system, whereas the mixture of isomers **3b** and **4b** enhanced chemiluminescence, acting as an oxidant.

The resulting data show that the synthesized 6-methyluracil derivatives are promising objects for further biological activity research.

Synthesis of compounds 3 and 4. A mixture of 0.05 mol of 6-methyluracil **1**, 0.065 mol of K_2CO_3, 0.15 g of triethylbenzylammonium chloride, and 18 mL of DMF was stirred at room temperature for 2 h and allowed to stand at that temperature for 8 h. Alkylating agent **2a** (or **2b**), 0.055 mol, was then added, the mixture was vigorously stirred for 4 (**2a**) or 8 h (**2b**) at 90°C, cooled down, and allowed to stand for 8 h. The precipitate was filtered off, and the filtrate was evaporated. The residue was treated with 15 mL of 10% KOH, treated with chloroform (3×10 mL), and the combined extract was dried over $MgSO_4$. The solvent was distilled off, and the residue was chromatographed on KSKG silica (63–200 μm), eluent benzene–ethanol (19 : 1). The target compounds were isolated as isomer mixtures **3a**/**4a** and **3b**/**4b**.

Changes in the total chemiluminescence (S) and maximum flash amplitude (I_{max}) of the model systems generating ROS and mimicking LPO in the presence of 6-methyluracil derivatives **3**–**6**[a]

Compound	ROS model		LPO model	
	S, %	I_{max}, %	S, %	I_{max}, %
Control	100	100	100	100
5-Hydroxy-6-methyluracil	32	39	49	51
3a + **4a**	82	84	90	86
3b + **4b**	62	64	151	123
5	62	66	78	69
6	22	42	87	87

[a] Data are presented as the percentage of control. Sample volume 0.01 mL.

1-[(2,2-Dichlorocyclopropyl)methyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (3a) and 3-[(2,2-dichlorocyclopropyl)methyl]-6-methylpyrimidine-2,4-(1*H*,3*H*)-dione (4a). Yield 30%, mp 130–131°C. **Compound 3a.** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.51 (1H, $C^{3'}H_A$, ^2J = 10.0, ^3J = 7.2), 1.59 d.d (1H, $C^{3'}H_B$, ^2J = 10.0, ^3J = 4.7), 2.06–2.14 m (1H, $C^{2'}H$), 2.17 s (3H, C^7H_3), 4.0 d.d (1H, $C^{4'}H_A$, ^2J = 13.6, ^3J = 9.7), 4.18 d.d (1H, $C^{4'}H_A$, ^2J = 13.6, ^3J = 5.1), 5.61 s (1H, C^5H), 10.20 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.75 (C^7), 26.28 ($C^{3'}$), 28.26 ($C^{2'}$), 40.32 ($C^{4'}$), 58.6 ($C^{1'}$), 100.1 (C^5), 150.4 (C^6), 153.1 (C^2), 162.4 (C^4). **Compound 4a.** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.52 m (1H, $C^{3''}H_B$), 1.75 d.d (1H, $C^{3''}H_A$, ^2J = 10.3, ^3J = 7.4), 1.94–1.99 m (1H, $C^{2''}H$), 2.35 s (3H, C^7H_3), 4.12 d.d (1H, $C^{4''}H_A$, ^2J = 14.0, ^3J = 4.8), 4.30 d.d (^2J = 14.0, ^3J = 4.5), 5.63 s (1H, C^5H), 9.70 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.5 (C^7), 26.1 ($C^{3''}$), 34.5 ($C^{2''}$), 45.2 ($C^{4''}$), 62.8 ($C^{1''}$), 100.1 (C^5), 151.4 (C^2), 154.4 (C^6), 164.4 (C^4).

1-(1,3-Dioxolan-4-ylmethyl)-6-pyrimidine-2,4-(1*H*,3*H*)-dione (3b) and 3-(1,3-dioxolan-4-ylmethyl)-6-pyrimidine-2,4(1*H*,3*H*)-dione (4b). Yield 25%, mp 122–123°C. **Compound 3b.** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.27 s (3H, C^7H_3), 3.42–3.56 m (2H, $C^{6'}H_2$), 3.65 d.d (1H, $C^{5'}H_A$, ^2J = 9.1, ^3J = 7.4), 3.72 d.d (1H, $C^{5'}H_B$, ^2J = 9.1, ^3J = 5.2), 4.16 t.d (1H, $C^{4'}H$, ^3J = 7.4, 5.2, 3.8), 4.62 s (1H, $C^{2'}H_A$), 4.68 s (1H, $C^{2'}H_B$), 5.55 s (1H, C^5H), 10.57 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 17.9 (C^7), 44.4 ($C^{6'}$), 73.5 ($C^{5'}$), 74.4 ($C^{4'}$), 94.7 ($C^{2'}$), 98.2 (C^5), 151.4 (C^6), 152.8 (C^2), 160.9 (C^4). **Compound 4b.** ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.27 s (3H, C^7H_3), 3.45–3.61 m (2H, $C^{6''}H_2$), 3.62 d.d (1H, $C^{5''}H_A$, ^2J = 8.9, ^3J = 4.9), 3.69 d.d (1H, $C^{5''}H_B$, ^2J = 8.9, ^3J = 6.8), 4.10 t.d (1H, $C^{4''}H$, ^3J = 6.8, 4.9, 4.2), 4.62 s (1H, $C^{2''}H_A$), 4.68 s (1H, $C^{2''}H_B$), 5.59 s (1H, C^5H), 9.57 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9 (C^7), 41.6 ($C^{6''}$), 70.6 ($C^{4''}$), 76.1 ($C^{5''}$), 95.1 ($C^{2''}$), 103.2 (C^5), 151.2 (C^6), 152.8 (C^2), 162.4 (C^4).

Compounds **5** and **6** were prepared in a similar way using a double excess (0.11 mol) of the corresponding alkylating agent.

1,3-Bis[(2,2-dichlorocyclopropyl)methyl]-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (5). Yield 40%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 1.48–1.58 m (2H, $C^{3'}H_2$), 1.69–1.78 m (2H, $C^{3''}H_2$), 1.92–2.10 m (1H, $C^{2'}H$), 2.08–2.17 m (1H, $C^{2''}H$), 2.32 s (3H, C^7H_3), 3.95–4.04 m (2H, $C^{4'}H_2$), 4.15 d.d (1H, $C^{4''}H_A$, J = 4.8, 13.4), 4.35 d.d (1H, $C^{4''}H_B$, J = 2.6, 4.5), 5.65 s (1H, C^5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.21 (C^7), 26.21 ($C^{3''}$), 26.52 ($C^{3'}$), 28.39 ($C^{2'}$), 28.84 ($C^{2''}$), 41.40 ($C^{4''}$), 44.92 ($C^{4'}$), 59.65 ($C^{1''}$), 68.15 ($C^{1'}$), 102.2 (C^5), 151.1 (C^6), 152.3 (C^2), 161.8 (C^4).

1,3-Bis(1,3-dioxolan-4-ylmethyl)-6-methylpyrimidine-2,4(1*H*,3*H*)-dione (6). Yield 35%. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 2.22 s (3H, C^7H_3), 3.61–3.68 m (2H, $C^{6''}H_2$), 3.69–3.75 m (2H, $C^{6'}H_2$), 3.86 d.d (1H, $C^{5'}H_A$, ^2J = 8.6, ^3J = 4.7), 3.97 d.d (1H, $C^{5'}H_B$, ^2J = 8.6, ^3J = 4.7), 4.05 d.d (1H, $C^{5''}H_A$, ^2J = 9.0, ^3J = 5.0), 4.24 d.d (1H, $C^{5''}H_B$, ^2J = 9.0, ^3J = 6.6), 4.32–4.37 m (2H, $C^{4'}H$, $C^{4''}H$), 4.76 s (1H, $C^{2'}H_A$), 4.84 s (1H, $C^{2'}H_B$), 4.98 s (1H, $C^{2''}H_A$), 5.00 s (1H, $C^{2''}H_B$), 5.55 s (1H, C^5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.3 (C^7), 42.2 ($C^{6'}$), 47.2 ($C^{6''}$), 67.3 ($C^{5'}$), 67.6

($C^{5''}$), 72.8 ($C^{4''}$), 73.5 ($C^{4'}$), 94.7 ($C^{2'}$), 95.1 ($C^{2''}$), 101.6 (C^5), 152.1 (C^2), 152.3 (C^6), 161.8 (C^4).

Chromatographic analysis of the reaction products was performed on a CarloErba HRGC 5300 Mega Series chromatograph with FID, carrier gas helium, flow rate 30 mL/min, column length 25 m, oven temperature program programmed temperature from 50 to 280°C at 8 deg/min, detector temperature 250°C, injector temperature 300°C. The EI mass spectra were measured on Fisons (50 m DB 560 quartz capillary column) and Thermo Focus DSQ II GC-MS systems (ion source temperature 200°C, direct probe temperature 50–270°C, heating rate 10 deg/min, 50(2.5×10^{-4}) m ThermoTR-5MS column, helium flow rate 0.7 mL/min). The NMR spectra were obtained on a Bruker AVANCE-500 spectrometer in $CDCl_3$.

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REFERENCES

1. Munasipova, D.A., Meshheryakova, S.A., and Kataev, V.A., *Bash. Khim. Zh*., 2013, vol. 20, no. 1, p. 11.
2. Azas, N.,Rathelot, P., Djekou, S., Delmas, F.,Gellis, A., Di Giorgio, C., Vanelle, P., and Timon-David, P., *Farmaco,* 2003, vol. 58, no. 12, p. 1263. doi 10.1016/j.farmac.2003.07.009.
3. Krivonogov, V.P., Kozlova, G.G., Belaya, E.A., Spirikhin, L.V., and Abdrakhmanov, I.B., *Russ. J. Gen. Chem*., 2004, vol. 74, no. 5, p. 830. doi 10.1023/B:RUGC.0000039091.94471.75
4. Fattakhov, A.H., Lobov, A.N., Gimadieva, A.R., Mustafin, A.G., and Abdrakhmanov, I.B., *Vestn. Bash. Univ*., 2012, vol. 17, no. 4, p. 1710.
5. Petrova, I.V., Kataev, V.A., Meshheryakova, S.A., Nikolaeva, K.V., Munasipova, D.A., and Farkhutdinov, R.R., *Med. Vestn. Bashkortost*., 2013, vol. 8, no. 4, p. 64.
6. Petrova, I.V., Kataev, V.A., Meshheryakova, S.A., Nikolaeva, K.V., Munasipova, D.A., and Farkhutdinov, R.R., *Med. Vestn. Bashkortost*., 2013, vol. 8, no. 6, p. 163.
7. Borisova, Y.G., Raskildina, G.Z., Kazakova, A.N., and Zlotsky, S.S., *Russ. J. Gen. Chem*., 2015, vol. 85, no. 1, p. 200. doi 10.1134/S1070363215010351