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Synthesis of 1,3-Bis[2-hydroxy-3-(3-methyl-5-oxo-2,5-dihydro-1-pyrazolyl)propyl]uracils

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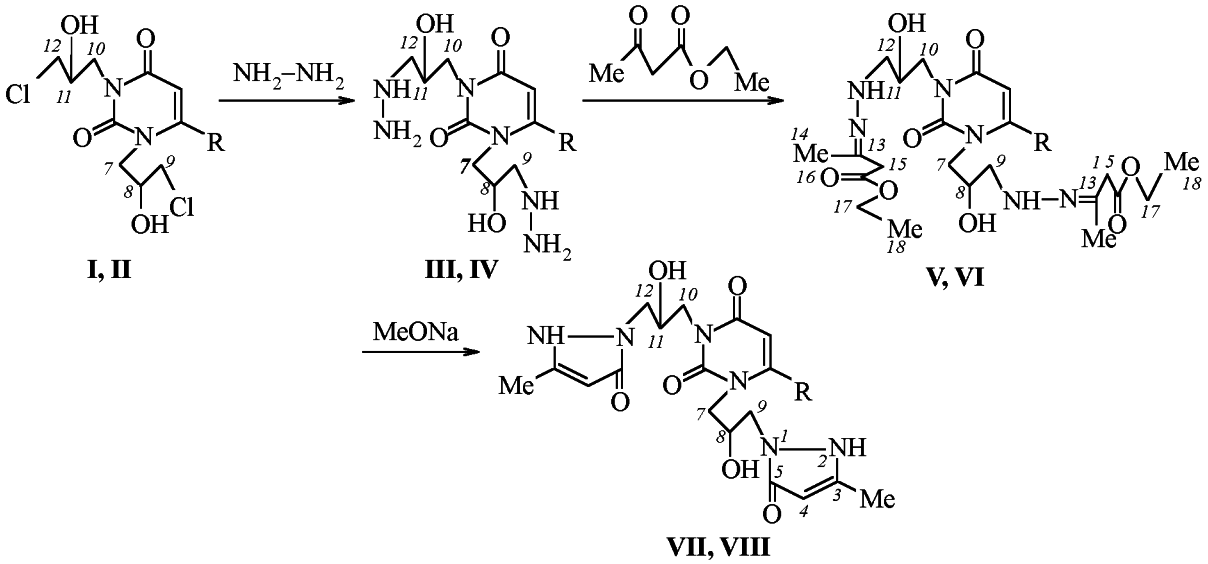
Abstract—A reaction was studied of newly synthesized 1,3-bis(2-hydroxy-3-chloropropyl)uracil and 1,3-bis(2-hydroxy-3-chloropropyl)-6-methyluracil with hydrazine hydrate followed by treating the compounds formed with ethyl acetoacetate. The hydrazones obtained cyclized into pyrazolones in the presence of sodium methylate.

Pyrimidine derivatives possess antiphlogistic activity [1, 2]. Among them stands out 1-[2-(3-methyl-5-methoxy-1-pyrazolyl)-6-methyl-4-methoxy]pyrimidine (mebrone) that is used as antiphlogistic medicine [4]. The antiphlogistic activity was also observed in 4-substituted 2-isopropylthiopyrimidines [4].

We showed formerly that pyrimidine derivatives possessed immunotropic, antiphlogistic, membrane-stabilizing, and antiradical activity [5–9]. One among them (oxymethyluracil) was authorized for wide medical application and industrial production.

With the goal of looking for new pyrimidine derivatives with possible immunotropic and antiphlogistic properties we synthesized a number of 1,3-bis[2-hydroxy-3-(3-methyl-5-oxo-2,5-dihydro-1-pyrazolyl)-propyl]uracils **VII, VIII** along the following scheme.

As starting compounds were used 1,3-bis(2-hydroxy-3-chloropropyl)uracil (**I**) and 1,3-bis(2-hydroxy-3-chloropropyl)-6-methyluracil (**II**) prepared by reaction between uracil and 6-methyluracil with epichlorohydrin. The replacement of chlorine in compounds **I, II** with hydrazine group occurs readily at 40–60°C in the presence of potassium carbonate. The hydrazine group in compounds **III, IV** reacts with ethyl acetoacetate at room temperature yielding hydrazones **V, VI** that in the presence of sodium methylate cyclize into pyrazolones **VII, VIII**.



R = H (**I, III, V, VII**), Me (**II, IV, VI, VIII**).

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The structure of compounds obtained was proved by ^{1}H and ^{13}C NMR, IR, and UV spectra, and the composition was confirmed by elemental analyses.

In the IR spectra of all compounds are present absorption bands in the region 1620–1720 cm^{-1} characteristic of the pyrimidine moiety [ν(C=O, =NC=O)]. The absorption bands in the 1060–1240 cm^{-1} region are common for molecules containing a tertiary nitrogen atom (–N=); absorption bands in the region 3300–3500 cm^{-1} correspond to stretching vibrations of OH and NH bonds. Thus in the spectra of compounds **I, II, V, VII** at 3400 cm^{-1} is observed an absorption band of the hydroxy group attached to C^{11} that take part in a hydrogen bond. In the spectra of compounds **III, IV** the absorption bands of the stretching vibrations of NH–NH$_2$ groups appear in the region 3200–3300 cm^{-1}; in the spectra of compounds **V–VIII** the absorption bands of NH bonds are present at 3260–3300 cm^{-1}. The absorption in the region 500–840 [ν(CCl)], 1280–1290 cm^{-1} [ω(CH$_2$Cl)] is characteristic of compounds **I, II**.

In the ^{13}C NMR spectra of all compounds the carbon atoms of the uracil fragment give usual peaks of this moiety at 164.4 (C^4), 157.0 (C^2), and 153.0 ppm (C^6). In the spectra of compounds **II, IV, VI, VIII** are also observed signals at 14.0 (CH$_3$C^6), 98.0 ppm (C^5), in the spectra of uracil derivatives **I, III, V, VII** the peak of C^5 atom appears at 102.87 ppm.

In the molecules of the compounds obtained exist strong intramolecular hydrogen bonds between the hydroxy groups of the substituents and oxo groups. These hydrogen bonds are not destroyed in solutions, and as a result in the ^{13}C NMR spectra the signals of the corresponding carbon atoms attached to N^1 and N^3 of the pyrimidine moiety are very dissimilar, and the signals of C^2 and C^5 are shifted upfield compared to their positions in the spectra of unsubstituted uracil and 6-methyluracil. In the spectra of compounds **VII, VIII** the signals of carbon atoms from the N–C=O groups in pyrazole substituents are observed in 167 ppm region, and the signals of C^4 atoms from the pyrazole fragment are around 100 ppm.

In the ^{1}H NMR spectra of compounds **I, III, V, VII** the signals of protons in positions *5* and *6* of the uracil moiety appear as doublets with *J* 6–7.5 Hz.

EXPERIMENTAL

IR spectra were recorded on spectrometer UR-20 equipped with prisms of NaCl and LiF from mulls in mineral oil or liquid films of compounds. UV spectra of 0.001% water solutions were registered on Specord M-400 instrument. Melting points were measured on Boetius heating block. ^{1}H and ^{13}C NMR spectra were registered on spectrometer Bruker AM-300 (operating frequencies 300 and 75.5 MHz respectively) from solutions in $CDCl_3$ or DMSO-d_6 containing 1% of compound for ^{1}H spectra, 10–20% for ^{13}C spectra. The chemical shifts of carbon nuclei are related to TMS. The monitoring of reactions progress and checking of products homogeneity was carried out by TLC on Silufol UV-254 plates, eluent ethanol–ammonia, 4:1, development in iodine vapor.

1,3-Bis(2-hydroxy-3-chloropropyl)uracil (I). To a mixture of 112 g (1 mol) of uracil, 30 g (0.22 mol) of K_2CO_3 in 500 ml of DMF within 10 min was added 239 g (2.58 mol) of epichlorohydrin. The reaction mixture was heated to 70°C with stirring on a water bath for 13 h. Insoluble crystals were filtered off and washed with DMF. From the filtrate the solvent was distilled off to afford 284.6 g (96%) of compound **I** as thick fluid, well soluble in water, alcohol, acetone, chloroform, insoluble in hexane. R_f 0.9. IR spectrum, ν, cm^{-1}: 580, 700 [ν(CCl)], 1248, 1260 [ω(CH$_2$Cl)], 1624, 1656 [ν(C=C), ν(C=O, =NC=O)], 1130, 1200, 3250 [ν(OH)]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.72–2.78 m (2H, C^{8,11}H), 3.46–3.96 m (4H, C^{9,12}H), 4.30–4.57 m (4H, C^{7,10}H), 5.37–5.50 br.s (2H, C^{8,11}OH), 5.7 d (1H, C^{5}H, *J* 7 Hz), 7.53 d (1H, C^{6}H, *J* 7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 44.12 (C^{10}), 46.34 (C^{9,12}), 48.10 (C^7), 67.47 (C^{11}), 69.90 (C^8), 99.63 (C^5), 145.34 (C^6), 150.97 (C^2), 161.30 (C^4). Found, %: C 40.00; H 5.10; Cl 23.61; N 9.70. $C_{10}H_{14}Cl_2N_2O_4$. Calculated, %: C 40.42; H 4.75; Cl 23.86; N 9.43.

1,3-Bis(2-hydroxy-3-chloropropyl)-6-methyluracil (II) was prepared similarly to compound **I** by mixing 252 g (2 mol) of 6-methyluracil, 214 g (2.27 mol) of epichlorohydrin, 30 g (0.22 mol) of K_2CO_3 in 1.9 l of DMF. The reaction time 20 h, yield of compound **II** 54%.

The presence of a methyl group in position *6* of the pyrimidine ring considerably decelerated alkylation of position *1* presumably due to steric hindrances. Therefore in the course of the reaction arise both mono- and disubstituted 6-methyluracils [10]. R_f 0.25. IR spectrum, ν, cm^{-1}: 560, 616, 690 [ν(CCl)], 1248 (N=), 1288 [ω(CH$_2$Cl)], 1640, 1656 [ν(C=C), ν(C=O, =NC=O)], 1130, 1200, 3250 [ν(OH)]. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.37 s (3H, C^{6}CH$_3$), 2.8–3.01 m (2H, C^{8,11}H), 3.71 d (4H, C^{9,12}H, *J* 5.6 Hz), 4.3–4.53 m (4H, C^{7,10}H), 4.8 s (2H, C^{8,11}OH), 5.73 s (1H, C^{5}H). ^{13}C NMR spec-

trum ($CDCl_3$), δ_C, ppm: 14.62 ($H_3\underline{C}C^6$), 44.12 (C^{10}), 46.34 ($C^{9,12}$), 52.40 (C^7), 67.47 (C^{11}), 69.90 (C^8), 100.25 (C^5), 151.19 (C^2), 152.93 (C^6), 161.27 (C^4). Found, %: C 36.15; H 6.33; Cl 19.00; N 7.67. $C_{11}H_{16}Cl_2N_2O_4{\cdot}3H_2O$. Calculated, %: C 36.18; H 6.07; Cl 19.41; N 7.67.

1,3-Bis(3-hydrazino-2-hydroxypropyl)uracil (III). To a dispersion of 112.1 g (1 mol) of compound **I** and 200 g (1.45 mol) of K_2CO_3 in 300 ml of anhydrous ethanol was added by portions 136 g (1.05 mol) of $H_2NNH_2{\cdot}H_2SO_4$ at 40–60°C within 4 h. Then the reaction mixture was stirred at this temperature for 1 h, the precipitate was filtered off and washed with hot ethanol(2×100 ml) and DMF (3×100 ml). From the filtrate the solvent was distilled off to afford 61 g (96%) of thick fluid. R_f 0.72. IR spectrum, ν, cm^{-1}: 1260 (–N=), 1620, 1690, 1700 [ν(C=O, =NC=O)], 3250–3300 [ν($NHNH_2$)], 3400–3450 [ν(OH)]. UV spectrum (H_2O), λ_{max}, nm: 265.7. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.72–2.88 m (2H, $C^{8,11}H$), 3.46–3.96 m (6H, $C^{9,12}H$, $C^{8,11}OH$), 3.95–4.2 m (4H, $C^{7,10}H$), 4.2–4.5 s (3H, $NHNH_2$), 5.61 d (1H, C^5H, *J* 7.9 Hz), 7.51 d (1H, C^6H, *J* 7.9 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 49.10 (C^{10}), 52.2 (C^7), 56.3 (C^{12}), 60.6 (C^9), 65.00 (C^{11}), 68 (C^8), 99.52 (C^5), 144.66 (C^6), 153.25 (C^2), 162.44 (C^4). Found, %: C 41.20; H 7.20; N 28.80. $C_{10}H_{20}N_6O_4$. Calculated, %: C 41.66; H 6.99; N 29.14.

1,3-Bis(3-hydrazino-2-hydroxypropyl)-6-methyluracil (IV) was prepared in similar way as compound **III** from 14.5 g (0.047 mol) of compound **II**, 26.5 g (0.19 mol) of K_2CO_3, and 19 g (0.146 g) of hydrazine sulfate. Yield 87%. R_f 0.71. Compound **IV** is well soluble in DMF, alcohol, water, sparingly soluble in benzene, hexane. IR spectrum, ν, cm^{-1}: 1260 (–N=), 1640, 1700 [ν(C=O, =NC=O)], 3250–3300 [ν($NHNH_2$)]. UV spectrum (H_2O), λ_{max}, nm: 264.5. ^1H NMR spectrum (D_2O), δ, ppm: 2.05 s (3H, C^6CH_3), 2.72–2.88 m (2H, $C^{8,11}H$), 3.46–3.96 m (4H, $C^{9,12}H$), 3.9– 4.2 m (4H, $C^{7,10}H$), 4.2–4.90 m (8H, $2NHNH_2$, $C^{8,10}OH$), 5.63 s (1H, C^5H). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 14.6 ($\underline{C}H_3C^6$), 48.00 ($C^{7,10}$), 56.00 ($C^{9,12}$), 66.50 ($C^{8,11}$), 98.45 (C^5), 153.6 (C^6), 157.00 (C^2), 162.4 (C^4). Found, %: C 43.50; H 7.00; N 27.50. $C_{11}H_{22}N_6O_4$. Calculated, %: C 43.70; H 7.33; N 27.80.

1,3-Bis[2-hydroxy-3-(1-methyl-2-ethoxycarbonylethylidenehydrazino)propyl]uracil (V). To a solution of 6.25 g (0.0215 mol) of compound **III** in 200 ml of methanol was added 8 ml (0.062 mol) of ethyl acetoacetate, The reaction mixture was stirred for 4 h at room temperature and left overnight. On the next day the solvent was distilled off, the residue (9.8 g) was treated with pentane (2×30 ml), the pentane was decanted, and the residual solvent was distilled off in a vacuum. We obtained 8.6 g (77%) of thick fluid. IR spectrum, ν, cm^{-1}: 1060–1200 [ν(C–O)], 1660–1700 [ν(C=O, =NC=O)], 1700–1720 [ν(C=O)], 3320–3350 [ν(NHN)], 3400, 3450 [ν(OH)]. UV spectrum (H_2O), λ_{max}, nm: 269.5. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 t, (6H, $C^{18}H$, *J* 6.5 Hz), 2.1 s (6H, $C^{14}H$), 2.8–3.1 m (4H, $C^{9,12}H$), 3.3–3.4 m (4H, $C^{15}H$), 3.43– 3.88 m (6H, $C^{7,10}H$, $C^{8,11}H$), 4.0 q (4H, $C^{17}H$, *J* 6.5 Hz), 5.13 s (4H, NH, OH), 5.74 d (1H, C^5H, *J* 7.3 Hz), 8.1 d (1H, C^6H, *J* 7.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.11 (C^{18}), 20.5 (C^{14}), 42.5 (C^{15}), 48.8 ($C^{7,10}$), 50.00 ($C^{9,12}$), 60.2 (C^{17}), 68.5 ($C^{8,11}$), 106.42 (C^5), 144.66 (C^6), 153.26 (C^2), 158.40 (C^{13}), 162.44 (C^4), 167.70 (C^{16}). Found, %: C 44.9; H 7.20; N 14.6. $C_{22}H_{36}N_6O_8{\cdot}4H_2O$. Calculated, %: C 45.29; H 7.60; N 14.47.

1,3-Bis[2-hydroxy-3-(1-methyl-2-ethoxycarbonylethylidenehydrazino)propyl]-6-methyluracil (VI) was obtained in the same way as compound **V** from 8 g (0.277 mol) of compound **IV** and 9 ml of ethyl acetoacetate in 200 ml of methanol. Yield 73%. R_f 0.73. Compound **VI** is well soluble in alcohol, acetone, water, insoluble in hexane. IR spectrum, ν, cm^{-1}: 1060–1200 [ν(C–O)], 1660–1700 [ν(C=O, =NC=O)], 1700– 1720 [ν(C=O)], 3320–3350 [ν(NHN)], 3400, 3450 [ν(OH)]. UV spectrum (H_2O), λ_{max}, nm: 270. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.1 t (6H, $C^{18}H$, *J* 6.5 Hz), 2.05 s (3H, CH_3C^6), 2.1 s (6H, $C^{14}H$), 2.8–3.1 m (4H, $C^{9,12}H$), 3.3–3.4 m (4H, $C^{15}H$), 3.43–3.88 m (6H, $C^{7,10}H$, $C^{8,11}H$), 4.05 t (4H, $C^{17}H$, *J* 6.5 Hz), 5.13 s (4H, NH, OH), 5.69 s (1H, C^5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.0 (C^{18}), 14.61 (C^6CH_3), 20.5 (C^{14}), 42.5 (C^{15}), 48.8 (C^{10}), 50.00 ($C^{9,12}$), 51.00 (C^7), 60.2 (C^{17}), 68.5 ($C^{8,11}$), 99.53 (C^5), 153.47 (C^6), 157.82 (C^2), 158.40 (C^{13}), 162.44 (C^4), 167.70 (C^{16}). Found, %: C 52.00; H 6.87; N 15.60. $C_{23}H_{38}N_6O_8$. Calculated, %: C 52.46; H 7.27; N 15.96.

1.3-Bis[2-hydroxy-3-(3-methyl-5-oxo-2,5-dihydro-1-pyrazolyl)propyl]uracil (VII). To a solution of 10.5 g (0.02 mol) of compound **V** in 120 ml of DMF and 100 ml of methanol was added dropwise within 1 h a solution of 1.18 g of sodium methylate in 50 ml of methanol. The mixture was left overnight. On the next day to the reaction mixture was added 12 ml of concn. HCl, and then the solvent was distilled off, the residue was dissolved in methanol,

the separated crystals were filtered off and washed with methanol; we obtained 6.3 g of NaCl. From the filtrate methanol was distilled off, and the residue was subjected to azeotrope drying with acetone and methanol. We obtained finally 6.6 g of viscous fluid. R_f 0.79. IR spectrum, ν, cm^{-1}: 1060–1240 (–N=), 1660–1700 [ν(C=O, =NC=O)], 3304 [ν(NHN)], 3600 [ν(OH)]. UV spectrum (H_2O), λ_{max}, nm: 261.5, 298. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.11 c (6H, CH_3 pyrazole), 3.05–3.3 m (4H, $C^{9,12}H$), 3.5–3.9 m (4H, $C^{7,10}H$), 3.9–4.2 m (2H, $C^{8,11}H$), 4.2 s (4H, NH, OH), 5.2 s (2H, C^4H pyrazole), 5.74 d (1H, C^5H, *J* 7.3 Hz), 8.1 d (1H, C^6H, *J* 7.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 15.66 (CH_3C^3 pyrazole), 36.8 ($C^{9,12}$), 48.5 ($C^{7,10}$), 64.2 ($C^{8,11}$), 156.4 (C^3 pyrazole), 108.4 (C^4 pyrazole), 103.2 (C^5), 144.66 (C^6), 152.40 (C^2), 162.44 (C^4), 168.37 (C^5 pyrazole). Found, %: C 51.10; H 6.00; N 19.50. $C_{18}H_{24}N_6O_6$. Calculated, %: C 51.42; H 5.75; N 19.99.

1.3-Bis[2-hydroxy-3-(3-methyl-5-oxo-2,5-dihydro-1-pyrazolyl)propyl]-6-methyluracil (VIII) was prepared analogously to compound **VII** from 10.5 g (0.02 mol) of compound **VI**. Yield 38%. R_f 0.71. Compound **VIII** is well soluble in water, alcohol, insoluble in hexane. IR spectrum, ν, cm^{-1}: 1060–1240 (–N=), 1640–1710 [ν(C=O, =NC=O)], 3300 [ν(NHN)], 3600 [ν(OH)]. UV spectrum (H_2O), λ_{max}, nm: 261.0, 299.5. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.05 s (3H, CH_3C^6), 2.11 s (6H, CH_3 pyrazole), 3.15–3.3 m (4H, $C^{9,12}H$), 3.5–3.7 m (4H, $C^{7,10}H$), 3.8–3.9 m (2H, $C^{8,11}H$), 4.2–4.4 m (4H, NH, OH), 5.4 s (2H, C^4 pyrazole), 5.68 s (1H, C^5H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.28 (CH_3C^3 pyrazole), 14.62 (CH_3C^6), 36.9 ($C^{9,12}$), 44.23 (C^{10}), 50.75 (C^7), 60.90 (C^{11}), 61.27 (C^8), 98.53 (C^5), 114.6 (C^4 pyrazole), 152.5 (C^3 pyrazole), 153.47 (C^2), 143.50 (C^6), 162.44 (C^4), 168.37 (C^5 pyrazole). Found, %: C 52.70; H 6.50; N 19.70. $C_{19}H_{26}N_6O_6$. Calculated, %: C 52.53; H 6.03; N 19.34.

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