Russian Journal of Organic Chemistry, Vol. 40, No. 3, 2004, pp. 417–420. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 3, 2004, pp. 444–447.

Synthesis of 5-Alkyl-1,3-bis[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-diones

V. P. Krivonogov, G. G. Kozlova, E. A. Belaya, G. A. Sivkova, L. V. Spirikhin, I. B. Abdrakhmanov, and V. V. Plechev

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia

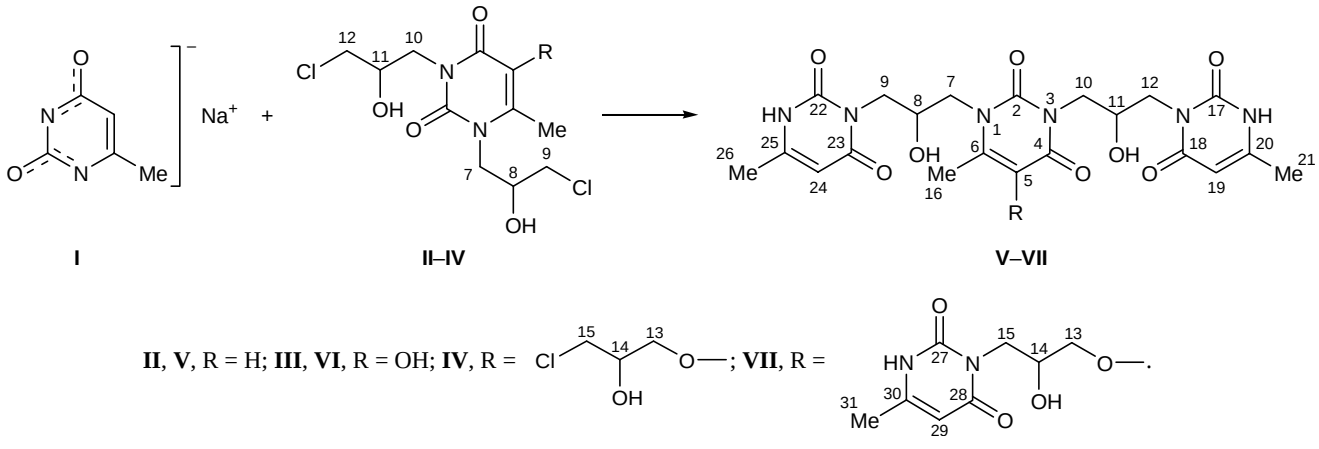
Received January 22, 2003

Abstract—6-Methyluracil sodium salt reacts with 1,3-bis(3-chloro-2-hydroxypropyl)-6-methyluracils in DMF, yielding products of alkylation at the nitrogen atom in position *3* of the uracil ring.

Derivatives of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine (uracil) in which the heterocyclic fragments are linked through a hydrocarbon bridge attract interest not only as immunotropic and antiphlogistic agents but also as model compounds for studying interactions between pyrimidine bases in nucleic acids [1]. We previously synthesized a series of pyrimidine derivatives which exhibited immunotropic, antiphlogistic, membrane-stabilizing, and antiradical activity [2–7], as well as extracting ability with respect to noble metals [8, 9].

In continuation of our studies on the synthesis of pyrimidine derivatives as potential immunotropic and antiphlogistic agents we examined the reaction of 6-methyluracil sodium salt (**I**) with 1,3-bis(3-chloro-2-hydroxypropyl)-6-methyluracil (**II**), 1,3-bis(3-chloro-2-hydroxypropyl)-5-hydroxy-6-methyluracil (**III**), and 1,3-bis(3-chloro-2-hydroxypropyl)-5-(3-chloro-2-hydroxypropoxy)-6-methyluracil (**IV**) in dimethylformamide (DMF). Sodium salt **I** reacted with compounds **II** and **III** at a reactant ratio of 2:1 to give, respectively, 1,3-bis[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**V**) and 1,3-bis-[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-5-hydroxy-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**VI**). The reaction of salt **I** with compound **IV** at a reactant ratio of 3:1 afforded compound **VII** (Scheme 1). In none of the cases O-alkylation products were formed. The purity of the products was checked by thin-layer chromatography. Compounds **V**–**VII** are thick liquids which are

Scheme 1.



1070-4280/04/4003-0417 © 2004 MAIK “Nauka/Interperiodica”

readily soluble in water, DMF, and alcohols and insoluble in chloroform.

The structure of the products was confirmed by the data of elemental analysis and IR, ^{1}H and ^{13}C NMR, and UV spectroscopy. The IR spectra of compounds **V** and **VII** contained absorption bands in the regions 3100–3600 [ν(NH)], 3060–3100 cm^{-1} [ν(CH)], 1615, and 760 cm^{-1} (uracil ring) [1]. All compounds showed in the IR spectra absorption bands at 1620–1720 cm^{-1}, which are typical of vibrations of the pyrimidine fragment [ν(C=O), ν(=N–C=O)]. Absorption bands in the region 1060–1240 cm^{-1} are usually observed for compounds whose molecules contain tertiary nitrogen atoms (–N=); stretching vibrations of the hydroxy groups appeared at 3300–3400 cm^{-1}, and the band at 3500 cm^{-1} belongs to ν(OH) of the hydrate water. In the spectra of all the products we observed a band at 3400 cm^{-1} due to stretching vibrations of the hydroxy group at C^{11}, which is involved in formation of hydrogen bond, and a band centered at 3090–3100 cm^{-1}, which corresponds to ν(NH).

With the goal of determining the site of alkylation, i.e., whether it occurred at N^1 or N^3, we recorded the UV spectra of compounds **V**–**VII** at different pH values. We found that the UV absorption maximum shifts toward longer wavelengths by 19–22 nm on variation of pH from 2 to 12: λ_{max} = 261–263 nm (pH 2), λ_{max} = 280–283 nm (pH 12). This pattern is typical of uracil derivatives substituted at the nitrogen atom in position *3* [10]. We were the first to reveal that the site of alkylation can be determined from the ^{1}H NMR spectra. If a substituent is attached to N^3, the 1-H signal appears at δ 8–9 ppm, while the 3-H signal of N^1-substituted analogs is located in the δ region 10–11 ppm. The positions of signals from the ring carbon atoms in the ^{13}C NMR spectra were typical of uracil derivatives, δ_C, ppm: 163.2, 162.4 (C^4, C^{18}, C^{23}, C^{28}); 157.7, 151.4 (C^6, C^{20}, C^{25}, C^{30}); 153.0 (C^2, C^{17}, C^{22}, C^{27}); 98.53 (C^5, C^{19}, C^{24}, C^{29}). Also, signals at δ_C 12.98–17.2 ppm were present (CH$_3$, C^{16}, C^{21}, C^{26}, C^{31}).

Compounds **V**–**VII** are characterized by a strong intramolecular hydrogen bond which involves hydroxy groups in the substituents and endocyclic C=O groups. The hydrogen bond persists in solution; therefore, the substituents at N^1 and N^3 give different signals from their carbon atoms in the ^{13}C NMR spectra, and signals from C^{16} and C^{31} shift upfield relative to the corresponding signals of unsubstituted uracil and 6-methyluracil.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ or D_2O (1% solutions for ^{1}H and 10–20% solutions for ^{13}C) using a Bruker AM-300 spectrometer (300 and 75 MHz, respectively); the chemical shifts were measured relative to TMS. The IR spectra of compounds dispersed in mineral oil (or neat) were obtained on a UR-20 spectrometer (Carl Zeiss Jena) with NaCl and LiF prisms. The melting points were determined on a Boetius device. Elemental analysis was performed using a C–N–H Analyzer M-185B. The progress of reactions was monitored (and the purity of products was checked) by TLC on Silufol UV-254 plates using ethanol–aqueous ammonia (4:1) as eluent; spots were visualized by UV irradiation (λ 254 nm) or treatment with iodine vapor. The UV spectra were measured on a Specord M-400 spectrophotometer. Silica gel was used for preparative column chromatography.

1,3-Bis[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (V). 6-Methyluracil sodium salt, 3.14 g (0.212 mol), was added to 33.0 g (0.106 mol) of 1,3-bis(3-chloro-2-hydroxypropyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**II**) in 400 ml of DMF. The mixture was heated for 15–20 h on a boiling water bath until it became neutral (against litmus), cooled, and diluted with 100 ml of acetone. The precipitate of sodium chloride was filtered off and washed with acetone, the filtrate was acidified with 3–5 ml of hydrochloric acid, and the crystals of initial methyluracil (7 g) were filtered off. The filtrate was evaporated to obtain 43 g (83%) of compound **V** as a thick yellow liquid. IR spectrum, cm^{-1}: 540, 608, 768 (uracil); 1064–1272 (=N–), 1352, 1376 (δCH$_3$); 1400, 1460, 1664, 1704, 1716 [ν(C=O, =N–C=O)]; 3100 [ν(NH)]; 3400, 3560 [ν(OH)]. UV spectrum, λ_{max}, nm: 261 (pH 2), 283 (pH 12). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.05 s (3H, 6-CH$_3$), 2.4 s (6H, C^{20}H$_3$, C^{25}H$_3$), 2.8 d (1H, 8-H, *J* = 7.7 Hz), 3.0 d (1H, 11-H, *J* = 7.7 Hz), 3.5–3.7 m (4H, C^{9}H$_2$ and C^{12}H$_2$), 3.7 d (4H, C^{7}H$_2$, *J* = 7.7 Hz), 5.5–5.7 m (3H, 5-H, 19-H, 24-H), 6.07 s (2H, 8-H, 11-H), 8.4 s (2H, NH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 14.6 (C^{16}), 17.00 (C^{21}, C^{26}), 45.10 (C^9, C^{12}), 46.2 (C^{10}), 48.0 (C^7), 64.00 (C^8, C^{11}), 98.5 (C^5), 99.2 (C^{19}, C^{24}), 151.4 (C^{20}, C^{25}), 153.47 (C^2), 154.4 (C^{17}, C^{22}), 157.8 (C^6), 162.4 (C^4), 163.2 (C^{18}, C^{23}). Found, %: C 45.30; H 5.84; N 14.40. $C_{21}H_{24}N_6O_8 \cdot 4H_2O$. Calculated, %: C 45.00; H 5.75; N 14.99.

1,3-Bis[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-5-hydroxy-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (VI). 6-Methyluracil sodium salt, 31.7 g (0.22 mol), was added to 36.2 g (0.11 mol) of 1,3-bis(3-chloro-2-hydroxypropyl)-5-hydroxy-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**III**) and 400 ml of DMF. The mixture was heated on a boiling water bath and stirred until pH 7–8 was attained (~20 h). It was then cooled, 3 ml of concentrated hydrochloric acid was added to pH 6, and the crystals were filtered off. The filtrate was evaporated to obtain 21.7 g of compound **VI** as a thick liquid. The crystals were treated with 800 ml of hot alcohol, and the mixture was filtered from NaCl (35 g) through a glass filter. The filtrate was evaporated, and the residue, 23.9 g of a thick liquid, was treated with hot acetone. The mixture was cooled, and crystals of methyluracil (6.1 g, R_f 0.78) were filtered off. The filtrate was evaporated to obtain an additional portion (16.9 g) of compound **VI**. Overall yield 69%. The product is readily soluble in water, DMF, and alcohol and insoluble in chloroform, benzene, acetone, and hexane. The crude product was dissolved in water and subjected to column chromatography on Al_2O_3 of activity grade II. Removal of the solvent gave 23.3 g (42%) of compound **VI**, R_f 0.42. UV spectrum, λ_{max}, nm: 265 (pH 2), 280 (pH 12). IR spectrum, cm^{-1}: 540, 608, 760 (uracil); 1064–1272 (=N–); 1352, 1380 (δCH_3); 1400, 1460, 1664, 1704, 1716 [ν(C=O, =N–C=O)]; 3100 [ν(NH)]; 3400, 3600 [ν(OH)]. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.87 s (3H, 6-CH_3), 2.4 s (6H, $C^{20}H_3$ and $C^{25}H_3$), 2.8 d (1H, 8-H, J = 7.7 Hz), 3.5 d (1H, 11-H, J = 7.7 Hz), 3.5–3.7 m (4H, C^9H_2 and $C^{12}H_2$), 3.8 d (4H, C^7H_2 and $C^{10}H_2$, J = 7.7 Hz), 5.5 s (2H, 19-H, 24-H), 8.0 s (3H, 5-OH, 8-OH, 11-OH), 8.4 s (2H, N^1H). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 12.6 (C^{16}), 17.90 (C^{21}, C^{26}), 45.10 (C^9, C^{12}), 46.4 (C^{10}), 48.0 (C^7), 63.50 (C^8, C^{11}), 99.2 (C^{19}, C^{24}), 130.0 (C^5), 142.10 (C^6), 151.4 (C^{20}, C^{25}), 153.47 (C^2), 154.4 (C^{17}, C^{22}), 163.6 (C^4, C^{18}, C^{23}). Found, %: C 45.56; H 5.75; N 14.50. $C_{21}H_{26}N_6O_9 \cdot 3H_2O$. Calculated, %: C 45.00; H 5.75; N 14.99.

1,3-Bis[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propyl]-5-[2-hydroxy-3-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-3-yl)propoxy]-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (VII). 6-Methyluracil sodium salt, 22.5 g (0.15 mol), was added to 22.0 g (0.05 mol) of 1,3-bis-(3-chloro-2-hydroxypropyl)-5-(3-chloro-2-hydroxypropoxy)-6-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione (**IV**) in 400 ml of DMF, and the mixture was heated for 20 h on a boiling water bath (until pH 7) and was left overnight. The mixture was diluted with 300 ml of acetone, and the crystals of NaCl (15.6 g) were filtered off. The solvent was distilled off from the filtrate, the residue was treated with hot acetone (2×200 ml), and the extract was filtered while hot. After cooling, the precipitate of compound **VII**, 11.0 g, was filtered off. Evaporation of the mother liquor gave an additional portion of **VII**, 20.6 g. Overall yield 31.6 g (92%). Found, %: C 45.96; H 5.80; N 14.64. $C_{29}H_{36}N_8O_{12} \cdot 4H_2O$. Calculated, %: C 45.77; H 5.87; N 14.72.

The crude product was dissolved in 23 ml of water, the solution was passed through a column charged with 50 g of silica gel, and the column was washed with water. From the eluate we isolated 15 g (44%) of the product as a thick liquid, R_f 0.37 (alcohol–aqueous ammonia, 4:1). UV spectrum, λ_{max}, nm: 265 (pH 2), 283 (pH 12). IR spectrum, cm^{-1}: 540, 608, 768 (uracil); 1064–1272 (=N–); 1352, 1380 (δCH_3); 1400, 1460, 1664, 1704, 1716 [ν(C=O, =N–C=O)]; 3112 [ν(NH)]; 3400, 3560 [ν(OH)]. ^{1}H NMR spectrum (D_2O), δ, ppm: 1.8 s (3H, 6-CH_3), 2.4 s (9H, $C^{20}H_3$, $C^{25}H_3$, $C^{30}H_3$), 2.9 d (1H, 8-H, J = 7.7 Hz), 3.5 d (2H, 11-H, 14-H, J = 7.7 Hz), 3.6–3.8 m (8H, 7-H, 9-H, 10-H, 12-H), 3.9–4.2 m (4H, $C^{13}H_2$ and $C^{17}H_2$), 5.58 s (3H, 19-H, 24-H, 29-H), 6.17 s (3H, 8-OH, 11-OH, 14-OH), 8.47 s (3H, NH). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 11.9 (C^{16}), 14.62 (C^{21}, C^{26}, C^{31}), 45.70 (C^9, C^{12}), 47.8 (C^7, C^{10}), 48.6 (C^{15}), 63.2 (C^8, C^{11}, C^{14}), 69.30 (C^{13}), 99.2 (C^{19}, C^{24}, C^{29}), 127.4 (C^5), 142.0 (C^6), 151.40 (C^{20}, C^{25}, C^{30}), 152.40 (C^{23}), 153.0 (C^2), 154.4 (C^{17}, C^{22}), 161.8 (C^{28}), 163.0 (C^4, C^{18}, C^{23}). Found, %: C 48.23; H 5.62; N 15.48. $C_{29}H_{36}N_8O_{12} \cdot 2H_2O$. Calculated, %: C 48.06; H 5.56; N 15.46.

REFERENCES

1. Reznik, V.S., Salikhov, I.Sh., Shvetsov, Yu.S., Shirshov, A.N., Bakulin, V.S., and Ivanov, B.E., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1977, p. 880.
2. Krivonogov, V.P., Tolstikov, G.A., Murinov, Yu.I., Zarudii, F.S., Lazareva, D.N., Ismagilova, A.F., Volkova, S.S., Sakhautdinova, G.M., Spirikhin, L.V., and Krivonogova, I.I., *Khim.-Farm. Zh.*, 1993, vol. 27, p. 41.
3. Krivonogov, V.P., Tolstikov, G.A., Murinov, Yu.I., Zarudii, F.S., Lazareva, D.N., Ismagilova, A.F., Volkova, S.S., Sakhautdinova, G.M., Spirikhin, L.V., and Krivonogova, I.I., *Khim.-Farm. Zh.*, 1996, vol. 30, p. 39.

4. Tolstikov, G.A., Krivonogov, V.P., Murinov, Yu.I., Galimov, B.I., Lazareva, D.N., Davydova, V.A., and Krivonogova, I.I., *Khim.-Farm. Zh.*, 1995, vol. 29, p. 14.
5. Krivonogov, V.P., Tolstikov, G.A., Murinov, Yu.I., Zarudii, F.S., Lazareva, D.N., and Abdrakhmanov, I.B., *Khim.-Farm. Zh.*, 1997, vol. 31, p. 24.
6. Krivonogov, V.P., Sivkova, G.A., Kozlova, G.G., Abdrakhmanov, I.B., Spirikhin, L.V., and Afzaletdinova, N.G., *Russ. J. Org. Chem.*, 2002, vol. 38, p. 286.
7. Krivonogov, V.P., Sivkova, G.A., and Kozlova, G.G., *Khim.-Farm. Zh.*, 2002, vol. 36, p. 8.
8. Khisamutdinov, R.A., Potapov, V.V., Murinov, Yu.I., and Krivonogov, V.P., *Zh. Neorg. Khim.*, 2001, vol. 46, p. 517.
9. Khisamutdinov, R.A., Potapov, V.V., Murinov, Yu.I., and Krivonogov, V.P., *Zh. Neorg. Khim.*, 2001, vol. 46, p. 513.
10. Shugar, D. and Fox, J., *Biochim. Biophys. Acta*, 1952, vol. 9, p. 199.