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Polyfunctional Isocytosine Derivatives: II.[1] Regioselectivity of Methylation of 2-(2-Hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one in Different Media

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Abstract—High regioselectivity in the methylation of 2-(2-hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one at the N^3 atom in water and ethanol in the presence of inorganic bases is determined by participation of the oxygen atom in hydrogen bonding and its coordination to metal cation, respectively. In going to aprotic dimethylformamide which is capable of solvating cations, the regioselectivity decreases, and a mixture of N^3- and *O*-methyl isomers is formed.

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Isocytosines are unsymmetrical 2-aminopyrimidines, and their alkylation constitutes a difficult problem, taking into account possible formation and subsequent separation of isomeric products. According to published data [2–13], alkylation of these compounds is characterized by poor regioselectivity which is determined in each case by a number of factors, including the substrate structure. Unfortunately, no analysis of the latter factor on the direction of alkylation of even the simplest isocytosines was performed in the cited studies; correspondingly, the behavior of more complex substrates in analogous reactions cannot be predicted. The above stated prompted us to examine the regioselectivity of methylation of a functionalized isocytosine derivative, 2-(2-hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (**I**) in different media.

Methylation of compound **I** with dimethyl sulfate in aqueous sodium hydroxide (method *a*), as well as with methyl iodide in ethanol in the presence of potassium hydroxide (method *b*), afforded exclusively 2-(2-hydroxyethylamino)-3,6-dimethylpyrimidin-4(3*H*)-one (**II**). Treatment of the same substrate with methyl iodide in dimethylformamide (DMF) in the presence of potassium carbonate (method *c*) gave a mixture of compound **II** and 2-(6-methyl-4-methoxypyrimidin-2-ylamino)ethanol (**III**). The structure of products **II** and **III** was proved, respectively, by independent synthesis, i.e., amination of 3,6-dimethyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**) with 2-aminoetanol, and alkaline hydrolysis of 2-(6-methyl-4-methoxypyrimidin-2-ylamino)ethyl acetate (**V**). The latter was synthesized by successive acetylation of substituted isocytosine **I** with excess acetic anhydride in anhydrous pyridine, exchange chlorination of 2-(2-acetoxyethylamino) derivative **VI** with phosphorus pentachloride, and methoxylation of 2-(4-chloro-6-methylpyrimidin-2-ylamino)ethyl acetate (**VII**) with sodium methoxide in anhydrous methanol. Insofar as *O*-methylisocytosine **III** and its hydrochloride are difficult to isolate in the crystalline form [14], samples of **III** obtained by the two methods were characterized as picrates (see scheme).

The high regioselectivity in the methylation of substituted isocytosine **I** according to method *a* can be rationalized in terms of specific hydration of the corresponding anion (λ_{max} 277 nm). Just the anionic form should be assumed to act as reacting species, for its concentration in the reaction mixture exceeds 99.9%. The negative charge in the anion is localized mainly on the oxygen atom which is involved in strong hydrogen bonding with the solvent. This follows from the red shift (Fig. 1a) of the absorption maximum of substituted isocytosine **I**, which approaches the absorption maximum of *N*-methylisocytosine (**II**) [λ_{max} 289 nm (MeCN)], and from the concomitant hypochromic effect (Fig. 1b) as the concentration of aprotic acetonitrile in aqueous–alkaline solutions of compound **I** rises.

Methylation of **I** according to method *b* also gave *N*-methylisocytosine (**II**) as the only product. However, in this case, the high regioselectivity originates

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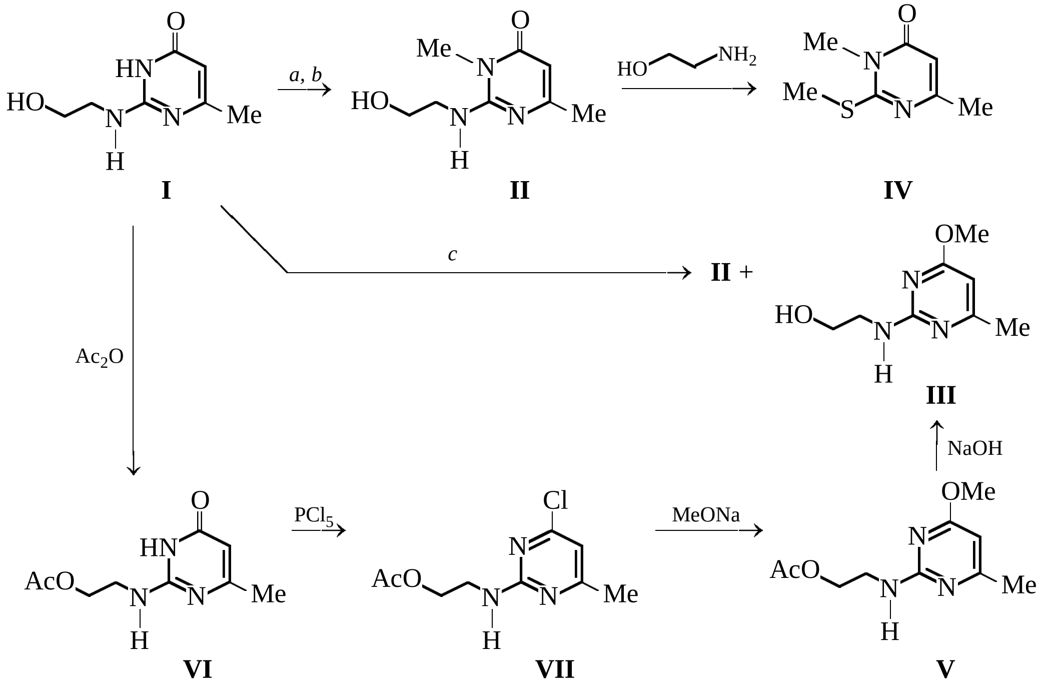
[1] For communication I, see [1].



from participation of the oxygen atom in complex formation with the base. Such association becomes possible due to considerably lower dielectric constant of ethanol (ε = 24.55) as compared to water (ε = 78.3) and increase in the energy of solvation of potassium cation in going from water to ethanol (ΔG = 16.4 kJ mol^{-1}) [15]. The amide moiety in **I** does not undergo ionization under these conditions, and it acts as a donor of electron density, thus favoring complex formation between the substrate and alkaline agent with a composition of 1 : 1. This follows from the absence of shift of the absorption maximum of compound **I** in the presence of an equimolar amount of alkali (λ_{max} 289 nm) and from the appearance of an inflection point on the plot of the optical density D_{290} of ethanolic solutions of substituted isocytosine **I** and potassium hydroxide vs. molar ratio of the components (n) at n ~1 (Fig. 2).

Considerable reduction of the regioselectivity is observed in the methylation of compound **I** according to procedure *c*. Despite similar dielectric constants of ethanol and DMF (ε = 36.71), the oxygen atom in the substrate is not blocked by the base, as it occurs in ethanol, for potassium cation is solvated by DMF. As a result, the reaction mixture contains both *N*- and *O*-methyl derivatives **II** and **III**. Unfortunately, the latter is difficult to isolate as free base; therefore, we failed to determine the isomer ratio and thus estimate the reactivity of different nucleophilic centers in molecule **I** toward the methylating agent.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Shimadzu FTIR-8400 spectrometer. The ^{1}H NMR spectra were obtained on a Bruker AC-200 instrument at

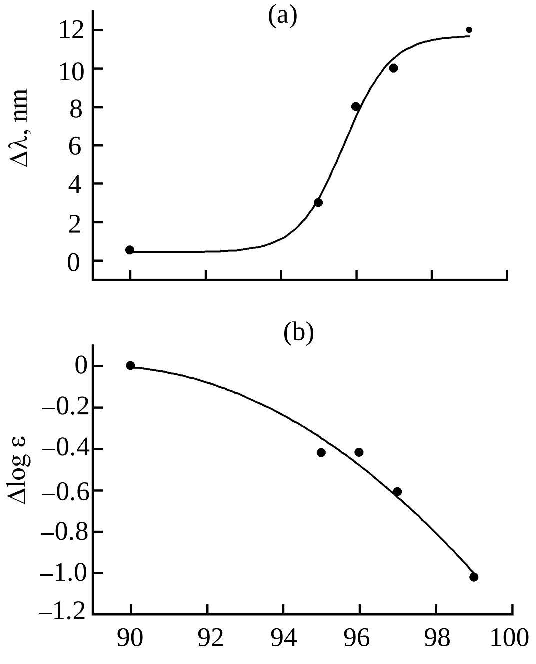


Fig. 1. Plots of the (a) position and (b) intensity of the absorption maximum of 2-(2-hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (**I**) anion versus volume fraction of acetonitrile in the solvent.

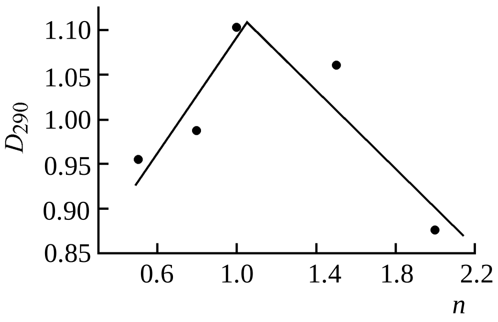


Fig. 2. Plot of the optical density of solutions of 2-(2-hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (**I**) in ethanol vs. concentration of potassium hydroxide; *n* is KOH-to-**I** molar ratio.

200.13 MHz from solutions in DMSO-d_6 using the signal from residual protons in the solvent as reference. The UV spectra were measured on an SF-26 spectrophotometer from solutions with a concentration of 10^{-4} M. The purity of the products was checked by TLC on Silufol UV-254 plates using 1-butanol–acetic acid–water (1 : 1 : 1, A) and chloroform–methanol (9 : 1, B) as eluents; spots were visualized under UV light. The elemental analyses were obtained on a Perkin–Elmer-240 CHN analyzer.

The concentration of the ionized form of 2-(2-hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (**I**) was calculated by the standard procedure [16] from the mixed ionization constant of substituted isocytosine **I** in water (pK_a = 9.96 ± 0.07). The latter was determined by spectrophotometry from the optical densities of buffer solutions of **I** with pH values varied from 9.0 to 12.6 (λ = 277 nm); the results were processed by the graphical method [17], taking into account variable molar absorption coefficient of the anionic form of **I**.

The absorption maximum of substituted isocytosine **I**, which is insoluble in anhydrous acetonitrile, was assumed to be equal to that indicated above, since its position was found to be independent of the polarity of the medium in the E_T^N range from 0.65–0.40 (E_T^N is the Dimroth–Reichardt normalized polarity parameter; E_T^N for acetonitrile is equal to 0.46) [15].

2-(2-Hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (**I**), 2-(4-methoxy-6-methylpyrimidin-2-ylamino)ethyl acetate (**V**), and 2-(4-oxo-6-methyl-3,4-dihydropyrimidin-2-ylamino)ethyl acetate (**VI**) were synthesized by the procedures described in [14], and 3,6-dimethyl-2-(methylsulfanyl)pyrimidin-4(3*H*)-one (**IV**) was prepared as reported in [18].

2-(2-Hydroxyethylamino)-3,6-dimethylpyrimidin-4(3*H*)-one (II). *a*. Dimethyl sulfate, 1.26 g, was added to a solution of 1.69 g of compound **I** in 7.6 ml of water containing 0.4 g of sodium hydroxide. The mixture was stirred for 120 h at room temperature, and the precipitate was filtered off, dried over phosphoric anhydride under reduced pressure, and extracted with anhydrous acetonitrile. The precipitate was recrystallized from water and dried over phosphoric anhydride under reduced pressure. Yield 294 mg (16%), mp 191°C (mixed sample: mp 191°C), R_f 0.44 (A). IR spectrum, ν, cm^{-1}: 1373.2, 1346.2, 1253.6, 1222.8, 1143.7, 1082.0, 1062.7, 1029.9, 1012.6, 958.6, 869.8, 819.7, 771.5, 763.8.

b. Methyl iodide, 1.42 g, was added to a solution of 1.69 g of compound **I** in 10 ml of anhydrous ethanol containing 0.56 g of potassium hydroxide. The mixture was kept for 120 h at room temperature, and the precipitate was filtered off, dried over phosphoric anhydride under reduced pressure, and extracted with anhydrous acetonitrile. The precipitate was recrystallized from water and dried over phosphoric anhydride under reduced pressure. Yield 324 mg (18%), mp 192°C (mixed sample: mp 192°C), R_f 0.44 (A). IR spectrum, ν, cm^{-1}: 1373.2, 1346.2, 1253.6, 1222.8, 1143.7, 1082.0, 1062.7, 1029.9, 1012.6, 958.6, 869.8, 819.7, 771.5, 763.8. The ethanol solution was evaporated to dryness under reduced pressure, the residue was crystallized by adding anhydrous acetonitrile, and the precipitate was filtered off, recrystallized from water, and dried over phosphoric anhydride under reduced pressure to isolate an additional portion, 102 mg (5%), of compound **II**, mp 192°C, R_f 0.44 (A). No depression of the melting point was observed on mixing with the main portion of the product.

2-(2-Hydroxyethylamino)-3,6-dimethylpyrimidin-4(3*H*)-one (II) and 2-(4-methoxy-6-methylpyrimidin-2-ylamino)ethanol (III). *c*. Compound **I**, 1.69 g, was dispersed in 15 ml of anhydrous DMF, and 1.38 g of potassium carbonate and 1.42 g of methyl iodide were added in succession to the suspension. The mixture was stirred for 120 h at room temperature, the precipitate was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The residue was made crystalline by adding anhydrous acetonitrile, and the precipitate was filtered off, recrystallized from water, and dried over phosphoric anhydride under reduced pressure. We thus isolated 125 mg (6.8%) of compound **II**, mp 192°C (mixed sample: mp 192°C), R_f 0.44 (A). IR spectrum, ν, cm^{-1}: 1373.2, 1340.4, 1253.6, 1220.9, 1143.7, 1082.0, 1062.7, 1029.9, 1012.6, 956.6, 869.8, 819.7, 771.5, 763.8. The acetonitrile solution was evaporated to dryness under reduced pressure, the residue was dissolved in 5 ml of acetone, the solution was filtered, and a solution of 0.55 g of picric acid in 5 ml of acetone was added to the filtrate. The mixture was heated for 15 min under reflux and cooled to 5°C, and the precipitate was filtered off, recrystallized from acetone, and dried under reduced pressure. Yield of compound **III** picrate 83 mg, mp 169°C (mixed sample: mp 168°C), R_f 0.86 (A). IR spectrum, ν, cm^{-1}: 1363.6, 1340.4, 1317.3, 1301.9, 1257.5, 1199.6, 1166.9, 1083.9, 1053.1, 902.6, 821.6, 790.8, 746.4. ^1H NMR spectrum, δ, ppm: 2.39 s (3H, Me), 3.97 s (3H, OMe), 6.32 s (1H, CH), 8.02 br.s (1H, NH), 8.57 s (2H, H_{arom}). Found, %: C 40.66; H 3.85; N 20.47. $C_8H_{13}N_3O_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 40.77; H 3.88; N 20.38.

2-(2-Hydroxyethylamino)-3,6-dimethylpyrimidin-4(3*H*)-one (II) was also synthesized from 3,6-dimethyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**) and 2-aminoethanol according to the procedure reported in [14]. mp 193°C, R_f 0.44 (A). IR spectrum, ν, cm^{-1}: 1373.2, 1346.2, 1253.6, 1222.8, 1143.7, 1082.0, 1062.7, 1029.9, 1012.6, 958.6, 869.8, 817.8, 771.5, 763.8.

2-(4-Methoxy-6-methylpyrimidin-2-ylamino)-ethanol (III) *(independent synthesis).* A solution of 0.5 g of sodium hydroxide in 4.5 ml of water was heated to 50°C, and 0.3 g of compound **V** was added in portions over a period of 1 h under vigorous stirring. The mixture was kept for an additional 1 h at 50°C and was evaporated to dryness under reduced pressure. The residue was treated with 5 ml of boiling acetone, the undissolved material was filtered off, and a solution of 0.30 g of picric acid in 5 ml of acetone was added to the filtrate. The mixture was heated for 15 min under reflux and cooled to 5°C, and the precipitate was filtered off, recrystallized twice from acetone, and dried under reduced pressure. Yield of picrate 54 mg (9.8%, calculated on initial compound **V**), mp 166°C, R_f 0.86 (A). ^1H NMR spectrum, δ, ppm: 2.37 s (3H, Me), 4.01 s (3H, OMe), 6.30 s (1H, CH), 8.06 br.s (1H, NH), 8.56 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 1363.6, 1340.4, 1317.3, 1298.0, 1259.4, 1199.6, 1164.9, 1083.9, 1053.1, 902.6, 821.6, 788.8, 746.4. Found, %: C 40.79; H 3.84; N 20.41. $C_8H_{13}N_3O_2 \cdot C_6H_3N_3O_7$. Calculated, %: C 40.77; H 3.88; N 20.38.

2-(4-Chloro-6-methylpyrimidin-2-ylamino)ethyl acetate (VII). A mixture of 2.53 g of acetate **VI** and 2.5 g of phosphorus pentachloride was heated to 120–130°C and was kept for 30 min at that temperature. The mixture was cooled, treated with crushed ice, and neutralized with 25% aqueous ammonia, maintaining the temperature not higher than 15–20°C. The precipitate was filtered off, washed with water, and dried under reduced pressure over phosphoric anhydride. The dry product was recrystallized from ethanol, and dried under reduced pressure over phosphoric anhydride. Yield 1.36 g (49%), mp 124°C, R_f 0.52 (B). No depression of the melting point was observed on mixing with a sample prepared by chlorination of acetate **VI** with phosphoryl chloride as described in [14].

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