with HCl solution in C_2H_5OH, and the precipitated solid rapidly filtered off and dried in vacuo (over H_2SO_4) to give a mixture of the hydrochlorides of III and IV (0.2 g). The mixture was dissolved in 48% HBr (6 ml), refluxed for 4.5 h, cooled to 20°C, and the solution basified with 2N NaOH to pH 9. It was extracted with $CHCl_3$ (5 × 35 ml), washed with water (2 × 25 ml), dried (Na_2SO_4), evaporated to dryness and further dried in vacuo (H_2SO_4) to give a mixture of V and VI (0.1 g). The mixture was separated by preparative chromatography on bonded layer silica gel (DC-Fertigplatten Kieselgel 60 F_{254} Merck) using chloroform—methanol (3:1) as eluent to give V and VI. Isomer V (0.05 g, 50%) had mp 178-180°C and PMR spectrum (DMSO-d_6): 2.18 (6H, s, CH_3); 2.64 (2H, t, CH_2—NMe_2); 4.61 (2H, t, CH_2); 6.16 (1H, d, J_{32} = 2.9 Hz, 3-H); 7.43 (1H, d, 2-H); 7.16 (1H, m, 7-H); 7.54 (2H, m, 5-H, 6-H); 8.25 (1H, d, 8-H); 11.90 ppm (1H, br s, NH). Isomer VI (0.02 g, 20%) had mp 220-222°C and PMR spectrum (DMSO-d_6); 2.26 (6H, s, CH_3); 2.61 (2H, t, CH_2—NMe_2); 4.47 (t, 2H, CH_2); 6.43 (1H, d, $^3J_{32}$ = 2.9 Hz, 3-H); 7.46 (1H, d, 2-H); 7.26 (1H, m, 7-H); 7.70 (2H, m, 5-H, 6-H); 8.39 (1H, d, 8-H); 12.02 ppm (1H, br. s, NH).

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4-METHYL-5-HYDROXYPYRIMIDINE AND ITS N-OXIDES: SYNTHESIS AND INVESTIGATION OF THE REACTIVITIES IN ELECTROPHILIC SUBSTITUTION

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UDC 547.854.07

A new more accessible method for the synthesis of 4-methyl-5-hydroxypyrimidine is proposed; its 1- and 3-oxides were obtained. An attempt was made to evaluate the reactivities of the individual positions of the heterocyclic ring of pyrimidine and its 3-oxide in aminomethylation.

5-Hydroxypyrimidines, which have a symmetrical (relative to the two heteroatoms) meta position that is the only one capable of electrophilic substitution in the unactivated molecule, but is occupied by an electron donor in this case,* occupy a special place among diazines. Therefore, only the remaining three even-numbered positions (2, 4, and 6), two of which are symmetrical (4 and 6), can also be the subject of the resultative attack by electrophiles. We have previously [1, 2] demonstrated for the first time the possibility of the aminomethylation, diazo coupling, and iodination of the even-numbered positions of the ring in the case of 5-hydroxypyrimidine (I), 4,6-dimethyl-5-hydroxypyramidine (II), 4-phenyl-5-hydroxypyrimidine, and the 1-oxide of II.

The aims of the present research were to compare the relative activities of the unsymmetrical 2 and 6 positions of the pyrimidine ring vis-a-vis an occupied 4 position and, chiefly, to ascertain the effect on them of N-oxidation of each of the nitrogen atoms (as a result of which significant redistribution of the electron density of the heterocyclic ring occurs) under competitive conditions of electrophilic substitution. We also attempted to evaluate this relationship previously when we carried out hydrogen-isotope exchange of the 1-oxides of I and II [3, 4].

*5-Amino and other substituted pyrimidines that have an electron-donor substituent in the 5 position can be assigned to this classification.

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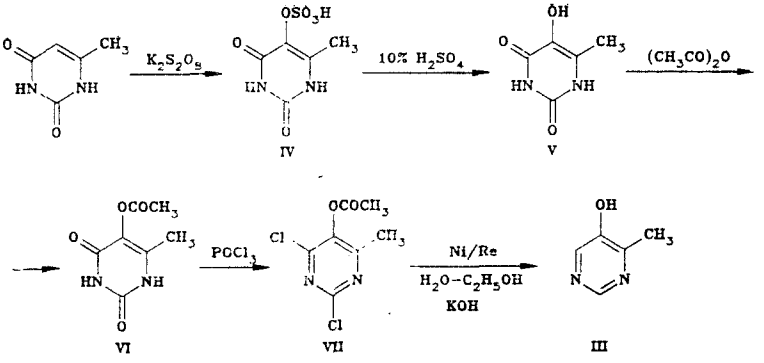
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 636-640, May, 1989. Original article submitted November 9, 1987.

0009-3122/89/2505-0530$12.50

The K_{eff} values obtained for the 2 and 4 positions of 5-hydroxypyrimidine 1-oxide proved to be close (within the limits of the predictive ability of the method); this made it impossible to draw an unequivocal conclusion regarding the relationship of the reactivities of these positions.

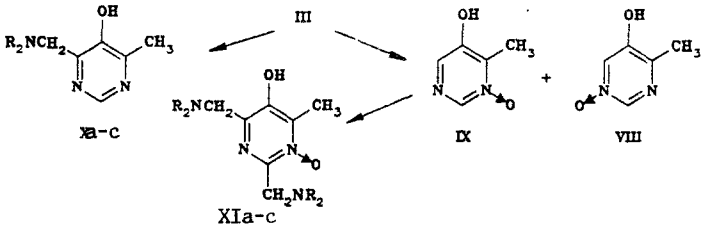
We selected 4-methyl-5-hydroxypyrimidine (III) as a model compound, since it was assumed that the methyl group introduces minimal changes from the point of view of the electron and three-dimensional structures of the molecule and therefore will not cause appreciable distortion due to the effect of the substituent itself on the examined relationship of the reactivities of the 2 and 6 positions of the ring.

The synthesis of III was described in [5]; however, the complexity, the many steps involved, and the low overall yield make it, from our point of view, a nonpreparative method. In this connection we propose another method that starts from the accessible 6-methyluracil. As a result of persulfate oxidation and subsequent hydrolysis, the starting compound is converted to 5-hydroxy-6-methyluracil (V), which, after acylation, is treated with $POCl_3$ and is then dechlorinated with the simultaneous removal of the acyl protective group over a Raney nickel catalyst in an alkaline medium.



Although each of these transformations, except for the last step, has been described in the literature, the method that we are proposing for obtaining simple derivatives of 5-hydroxypyrimidine has not been used. In the step involving persulfate oxidation, instead of the previously used solution of $K_2S_2O_8$ in a large volume of water, we introduced dry $K_2S_2O_8$ in portions in accordance with the rate of which it dissolved, thereby maintaining the temperature of the exothermic reaction at a certain level. Since the reaction product precipitates upon acidification of the reaction mixture, evaporation of the solution is not necessary. We also showed that trihydroxy derivative V is formed when sulfonate ester IV is heated in 10% sulfuric acid up to 85°C, but not when it is refluxed for 2 h in hydrochloric acid [6], and precipitates from the solution in 80% yield (the yield previously was ~50%). The acylation of V is carried out conveniently in a Soxhlet apparatus, in the sleeve of which the starting substance is placed. The amount of acetic anhydride necessary for the reaction decreases by a factor of four to five; one is also able to eliminate the 6-methyluracil impurity. In obtaining dichloro derivative VII by means of the described method the reaction mass was poured gradually over ice at 0-5°C; in this case extraction with ether is not necessary, and the dichloride precipitates completely. The dehalogenation of the chloropyrimidines was previously carried out by the action of zinc in an alkaline medium in low yields or by hydrogenation over palladium. We were able to carry out the dechlorination of VII using inexpensive industrial-grade Raney nickel. By varying the water–alcohol–NaOH ratio and by selecting the optimal temperature we found conditions under which removal of the acyl protective group occurs simultaneously with dehalogenation, and 4-methyl-5-hydroxypyrimidine is obtained in good yield. The reaction does not go to completion in the case of other parameters, and 2-chloro-6-ethoxy-5-hydroxy-4-methylpyrimidine or a mixture of the latter with the principal reaction product is formed.

4-Methyl-5-hydroxypyrimidine is converted to a mixture of isomeric 1- and 3-oxides VIII and IX by the action of peracids. Their separation presents certain difficulties, since the low solubilities of the N-oxides in organic solvents makes it impossible to use column chromatography. As a result, the mixture could be separated by means of a number of successive treatments with several solvents. In the individual state these compounds differ appreciably with respect to their solubilities, melting points, and spectral characteristics.

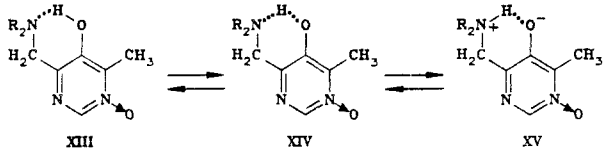


XIa $R_2 = -(CH_3)_2$; b $R_2 = -(CH_2)_5$; c $R_2 = (CH_2)_2O(CH_2)_2$

The assignment of the signals of the 6-H and 2-H protons in the PMR spectra of 4-methyl-5-hydroxypyrimidine 1-oxide and 3-oxide was made on the basis of the spin-spin coupling constants (SSCC) of the indicated meta protons. As previously demonstrated for derivatives of pyrimidine and their N-oxides [7], in the case of the 3-oxide the J_{26} value is close to zero, and the 6-H and 2-H signals are singlets, while in the case of the 1-oxide J_{26} = 2.0 Hz, and the signals are doublets.

An investigation of the reactivity of 4-methyl-5-hydroxypyrimidine showed that aminomethylation, for example, proceeds exclusively in the 6 position of the ring. An excess amount of the aminomethylating reagents or the use of more severe reaction conditions does not lead to the formation of either a mixture of 2- and 6-substituted compounds or traces of a bis(aminomethyl) derivative. A bis(substitution) product is formed in the aminomethylation of 4-methyl-5-hydroxypyrimidine 3-oxide even under mild reaction conditions, whereas a mixture of the starting compound and bis(aminomethyl) compounds without admixed monosubstitution products is formed in the case of an equimolar amount or when insufficient amounts of the reagents are used; this remained unexplainable for us for a long time.*

From our point of view the explanation of this fact should include activation of the free position of the ring as a result of the incorporation of the first aminomethyl substituent. According to the scheme that we propose the formation of a hydrogen bond that was previously observed for o-oriented aminomethyl and hydroxy groups in 5-hydroxypyrimidines, is the first link in the chain of tautomeric transformations (XIII). In connection with the fact that 5-hydroxypyrimidine N-oxides have pronounced acidic properties [8] intramolecular protonation with the production, in the limiting case, of structure XV seems possible. As a result of ionization, the donor properties of the hydroxy group increase, which leads to an increase in the electron density, particularly in the 2 position, evidently to such an extent that it makes electrophilic attack at it more preferable than primary attack on the ring in the 6 position. As a result of this, the aminomethylating reagent is consumed completely in the production of the bis(substituted) derivative.†



A study of the chemical behavior of 4-methyl-5-hydroxypyrimidine provides evidence for weak interpolation of the chemical properties in the homologous series of compounds I—III—II.‡ We also arrive at the same conclusion when we examine some physicochemical properties of this compound and its N-oxides (solubilities, TLC constants, PMR spectra, and pK_{HA} values).

*The same reaction with the 1-oxide gives a product that darkens rapidly, even in the hydrochloride form, and could not be identified.

†An alternative variant of the explanation in this case involves regarding the molecule with an annelated six-membered ring (XIV) as a system that is isoelectronic with respect to naphthalene; this also explains the ease of occurrence of the second step in the consecutive aminomethylation reactions.

‡5-Hydroxypyrimidine (I), which does not contain methyl groups, upon aminomethylation gives both monosubstituted compound and a bis(substituted) compound (in the 4 and 6 positions), 4,6-dimethyl-5-hydroxypyrimidine (II) is readily aminomethylated in the 2 position, while pyrimidine III, which contains one methyl group gives only a monoaminomethyl derivative (substituted in the 6 position of the ring).

We were unable to solve the problem of differentiating with respect to the reactivities of the free 2 and 6 positions in 4-methyl-5-hydroxypyrimidine 1- and 3-oxides, since it was difficult to propose an anomalous course of the reaction with the formation immediately of bis derivatives; however, this problem — the redistribution of the sensitivities of the individual positions of the 5-hydroxypyrimidine ring to electrophilic attack as a result of N-oxidation of one or the other nitro atom — seems to us worthy of elucidation and additional experimental efforts.

EXPERIMENTAL

The PMR spectra of solutions (0.2 mole/liter) of the compounds were recorded with a Varian HA-60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The results of elementary analysis of the synthesized compounds for C and H were in agreement with the calculated values.

6-Methyluracil 5-Sulfate (IV). A 200-g (0.74 mole) sample of potassium persulfate was added in small portions with stirring at 18-20°C to a solution of 63 g (0.5 mole) of 6-methyluracil in 1.5 liters of 2 N NaOH in the course of 6 h. The reaction mass was allowed to stand overnight at room temperature, after which it was acidified to pH 4 with concentrated HCl and stirred for 2 h. The resulting precipitate was removed by filtration and washed with water, and dried to give 26.6 g (24%, 62% based on the amount of starting compound that underwent reaction) of a product with mp > 320°C.

5-Hydroxy-6-methyluracilyl(6-methylisobarbituric Acid) (V). A 26.6 g (0.12 mole) sample of 6-methyluracil 5-sulfate was added at 75-80°C to 400 ml of 10% H_2SO_4. After the solid material had dissolved, the mixture was heated to 85-90°C and stirred until a precipitate began to form (5-10 min). The reaction mass was cooled, and the precipitate was removed by filtration, washed with water, and dried at 80°C. The principal filtrate can be used several times; the yield in this case is increased somewhat. This procedure gave 15.1 g (78%) of a product with mp > 300°C (mp > 300°C [6]).

5-Acetoxy-5-methyluracil (VI). A 4-g (28 mmole) sample of 5-hydroxy-6-methyluracil in a porous glass small beaker was placed in a Soxhlet extractor and extracted with acetic anhydride for 8-10 h. The precipitated crystals of 5-acetoxy-6-methyluracil was removed by filtration and dried at 80°C to give 4.6 g (81%) of a product with mp 295°C (from water, dec.) (mp 295°C (dec.) [9]).

2,6-Dichloro-4-methyl-5-hydroxypyrimidine (VII). A mixture of 7.9 g (40 mmole) of VI, 80 ml of $POCl_3$, and 5 ml of dimethylaniline was refluxed for 2 h, after which the excess $POCl_3$ was removed by distillation in vacuo. The residue was poured over 100 g of finely ground ice, and the aqueous mixture was stirred until the viscous oil began to solidify. The resulting precipitate was separated, washed with cold water, and dried in vacuo at room temperature to give 7.89 g (84%) of a product with mp 78-80°C (from hexane) and bp 108°C (2 mm) [bp 135-137°C (6 mm), mp 79-80°C].

4-Methyl-5-hydroxypyrimidine (III, $C_5H_6N_2O$). A 0.22-g (1 mmole) sample of 2,6-dichloro-4-methyl-5-acetoxypyrimidine was added cautiously (because of foaming) to a refluxing mixture of 0.7 g (12 mmole) of KOH, 18 ml of water, 5 ml of alcohol, and 1 g of an aqueous paste of Raney nickel, after which the reaction mixture was refluxed for 2 h and filtered hot. The aqueous alcohol filtrate was evaporated until drops of water appeared in the condenser. The residue was cooled and neutralized to pH 4-5 with sulfuric acid, and the resulting suspension was evaporated to dryness. The residue was sublimed at 150-175°C (2 mm) to give 0.09 g (83%) of 4-methyl-5-hydroxypyrimidine with mp 187-189°C (mp 190°C [5]). PMR spectrum (D_2O): 2.40 (3H, s, 4-CH), 8.15 (1H, s, 6-H), 8.46 ppm (1H, s, 2-H).

6-Dimethylaminomethyl-4-methyl-5-hydroxypyrimidine Hydrochloride (Xa, $C_8H_{13}N_3O \cdot HCl$). A mixture of 0.11 g (1 mmole) of III and 0.5 ml of N,N,N',N'-tetramethylmethylenediamine was refluxed in a water bath for 2 h, after which it was evaporated to dryness. Absolute alcohol saturated with HCl was added to the resulting oily residue, and the mixture was refluxed for 15-20 min. The resulting precipitate was removed by filtration to give 0.15 (60%) with mp 149-151°C (from isopropyl alcohol). PMR spectrum (D_2O): 2.80 (3H, s, 4-CH_3), 3.16 [6H, s $(CH_3)_2N$], 9.02 ppm (1H, s, 2-H).

6-Morpholinomethyl-4-methyl-5-hydroxypyrimidine Hydrochloride (Xb, $C_{10}H_{15}N_3O_2 \cdot HCl$). A mixture of 0.11 g (1 mmole) of III, 0.1 ml of morpholine, 0.06 g of paraformaldehyde, 0.01 ml of triethylamine, and 2 ml of dioxane was refluxed for 5 h, after which the solvent was

removed by distillation, and absolute alcohol saturated with HCl was added to the oily residue. The mixture was then worked up as in the preceding experiment to give 0.2 g of a crystalline precipitate (90%) with mp 162-164°C. PMR spectrum (D_2O): 2.74 (3H, s, 4-CH_3), 3.56 (4H, m, CH_2—N—CH_2), 4.06 (4H, m, CH_2—O—CH_2), 4.72 (2H, s, CH_2N), 8.85 ppm (1H, s, 2-H).

6-Piperidinomethyl-4-methyl-5-hydroxypyrimidine Hydrochloride (Xc, $C_{11}H_{17}N_3O \cdot HCl$). A mixture of 0.22 g (2 mmole) of III, 0.38 ml of N,N'-methylenebispiperidine, and 4 ml of dioxane was refluxed for 8 h and worked up as in the preceding experiment. The precipitate was washed with acetone and recrystallized from isopropyl alcohol to give 0.48 g (90%) of a product with mp 158-160°C. PMR spectrum (D_2O): 2.60 (3H, s, 4-CH_3), 1.75 (6H, m, β,γ-CH_2), 3.45 (4H, m, α-CH_2), 4.55 (2H, s, CH_2—N), 8.85 ppm (1H, s, 2-H).

4-Methyl-5-hydroxypyrimidine 1- and 3-Oxides (VIII, IX. $C_5H_6N_2O_2$). A 5.5-g (20 mmole) sample of p-nitroperbenzoic acid was added to a solution of 1.1 g (10 mmole) of 4-methyl-5-hydroxypyrimidine in 100 ml of alcohol, and the mixture was stirred until the solid material had dissolved completely, after which the reaction mixture was allowed to stand overnight. The alcohol was removed by distillation to dryness. The residue was mixed with 5 ml of ice water, the undissolved part was removed by filtration, and the precipitate was washed with 5 ml of ice water. The filtrate was evaporated to a volume of ∿3 ml; cooling of this concentrate led to the partial precipitation of the 3-oxide, which was separated, and the filtrate was evaporated to dryness. Dry acetone (5 ml) was added to the resulting oily residue, and the mixture was triturated until a precipitate containing the 1-oxide with admixed 3-oxide was obtained; it was removed by filtration, washed with cold acetone, and dried to give 0.54 g (43%) of product. The filtrates were combined and evaporated to dryness, and the residue was combined with the 3-oxide, which was recrystallized from a small amount of water. This procedure gave 0.33 g (26%) of a product with mp 256-260°C (dec.).

4-Methyl-5-hydroxypyrimidine 1-oxide was purified by dissolving in dioxane, from which, by means of the careful addition of hexane, a pure substance with mp 175-177°C (dec.) crystallized out. PMR spectrum (D_2O): 2.44 (3H, s, 4-CH_3), 8.15 (1H, d, J = 2.0 Hz, 6-H), 8.60 ppm (1H, d, 2-H). PMR spectrum of the 3-oxide (D_2O): 2.45 (3H, s, 4-CH_3), 8.12 (1H, s, 6-H), 8.69 ppm (1H, s, 2-H).

2,6-Bis(dimethylaminomethyl)-4-methyl-5-hydroxypyrimidine Hydrochloride (XIa, $C_{11}H_{20}N_4O_2 \cdot HCl$). A mixture of 0.063 g (5 mmole) of 4-methyl-5-hydroxypyrimidine 3-oxide and 0.29 ml of N,N,N',N'-tetramethylmethylenediamine was refluxed for 15-20 min and then evaporated to dryness in vacuo. Absolute alcohol saturated with HCl was added to the resulting oil, the mixture was refluxed for 10 min and then cooled, and the resulting precipitate was removed by filtration to give 0.06 g (46%) of a product with mp 179-180°C (from alcohol). PMR spectrum (D_2O): 2.66 (3H, s, 4-CH_3), 3.18 (12H, s, Me_2N), 4.70 ppm (4H, s, CH_2—N).

2,6-Bis(piperidinomethyl)-4-methyl-5-hydroxypyrimidine 3-Oxide Hydrochloride (XIb, $C_{17}H_{28}N_4O_2 \cdot HCl$). A mixture of 0.063 g (5 mmole) of IX, 0.098 ml of N,N'-methylenebispiperidine, and 2 ml of dioxane was refluxed for 5 min. Compared XIb was isolated and purified as in the preceding experiment to give 0.09 g (50%) of a product with mp 255-257°C (from alcohol with charcoal). PMR spectrum (D_2O): 1.95 (12H, m, β,γ-CH_2), 2.63 (3H, s, 4-CH_3), 3.50 (8H, m, α-CH_2), 4.62 ppm (4H, s, CH_2—N).

2,6-Bis(morpholinomethyl)-4-methyl-5-hydroxypyrimidine 3-Oxide Hydrochloride (XIc, $C_{15}H_{24}N_4O_4 \cdot HCl$). A mixture of 0.063 (5 mmole) of IX, 0.04 g of paraformaldehyde, 0.06 ml of morpholine, 10 ml of chlorobenzene, and 0.02 ml of triethylamine was refluxed for 15 min and was then worked up as in the preceding experiment to give 0.13 g (70%) of a product with mp 198-200°C (from alcohol). PMR spectrum (D_2O): 2.78 (3H, s, 4-CH_3), 3.74 (8H, m, CH_2—N—CH_2), 4.10 (8H, m, CH_2—O—CH_2), 4.78 ppm (2H, s, CH_2N).

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ANALOGS OF PURINE NUCLEOSIDES.

4.* 7-ALKYLATED 9-(2-HYDROXYMETHYL)GUANINE

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UDC 547.857.7:543.422.07

7,9-Disubstituted guaninium hydrohalides were synthesized by the reaction of 9- and 7-(2-hydroxymethyl)guanines with alkyl halides. The effect of the structure of the alkylating agent on the direction and yield of the alkylation reaction was established. The possibility of the conversion of the salts obtained to the free bases in a weakly alkaline medium was investigated. The synthesized compounds were characterized by the UV and ^{1}H and ^{13}C NMR spectra. The ability of the synthesized compounds to inhibit replication of the herpes virus (VPG-1) was demonstrated.

7-Substituted 9-alkoxyalkyl derivatives of purines constitute a new little-studied class of acyclic analogs of purine nucleosides. The present research was devoted to the synthesis and study of 9-(2-hydroxyethoxymethyl)guanine derivatives alkylated in the 7 position of the purine ring and of interest as potential antiviral preparations, as well as model compounds for the study of the mechanisms of the action of alkylating anticancer agents.

For the synthesis of 7-alkyl-9-alkoxyalkylguanines we used the alkylation of 9-(2-hydroxyethoxymethyl)guanine (I) in DMF or in dimethylacetamide. The formation of 7,9-disubstituted derivatives in reactions involving the alkylation of purines is well-known. 7,9-Dialkylguanines were obtained in the reaction of guanine and some of its 7- or 9-alkyl derivatives with dimethyl sulfate [2] or alkyl esters of p-toluenesulfonic acid [3, 4] in a neutral medium. The alkylation of guanosine under similar conditions also leads to the formation of 7-substituted derivatives of the nucleoside [5-8]. The reaction of 9-alkoxyalkylguanines with alkylating agents in a neutral medium has not been studied.†

By alkylation of I with methyl iodide, ethyl iodide, and benzyl iodide at room temperature we synthesized 7-methyl- and 7-ethyl-9-(2-hydroxyethoxymethyl)guaninium hydriodides (IIa, b) and 7-benzyl-9-(2-hydroxyethoxymethyl)guaninium hydrobromide (IIc) in 80% yields. The yields of the products and the reaction times depend on the reactivity of the alkylating agent. The less active the alkylating agent, the greater the excess amount of it that must be used in the reaction and the longer the time required for the disappearance of the starting compound. For example, with a threefold excess of methyl iodide the reaction takes 24 h, while with a sixfold excess of ethyl iodide the reaction takes 4-6 days. The reaction could not be accomplished with ethyl bromide, diethyl α-bromomalonate, and α-bromobutyrolactone.

The reaction of 9-alkoxyalkylguanine I with ethyl p-toluenesulfonate and 2-bromoethanol proceeds only at 130-150°C. 7,9-Diethylguaninium p-toluenesulfonate (IIIa) and 7,9-bis(2-hydroxyethyl)guaninium hydrobromide (IIIb), respectively, were obtained as the principal reaction products in 30-40% yields with a threefold excess of the alkylating agent. Thus

*See [1] for Communication 3.
†While the present research was being carried out, a description of the alkylation of some 9-alkoxyalkyl- and 9-hydroxyalkylguanines with alkyl halides were published [9].

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 641-646, May, 1989. Original article submitted December 21, 1987.

0009-3122/89/2505-0535$12.50