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ANALOGS OF PURINE NUCLEOSIDES.

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

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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-di-substituted 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

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*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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transalkylation at the nitrogen atom in the 9 position of the purine ring occurs at elevated temperatures.
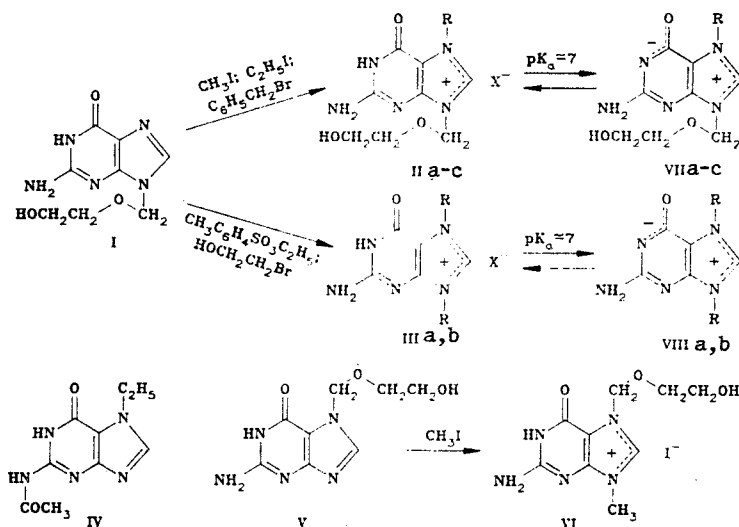
IIa, VIIa R=CH₃; IIb, VIIb IIIa, VIIIa R=C₂H₅; IIc. VIIc R=CH₂C₆H₅; IIIb, VIIIb R=CH₂CH₂OH; IIa,b X=I; IIc, IIIb X=Br; IIIa X=SO₃C₆H₄CH₃

In the reaction of I with ethyl p-toluenesulfonate in dimethylacetamide yet another alkylation product — IV, the structure of which was established on the basis of the results of physicochemical analysis — was isolated from the reaction mixture by preparative column chromatography on silica gel. Its PMR spectrum showed the presence of acetyl (2.16 ppm) and ethyl (1.41, 4.29 ppm) groups in the guanine ring. The absence of a singlet of protons of an amino group in the ~7 ppm region and the presence of signals of protons of two NH groups at 11.53 and 11.99 ppm confirmed the presence of a substituent in the exocyclic amino group. Absorption maxima at 264 (pH 2 and 7) and 269 nm (pH 12), which correspond to the absorption maxima of 2-acetyl-7-substituted guanines and differ substantially from those for 2-acetyl-9-substituted guanines [10], as well as for other possible guanine derivatives (2-alkyl, 6-alkoxy, etc.) in this case [11], are observed in the UV spectrum of IV. On the basis of this, the 2-acetyl-7-ethylguanine structure, to which the results of elementary analysis correspond, was assigned to IV. The formation of IV evidently occurs as a result of alkylation of the 7 position of the ring, dealkoxyalkylation of the $N_{(9)}$ atom, and acylation of the exocyclic amino group by dimethylacetamide.

In the reaction of guanine I with a small excess (1.2 equivalents of ethyl p-toluenesulfonate or 2-bromoethanol we obtained a mixture consisting of starting I, alkylation products IIIa and IV or IIIb, as well as a number of unidentified impurities.

We also studied the alkylation of 7-(2-hydroxyethoxymethyl) guanine (V), the synthesis of which we previously described in [10]. The reactivity of 7-substituted isomer V proved to be considerably lower than that of 9-substituted isomer I. The alkylation could be accomplished only with an excess (4-equivalents) of methyl iodide in 6 days; the yield of 7-(2-hydroxyethoxymethyl)-9-methylguaninium hydriodide (VI) did not exceed 30%.

The individuality and purity of salts IIa-c, IIIa, b, and VI obtained were confirmed by TLC and the results of elementary analysis (Table 1). The absorption maxima in the UV spectra of IIa-c, and VI at 257 and 280 nm (pH 2 and 7) and 254 and 287 nm (pH 9) coincide with the absorption maxima of other 7,9-disubstituted guaninium salts [8, 11]. The UV spectra of derivatives IIIa,b correspond to the data in [11]. A characteristic feature of the PMR spectra of 7,9-disubstituted guaninium salts II, III, and VI (Table 2) is a substantial shift to weak field of the signals of the 8-H protons of the ring (by ∿1.5 ppm) and the protons of the NH₂ group (by ∿1.0 ppm) as compared with the corresponding signals for the starting 9- and 7-alkoxyalkylguanines I and V [10]. In the case of IIa, c we studied the ¹³C NMR spectra (Table 3), which definitively confirmed the structures of the alkylation products. The positions of the substituents attached to the $N_{(7)}$ and $N_{(9)}$ atoms were proved by the constants of long-range spin—spin coupling (SSC) of the ring $C_{(4)}$, $C_{(5)}$, and $C_{(8)}$ atoms with the protons of the NCH₂ groups of the substituents. The equivalence of the constants $^3J_{C(4)H(8)} \simeq {}^3J_{C(5)H(8)}$ constitutes evidence for delocalization of the multiple bond in the imidazole part of the molecule.

TABLE 1. Characteristics of 7,9-Disubstituted
Guaninium Salts IIa-c, IIIa,b, and VI

Com-pound	Empirical formula	mp, °C (ethanol)	R_f A	R_f B	Yield, %
IIa	$C_9H_{13}N_5O_3 \cdot HI$	154...155 (dec.)	0,14	0,28	88
IIb	$C_{10}H_{15}N_5O_3 \cdot HI$	163...164 (dec.)	0,15	0,30	81
IIc	$C_{15}H_{17}N_5O_3 \cdot HBr$	122 (dec.)	0,34	0,54	79
IIIa	$C_9H_{13}N_5O \cdot C_7H_8O_3S$	249...251*	0,22	0,64	43
IIIb	$C_9H_{13}N_5O_3 \cdot HBr$	221...221,5	0,15	0,28	30
VI	$C_9H_{13}N_5O_3 \cdot HI$	149...152	0,16	0,29	31

*According to the data in [11], this compound
had mp 248°C.

TABLE 2. PMR Spectra of 7,9-Disubstituted Guanine Derivatives
IIa-c, VI, IIIa,b and VIIIa,b

Com-pound	Chemical shift, δ, ppm				
	NH (s, 1H)	8-H (s, 1H)	NH₂ (s, 2H)	NCH₂ (2H)*	remaining protons
IIa	11,68	9,40	7,22	5,57 s	3,58 (4H, m, CH₂)
IIb	11,62	9,40	7,16	5,53 s; 4,39 q	3,57 (4H, m, CH₂), 1,48 (3H, t, CH₃)
IIc	11,67	9,70	7,29	5,64 s; 5,58 s	7,40 (5H, m, arom. protons), 3,59 (4H, m, CH₂)
VI	11,61	9,37	7,16	5,67 s	3,56 (4H, m, CH₂)
IIIa	11,53	9,21	7,13	4,32 q; 4,09 q	7,43; 7,13 (4H, m, arom. protons), 2,27 (3H, s, CH₃), 1,42 (6H, m, CH₃)
IIIb	11,60	9,19	7,16	4,41 t; 4,18 t	3,77 (4H, m, CH₂)
VIIIa	—	8,82	5,59	4,39 q; 4,07 q	1,42 (6H, m, CH₃)
VIIIb	—	8,71	5,66	4,42 t; 4,10 t	3,74 (4H, m, CH₂)

*4.03 ppm (s, 3H, NCH₃) for IIa, and 3.73 ppm (s, 3H, NCH₃)
for VI.

It is known that 7,9-disubstituted guaninium salts in aqueous solutions exist in equilibrium with the corresponding deprotonated forms — purinyl betaines [2, 3, 7]. We studied the possibility of obtaining 7-alkyl-9-(2-hydroxyethoxymethyl)guanines in the form of free bases VIIa-c from the corresponding hydrohalides IIa-c by the methods in [3, 5, 7]. A product that differed from the starting compound with respect to its melting point, R_f value in TLC, and PMR spectrum (disappearance of the signal of the proton of the endocyclic NH group, 0.2 ppm shift to strong field of the signal of the ring 8-H proton) was obtained by treatment of an aqueous or alcohol solution of hydriodide IIa with ammonium hydroxide or methylamine. However, the shift of the frequencies of the vibrations of the carbonyl group in the 6 position of the ring that is characteristic for purinyl betaines was not observed in the IR spectra of the product [2]. The results of elementary analysis also did not correspond to the structure of VIIa and indicated the presence of halogen in the molecule; the elementary composition of the product did not change when it was crystallized repeatedly from aqueous ethanol. It is possible that the reaction product in this case is a mixture of 7-methyl-9-(2-hydroxyethoxymethyl)guanine (VIIa) and the corresponding hydriodide (IIa, 1:1). The formation of such mixtures in an attempt to synthesize 7-benzylguanosine from the corresponding hydrobromide was noted in [12]. Complexes of purinyl betaines with the corresponding salts are formed under similar conditions also from IIb,c and IIIa,b. 7-Methylguanosinium hydriodide in all cases undergoes quantitative conversion to 7-methylguanosine, identical to the compound described in [5].

7,9-Diethyl- and 7,9-bis(2-hydroxyethyl)guanines (VIIIa,b) were obtained in good yields

TABLE 3. ^{13}C NMR Spectra of Guanine Derivatives IIa,c

Com-pound	Chemical shift, σ, ppm					
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(8)}$	carbons atoms of the substituents*
IIa	153,34	149,57	107,35	156,72	138,38	74,43 ($C_{(1')}$), 71,63 ($C_{(3')}$), 59,79 ($C_{(4')}$), 35,72 (CH_3)
IIc	153,02	149,92	106,52	155,99	138,27	74,73 ($C_{(1')}$), 71,84 ($C_{(3')}$), 59,85 ($C_{(4')}$), 51,46 ($C_{(1'')}$), 134,39 ($C_{(2'')}$), 128,33 ($C_{(3'')}$), 128,86 ($C_{(4'')}$), 128,70 ($C_{(5'')}$)

*Numbering of the carbon atoms in the substituents $-CH_2OCH_2CH_2OH$.

when aqueous solutions of salts IIIa,b were passed through a column packed with Dowex 1 × 4 (OH⁻) anion-exchange resin [3]. The structures of purinyl betaines VIIIa,b were confirmed by data from the UV, IR, and PMR spectra and the results of elementary analysis. The most substantial changes in the PMR spectra are observed on passing from the salt to the purinyl betaine (Table 2). A shift of the signals of the ring 8-H proton (by 0.4-0.5 ppm) and the protons of the NH_2 group (by 1.5 ppm) to stronger field as compared with the signals of the corresponding protons of the starting salts IIIa,b is characteristic for products VIIIa,b. A shift of the band of the vibrations of the carbonyl group is also observed [1717 (IIIa) and 1625 cm⁻¹ (VIIIa) and 1710 (IIIb) and 1615 cm⁻¹ (VIIIb)], in agreement with the data in [2].

Betaine VIIa with unidentified impurities (possibly destruction products) was obtained in low yield (<10%) according to the PMR spectral data when an aqueous or aqueous alcohol solution of hydroiodide IIa was passed through a column packed with the anion-exchange resin with subsequent lyophilization. A complex of VIIa and IIa was obtained when an aqueous or aqueous alcohol solution of salt IIa was treated with Dowex 1 × 4 (OH⁻) anion-exchange resin by the method in [7].

A study of the antiviral activity of the synthesized 7-alkyl-9-(2-hydroxyethoxymethyl)-guaninium salts IIa-c showed that these compounds inhibit replication of the herpes virus (VPG-1) in a culture of chicken fibroblast cells; however, they are inferior in activity to the preparation acycloguanosine.

EXPERIMENTAL

The UV spectra were recorded with a Unicam-SP 1800 spectrophotometer. The IR spectra of mineral oil suspensions were obtained with a UR-20 spectrometer. The PMR spectra of solutions in d_6-DMSO were obtained with a Bruker WH-90/DS spectrometer (90 MHz) with tetramethylsilane as the internal standard. The ^{13}C NMR spectra were recorded with a Bruker WM-360 spectrometer; the ^{13}C chemical shifts were measured relative to the signal of the solvent (d_6-DMSO) and were rescaled relative to TMS (δ, 39.6 ppm). The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates in chloroform-acetic acid-methanol-water (5:6:1:1) (A) and chloroform-methanol (10:2) (B) and on Lucefol cellulose plates in a butanol-acetic acid-water (4:1:5) (C). For preparative column chromatography we used L 40/100 silica gel (Czechoslovakian SSR); Dowex 1 × 4 anion-exchange resin (20-50 mesh) was used for ion-exchange chromatography.

The results of elementary analysis of the compound for C, H, and N were in agreement with the calculated values.

7-Methyl-9-(2-hydroxyethoxymethyl)guaninium Hydroiodide (IIa). A 4.0-g (17.8 mmole) sample of I was suspended in 160 ml of DMF, 3.4 ml [7.5 g (54.6 mmole)] of methyl iodide was added, and the mixture was stirred at 20°C for 24 h. The resulting solution was diluted with 900 ml of chloroform, the mixture was cooled to 0°C, and the precipitate was removed by filtration and dried to give 5.63 g of IIa. UV spectrum, λ_{max} (log ε): 257 (4.06), 279 nm (3.88) (pH 2); 254 (3.77), 287 nm (3.92) (pH 9).

7-Ethyl-9-(2-hydroxyethoxymethyl)guaninium Hydroiodide (IIb). A 2.0-g (8.9 mmole) sample of I was dissolved in 80 ml of DMF. 4.3 ml [8.31 g (53.5 mmole)] of ethyl iodide was added, and the mixture was stirred at 20°C until I had dissolved completely (4-6 days). The solution was diluted with 450 ml of chloroform, the mixture was cooled to 0°C, and the precipitate was removed by filtration and dried to give 2.7 g of IIb. UV spectrum, λ_{max} (log ε): 256 (4.06), 280 nm (3.81) (pH 2); 254 (3.77), 285 nm (3.89) (pH 9).

SSCC for ^{13}C-^{1}H, J, HZ			
$C_{(8)}$—$H_{(8)}$	$C_{(4)}$—$H_{(8)}$	$C_{(5)}$—$H_{(8)}$	$C_{(X)}$—$C_{(Y)}H_2$
223,4	6,0	5,8	1,5 ($C_{(8)}$—$C_{(1')}H_2$), 4,8 ($C_{(4)}$—$C_{(1')}H_2$), 3,8 ($C_{(8)}$—CH_3), 2,2 ($C_{(5)}$—CH_3)
223,6	6,9	5,5	5,1 ($C_{(8)}$—$C_{(1')}H_2$), 2,6 ($C_{(4)}$—$C_{(1')}H_2$), 5,1 ($C_{(8)}$—$C_{(1'')}H_2$), 2,6 ($C_{(5)}$—$C_{(1'')}H_2$)
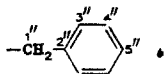
7-Benzyl-9-(2-hydroxyethoxymethyl)guaninium Hydrobromide (IIc). A 2.0-g (8.9 mmole)
sample of I was suspended in 80 ml of DMF, 6.3 ml [9.13 g (53.4 mmole)] of benzyl bromide
was added, and the mixture was stirred at 20°C until I had dissolved completely, after
which it was stirred for an additional 24 h. Dry ether (400 ml) was added to the solution,
and the mixture was cooled to 0°C. The solvent was decanted, and the oily residue was tri-
turated with a small amount of acetone and cooled. The precipitate was removed by filtration,
suspended in 125 ml of acetone—ethanol (4:1), stirred, and again removed by filtration to
give 2.76 g of IIc. UV spectrum, λ_{max} (log ε): 259 (4.05), 281 nm (3.84) (pH 2); 255 (3.74),
288 nm [3.86 (pH 9].

7-9-Diethylguaninium p-Toluenesulfonate (IIIa) and 2-Acetyl-7-ethylguanine (IV, $C_9H_{11}N_5O_2$).
A mixture of 2.0 g (8.9 mmole) of I, 5.35 g (26.7 mmole) of ethyl p-toluenesulfonate, and 60
ml of dimethylacetamide was refluxed for 2 h, after which the solvent was removed by
distillation in vacuo. The oily residue was washed several times with dry ether, after which
it was treated with acetone and cooled to 0°C. The resulting precipitate was removed by fil-
tration and recrystallized from ethanol to give 1.45 g of IIIa.

The filtrate was evaporated in vacuo, the residue was dissolved in 15 ml of chloroform,
and the chloroform solution was applied to a column packed with 100 g of silica gel. The
column was washed with chloroform, and product IV was eluted with chloroform—methanol (40:1).
The product had mp > 300°C (dec.) and R_f 0.77 (B). UV spectrum, λ_{max}: 263 (pH 2), 265 nm
(pH 7), 269 nm (pH 12). PMR spectrum (d_6-DMSO): 11.99 (1H, s, NH), 11.53 (1H, s, NH), 8.14
(1H, s, 8-H), 4.29 (2H, q, CH_2), 2.16 (3H, s, $COCH_3$), 1.41 ppm (3H, t, CH_3).

7-9-Bis(2-hydroxyethyl)quaninium Hydrobromide (IIIb). A mixture of 4.0 g (17.8 mmole)
of I, 3.8 ml [6.69 g (53.6 mmole)] of 2-bromoethanol, and 75 ml of DMF was heated at 125–
135°C for 3.5 h, after which the solvent was removed by distillation in vacuo, and the oily
residue was washed with cooled acetone (three 25-ml portions). It was then extracted with
250 ml of boiling ethanol, and the ethanol solution was maintained at 20°C for 24 h and
filtered. The filtrate was concentrated to a volume of ≃50 ml and cooled to —5°C, and the
resulting precipitate was removed by filtration and recrystallized from ethanol to give 1.82
g of IIIb.

7-(2-Hydroxyethoxymethyl)-9-methylguaninium Hydroiodide (VI). A 1.0-g (4.4 mmole) sample
of V was suspended in 30 ml of DMF, 1.2 ml [2.73 g (19.3 mmole)] of methyl iodide was added,
and the mixture was stirred at 20°C until V had dissolved completely (∿ 6 days). Dry ether
(200 ml) was added to the resulting solution, and the mixture was cooled to 0°C. The solvent
was decanted, the oily residue was triturated with a small amount of ether, and the mixture
was cooled. The precipitate was removed by filtration and recrystallized twice from ethanol
to give 0.5 g of VI.

7,9-Diethylguanine (VIIIa). This compound was obtained by passing an aqueous solution of
p-toluenesulfonate IIIa [1.0 g (2.64 mmole)] through a column packed with Dowex 1 × 4 (OH⁻)
anion-exchange resin as described in [3]. Workup gave 0.44 g (71.3%) of VIIIa with mp > 270°C
(dec.) [mp 274°C (dec.) [3]].

7,9-Bis(2-hydroxyethyl)guanine (VIIIb). This compound was synthesized as in the case
of VIIIa from 1.0 g (3.12 mmole) of hydrobromide IIIb. Workup gave 0.56 g (64.7%) of VIIIb
with mp > 300°C (dec.) (mp 320°C [11]).

<u>Reaction of Hydrohalides IIa, c with Ammonium Hydroxide.</u> A 2.94-g (8.0 mmole) sample of hydroiodide IIa was suspended in 100 ml of ethanol, the pH of the suspension was brought up to 9 by the addition of concentrated NH_4OH, and the mixture was stirred at 20°C for 15 min. The precipitate was removed by filtration, washed with a small amount of ethanol, and recrystallized twice from aqueous ethanol to give 1.87 g of a product that was found to be a mixture of IIa and VIIa (1:1) with mp > 280°C (dec.). $C_9H_{13}N_5O_3 \cdot 0.5HI$. PMR spectrum ($d_6$-DMSO): 9.22 (1H, s, 8-H), 7.24 (2H, s, NH_2), 5.54 (2H, s, NCH_2), 4.04 (3H, s, CH_3), 3.57 ppm (4H, m, CH_2).

Hydrobromide IIc [0.85 g (2.0 mmole)] was dissolved in 150 ml of acetone—ethanol (4:1), the solution was filtered, and the filtrate was made alkaline to pH 9 by the addition of concentrated NH_4OH and cooled to —5°C. The resulting precipitate was removed by filtration, washed with acetone, and recrystallized from aqueous ethanol to give 0.4 g of product that was identified as a complex of IIc and VIIc with mp > 280°C (dec.). $C_{15}H_{17}N_5O_3 \cdot 0.5 HBr$. PMR spectrum ($d_6$-DMSO): 9.41 (1H, s, 8-H), 7.43 (5H, m, aromatic protons), 7.04 (2H, s, NH_2), 5.67 (2H, s, NCH_2), 5.53 (2H, s, NCH_2), 3.56 ppm (4H, m, CH_2).

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