PURINE NUCLEOSIDE ANALOGS. 6.* CHLORINATION OF ACYCLOGUANOSINE AND SOME OF ITS DERIVATIVES WITH THIONYL CHLORIDE

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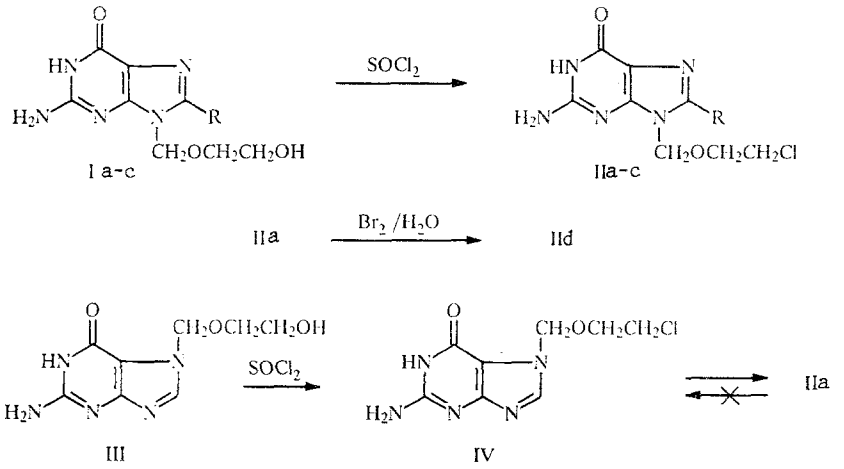
The reaction of 9- and 7-(2-hydroxyethoxymethyl)guanines and some of their derivatives with thionyl chloride inhexamethylphosphorustriamide was investigated. 9- and 7-(2-Chloroethoxymethyl)- and 8-chloro-, 8-bromo-, and 8-mercapto-9-(2-chloroethoxymethyl)guanines were synthesized. The structure of the compounds was confirmed by the UV and ESR spectra.

Acycloguanosine — 9-(2-hydroxyethoxymethyl)guanine — is a well-known antiviral drug [2], and the search for new potentially biologically active compounds based on it is thus of great interest. We synthesized some halogen-containing derivatives of 9-(2-hydroxyethoxymethyl)guanine which can be used as intermediate compounds for preparation of different acyclic analogs of guanosine.

Synthesis of 8-halogenated derivatives of acycloguanosine by halogenation of 9-(2-hydroxyethoxymethyl)guanine in position 8 of the ring is described in [3]. We also previously prepared 9-(2-chloroethoxymethyl)guanine by alkylation of the silyl derivative of guanine with 2-chloroethylchloromethyl ether [4]. A similar reaction in the presence of a catalyst — tetrabutylammonium fluoride — was mentioned in [5]. Halogenation of 9-(2-hydroxyethoxymethyl)guanine in the acyclic part of the molecule is not described



Ia, IIa R=H; Ib, IId R=Br; Ic, IIc R=SH; II b R=Cl

*See [1] for Communication 5.

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TABLE 1. Properties of Guanine Derivatives IIa-d and IV

Compound	Empirical formula	Mp, °C (decomp.)	R_f*	UV spectrum, λ_{max}, nm		Yield, %
				pH 2	pH 12	
IIa	$C_8H_{10}N_5ClO_2 \cdot H_2O$	>280	0,65	255, 272	258, 267	78,0
IIb	$C_8H_9N_5Cl_2O_2$	>280	0,72	259, 269	269	72,3
IIc	$C_8H_{10}N_5ClO_2S$	>300	0,73	231, 282, 304	294	57,7
IId	$C_8H_9N_5BrClO_2$	>265	0,73	262, 272	273	74,5
IV	$C_8H_{10}N_5ClO_2$	>300	0,72	252, 272	238, 284	61,9

*In system A for compounds IIa-d, in system B for compound IV.

TABLE 2. ESR Spectra of Guanine Derivatives IIa-d and IV

Compound	Chemical shifts, δ, ppm				
	NH (s 1H)	8-H (s 1H)	NH_2 (s 2H)	NCH_2 (s 2H)	OCH_2CH_2 (m. 4H)
IIa	10,60	7,79	6,52	5,38	3,71
IIb	10,70	—	6,62	5,33	3,71
IIc	12,90; 10,78	—	6,67	5,40	3,88 (m. 2H); 3,69 (m. 2H)
IId	10,67	—	6,60	5,31	3,70
IV	10,78	8,09	6,18	5,61	3,71

We investigated the reaction of acylguanosine, its 7-isomer, and some 8-substituted derivatives with thionyl chloride in hexamethylphosphorus triamide (hexametapol) in the conditions widely used for synthesis of 5′-chloro-5′-deoxynucleosides [6]. 9-(2-Chloroethoxymethyl)guanine (IIa), identical to the compound previously obtained in [4], was synthesized when 9-(2-hydroxyethoxymethyl)guanine (Ia) was treated with thionyl chloride in hexametapol. The reaction takes place at room temperature with a yield of approximately 80%. In similar conditions, 8-bromo-9-(2-hydroxyethoxymethyl)guanine (Ib) is converted into 8-chloro-9-(2-chloroethoxymethyl)guanine (IIb), i.e., substitution of bromine in position 8 of the ring takes place simultaneously with chlorination in the acyclic part of the molecule, which is in agreement with the published data on chlorination of 8-bromoadenosine [7]. 8-Bromo-9-(2-chloroethoxymethyl)guanine (IId) was synthesized by bromination of compound IIa with bromine water for comparison.

The corresponding 8-mercapto-9-(2-chloroethoxymethyl)guanine (IIc) is obtained in the reaction of 8-mercapto-9-(2-hydroxyethoxymethylguanine (Ic) with thionyl chloride. In this case, substitution of the mercapto group by chlorine in position 8 was not observed, in contrast to position 6, where this took place [8].

7-(2-Chloroethoxymethyl)guanine (IV) is formed in the reaction of 7-(2-hydroxyethoxymethyl)guanine (III) with thionyl chloride in hexametapol, but it is easily isomerized into the corresponding 9-isomer IIa in the conditions of separation and purification (evaporation of acid solution). Changing the conditions of separation, i.e., neutralization of the reaction mixture before evaporation, prevented isomerization, and target product IV was obtained with a 60% yield. The reverse reaction, i.e., isomerization of 9-isomer IIa into 7-isomer IV, was not observed.

The individuality and purity of these guanine derivatives IIa-d and IV was confirmed by TLC and the data from elemental analysis (Table 1). The absorption maxima in the UV spectra of the compound at pH 2 and pH 12 (see Table 1) correspond to the maxima of the other 7- and 9-substituted and the 8,9-disubstituted guanine derivatives [3, 9, 10]. The ESR spectra of products IIa-d and IV are reported in Table 2.

EXPERIMENTAL

The UV spectra were made on a Unicam-SP 1800 spectrophotometer. The ESR spectra were made on a Bruker WH-90/DS spectrometer (90 MHz) in DMSO-D_6 with TMS as the internal standard. The purity of the compounds was monitored

by TLC on Silufol UV-254 plates in chloroform—methanol, 5:1 (A) and isopropanol—ammonia—water, 7:1:2 (B) solvent systems.

The data from elemental analysis for C, H, N, Cl, and S corresponded to the calculations.

9-(2-Chloroethoxymethyl)guanine (IIa). While stirring and heating, 10.0 g (44.4 mmole) of compound Ia was dissolved in 100 ml of hexametapol. It was cooled to 20°C and a solution of thionyl chloride (19 ml; 31.4 g; 264 mmole) in 100 ml of hexametapol, previously prepared and cooled to 20°C, was added. After stirring (24 h at 20°C), the reaction mixture was poured into 700 ml of ice water. The solution was concentrated in a vacuum to ~ 1/2 the volume, neutralized by addition of conc. NH_4OH, and cooled. The sediment formed was filtered off, washed with cold water, and recrystallized from ethanol, yielding 8.44 g of compound IIa.

8-Chloro-9-(2-chloroethoxymethyl)guanine (IIb) was synthesized similar to compound IIa from 1.3 g (4.3 mmole) of compound Ib [3] and 1.8 ml (2.89 g; 25 mmole) of thionyl chloride. After stirring (48 h at 20°C), the reaction mixture was poured into 100 ml of ice water. The sediment formed was filtered off and washed with water. The product was recrystallized from water, yielding 0.86 g of compound IIb.

8-Mercapto-9-(2-chloroethoxymethyl)guanine (IIc) was synthesized similar to compound IIb from 1.0 g (3.6 mmole) of compound Ic [9] and 1.7 ml (2.81 g; 24 mmole) of thionyl chloride. The product was recrystallized from water, yielding 0.62 g of compound IIc.

7-(2-Chloroethoxymethyl)guanine (IV) was synthesized similar to compound IIa from 1.6 g (7.0 mmole) of compound III [10] and 3.0 ml (4.97 g; 42 mmole) of thionyl chloride. After diluting the reaction mixture with 180 ml of ice water, the solution was immediately neutralized by addition of conc. NH_4OH. It was cooled in a condenser, and the sediment formed was filtered off and washed with water. It was recrystallized from water, yielding 1.07 g of compound IV.

8-Bromo-9-(2-chloroethoxymethyl)guanine (IId). Bromine water was added by small portions to a suspension of 1.3 g (5.3 mmole) of compound IIa in 250 ml of water while intensely stirring until discoloration stopped. Stirring was continued for 2 h at 20°C. The sediment was filtered off, washed with cold water, and recrystallized from water—ethanol mixture, 1:2, yielding 1.28 g of compound IId.

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