SYNTHESIS OF 6-SUBSTITUTED 9-(DIHYDROXYALKYL)PURINES

M. Yu. Lidak, Ya. Ya. Shluke,
B. V. Zarinya, and S. E. Poritere

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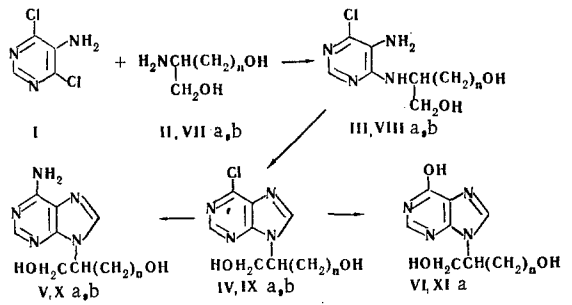
5-Amino-6-chloro-4-dihydroxyalkylaminopyrimidines, which are cyclized to 6-chloro-9-(dihydroxyalkyl)purines, were obtained by the condensation of 5-amino-4,6-dichloropyrimidine with 2-amino-1,3-dihydroxypropane or with 2-amino-1,4-dihydroxybutane. The corresponding 6-hydroxy and 6-amino derivatives were obtained by replacement of the chlorine.

On the basis of modern concepts regarding the probable significance of epigenomic changes in carcinogenesis, impetus was given to a search for new types of anticancer substances – model analogs of oligonucleotides which have a conformation similar to natural nucleic acids and a sequence of pyrimidine and purine bases which is complementary with respect to the responsible operon [1].

In this paper we describe routes for the synthesis of fragments of the purine portion of analogs of nucleotides, viz., 6-substituted 9-(1,3-dihydroxypropyl)purines (IV-VI) and 6-substituted 9-(1,4-dihydroxybutyl)purines (IX-XI). To obtain these compounds, we used the method of condensation of 5-amino-4,6-dichloropyrimidine with the appropriate amine, first used for the synthesis of 9-substituted purines by Montgomery and Temple [2] and later employed by Schaeffer and co-workers [3] to obtain 6-substituted 9-(2,3-dihydroxypropyl)purines. As shown in the scheme, condensation of 5-amino-4,6-dichloropyrimidine (I) with 2-amino-1,3-dihydroxypropane (II) or, respectively, with 2-amino-1,4-dihydroxybutane (VII) gives 5-amino-6-chloro-4-dihydroxyalkylaminopyrimidines (III and VIII), which undergo cyclization with ethyl orthoformate to form 6-chloro-9-(1,3-dihydroxypropyl)purine (IV) and 6-chloro-9-(1,4-dihydroxybutyl)-purine (IX).



II-VI n=1; VII-XI n=2; a-D, L-isomer; b-L-isomer

The corresponding 6-hydroxy (VI and XI) and 6-amino derivatives (V and X) are obtained by nucleophilic substitution of the labile chlorine in IV and IX. The optically active L-6-chloro-9-(1,4-dihydroxybutyl)purine (IXb) with $[\alpha]^{20} = -29.5$ deg and L-6-amino-9-(1,4-dihydroxybutyl)purine (Xb) with $[\alpha]^{20} = -38$ deg (C = 1, water) were obtained by synthesis with L-2-amino-1,4-dihydroxybutane. The structures of the compounds obtained were confirmed by their UV spectra and microanalysis (Table 1). The UV spectra of the new purine derivatives are characteristic for these compounds and differ markedly from the spectra of the starting

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TABLE 1. Characteristics of the Compounds Obtained

Compound	R_f in system *		UV spectra					Empirical formula	Found, %			Calculated, %		
			0,1N HCl		H_2O		0,1N NaOH							
	1	2	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε	λ_{max}, nm	lg ε		C	H	N	C	H	N
III	0,92	0,76	303	3,85	260	3,66	260; 292	3,83; 3,91	$C_7H_{11}ClN_4O_2$	38,30	5,32	26,01	38,44	5,07	25,62
IV	0,85	0,70	265	3,63			264	3,60	$C_8H_9ClN_4O_2 \cdot HCl$	36,03	3,60	26,43	36,24	3,80	26,75
V	0,64	0,48	260	3,86	261	3,86	261	3,87	$C_8H_{11}N_5O_2 \cdot HCl$	39,04	5,40	28,15	39,11	4,92	28,50
VI	0,51	0,49	246	3,84	249	3,81	254	3,81	$C_8H_{10}N_4O_3 \cdot HCl$	38,55	4,22	22,23	38,95	4,50	22,72
VIII	0,82	0,81	303	4,31	262; 291	4,14; 4,16	262; 292	4,16; 4,18	$C_8H_{13}ClN_4O_2$	41,57	5,57	24,15	41,25	5,63	24,08
IX	0,80	0,81	264	3,43	265	3,63	265	3,63	$C_9H_{11}ClN_4O_2 \cdot HCl$	38,50	4,60	19,63	38,73	4,33	20,16
X	0,59	0,71	260	3,80	261	3,76	262	3,82	$C_9H_{13}N_5O_2$	48,15	5,85	31,25	48,43	5,86	31,38
XI	0,53	0,55	250	3,67	248	3,88	254	3,78	$C_9H_{12}N_4O_3 \cdot HCl$	41,29	4,99	20,90	41,46	5,03	21,49

* System 1: iso-$C_3H_7OH-NH_4OH-H_2O$ (7:1:2); system 2: n-$C_3H_7OH-NH_4H-H_2O$ (6:3:1).

pyrimidines; this makes it possible to determine the course of the cyclization and identify the final products obtained.

EXPERIMENTAL

5-Amino-4-(1,3-dihydroxypropylamino)-6-chloropyrimidine (III). A mixture of 6 g (0.037 mole) of I, 3.36 g (0.037 mole) of II, 3.7 g (0.037 mole) of triethylamine, and 40 ml of butanol was refluxed for 24 h. The solvent was removed by distillation, and the residue was crystallized from water to give 4.3 g (47%) of III with mp 206 deg.

6-Chloro-9-(1,3-dihydroxypropyl)purine (IV). A solution of 4.3 g (0.02 mole) of III in 86 ml of triethyl orthoformate and 1.9 ml of hydrochloric acid (sp. gr. 1.175) was held at room temperature for 5 h. The solvent was removed by distillation, and the residue was crystallized from acetone to give 3.88 g (71%) of IV with mp 184-185 deg. The hydrochloride was obtained as follows. Compound IV was dissolved in ether–chloroform (1:1), and the hydrochloride was precipitated with hydrogen chloride. The reaction mass was crystallized from methanol–ether to give 3.3 g (52%) of the hydrochloride of IV with mp 190-195 deg.

6-Amino-9-(1,3-dihydroxypropyl)purine (V). A solution of 1.95 g (0.0085 mole) of IV in 30 ml of methanol saturated with ammonia at 0 deg was held at 65 deg in a sealed ampule for 22 h. The solvent was removed by distillation, and the residue was crystallized from methanol to give 1.0 g of crystals of V with mp 182-184 deg. Compound V was treated with 3 N hydrochloric acid, the excess acid was removed by distillation, and the residue was crystallized from methanol–ether to give 1.0 g (49%) of the hydrochloride of V with mp 204-206 deg.

6-Hydroxy-9-(1,3-dihydroxypropyl)purine (VI). The hydrochloride was obtained as follows. A solution of 1.3 g (0.0049 mole) of IV in 38 ml of 1 N hydrochloric acid was refluxed for 2 h. The hydrochloric acid was removed by distillation, and the residue was crystallized from methanol–ether to give 0.9 g (74%) of the hydrochloride of VI with mp 173-175 deg.

5-Amino-4-(1,4-dihydroxybutylamino)-6-chloropyrimidine (VIIIa). A mixture of 12.6 g (0.077 mole) of I, 8.3 g (0.078 mole) of VIIa, and 7.8 g (0.077 mole) of triethylamine was treated as in the preparation of III to give 8.0 g (43%) of VIIIa with mp 144 deg.

L-5-Amino-4-(1,4-dihydroxybutylamino)-6-chloropyrimidine (VIIIb). This was obtained in the same way as VIIIa from VIIb. Compound VIIIb had $[\alpha]^{27} = +30.5$ deg (C = 1, water).

6-Chloro-9-(1,4-dihydroxybutyl)purine (IXa). The hydrochloride was obtained as follows. A solution of 5.6 g of VIIIa in 110 ml of triethyl orthoformate and 2.4 ml of hydrochloric acid (sp. gr. 1.175) was treated in the same way as that used to obtain IV without isolation of the base to give 5.8 g (86.5%) of the hydrochloride of IXa with mp 110-112 deg.

L-6-Chloro-9-(1,4-dihydroxybutyl)purine (IXb). The hydrochloride was obtained in the same way as that used to obtain IXa by subjecting VIIIb to cyclization. Deriviative IXb had $[\alpha]^{20} = -29.5$ deg (C = 1, water) and mp 95 deg.

6-Amino-9-(1,4-dihydroxybutyl)purine (Xa). A solution of 1.0 g (0.0036 mole) of IXa in 30 ml of methanol saturated with ammonia at 0 deg was held at 95 deg in a sealed ampule for 24 h. The solvent was removed by distillation, and an aqueous solution of the residue was passed through a column containing Dowex 50 W ion-exchange resin. The solvent was removed from the eluate (1 N NH_4OH) by distillation, and the residual Xa was crystallized from methanol to give 0.4 g (50%) of a product with mp 181 deg.

L-6-Amino-9-(1,4-dihydroxybutyl)purine (Xb). This was obtained in the same way as Xa from IXb and had $[\alpha]^{20} = -38$ deg (C = 1, water) and mp 181 deg.

6-Hydroxy-9-(1,4-dihydroxybutyl)purine (XIa). The hydrochloride was obtained as follows. A solution of 1.45 g (0.0058 mole) of IXa in 45 ml of 1 N HCl was treated in the same way as VI to give 0.95 g (72.5%) of XIa with mp 131-133 deg.

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