NEW METHOD FOR THE SYNTHESIS OF 2-(9-ADENINYL)ALKANEDIOLS

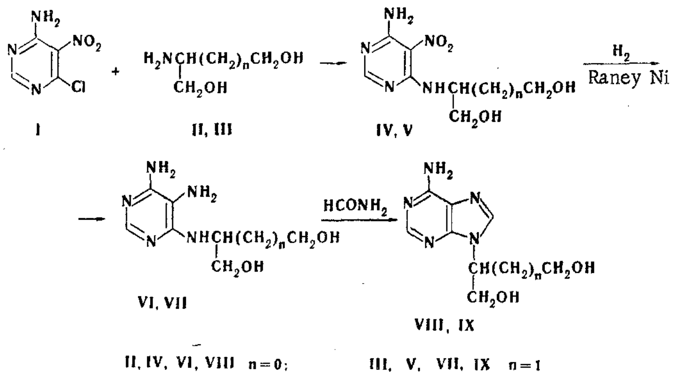
M. Yu. Lidak, B. V. Zarinya,
and Ya. Ya. Shluke

UDC 547.857.7.07:542.953

Condensation of 4-amino-5-nitro-6-chloropyrimidine with 2-amino-1,3-dihydroxypropane and 2-amino-1,4-dihydroxybutane gave 4-amino-5-nitro-6-dihydroxyalkylpyrimidines, which are cyclized to 2-(9-adeninyl)alkanediols after reduction of the nitro group.

We have already reported the synthesis of fragments of the purine portion of analogs of nucleosides – 2-(6-substituted-9-purinyl)alkanediols [1].

The present paper is devoted to an investigation of another route to 2-(9-purinyl)alkanediols, which are previously described for the synthesis of 2-(9-adeninyl)-1,3-cyclohexanediol [2]. The starting material was 4-amino-5-nitro-6-chlorpyrimidine (I) [3], in which the chlorine atom attached to $C_{(6)}$ is replaced by the residue of the appropriate aminoalkanediol. In connection with the activating effect of the nitro group attached to $C_{(5)}$, substitution proceeds readily, and the corresponding aminoalkanediols (IV, V) are obtained in good yields.



The nitro group of pyrimidines IV and V was reduced by molecular hydrogen at atmospheric pressure in the presence of Raney nickel.

Formamide was used as the cyclizing agent for closing of the imidazole ring. Formic acid or a mixture of formic acid and formamide gave a resinous product that was difficult to separate.

Thus, as compared with a previous method [1] (20% yield), we were able to raise the yield of VIII and IX by a factor of three, based on the starting pyrimidine.

The location of the alkanediol residue at $N_{(9)}$ of the purine ring was proved by analysis of the UV spectra and alternative synthesis via the method in [1].

Some characteristics of the synthesized derivatives are given in Table 1.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 129-130, January, 1973. Original article submitted October 18, 1971.

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C (crystallization solvent)	Rf in system*			Empirical formula
		1	2	3	
IV	242—243 (water)	—	0,78	0,70	$C_7H_{11}N_5O_4$
V	170—171 (water)	—	0,84	0,80	$C_8H_{13}N_5O_4$
VI	168—169 (ethanol)	—	0,54	0,50	$C_7H_{13}N_5O_2$
VII	124—125 (methanol)	—	0,70	0,37	$C_8H_{15}N_5O_2 \cdot H_2O \cdot H_2SO_4$
VIII	183—184 (methanol+ ether)	0,48	0,64	—	$C_8H_{11}N_5O_2$
IX	181 (methanol+ether)	0,71	0,59	—	$C_9H_{13}N_5O_2$

TABLE 1 (continued)

Compound	Found, %			Calc., %			UV spectra						Yield, %
							0,1 *N* HCl		H_2O		0,1 *N* NaOH		
	C	H	N	C	H	N	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	λ_{max}, nm	$\varepsilon \cdot 10^{-3}$	
IV	36,64	4,83	30,28	36,68	4,84	30,56	339	6,05	341	16,50	341	7,40	88
V	39,43	5,55	28,81	39,50	5,39	28,80	340	7,35	339	9,54	339	8,0	90
VI	42,16	6,29	35,20	42,20	6,50	35,16	384	10,22	386	10,48	385	8,96	75
VII	29,17	5,50	21,12	29,17	5,81	21,24	283	9,96	288	10,28	280	6,28	73
VIII	45,90	5,20	33,31	45,92	5,30	33,48	260	14,49	261	14,49	261	14,83	68
IX	48,41	5,79	31,16	48,43	5,86	31,38	260	12,62	261	11,51	262	13,21	64

---

*System 1: $C_3H_7OH-NH_4OH-H_2O$ (6:3:1); system 2: iso-$C_3H_7OH-NH_4OH-H_2O$ (7:1:2); system 3: $C_4H_9OH-CH_3COOH-H_2O$ (5:3:2).

EXPERIMENTAL

2-[(4-Amino-5-nitro-6-pyrimidinyl)amino]-1,3-propanediol (IV). A solution of 10 g (44 mmole) of I, 8 g (88 mmole) of II, and 13.36 g (132 mmole) of triethylamine in 176 ml of Methyl Cellosolve was refluxed for 2 h, and the precipitated crystals were removed by filtration and recrystallized to give 11.52 g of IV.

2-[(4-Amino-5-nitro-6-pyrimidinyl)amino]-1,4-butanediol (V). A solution of 7.7 g (73 mmole) of III, 8.4 g (37 mmole) of I, and 11.1 g (0.011 mole) of triethylamine in 148 ml of Methyl Cellosolve was refluxed for 2 h. The solvent was removed by distillation, and the residue was crystallized to give 10.2 g of V.

2-[(4,5-Diamino-6-pyrimidinyl)amino]-1,3-propanediol (VI). A 3-g sample of Raney nickel was added to a suspension of 9.17 g (0.04 mole) of IV in 300 ml of absolute ethanol, and the hydrogenation was carried out at atmospheric pressure for 8 h. The catalyst was removed by filtration, the solvent was removed by vacuum distillation, and the residue was recrystallized to give 6.7 g of VI.

2-[(4,5-Diamino-6-pyrimidinyl)amino]-1,4-butanediol (VII) Hydrosulfate. A 1-g sample of Raney nickel was added to a suspension of 2.7 g (0.011 mole) of V in 120 ml of absolute ethanol, and the hydrogenation was carried out with molecular hydrogen at atmospheric pressure for 2 h. The catalyst was removed by filtration, the solvent was removed by vacuum distillation, and the syrupy residue was dissolved in 45 ml of methanol. The pH of the solution was adjusted to three by the addition of 10 N sulfuric acid, and the resulting precipitate was removed by filtration and recrystallized to give 2.7 g of the hydrosulfate of VII.

2-(9-Adeninyl)-1,3-propanediol (VIII). A solution of 0.8 g (4 mmole) of VI in 8 ml of formamide was held at 170° for 2 h. The solvent was then removed by distillation, and the residue was crystallized to give 0.57 g of VIII.

2-(9-Adeninyl)-1,4-butanediol (IX). A solution of 0.7 g (2.1 mmole) of the hydrosulfate of VII in 7 ml of formamide was held at 170° for 2 h. The solvent was removed by vacuum distillation, and the syrupy residue was dissolved in 20 ml of water and passed through Dowex 50w (H^+) ion-exchange resin. The column was washed with water until the exiting liquid gave a negative test for sulfate ions. The material on the column was then eluted with 1 N ammonium hydroxide, the solution was vacuum evaporated to dryness, and the residue was crystallized to give 0.32 g of IX.

LITERATURE CITED

1. M. Yu. Lidak, Ya. Ya. Shluke, B. V. Zarinya, and S. E. Poritere, Khim. Geterotsikl. Soedin., 2, 262 (1971).

2. T. Suami, Y. Sato, Y. Fukai, and Y. Sakota, J. Heterocycl. Chem., 6, 663 (1969).
3. W. R. Boon, W. G. M. Jones, and G. R. Ramage, J. Chem. Soc., 99 (1951).