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ANALOGS OF PURINE NUCLEOSIDES AND PURINE MONO- AND POLYNUCLEOTIDES

V.* PREPARATION OF 9-(1,5-DIHYDROXY-3-PENTYL)-PURINES

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A number of 6-substituted 9-(1,5-dihydroxy-3-pentyl)purines were obtained from 5-amino-4,6-dichloropyrimidine. 5-Amino-4,6-dichloropyrimidine reacts with 2-hydroxymethylpyrrolidine to give 4-chloro-5-amino-6-(2-hydroxymethylpyrrolidino)pyrimidine.

As previously reported in [2], the synthesis of analogs of oligonucleotides with a modified pentose residue seems of interest in order to study the effect of such oligomers on biologically important systems, the functioning of which is associated with nucleic acids. Replacement of the ribose or deoxyribose of natural polynucleotides by dihydroxyalkyl groups of corresponding length and conformation may lead to analogs of nucleotides that to a greater or lesser extent are capable of complexing with natural polynucleotide matrices.

The synthesis and subsequent polycondensation of 1'5'-diphosphates of 1',5'-dihydroxypentylpurines also seems of definite interest, since it is possible that synthetic polynucleotides containing a pentamethylene chain instead of a ribose (deoxyribose) residue will prove to be conformationally closer to natural prototypes.

9-(1,5-Dihydroxy-3-pentyl)purines, the synthesis of which is possible by two methods – by alkylation of purine derivatives (for example, see [3, 4]) or by adding an imidazole ring to the corresponding pyrimidine derivatives (for example, see [5]) – can be used as the starting materials for the preparation of such compounds.

Our attempts to alkylate 6-fluoropurine with diethyl α- or β-bromoglutarates in the presence of sodium hydride or potassium carbonate [4, 6] in dimethylformamide (DMF) with subsequent reduction of the ester

*See [1] for communication IV.
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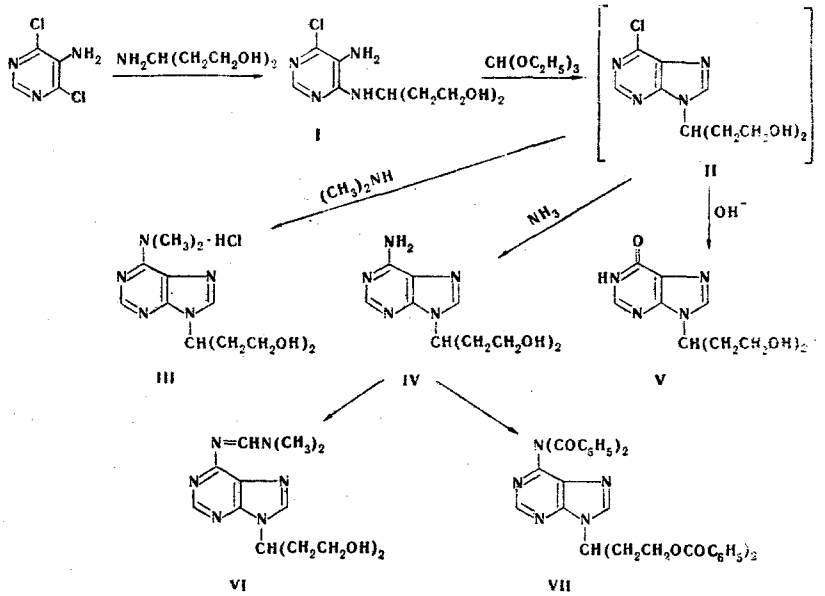
groupings proved to be unsuccessful. Only the second method gave positive results. The reaction of 3-amino-1,5-pentanediol with 5-amino-4,6-dichloropyrimidine and subsequent cyclization of 5-amino-6-(1,5-dihydroxy-3-pentyl)amino-4-chloropyrimidine (I) with ethyl orthoformate in the presence of acetic anhydride gives purine II. As shown in [7], it is not expedient to isolate the intermediate 6-chloro-9-hydroxyethylpurine in the synthesis of 6-amino-9-hydroxyethylpurine. In the synthesis of 6-amino-9-(1,5-dihydroxy-3-pentyl)purine the reaction mixture was therefore treated with ethanol saturated with ammonia immediately after the cyclization step. We were thus able to obtain 6-amino-9-(1,5-dihydroxy-3-pentyl)purine (IV) in 80% yield.

It is necessary to protect the amino group of the purine for the subsequent utilization of the resulting monomers in polycondensation reactions. For this purpose base IV was treated with DMF dimethylacetal, and 6-N-dimethylaminomethyleneamino-9-(1,5-dihydroxy-3-pentyl)purine (VI) was obtained. Acylation with benzoyl chloride gave tetrabenzoyl derivative VII.

In addition to the preparation of adenine derivatives IV, VI, and VII, it seemed expedient also to synthesize 6-oxo- and 6-dimethylamino-9-(1,5-dihydroxy-3-pentyl)purines. They do not need protection of their functional groupings, and this considerably facilitates the subsequent synthesis of the analogs of oligonucleotides. In addition, a comparative study of the capacities for association and complexing of these compounds with complementary polynucleotides seems of definite interest. 6-Oxo-9-(1,5-dihydroxy-3-pentyl)purine (V) was obtained after elution with 1 N ammonium hydroxide of the cyclization product II adsorbed on Dowex. Direct hydrolysis of purine II with 2 N HCl leads to the same substance but in considerably lower yield.



An attempt to use the method described here for the preparation of 6-substituted 9-(1,5-dihydroxy-2-pentyl)purine by condensation of 5-amino-4,6-dichloropyrimidine with 2-amino-1,5-pentanediol is complicated by the fact that the latter compound is very easily cyclized to 2-hydroxymethylpyrrolidine. 4-Chloro-5-amino-6-(2-hydroxymethylpyrrolidino)pyrimidine (VIII), which can be selectively benzoylated at the amino group to give N,N-dibenzoyl derivative IX or simultaneously benzoylated at the amino and hydroxy groups to give X, is obtained as a result of the reaction carried out in this way. The structure of IX was confirmed by the IR spectrum, in which the characteristic bands of monoacylated amines are absent.

EXPERIMENTAL METHOD

The UV spectra of the compounds were recorded with a Specord spectrophotometer. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The melting points were determined with a Boetius apparatus.

Paper chromatography was carried out with Filtrax FN-3 paper [system A: isopropyl alcohol – H_2O – concentrated NH_4OH (7 : 2 : 1)] and Whatman 3-mm paper [system B: 1 M CH_3COONH_4 – ethanol (1 : 1); system C: isobutyric acid – 0.5 N NH_4OH (10 : 6)]. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in a chloroform – methanol system (9 : 1).

The characteristics of the purine derivatives obtained in this research are presented in Table 1.

TABLE 1. 9-(1,5-Dihydroxy-3-pentyl)purine Derivatives

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
II	175[a]	$C_{12}H_{19}N_5O_2 \cdot HCl$	48,2	6,8	23,4	47,8	6,7	23,2	80
IV	124,5—125[b]	$C_{10}H_{15}N_5O_2$	50,4	6,4	29,2	50,6	6,4	29,5	78
V	214,5—215[c]	$C_{10}H_{14}N_4O_3$	50,0	6,1	23,3	50,4	5,9	23,5	45
VI	138,5—139	$C_{13}H_{20}N_6O_2$	53,9	7,1	28,5	53,4	6,9	28,8	62
VII	154—155	$C_{38}H_{31}N_5O_6$	70,1	4,3	10,7	69,8	4,8	10,7	80

[a] With decomposition. This compound had R_f 0.88 (A), 0.91 (B), and 0.85 (C). UV spectrum, λ_{max}, NM ($\varepsilon \cdot 10^{-3}$): 277 (17.7) in 0.1 N HCl, 277 (44) in water, 280 (9.5) in 0.1 N NaOH.

[b] This compound had R_f 0.73 (A), 0.78 (B), and 0.80 (C). UV spectrum, λ_{max}, NM ($\varepsilon \cdot 10^{-4}$): 260 (2.5) in 0.1 NHCl, 262 (2.0) in water, 265 (1.5) in 0.1 N NaOH.

[c] This compound had R_f 0.67 (A), 0.78 (B), and 0.65 (C). UV spectrum: λ_{max}, NM ($\varepsilon \cdot 10^{-3}$): 250 (6.0) in 0.1 N HCl, 250 (6.4) in water, and 257 (6.4) in 0.1 N NaOH.

4-Chloro-5-amino-6-(1,5-dihydroxy-3-pentyl)aminopyrimidine (I). A solution of 4.7 g (28.6 mmole) of 5-amino-4,6-dichloropyrimidine and 7.0 g (58.5 mmole) of 3-amino-1,5-pentanediol in 80 ml of dioxane was refluxed for 16 h, after which the resulting oily layer was separated from the dioxane by decantation and extracted with boiling dioxane (three 40-ml portions). Ether was added, with cooling, to the combined dioxane extracts and decanted solution. The resulting precipitate was removed by filtration, and the filtrate was evaporated to half its original volume and treated again with ether. The overall yield of colorless crystals with mp 140.5–141° (from ethyl acetate) and R_f 0.37 (TLC) was 4.12 g (59%).

6-Dimethylamino-9-(1,5-dihydroxy-3-pentyl)purine Hydrochloride (III). A solution of 3.0 g (12.1 mmole) of I in 15 ml of freshly distilled acetic anhydride and 15 ml of triethyl orthoformate was refluxed for 3 h, after which the solvent was removed by vacuum distillation, and the residue was dissolved in 200 ml of ethanol saturated with dimethylamine (at 0°). The resulting solution was heated at 100° in an autoclave for 14 h, after which it was evaporated to dryness. The residue was dissolved in the minimum amount of ethanol, and ethanol saturated with HCl was added to obtain the hydrochloride. The yield of colorless prisms with mp 175° (dec., from ethanol) was 2.9 g (80%).

6-Amino-9-(1,5-dihydroxy-3-pentyl)purine (IV). The dihydrochloride of base IV was obtained from 5.4 g (21.8 mmole) of I, 30 ml of ethyl orthoformate, 30 ml of acetic anhydride, and 200 ml of ethanol saturated with ammonia by a method similar to that in the synthesis of hydrochloride III. The yield of the dihydrochloride with mp 137° (dec., from ethanol) was 4.6 g (77%). For isolation of base IV, 2.0 g of the dihydrochloride was dissolved in 20 ml of water, and the solution was filtered and passed through a column filled with 90 ml of Dowex-50 · 8 resin. The column was washed with water to remove the chlorides, and the products were eluted with 1 N ammonium hydroxide. The fractions that fluoresced in UV light were evaporated to dryness. The residue was dissolved in a small amount of ethanol, and ether was added. Workup gave 1.2 g (78%) of colorless prisms with mp 124.5–125° and pK_a 3.84.

6-Oxo-9-(1,5-dihydroxy-3-pentyl)purine (V). The oily substance (obtained as in the preparation of III) prepared from 3.0 g (12.1 mmole) of I, 15 ml of ethyl orthoformate, and 15 ml of acetic anhydride was dissolved in 10 ml of ethanol, and 2 ml of 2 N HCl was added. The resulting solution was passed through a column filled with 50 ml of Dowex-50W · 8 resin. The column was washed out with 200 ml of distilled water, after which the hydrolysis product was eluted with 1 N ammonium hydroxide. The fractions that fluoresced in UV light were evaporated to dryness, and the residue was crystallized from ethanol to give 1.3 g (45%) of colorless prisms with mp 214.5–215° (from ethanol). IR spectrum: 1690 cm^{-1} (C=O).

6-(N,N-Dimethylaminomethyleneamino)-9-(1,5-dihydroxy-3-pentyl)purine (VI). Dimethylformamide dimethylacetal (1 ml) was added to a solution of 0.68 g (2.87 mmole) of base IV in 5 ml of DMF, and the solution was allowed to stand at room temperature for 2 days. The excess DMF was then removed in vacuo at 40–50°, and the residue was dissolved in chloroform. Ether was added to the chloroform solution to give 0.53 g (62%) of colorless crystals with mp 138.5–139° (from chloroform and ether).

6-Dibenzamido-9-(1,5-dibenzoxy-3-pentyl)purine (VII). A 0.5-g (2.1 mmole) sample of base IV was dissolved by gentle heating in 8 ml of pyridine, and 1.25 ml of benzoyl chloride was added dropwise. The mixture

was refluxed for 5 min, after which it was vacuum evaporated to dryness. Excess water was added to the residue, and the mixture was allowed to stand for a few hours. The precipitated crystals were removed by filtration to give 1.1 g (80%) of colorless prisms with mp 154-155° (from ethanol).

4-Chloro-5-6-(2-hydroxymethylpyrrolidino)pyrimidine (VIII). A mixture of 4.8 g (30 mmole) of 5-amino-4,6-dichloropyrimidine and 7.0 g (69 mmole) of 2-hydroxymethylpyrrolidine in 40 ml of dioxane was refluxed for 16 h, after which the solution was vacuum evaporated, and the residue was crystallized from water to give 5.1 g (44%) of colorless needles with mp 138° (from water) and R_f 0.45 (TLC). Found: C 47.2; H 5.4; N 24.4%. $C_9H_{13}ClN_4O$. Calculated: C 47.3; H 5.7; N 24.5%.

4-Fluoro-5-dibenzamido-6-(2-hydroxymethylpyrrolidono)pyrimidine (IX). A 0.4-ml (3.4 mmole) sample of benzoyl chloride was added to a solution of 0.23 g (1 mmole) of VIII in 2 ml of pyridine, and the mixture was refluxed for 5 min. It was then evaporated, and the excess benzoyl chloride was hydrolyzed with water. The resulting oil solidified on trituration to give 0.4 g (92%) of a product with mp 190° (from ethanol). IR spectrum: 1720 cm^{-1} (C=O). Found: C 62.9; H 4.8; N 12.8%. $C_{23}H_{21}ClN_4O_3$. Calculated: C 63.2; H 4.8; N 12.8%.

4-Chloro-5-dibenzamido-6-(2-benzoxymethylpyrrolidino)pyrimidine (X). A 3-ml sample of benzoyl chloride was added with shaking to a solution of 0.5 g (2.2 mmole) of VIII in 2 ml of pyridine, and the mixture was refluxed for 15 min. It was then cooled and evaporated, and the residue was treated with water. The product was removed by filtration and washed with boiling water to give 0.5 g (43%) of a product with mp 172° (from ethanol). IR spectrum: 1130 (ester C-O-C) and 1725 cm^{-1} (C=O). Found: C 66.2; H 4.5; N 10.2%. $C_{30}H_{25}ClN_4O_4$. Calculated: C 66.6; H 4.7; N 10.4%.

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