NUCLEIC ACID COMPONENTS AND THEIR ANALOGUES. CXXXIX.*

SYNTHESIS OF 1-DEOXY-1-(6-AMINO-9-PURINYL)-2,5-ANHYDRO-D-ALLITOL** ("HOMOADENOSINE")

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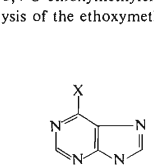
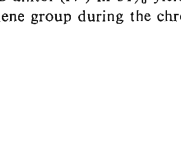
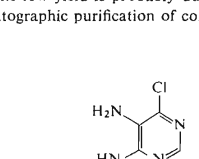
In the present paper, we wish to report the synthesis of 1-deoxy-1-(6-amino-9-purinyl)-2,5-anhydro-D-allitol*** (*I*, "homoadenosine") starting from 1-amino-1-deoxy-2,5-anhydro-D-allitol[3] (*II*), readily accessible by the lithium aluminum reduction of 2,5-anhydro-D-allonic nitrile[4]. The amine *II* has been used some time ago as the starting compound in syntheses of analogous "homonucleosides" of the uracil and cytosine series[3]. Compound *I* has been prepared by a procedure based on the imidazole ring closure of a pyrimidine precursor[5]. The same procedure has been used by Vince and Donovan[6] in the synthesis of 1-deoxy-1-(6-amino-9-purinyl)-2,6-anhydro-D-allitol and by Defaye[7] in the synthesis of 1-deoxy-1-(6-amino-9-purinyl)-2,5-anhydro-D-ribitol.

Reaction of the amine *II* and 5-amino-4,6-dichloropyrimidine afforded 1-deoxy-1-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-anhydro-D-allitol (*III*) the treatment of which with ethyl orthoformate in the presence of hydrogen chloride led to 1-deoxy-1-(6-chloro-9-purinyl)-2,5-anhydro-3,4-O-ethoxymethylene-D-allitol (*IV*) in 31% yield. The low yield is probably due to the hydrolysis of the ethoxymethylene group during the chromatographic purification of compound







I, R = H, X = NH_2 *II* *III*

IV, 2 R = $>CHOC_2H_5$, X = Cl

V, R = H, X = Cl

VI, R = H, X = OH

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*** When the manuscript of this paper was finished, Montgomery and Hewson[2] have reported another synthesis of "homoadenosine" which uses, in contrast to our procedure, 3,4-O-isopropylidene-1-amino-1-deoxy-2,5-anhydro-D-allitol as the starting compound.

IV on silica gel. On removal of the ethoxymethylene group from compound *IV* by the action of methanolic hydrogen chloride at room temperature, 1-deoxy-1-(6-chloro-9-purinyl)-2,5-anhydro-D-allitol (*V*) was obtained and converted with methanolic ammonia at 100°C to the desired "homoadenosine" *I*. 1-Deoxy-(6-hydroxy-9-purinyl)-2,5-anhydro-D-allitol (*VI*) was then prepared from the chloro derivative *V* by the hydrolytical removal of the chloro atom.

Compounds *I* and *VI* do not exhibit any inhibitory effect on the growth of *Escherichia coli* at a concentration as high as 1 mg per 1 ml.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 25°C/0·05 Torr Ultraviolet spectra were recorded on an Optica Milano CF-4 spectrophotometer. Infrared spectra were measured on a Zeiss (Jena) Model UR-10 double-beam spectrophotometer. Periodic acid oxidations were performed in 0·1M acetate buffer solution (pH 4·7) at 25°C. Descending chromatography was performed on paper Whatman No 1 in the solvent systems S_1, ethyl acetate–1-butanol–acetic acid–water (7 : 3 : 3 : 1), and S_2, 2-propanol–20% aqueous ammonia–water (7 : 1 : 2). Electrophoresis was carried out on paper Whatman No 1 (90 minutes at 30 volt per cm) in the buffer solutions E_1, 0.05M triethylammonium borate (pH 7·5), and$_2$ *E*, 0·05M sodium hydrogen citrate.

1-Deoxy-1-(5-amino-6-chloro-4-pyrimidinylamino)-2,5-anhydro-D-allitol (*III*)

A mixture of 5-amino-4,6-dichloropyrimidine (3·59 g; 0·022 mol), 1-amino-1-deoxy-2,5-anhydro-D-allitol (3·59 g; 0·022 mol), triethylamine (2·52 g; 0·025 mol), and ethanol (50 ml) was heated in a sealed tube at 100°C for 10 hours and evaporated under diminished pressure. The residual sirup was dissolved in a mixture (50 ml) of ethyl acetate and ethanol (4 : 1), the solution filtered, the filtrate evaporated under diminsihed pressure, and the residue chromatographed on a column of silica gel (200 g) in the solvent system ethyl acetate–ethanol (4 : 1) to afford 3·80 g (59%) of compound *III*, m.p. 183°C (183—183·5°C after recrystallisation from methanol). Optical rotation: $[\alpha]_D^{25} -27{\cdot}9°$ (*c* 0·5, water). For $C_{10}H_{15}ClN_4O_4$ (290·7) calculated: 41·32% C, 5·20% H, 19·28% N, 12·20% Cl; found: 41·69% C, 5·31% H, 19·25% N, 12·05% Cl. Ultraviolet spectrum (in water): λ_{max} 207 nm, 263 nm, and 292 nm (log ε 4·33, 4·05, and 4·08). Periodic acid uptake after 5 min, 60 min, and 360 min: 1·15 mol, 1·34 mol, and 1·83 mol.

1-Deoxy-1-(6-chloro-9-purinyl)-2,5-anhydro-3,4-O-ethoxymethylene-D-allitol (*IV*)

Compound *III* (1·00 g) was added to a mixture of ethyl orthoformate (10 ml) and dioxane presaturated with hydrogen chloride (0·2 ml). The whole mixture was stirred at room temperature for 2 hours until the solid dissolved, kept at room temperature for additional 12 hours, neutralised with triethylamine, and the precipitate of triethylamine hydrochloride filtered off. The filtrate was evaporated under diminished pressure and the residue chromatographed on silica gel in the solvent system benzene–ethyl acetate (2 : 1) to afford 0·385 g (31%) of compound *IV*, m.p. 162 to 163°C (ethanol). For $C_{14}H_{17}ClN_4O_5$ (356·8) calculated: 47·13% C, 4·80% H, 15·71% N, 9·94% Cl; found: 47·25% C, 4·94% H, 15·83% N, 9·88% Cl. Ultraviolet spectrum (in ethanol): λ_{max} 210 nm and 266 nm (log ε 4·13 and 3·97). Infrared spectrum (*c* 10^{-3}M; chloroform): 3 620 cm^{-1} (OH); 3 360 cm^{-1} (OH assoc).)

1-Deoxy-1-(6-chloro-9-purinyl)-2,5-anhydro-D-allitol (*V*)

Reaction of compound *III* (1·00 g) with ethyl orthoformate was performed analogously to the preceding paragraph. The resulting sirupous mixture was chromatographed on silica gel (100 g) in ethyl acetate. The fractions containing a mixture of compounds *IV* and *V* were evaporated

under diminished pressure, and the residue dissolved in a mixture of methanol (10 ml) and dioxane presaturated with hydrogen chloride (0·2 ml). The solution was allowed to stand at room temperature for 20 min and evaporated under diminished pressure. The residual sirup was dissolved in methanol (5 ml) and the solution kept at 0°C overnight to deposit 0·820 mg (79%) of compound *V*, m.p. 192°C (methanol). Optical rotation: $[\alpha]_D^{25}$ −21·2° (*c* 0·5; water). For C_{11}·$.H_{13}ClN_4O_4$ (300·7) calculated: 43·93% C, 4·36% H, 18·63% N, 11·79% Cl; found: 44,09% C, 4·41% H, 18·45% N, 11·42% Cl. Ultraviolet spectrum (in water): λ_{max} 206 nm and 266 nm (log ε 4·18 and 3·96). Periodic acid uptake after 5 min, 60 min, and 360 min: 1·05, 1·07 mol, and 1·06 mol.

TABLE I

Paper Chromatography and Electrophoretic Mobility

Compound	R_F		Mobility, cm	
	S_1	S_2	E_1	E_2
I	0·34	0·50	5·1	−4·8
III	0·47	0·73	6·0	0·0
V	0·50	0·73	5·5	0·0
VI	0·15	0·38	5·2	0·0
Adenosine	0·37	0·53	4·8	−2·7

1-Deoxy-(6-hydroxy-9-purinyl)-2,5-anhydro-D-allitol (*VI*)

A mixture of compound *V* (84 mg) and water (5 ml) was heated at 100°C for 10 hours, cooled to 20°C, passed through a column of Dowex-1 (acetate) ion exchange resin, and the column washed with water. Elution with 2% aqueous acetic acid afforded 35 mg (43%) of compound *VI*, m.p. 226—227°C (water). Optical rotation: $[\alpha]_D^{25}$ −25·9° (*c* 0·5; water). For $C_{11}H_{14}N_4O_5$ (282.2) calculated: 46·81% C, 5·00% H, 19·85% N; found: 46·74% C, 5·15% H, 19·83% N. Ultraviolet spectrum, in 0·1M-HCl: λ_{max} 251 nm (log ε 4·03); in 0·1M-NaOH: λ_{max} 207 nm and 255 nm (log ε 4·21 and 4·08). Periodic acid uptake after 5 min, 60 min, and 360 min: 1·06 mol, 1·10 mol and 1·15 mol.

1-Deoxy-(6-amino-9-purinyl)-2,5-anhydro-D-allitol (*I*)

A mixture of compound *V* (120·8 mg) and 2·5M methanolic ammonia (10 ml) was heated in a sealed tube at 100°C for 4 hours and evaporated under diminished pressure. After the addition of ethanol, the residue solidified; yield, 89·7 mg of a chromatographically homogeneous substance, m.p. 197°C. Recrystallisation from methanol afforded 58·2 mg (48%) of compound *I*, m.p. 202—203°C. Optical rotation: $[\alpha]_D^{25}$ −24·7° (*c* 0·5; water). For $C_{11}H_{15}N_5O_4$ (281·2) calculated: 46·97% C, 5·37% H, 24·90% N; found: 47·06% C, 5·41% H, 24·94% N. Ultraviolet spectrum, in 0·1M-HCl: λ_{max} 213 nm and 259 nm (log ε 4·24 and 4·17); in 0·05M-NaOH: λ_{max} 211 nm and 259 nm (log ε 4·24 and 4·17). Periodic acid uptake after 5 min, 60 min, and 360 min: 0·96 mol, 0·95 mol, and 0·97 mol.

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AMINO SUGARS. XXV.*

REACTION OF METHYL-6-DEOXY-2,3-O-ISOPROPYLIDENE-4-O-METHANESULFONYL-α-L-TALOPYRANOSIDE WITH AMMONIA AND HYDRAZINE

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In previous papers[1-3] we studied the reaction of methyl-2,3-O-isopropylidene-4-O-methanesulfonyl-α-L-rhamnopyranoside (*VIII*) with sodium azide and hydrazine with the aim of preparing the corresponding 4-amino sugar. However, in agreement with the investigations of other authors[4,5] the substitution had an anomalous course, accompanied by ring rearrangement. In order to check the effect of steric conditions on the course of this substitution reaction we synthesized methyl-6-deoxy-2,3-O-isopropylidene-4-O-methanesulfonyl-α-L-talopyranoside (*V*) which differs from rhamnopyranoside *VIII* only by its inverse configuration at $C_{(4)}$ and we also followed its reaction with ammonia and hydrazine.

As a starting compound for the synthesis of talopyranoside *V* we chose methyl-2,3-O-isopropylidene-α-L-rhamnopyranoside (*I*). Overend and coworkers[6,7] oxidised it with chromium trioxide in pyridine and obtained methyl-6-deoxy-2,3-O-isopropylidene-α-L-*lyxo*-hexopyranosid-4-ulose (*II*) and found that its reduction takes place stereospecifically to methyl-6-deoxy-2,3-O-isopropylidene-α-L-talopyranose (*IV*). We endeavoured to carry out the oxidation with a mixture of dimethyl sulfoxide and acetic anhydride. However, we isolated methyl-2,3-O-isopropylidene-4-O-methylthiomethyl-α-L-rhamnopyranoside (*III*) in 53% yield as the main product. The formation of methylthiomethyl ethers during the oxidation of alcohols with the mentioned reagent is known[8], but if they are formed at all, then only in low yields. We obtained an incompletely pure

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