SYNTHESIS OF N^1,N^2-BIS(9-β-D-RIBOFURANOSYLPURIN-6-YL)--1,5-DIAMINOPENTANE AND N^6-(5-AMINOPENT-1-YL)ADENOSINE*

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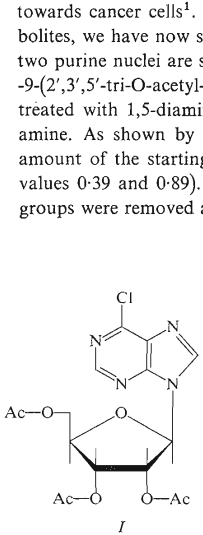
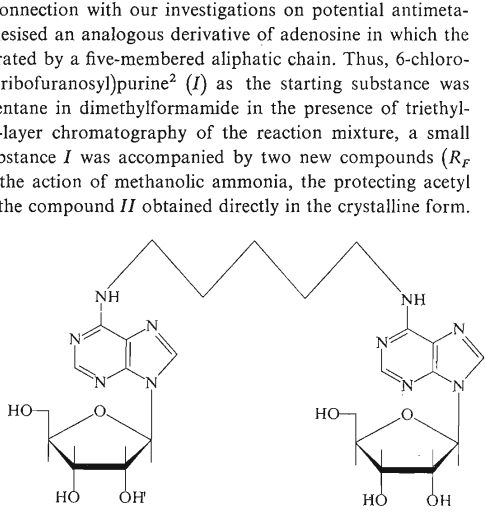
Received September 23rd, 1976

6-Chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)purin (*I*) affords by reaction with 1,5-diaminopentane and deblocking N^1,N^2-bis(9-β-D-ribofuranosylpurin-6-yl)-1,5-diaminopentane (*II*). Reaction of *I* with N^1-dimethoxytrityl-1,5-diaminopentane (*III*) and deblocking affords N^6-(5--aminopent-1-yl)adenosine (*IVb*).

N^1,N^2-Bis(purin-6-yl)ethylenediamine was reported to exhibit selective activity towards cancer cells[1]. In connection with our investigations on potential antimetabolites, we have now synthesised an analogous derivative of adenosine in which the two purine nuclei are separated by a five-membered aliphatic chain. Thus, 6-chloro--9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)purine[2] (*I*) as the starting substance was treated with 1,5-diaminopentane in dimethylformamide in the presence of triethylamine. As shown by thin-layer chromatography of the reaction mixture, a small amount of the starting substance *I* was accompanied by two new compounds (R_F values 0·39 and 0·89). By the action of methanolic ammonia, the protecting acetyl groups were removed and the compound *II* obtained directly in the crystalline form.



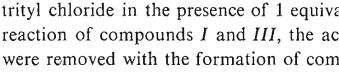
I



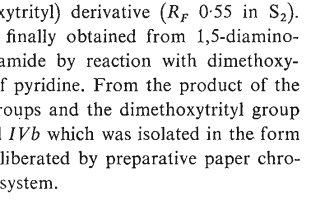
II

* Part CLXXXIX in the series Nucleic Acid Components and their Analogues; Part CLXXXVIII: This Journal *42*, 902 (1977).

The mother liquor contained additional *II* along with traces of adenosine and compound *IVb*. In the preparation of the pure compound *IVb*, the reaction of compound *I* with a monosubstituted diamine was used, namely, with N^1-dimethoxytrityl-1,5-diaminopentane (*III*). The attempted preparation of compound *III* by reaction of the diamine with dimethoxytrityl chloride in the presence of pyridine or triethylamine yielded as the main product the bis(dimethoxytrityl) derivative (R_F 0·55 in S_2). The mono(dimethoxytrityl) derivative *III* was finally obtained from 1,5-diaminopentane mono-trifluoracetate in dimethylformamide by reaction with dimethoxytrityl chloride in the presence of 1 equivalent of pyridine. From the product of the reaction of compounds *I* and *III*, the acetyl groups and the dimethoxytrityl group were removed with the formation of compound *IVb* which was isolated in the form of the crystalline hydrochloride; the base was liberated by preparative paper chromatography in an ammonia-containing solvent system.



III



IVa, $R^1 = -C(C_6H_5)(C_6H_4OCH_3)_2$
IVb, $R^1 = H$

Compounds *II* and *IVb* did not inhibit the growth of *Escherichia coli* in a synthetic medium.

EXPERIMENTAL

Unless stated otherwise, the chromatography was performed on ready-for-use Silufol UV_{254} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel sheets in the solvent systems S_1, chloroform–triethylamine (9 : 1); S_2, chloroform–methanol (9 : 1); S_3, chloroform–methanol (95 : 5); S_4, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2); and S_5, 1-butanol–water (85 : 15). Preparative runs were performed on loose 20 . 40 . 0·6 cm layers of the Pitra macroporous silica gel (produced by Service Laboratories of this Institute).

N^1,N^2-Bis(9-β-D-ribofuranosylpurin-6-yl)-1,5-diaminopentane (*II*)

1,5-Diaminopentane (5 mmol) and triethylamine (22 mmol) are added to an 1M solution (10 ml) of compound[1] *I* in dimethylformamide and the mixture is kept at room temperature for 3 days

to deposit triethylamine hydrochloride which is filtered off and washed with dimethylformamide. The filtrate and washings are combined, evaporated (40°C, 1 Torr), and the residue is dissolved in 6M methanolic ammonia (50 ml). The solution is set aside for one week to deposit crystals which are collected with suction, washed with methanol, and dried under diminished pressure. Yield, 950 mg (32%) of compound *II*, m.p. 222–225°C; R_F (paper) 0·15 in S_5 and 0·72 in S_4. UV spectrum (pH 1): λ_{max} 264 nm, λ_{min} 235 nm. Mol. extinction $34{\cdot}7 \cdot 10^3$ at 260 nm and $36{\cdot}4 \cdot 10^3$ at 264 nm. For $C_{25}H_{36}N_{10}O_8$ (604·3) calculated: 49·65% C, 5·99% H, 23·35% N; found: 49·29% C, 5·72% H, 22·97% N.

N^1-Dimethoxytrityl-1,5-diaminopentane (*III*)

Trifluoroacetic acid (10 mmol) and pyridine (10 mmol) are added to a solution of 1,5-diaminopentane (10 mmol) in dimethylformamide (10 ml). The flask is placed into an ethanol-Dry Ice bath, the solution stirred for several minutes, and treated with dimethoxytrityl chloride (10 mmol). When this reagent dissolves, the mixture is kept in the freezing bath for 1 h and at room temperature for 20 h, and finally evaporated. The residue is dissolved in chloroform (50 ml), the solution washed with 2·5M aqueous sodium hydroxide (100 ml) and twice with water, dried over anhydrous magnesium sulfate, and concentrated (40°C, 15 Torr) to the volume of about 10 ml. The concentrate is diluted with triethylamine (5 ml) and chromatographed on two layers of loose silica gel in the solvent system S_1. The dimethoxytrityl-positive bands (R_F value of about 0·30) are eluted with chloroform–methanol–triethylamine (50 : 45 : 5) and the eluate is evaporated (40°C, 15 Torr.) The residue is coevaporated with two portions of chloroform and finally maintained at 40°C/0·1 Torr to remove traces of solvents. Yield, 2·12 g (50%) of compound *III* in the form of a solid foam; R_F 0·26 in S_2. For $C_{26}H_{32}N_2O_2$ (404·5) calculated: 6·93% N; found: 6·75% N.

N^6-(5-Dimethoxytritylaminopent-1-yl)adenosine (*IVa*)

A solution of compound *III* (6 mmol) and 6-chloro-9-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranosyl)-purine[2] (6 mmol) in dimethylformamide (6 ml) is treated with triethylamine (2 ml) and kept at room temperature for 3 days. The precipitate of triethylamine hydrochloride is filtered off and washed with dimethylformamide (3 ml). The filtrate and washings are combined and evaporated (30°C, 1 Torr). The residue is dissolved in 6M methanolic ammonia, the solution kept at room temperature for 2 days, and then water (30 ml) and chloroform (50 ml) are added. The whole is briefly shaken, the chloroform layer separated, dried over anhydrous magnesium sulfate, evaporated (40°C, 15 Torr), and the residue dried (40°C, 0·1 Torr). Yield, 2·96 g (76%) of compound *IVa* in the form of a solid foam; R_F 0·55 in S_3. For $C_{36}H_{42}N_6O_6$ (654·7) calculated: 12·87% N; found: 12·45% N.

N^6-(5-Aminopent-1-yl)adenosine (*IVb*)

A solution of compound *IVa* (2·5 g) in 80% aqueous acetic acid (50 ml) is kept at room temperature 2 h, diluted with water (50 ml), extracted twice with ether, and the aqueous layer evaporated (40°C, 15 Torr). The residue is dissolved in methanol and conc. hydrochloric acid (0·6 ml) is added. The mixture is evaporated (20°C, 1 Torr), the residue triturated with 1 : 2 ethanol–acetone mixture (30 ml) and cooled down to 0°C. The crystalline material is collected with suction, washed with ethanol, and dried over phosphorus pentoxide. Yield, 1·2 g (83%) of the dihydrochloride of compound *IVb*, m.p. 176–177°C. For $C_{15}H_{24}N_6O_2.2\,HCl$ (425·3) calculated: 42·35% C, 6·12% H, 19·78% N, 16·70% Cl; found: 41·97% C, 6·06% H, 19·48% N, 16·25% Cl.

UV spectrum (pH 2): λ_{max} 265 nm, λ_{min} 232 nm. Mol. extinction 21·8 . 10^3 at 260 nm and 23·4 . . 10^3 at 265 nm. R_F value 0·27 (Silufol) and 0·50 (paper) in S_4.

Base. The dihydrochloride of compound *IVb* (200 mg) is chromatographed on 1 sheet of paper Whatman No 3 MM in S_4. The UV-absorbing band (R_F of about 0·5) is eluted with a 5 : 4 : 1 ethanol–water–conc. aqueous ammonia mixture, the eluate evaporated, and dried (40°C, 0·1 Torr). Yield, 158 mg of the crystalline compound *IVb*, m.p. 123—125°C. For $C_{15}H_{24}N_6O_4$ (352·4) calculated: 23·86% N; found: 22·58% N.

The author wishes to thank Professor J. Škoda of this Institute for inhibition assays and the staff of the Analytical Department (Dr J. Horáček, Head) of this Institute for elemental analyses.

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Translated by J. Pliml.