SYNTHESIS OF 5-PHENYLCYTOSINE NUCLEOSIDE DERIVATIVES

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Reaction of silylated 5-phenylcytosine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose, catalyzed with tin tetrachloride, and subsequent methanolysis afforded 5-phenylcytidine (**2**). This compound reacted with thionyl chloride in acetonitrile to give cyclic sulfite **3** which on heating in dimethylformamide was converted into 2,2′-anhydro-1-(β-D-arabinofuranosyl)-5-phenylcytosine (**4**). Analogous reaction of compound **2** with thionyl chloride at reflux gave 5′-chloro-5′-deoxy-2′,3′-cyclic sulfite **5**. Its heating in dimethylformamide afforded 5′-chloro-2,2′-anhydro derivative **6**, mild alkaline hydrolysis led to 5′-chloro-5′-deoxy-5-phenylcytidine (**7**). Alkaline hydrolysis of 5-phenyl-2,2′-anhydrocytidine (**4**) gave 5-phenylcytosine arabinoside **8**, whereas the 2,2′-anhydro derivative **6** afforded 1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)-5-phenylcytosine (**11**). At higher temperature, the final reaction product was 2,5′-anhydro-5-phenylcytidine (**12**). 5′-Chloro-5′-deoxynucleosides **7** and **11** reacted with tri-n-butylstannane to give 5′-deoxyribofuranosyl and 5′-deoxyarabinofuranosyl derivatives **15** and **16**. 5-Phenylcytidine (**2**) was converted into the N^4-acetate **17** with acetic anhydride. Further reaction with acetic anhydride and hydrogen bromide in acetic acid afforded a mixture of peracetylated 2′-bromo and 3′-bromo derivatives **18** and **19**. Reaction with Zn/Cu couple gave 5′-*O*-acetyl-5-phenyl-2′,3′-didehydro derivative **20** and 2′,3′,5′-tri-*O*-acetyl-5-phenylcytidine (**21**). Compound **20** was deblocked to 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-phenylcytosine (**22**). Catalytic hydrogenation of compound **20** over palladium and subsequent deblocking of the protected 2′,3′-dideoxy derivative **23** gave 1-(2, 3-dideoxy-β-D-*glycero*-pentofuranosyl)-5-phenylcytosine (**24**).

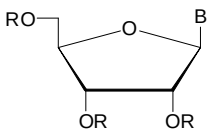
Key words: 5-Phenylcytosine; Nucleosides; Pyrimidine; 2′,3′-Dideoxynucleoside.

5-Substituted pyrimidine nucleosides with a natural or modified sugar component represent an important group of compounds with a wide spectrum of biological activities (for a review see refs[1,2]). Particular attention received the antiviral 5-halogeno-2′-deoxyuridines and 2′-deoxycytidines and analogous 5-alkyl derivatives (2″-bromovinyl, ethyl, trifluoromethyl, methoxymethyl, etc.). Some compounds of this group are also effective cytostatics (5-fluoro-, 5-alkynyl- and 5-perfluoroalkyl-2′-deoxyuridines, 2-deoxy-2-fluoroarabinosyl uracils and 2-deoxy-2-fluoroarabinosyl cytosines substituted in position 5 with iodine or an alkyl group).

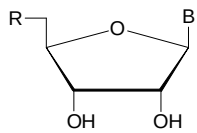
In spite of hundreds of publications of synthetic as well as purely biochemical character, devoted to 5-halogeno and 5-alkyl substituted derivatives, 5-aryl derivatives received relatively little attention. Only several nucleosides with phenyl or substituted phenyl

group have been synthesized: ribosides, 2′-deoxyribosides and 2′-deoxy-2′-fluoro-arabinosides[3,4]. In the series of 5-phenylcytosine nucleosides only 5-phenylcytidine[5], α- and β-anomer of 2′-deoxy-5-phenylcytidine[6–8] and 1-(2-deoxy-2-fluoroarabinosyl)-5-phenylcytosine[9] have been prepared. Also a large number of N^1-alkyl derivatives of 5-phenylcytosine have been described as cytidine deaminase inhibitors[10–13] and according to recent studies, various 5-heteroaryl-2′-deoxycytidines and 5-heteroaryl-2′-deoxyuridines appeared to be effective antivirals, particularly against herpesviruses[8,14–16].

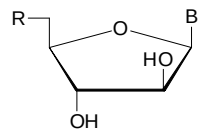
Since cytosine nucleosides are very effective and clinically employed cytostatics, we decided to extend our investigation of 5-aryl- and 5-benzylpyrimidine nucleoside analogs[17–19] to a series of 5-phenylcytosine nucleosides modified in the sugar part of the molecule and to study their cytostatic activity. In addition, we also focused our attention on the investigation of their potential inhibitory effects against uridine phosphorylase, an enzyme catalyzing the phosphorolysis of uracil nucleosides to uracil and



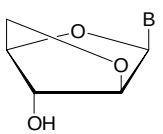
	R
1	Bz
2	H



	R
7	Cl
15	H



	R
8	OH
11	Cl
16	H



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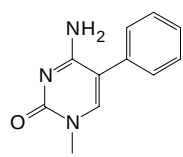
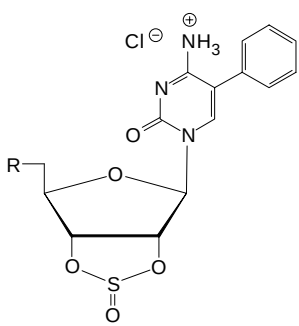
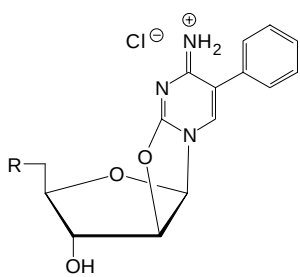
B =





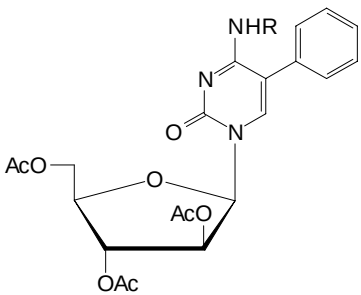
	R
3	OH
5	Cl



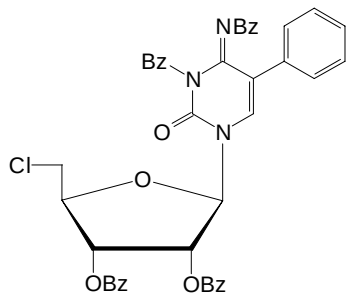
	R
4	OH
6	Cl

the sugar-1-phosphate and also cleaves many biologically active nucleoside analogs in the organism, reducing thus the in vivo activity of these compounds. Nucleoside inhibitors of uridine phosphorylase comprise analogs with hydrophobic groups, some 2,2′-anhydronucleosides and 2′-deoxyglucopyranosyl nucleosides. An extensive research has been devoted mainly to acyclic analogs derived from 5-benzyluridine (see ref.[20] and references therein).

Our synthesis of 5-phenylcytidine analogs, described in this paper, started from 5-phenylcytosine which can be easily prepared[21] from benzyl cyanide. Reaction of silylated 5-phenylcytosine with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose, catalyzed by tin tetrachloride, afforded nucleoside **1** which was debenzoylated with methanolic ammonia to give free 5-phenylcytidine (**2**). This on reaction with thionyl chloride in acetonitrile at room temperature afforded the 2′,3′-cyclic sulfite **3** which was converted into 2,2′-anhydro-5-phenylcytosine (**4**) by heating in dimethylformamide. When the reaction of 5-phenylcytidine with thionyl chloride was performed at reflux, the reaction product was the 2′,3′-cyclic sulfite **5**, bearing chlorine atom in the position 5′. Compound **5** was converted either into 5′-chloro-2,2′-anhydro derivative **6** by heating in dimethylformamide or into 5′-chloro-5′-deoxy-5-phenylcytidine (**7**) by reaction with Dowex 1 (CO_3^{2-} form).



	R
9	Ac
10	H



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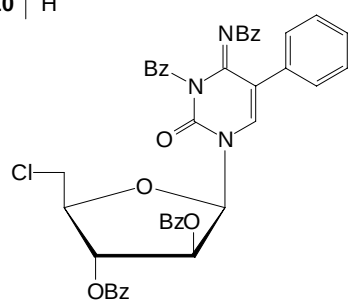
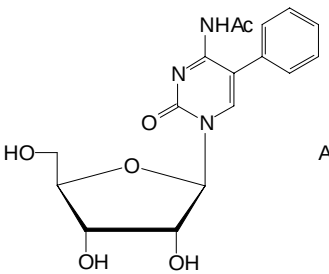


14

A similar reaction scheme has been described already earlier[22,23] for the preparation of some unsubstituted cytosine derivatives. The anhydro ring in 5-phenyl-2,2′-anhydrocytidine (**6**) was opened by treatment with Dowex 1 in the carbonate form. The resulting 5-phenylcytosine arabinoside (**8**) was acetylated with acetic anhydride in pyridine to afford a mixture of tetraacetyl **9** and triacetyl **10** derivatives.

1-(5-Chloro-5-deoxy-β-D-arabinofuranosyl)-5-phenylcytosine (**11**) was prepared similarly as the arabinosyl derivative **8** by alkaline hydrolysis of the corresponding 2,2′-anhydro derivative. The anhydro ring in 5′-chloro-5-phenyl-2,2′-anhydrocytidine (**6**) was opened by treatment with potassium carbonate solution at room temperature; the reaction with Dowex 1 in the carbonate form was less advantageous because the formed 5′-chloroarabinosyl derivative **11** was sparingly soluble and its isolation was difficult. At higher temperature (about 70 °C) the reaction with Dowex gave the well soluble 2′,5′-anhydro derivative **12** arising by subsequent cyclization of the compound **11**.

To prepare 5′-deoxyribofuranosyl and 5′-deoxyarabinofuranosyl derivatives **15** and **16**, we first benzoylated the starting 5′-chloro-5′-deoxynucleosides **7** and **11**. However, in



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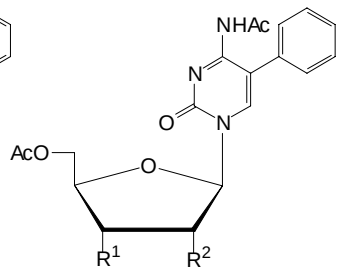
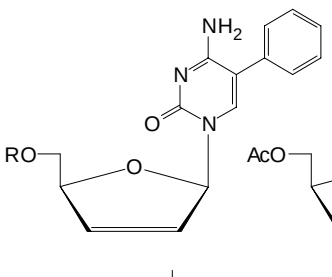
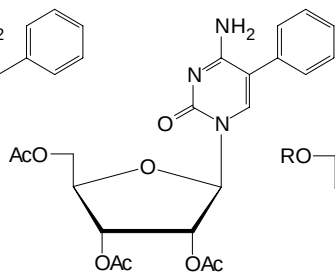


	R^1	R^2
18	Br	OAc
19	OAc	Br



	R
20	Ac
22	H



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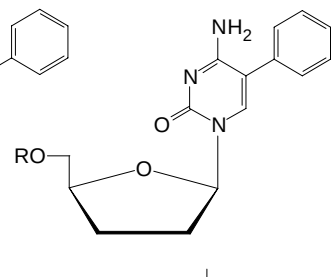

	R
23	Ac
24	H

both cases the usual benzoylation with benzoyl chloride in pyridine afforded the tetrabenzoyl derivatives **13** and **14**, i.e. compounds in which the base bears two benzoyl groups (see ref.[24]) which in the subsequent reaction with tributylstannane undergo total degradation. For this reason, we performed the reduction with tributylstannane with the free 5′-chloro derivatives **7** and **11**.

As the starting compound for the preparation of 2′,3′-dideoxy and 2′,3′-didehydro derivatives we used 5-phenylcytidine (**2**) which was first converted into the N^4-acetate **17** by reaction with acetic anhydride in boiling methanol. Treatment of the N^4-acetate with acetic anhydride and hydrogen bromide in acetic acid gave a mixture of peracetylated 2′- and 3′-bromo derivatives **18** and **19**. This mixture was subjected to elimination reaction with the Zn/Cu couple, leading to 2′,3′-didehydro derivatives[25]. We obtained the desired 5′-*O*-acetyl-5-phenyl-2′-3′-didehydro derivative **20**, together with 2′,3′,5′-tri-*O*-acetyl-5-phenylcytidine (**21**). On reaction with ammonia, the protected didehydro derivative **20** afforded 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-phenylcytosine (**22**). Compound **20** was converted into the protected 2′,3′-dideoxy derivative **23** by catalytic hydrogenation over palladium. Compound **23** reacted with methanolic ammonia to give 1-(2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-5-phenylcytosine (**24**).

The cytostatic activity of all the new 5-phenylcytosine nucleosides was studied on cell cultures L1210, HeLa and L929. Neither of the compounds exhibited any significant cytostatic effect. Also negative were the uridine phosphorylase inhibition assays (ref.[26]).

EXPERIMENTAL

Unless stated otherwise, the solutions were evaporated at 40 °C/2 kPa and the compounds were dried over phosphorus pentoxide at 13 Pa. Thin-layer chromatography was performed on Silufol UV 254 foils (Kavalier, Czech Republic) in the systems S1, ethyl acetate; S2, ethyl acetate–2-propanol 5 : 1; S3, toluene–acetone 10 : 1; S4, ethyl acetate–acetone–ethanol–water 18 : 3 : 1 : 1; S5, ethyl acetate–acetone–ethanol–water 18 : 3 : 2 : 2. Spots were detected by UV light at 254 nm. Preparative column chromatography was carried out on silica gel (30–60 μm, Service Laboratory of the Institute). ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian UNITY 200 spectrometer (200.01 MHz) in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Mass spectra were obtained with a ZAB-EQ spectrometer (VG Analytical) using the FAB method (Xe, 8 kV, glycerol as matrix).

5-Phenylcytidine (**2**)

A mixture of 5-phenylcytosine (15 g, 80.05 mmol), hexamethyldisilazane (120 ml) and a catalytic amount of ammonium sulfate was heated at 150 °C to homogeneity and then for further 1 h. The solution was taken down, the residue was codistilled with toluene (2 × 100 ml) and dried in vacuo for 1 h at 50 °C. The obtained silylated base was added to a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose (40.35 g, 80 mmol) in 1, 2-dichloroethane (400 ml), tin tetrachloride (52 ml, 44.4 mmol) was added and the reaction mixture was stirred at room temperature for 20 h. The solution was poured into saturated solution of sodium hydrogen carbonate (2 l) and the formed suspension was filtered through Celite. The organic layer was separated and the aqueous one extracted with chloro-

form (2 × 1 l). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (1 l), dried over magnesium sulfate and the solvent was evaporated. The residue (benzoyl derivative **1**, 56 g) was stirred with methanolic ammonia (500 ml) at room temperature for 5 days. The solution was taken down, the residue was partitioned between water (2 l) and ethyl acetate (1.5 l) and the aqueous layer was concentrated to about 400 ml. Crystallization in a refrigerator afforded the product which was collected and washed successively with ice-cold water, methanol and ether. Yield 19.7 g (77%) of compound **2**. Its physical constants corresponded to the published[5] values.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)-5-phenylcytosine Hydrochloride (**4**)

Thionyl chloride (0.8 ml, 11 mmol) was added to a suspension of compound **2** (2 g, 6.26 mmol) in dry acetonitrile. The mixture was stirred to dissolution and then for an additional hour at room temperature. Ether (100 ml) was added, the precipitate was filtered, washed with ether and dried. The obtained sulfite **3** was dissolved in dimethylformamide (60 ml) and heated for 1 h at 100 °C. The solvent was evaporated, the residue codistilled with toluene (2 × 50 ml) and ethanol (50 ml) and crystallized from aqueous ethanol. Yield 1.1 g (52%) of white crystals, m.p. 158–168 °C. ^{1}H NMR spectrum: 3.40 m, 2 H (H-5′); 4.25 m, 1 H (H-4′); 4.51 m, 1 H (H-3′); 5.13 t, 1 H, *J*(OH,5′) = 4.7 (5′-OH); 5.45 d, 1 H, *J*(2′,1′) = 6.0 (H-2′); 6.19 d, 1 H, *J*(OH,3′) = 4.4 (3′-OH); 6.56 d, 1 H, *J*(1′,2′) = 6.0 (H-1′); 7.39–7.57 m, 5 H (H arom.); 8.40 s, 1 H (H-6); 8.40–9.50 br, 1 H (NH). According to elemental analysis, the product contained a variable amount of HCl.

2,2′-Anhydro-1-(5-chloro-5-deoxy-β-D-arabinofuranosyl)-5-phenylcytosine Hydrochloride (**6**)

A mixture of compound **2** (5 g, 15.7 mmol), acetonitrile (60 ml) and thionyl chloride (2.5 ml) was refluxed for 1.5 h. After cooling to room temperature, the solution was concentrated to a half and added dropwise with stirring into ether (500 ml). The suspension was set aside in a refrigerator for 1 h, the product was collected, washed with ether and dried in vacuo. Yield 6.44 g (94%) of amorphous derivative **5**. A solution of this compound (3.86 g, 8.8 mmol) in dimethylformamide (80 ml) was heated at 110 °C for 1.5 h. After evaporation of the solvent, the residue was codistilled with xylene (100 ml) and ethanol, dissolved in methanol, briefly boiled with charcoal, filtered and the solvent was evaporated. The residue was dissolved in a small amount of ethanol and the solution was added dropwise under stirring into ether (200 ml). The precipitated product was filtered and dried in vacuo over potassium hydroxide. Yield 3.1 g (99%) of amorphous product which according to elemental analysis contained a variable amount of HCl.

5′-Chloro-5′-deoxy-5-phenylcytidine (**7**)

Dowex 1 (CO_3^{2-} form, 40 ml) was added to a solution of sulfite **5** (2.58 g, 5.91 mmol) in methanol (100 ml). After stirring at room temperature for 1.5 h, the mixture containing the precipitated product was diluted with aqueous ethanol (500 ml), filtered and the ion exchanger on the filter was washed with hot ethanol. The combined filtrates were taken down and the residue was crystallized from water to give 1.45 g (73%) of white crystalline compound, m.p. 213.5–215.5 °C. For $C_{15}H_{16}ClN_3O_4$ (337.8) calculated: 53.34% C, 4.77% H, 10.50% Cl, 12.44% N; found: 53.07% C, 4.77% H, 10.55% Cl, 12.52% N. ^{1}H NMR spectrum: 3.79 dd, 1 H, *J*(5′a,4′) = 4.6, *J*(gem) = 11.3 (H-5′a); 3.88–4.05 m, 3 H (H-3′, H-4′ and H-5′b); 4.18 dd, 1 H, *J*(2′,3′) = 10.4 (H-2′); 5.26 d, 1 H, *J* = 5.2 (OH); 5.42 d, 1 H, *J* = 5.8 (OH); 5.87 d, 1 H, *J*(1′,2′) = 5.2 (H-1′); 6.43 br, 1 H (NH); 7.29–7.56 m, 6 H (H arom. and NH); 7.61 s, 1 H (H-6).

1-(β-D-Arabinofuranosyl)-5-phenylcytosine (**8**)

A solution of anhydro derivative **4** (300 mg, 0.89 mmol) in water (10 ml) was stirred with Dowex 1 (CO_3^{2-} form; 10 ml) at room temperature for 1 h. The ion exchanger was filtered off, washed with water and the filtrate was concentrated. The residue was crystallized from ethanol to give hygroscopic product (210 mg, 72%), m.p. 203.5–205.5 °C. For $C_{15}H_{17}N_3O_5$. 0.5 H_2O (328.3) calculated: 54.87% C, 5.53% H, 12.80% N; found: 54.48% C, 5.63% H, 12.41% N. ^{1}H NMR spectrum: 3.55 m, 2 H (H-5′); 3.73 dd, 1 H (H-4′); 3.91 m, 1 H (H-3′); 4.00 m, 1 H (H-2′); 5.03 t, 1 H, *J*(OH,5′a) = 5.5, *J*(OH,5′b) = 5.2 (5′-OH); 5.43 d, 1 H, *J* = 4.3 (OH); 5.50 d, 1 H, *J* = 5.5 (OH); 6.12 d, 1 H, *J*(1′,2′) = 4.0 (H-1′); 6.32 br, 1 H (NH); 7.26–7.52 m, 6 H (H arom. and NH); 7.59 s, 1 H (H-6).

Acetylation of Derivative **8**

Compound **8** (100 mg, 0.30 mmol) was codistilled with dry pyridine (2 ml). The residue was dissolved in pyridine (1 ml), acetic anhydride (0.13 ml, 1.4 mmol) was added and the solution was stirred for 5 h at room temperature. The excess acetic anhydride was decomposed with methanol (1 ml), the solution was stirred for 15 min and the solvent was evaporated. Chromatography on silica gel (20 ml) in ethyl acetate afforded first N^4-acetyl-1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-phenylcytosine (**9**) (60 mg, 41%), R_F 0.35, as white foam. For $C_{23}H_{25}N_3O_9$ (487.5) calculated: 56.67% C, 5.17% H, 8.62% N; found: 56.12% C, 5.27% H, 8.35% N. ^{1}H NMR spectrum: 1.90 s, 6 H (2 × acetyl); 2.11 s, 6 H (2 × acetyl); 4.34 m, 3 H (H-5′ and H-4′); 5.24 t, 1 H, *J*(3′,4′) = 3.1 (H-3′); 5.49 dd, 1 H, *J*(2′,3′) = 2.8 (H-2′); 6.33 d, 1 H, *J*(1′,2′) = 4.9 (H-1′); 7.29–7.51 m, 5 H (H arom.); 7.81 s, 1 H (H-6); 9.58 s, 1 H (NH).

Further elution with ethyl acetate–2-propanol (5 : 1) gave 5-phenyl-1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)cytosine (**10**) (45 mg, 34%) as colorless sirup (R_F 0.32). ^{1}H NMR spectrum: 1.87 s, 3 H (acetyl); 1.93 s, 3 H (acetyl); 2.10 s, 3 H (acetyl); 4.19–4.23 m, 1 H (H-4′); 4.23–4.38 m, 2 H (H-5′); 5.18 m, 1 H (H-3′); 5.38 dd, 1 H, *J*(2′,3′) = 3.0 (H-2′); 6.30 d, 1 H, *J*(1′,2′) = 4.8 (H-1′); 6.47 br, 1 H (NH); 7.27–7.53 m, 6 H (H-6 and H arom.); 7.56 br, 1 H (NH).

1-(5-Chloro-5-deoxy-β-D-arabinofuranosyl)-5-phenylcytosine (**11**)

To a stirred solution of anhydro derivative **6** (850 mg, 2.39 mmol) in water (5 ml) was added 10% aqueous solution of potassium carbonate (10 ml). The reaction mixture was stirred at room temperature for 30 min, the deposited product was collected on filter, washed with water to neutral reaction of the filtrate and dried over phosphorus pentoxide. Yield 574 mg (71%) of white crystalline compound, m.p. 237–238 °C. For $C_{15}H_{16}ClN_3O_4$ (337.8) calculated: 53.34% C, 4.77% H, 10.50% Cl 12.44% N; found: 53.33% C, 4.88% H, 10.54% Cl, 12.45% N. ^{1}H NMR spectrum: 3.82 m, 2 H (H-5′); 3.94 m, 2 H (H-3′ and H-4′); 4.05 m, 1 H (H-2′); 5.68 d, 1 H, *J* = 3.8 (OH); 5.74 d, 1 H, *J* = 4.8 (OH); 6.18 d, 1 H, *J*(1′,2′) = 3.6 (H-1′); 6.40 br, 1 H (NH); 7.25–7.53 m, 7 H (H arom., NH and H-6).

2′,5′-Anhydro-1-(β-D-arabinofuranosyl)-5-phenylcytosine (**12**)

Dowex 1 (CO_3^{2-} form, 35 ml) was added to solution of anhydro derivative **6** (1 g, 2.8 mmol) in water (60 ml) and the mixture was stirred for 6 h at 70 °C. The reaction was followed by monitoring the disappearence of the 5′-chloro derivative **11** (TLC in S5; R_F: **11**, 0.47; **12**, 0.38). The reaction mixture was cooled and, together with the Dowex, set aside in a refrigerator overnight. The ion exchanger was filtered off and washed with hot ethanol and hot water. The filtrate was evaporated and the residue was crystallized from methanol–ethanol (1 : 1). The obtained crystalline product was dried in vacuo for 4 h at 70 °C. Yield 410 mg (45%), m.p. 261–263.5 °C. The product contained (NMR) crystal ethanol. For $C_{15}H_{15}N_3O_4$. 0.66 C_2H_5OH (332.0) calculated: 59.09% C, 5.57% H,

12.66% N; found: 58.40% C, 5.70% H, 12.67% N. ^{1}H NMR spectrum: 3.82 brd and 3.93 brd, 2 H, *J*(gem) = 9.0 (H-5′); 4.24 dd, 1 H, *J* = 0.8 and 2.4 (H-4′); 4.44 m, 2 H (H-2′ and H-3′); 5.97 d, 1 H, *J*(1′,2′) = 3.4 (H-1′); 6.11 s, 1 H (OH); 6.37 br, 1 H (NH); 7.27–7.52 m, 6 H (H arom. and NH); 7.63 s, 1 H (H-6).

N^3,N^4-Dibenzoyl-1-(2,3-di-*O*-benzoyl-5-chloro-5-deoxy-β-D-ribofuranosyl)-5-phenylcytosine (**13**)

Benzoyl chloride (1.4 ml, 12 mmol) was added at 0 °C to a solution of compound **7** (1 g, 2.96 mmol) in pyridine (40 ml). The mixture was stirred at 0 °C for 1 h and at room temperature for 24 h. The excess benzoyl chloride was decomposed with water (50 ml), the solution was stirred for 10 min and then the solvent was evaporated. The residue was partitioned between chloroform (200 ml) and 1% HCl (100 ml), the organic layer was washed with saturated solution of sodium hydrogen carbonate (3 × 100 ml) and dried over magnesium sulfate. Evaporation of the solvent and chromatography on silica gel (560 ml) in system S3 (R_F 0.29) afforded 1.65 g (74%) of compound **13** as white foam. For $C_{43}H_{32}ClN_3O_8$ (754.2) calculated: 68.48% C, 4.27% H, 4.70% Cl, 5.57% N; found: 67.94% C, 4.52% H, 5.27% Cl, 5.53% N. ^{1}H NMR spectrum: 4.04 dd, 1 H, *J*(5′a,4′) = 6.4 (H-5′a); 4.16 dd, 1 H, *J*(5′b, 4′) = 4.4, *J*(gem) = 11.7 (H-5′b); 4.37 m, 1 H (H-4′); 5.84 dd, 1 H, *J*(3′,4′) = 5.9, *J*(3′,2′) = 6.4 (H-3′); 6.05 dd, 1 H (H-2′); 6.33 d, 1 H, *J*(1′,2′) = 3.9 (H-1′); 7.05–7.70 m, 21 H (H arom.); 7.83–7.95 m, 4 H (H arom.); 8.50 s, 1 H (H-6).

N^3,N^4-Dibenzoyl-1-(2,3-di-*O*-benzoyl-5-chloro-5-deoxy-β-D-arabinofuranosyl)-5-phenylcytosine (**14**)

The title compound was prepared from arabinosyl derivative **11** (1.5 g, 4.44 mmol) analogously as described for compound **13**. Yield 2 g (60%) of white foam. TLC (S3, R_F 0.23). For $C_{43}H_{32}ClN_3O_8$ (754.2): calculated: 68.48% C, 4.27% H, 4.70% Cl, 5.57% N; found: 68.68% C, 4.55% H, 4.87% Cl, 5.63% N. ^{1}H NMR spectrum: 4.17 m, 2 H (H-5′); 4.67 m, 1 H (H-4′); 5.69 dd, 1 H, *J*(3′,4′) = 5.8 (H-3′); 5.97 dd, *J*(2′,3′) = 3.1 (H-2′); 6.62 d, 1 H, *J*(1′, 2′) = 5.2 (H-1′); 7.12–7.39 m, 10 H, 7.45–7.64 m, 10 H, 7.67–7.86 m, 3 H and 8.01–8.12 m, 2 H (H arom.); 8.39 s, 1 H (H-6).

5′-Deoxy-5-phenylcytidine (**15**)

To a stirred solution of 5′-chloro derivative **7** (700 mg, 2.07 mmol) in dioxane–dimethyl sulfoxide (1 : 1, 30 ml) was added at 130 °C 1 M solution of tributylstannane in toluene (8 ml), followed by azobis(isobutyronitrile) (350 mg). The solution was stirred for 1 h at 130 °C, cooled and the solvent was evaporated at 60 °C. The residue was codistilled with dimethylformamide (4 × 30 ml) and xylene (20 ml) and then chromatographed on silica gel (150 ml) in system S4 (R_F: **13**, 0.28; **7**, 0.36). Yield 353 mg (56%), m.p. 223–224 °C (ethanol). For $C_{15}H_{17}N_3O_4$ (303.3) calculated: 59.40% C, 5.65% H, 13.85% N; found: 58.99% C, 5.54% H, 13.77% N. ^{1}H NMR spectrum: 1.24 d, 3 H, *J*(5′,4′) = 6.4 (H-5′); 3.67 m, 1 H, *J*(3′,4′) = 6.1 (H-3′); 3.84 m, 1 H (H-4′); 4.10 m, 1 H, *J*(2′,3′) = 5.5 (H-2′); 4.97 d, 1 H, *J*(OH,3′) = 5.8 (3′-OH); 5.28 d, 1 H, *J*(OH,2′) = 5.2 (2′-OH); 5.74 d, 1 H, *J*(1′,2′) = 4.0 (H-1′); 6.38 br, 1 H (NH); 7.24–7.64 m, 7 H (H arom., NH and H-6).

1-(5-Deoxy-β-D-arabinofuranosyl)-5-phenylcytosine (**16**)

Compound **16** was prepared from compound **11** (574 mg, 1.7 mmol) analogously as described for compound **15**. Yield 295 mg (57%) of white crystalline compound, m.p. 242–244.5 °C (ethanol). TLC: R_F 0.24 (S4). For $C_{15}H_{17}N_3O_4$ (303.3) calculated: 59.40% C, 5.65% H, 13.85% N; found: 58.85% C, 5.61% H, 13.69% N. ^{1}H NMR spectrum: 1.26 d, 3 H, *J*(5′,4′) = 6.6 (H-5′); 3.68 m, 1 H, *J*(3′,4′) = 2.9 (H-3′); 3.82 m, 1 H (H-4′); 3.97 m, 1 H, *J*(2′,3′) = 2.1 (H-2′); 5.41 d, 1 H, *J*(OH,3′) = 4.0

(3′-OH); 5.49 d, 1 H, *J*(OH,2′) = 4.9 (2′-OH); 6.08 d, 1 H, *J*(1′,2′) = 3.8 (H-1′); 6.35 br, 1 H (NH); 7.25–7.54 m, 7 H (H arom., H-6 and NH).

N^4-Acetyl-5-phenylcytidine (**17**)

Acetic anhydride (3 ml) was added to a solution of compound **2** (700 mg, 2.19 mmol) in methanol (40 ml) and the reaction mixture was rapidly heated to the boil. After about 2 min of boiling, the mixture was allowed to cool down slowly. After evaporation of the solvent, the residue was codistilled with toluene (2 × 30 ml) and ethanol (30 ml). Crystallization from ethanol afforded 500 mg (63%) of the product, m.p. 151–153 °C. Further portion (160 mg, 20%) was obtained from the mother liquors after evaporation and chromatography on silica gel in system S5 (R_F 0.47). For $C_{17}H_{19}N_3O_6$ (361.4) calculated: 56.51% C, 5.30% H, 11.63% N; found: 56.30% C, 5.23% H, 11.34% N. ^{1}H NMR spectrum: 2.08 s, 3 H (acetyl); 3.51–3.65 m, 1 H (H-5′a); 3.67–3.81 m, 1 H (H-5′b); 3.93 m, 1 H (H-4′); 4.03 m, 2 H (H-2′ and H-3′); 5.04 d, 1 H, *J* = 5.5 (OH); 5.22 t, 1 H, *J*(OH,5′) = 4.6 (5′-OH); 5.57 d, 1 H, *J* = 4.6 (OH); 5.82 d, 1 H, *J*(1′,2′) = 2.4 (H-1′); 7.26–7.45 m, 5 H (H arom.); 8.56 s, 1 H (H-6); 9.66 s, 1 H (NH).

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-eno)-5-phenylcytosine (**20**) and 2′,3′,5′-tri-*O*-acetyl-5-phenylcytidine (**21**)

A mixture of *N*-acetyl derivative **17** (2.48 g, 6.86 mmol), acetic anhydride (2 ml) and 30% hydrogen bromide in acetic acid (20 ml) was heated under argon for 7 h at 50 °C and then allowed to stand overnight at room temperature. The mixture was diluted with dichloromethane (80 ml), washed with Sörensen phosphate buffer, pH 7, (100 ml portions) until the aqueous layer was neutral and then three times more. The organic extract was dried over magnesium sulfate and the solvent was evaporated to give a foam (2.75 g) of bromoacetyl derivatives **18** and **19**.

A mixture of acetic acid (23 ml) and copper(II) acetate monohydrate (0.32 g) was heated at 110 °C, zinc dust (1.89) was added and the mixture was heated at 110 °C for 1 min. The solid was filtered and washed successively with acetic acid, methanol and dimethylformamide. The thus-prepared Zn/Cu couple was transferred into the reaction flask and mixed with a solution of the above-described mixture of bromoacetyl derivatives **18** and **19** in dimethylformamide (15 ml). The reaction mixture was stirred at room temperature for 1 h, the solid was filtered off (Celite) and the filtrate was evaporated. The residue was dissolved in dichloromethane (100 ml) and the solution was washed with 5% solution of sodium ethylenediaminetetraacetate (Komplexon III, 100 ml). The aqueous phase was extracted with dichloromethane (2 × 50 ml), the combined extracts were dried over magnesium sulfate and the solvent was evaporated. Chromatography of the residue on silica gel (500 ml) in system S5 afforded compound **21** (R_F 0.58; 500 mg, 16%), m.p. 206.5–207.5 °C (2-propanol). For $C_{21}H_{23}N_3O_8$ (445.4) calculated: 56.63% C, 5.20% H, 9.43% N; found: 56.28% C, 5.17% H, 9.19% N. ^{1}H NMR spectrum: 1.90 s, 3 H (acetyl); 2.07 s, 6 H (2 × acetyl); 4.10–4.41 m, 3 H (H- 5′and H-4′); 5.38 m, 1 H (H-3′); 5.53 dd, 1 H, *J*(2′,3′) = 6.4 (H-2′); 5.91 d, 1 H, *J*(1′,2′) = 4.3 (H-1′); 6.54 br s, 1 H (NH); 7.27–7.53 m, 5 H (H arom.); 7.64 s, 2 H (NH and H-6).

Further elution gave didehydro derivative **20** (R_F 0.43; 700 mg, 31%) as a white foam which was crystallized from 2-propanol, m.p. 150.5–151.5 °C. ^{1}H NMR spectrum: 1.41 s, 3 H (acetyl); 4.08 dd, 1 H, *J*(5′a,4′) = 2.4 (H-5′a); 4.23 dd, 1 H, *J*(5′b,4′) = 3.4, *J*(gem) = 12.5 (H-5′b); 4.99 m, 1 H (H-4′); 6.06 dt, 1 H (H-3′); 6.33 dt, 1 H, *J*(2′,3′) = 6.1 (H-2′); 6.44 br, 1 H (NH); 6.95 m, 1 H, *J*(1′,2′) = 1.7, *J*(1′,3′) = 1.5, *J*(1′,4′) = 3.2 (H-1′); 7.22–7.49 m, 6H (H arom. and H-6); 7.53 br, 1 H (NH).

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-5-phenylcytosine (**22**)

A solution of acetyl derivative **20** (640 mg, 1.96 mmol) in ethanol–25% aqueous ammonia (1 : 1, 30 ml) was stirred at room temperature for 3.5 h and then the solvent was evaporated. The residue was codistilled with ethanol and crystallized from ethanol. Yield 300 mg (54%) of compound **22**, not melting up to 300 °C. For $C_{15}H_{15}N_3O_3$ (285.3) calculated: 63.15% C, 5.30% H, 14.73% N; found: 62.97% C, 5.25% H, 14.42% N. ^{1}H NMR spectrum: 3.57 dd, 2 H, *J*(5′,4′) = 3.1, *J*(5′,OH) = 5.2 (H-5′); 4.79 m, 1 H (H-4′); 4.97 t, 1 H (5′-OH); 5.93 dt, 1 H, *J*(3′,4′) = 2.1 (H-3′); 6.32 dt, 1 H, *J*(2′,3′) = 5.8, *J*(2′,4′) = 1.5 (H-2′); 6.41 br, 1 H (NH); 6.97 br pent, 1 H, *J*(1′,2′) = 1.8, *J*(1′,3′) = 1.5, *J*(1′,4′) = 3.1 (H-1′); 7.24–7.50 m, 6 H (H arom. and NH); 7.76 s, 1 H (H-6).

1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pentofuranosyl)-5-phenylcytosine (**23**)

Didehydro derivative **20** (1 g, 3.05 mmol) was hydrogenated in methanol (150 ml) over 10% palladium on carbon (150 mg) at atmospheric pressure and room temperature for 3.5 h. The catalyst was filtered off through Celite, the filter was washed with methanol and the combined filtrates were taken down. Chromatography of the residue on silica gel (200 ml) in system S5 afforded dideoxy derivative **23** (R_F 0.44; 320 mg, 32%). ^{1}H NMR spectrum: 1.67 s, 3 H (acetyl); 1.75 m, 1 H (H-2′a); 1.99 m, 2 H (H-2′b and H-3′a); 2.33 m, 1 H (H-3′b); 4.20 m, 3 H (H-4′and H-5′); 6.01 dd, 1 H, *J*(1′,2′a) = 6.7, *J*(1′,2′b) = 3.7 (H-1′); 6.33 br, 1 H (NH); 7.28–7.53 m, 6 H (H arom. and NH); 7.58 s, 1 H (H-6).

1-(2,3-Dideoxy-β-D-*glycero*-pentofuranosyl)-5-phenylcytosine (**24**)

Acetyl derivative **23** (320 mg, 0.97 mmol) was stirred with methanolic ammonia (100 ml) for 3 h at room temperature. The solvent was evaporated and the residue was crystallized from ethanol with addition of a small amount of ether (to slight turbidity). Yield: 190 mg (68%) of compound **24**, m.p. 197.5–199 °C. Mass spectrum (FAB, glycerol + methanol): 288 (M + H). ^{1}H NMR spectrum: 1.74–2.04 m, 3 H and 2.18–2.41 m, 1 H (H-2′and H-3′); 3.49 m, 1 H, *J*(5′a,4′) = 3.5 (H-5′a); 3.69 m, 1 H, *J*(5′b,4′) = 3.1, *J*(gem) = 11.8 (H-5′b); 4.03 m, 1 H (H-4′); 5.03 t, 1 H, *J*(OH, 5′a) = 5.3, *J*(OH,5′b) = 5.0 (5′-OH); 5.98 dd, 1 H (H-1′); 6.33 br, 1 H (NH); 7.12–7.52 m, 6 H (H arom. and NH); 8.09 s, 1 H (H-6).

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