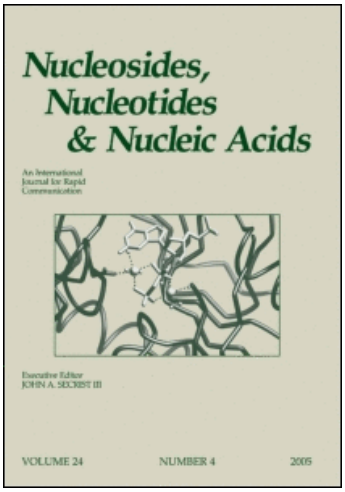

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New Pyrimidine Cyclonucleosides with Hydrogenated Aglycones: Synthesis and X-Ray Structures

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NEW PYRIMIDINE CYCLONUCLEOSIDES WITH HYDROGENATED AGLYCONES: SYNTHESIS AND X-RAY STRUCTURES

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ABSTRACT. Acid catalysed transformations of (6S)-6,5'-anhydro-6-hydroxy-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)hexahydropyrimidine-2-thione are studied. (6R)-6,2'-anhydro-6-hydroxy-1-(α-D-ribofuranosyl)hexahydropyrimidine-2-thione was formed as a thermodynamically stable product. Two intermediates, (6S)-6,5'-anhydro-6-hydroxy-1-(β-D-ribofuranosyl)hexahydropyrimidine-2-thione and 6-hydroxy-1-(D-ribosyl)hexahydropyrimidine-2-thione and products of cleavage of glycosidic bond were identified in the reaction mixtures. Results of X-ray structural determination of the synthesised nucleosides are presented.

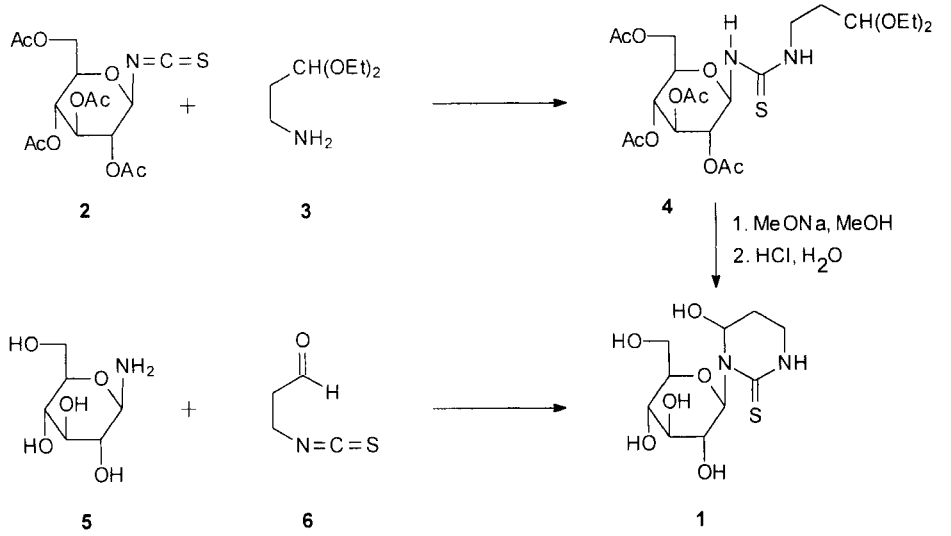
INTRODUCTION

The base-modified nucleoside analogues and, in particular, these containing hydrogenated aglycones attract significant attention as potential biologically active substances. Some of these compounds possess antiviral[1,2] and antitumor[3,4] activities and immuno-stimulating[5] and enzymatic inhibitory[6,7] properties. However, so far only few studies were concerned with the syntheses of nucleoside analogues derived from perhydrogenated heterocycles.

Previously, we reported two straightforward methods for synthesising 1-glycosyl-, 1-galactosyl-, and 1-ribosyl-6-hydroxyhexahydropyrimidine-2-thiones[5,8-10]. Exemplified in

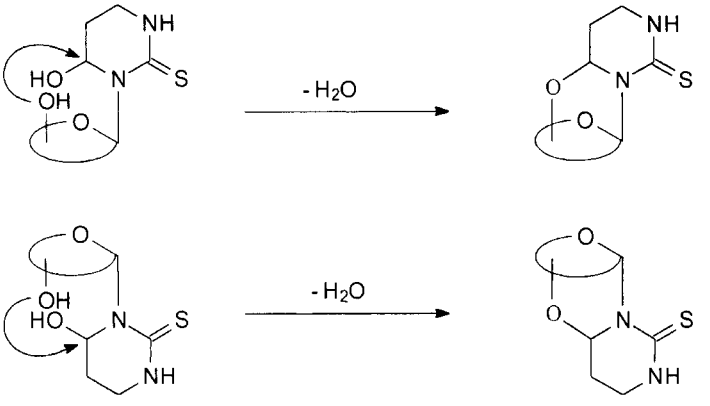
Scheme 1 for 1-glycosyl derivatives, the first method employs the reaction of **2** with **3** to give **4** and, after deprotection, the target nucleoside **1** in 63 % overall yield[9].

Scheme 1



In the second method, glycosylamines, for example, **5**, readily reacted with **6** in pyridine to give **1** in 79 % yield[10] (Scheme 1).

Scheme 2



One of the structural features of the obtained nucleoside analogues is the presence of the hemiacetal hydroxyl group at the pyrimidine ring along with several hydroxy groups

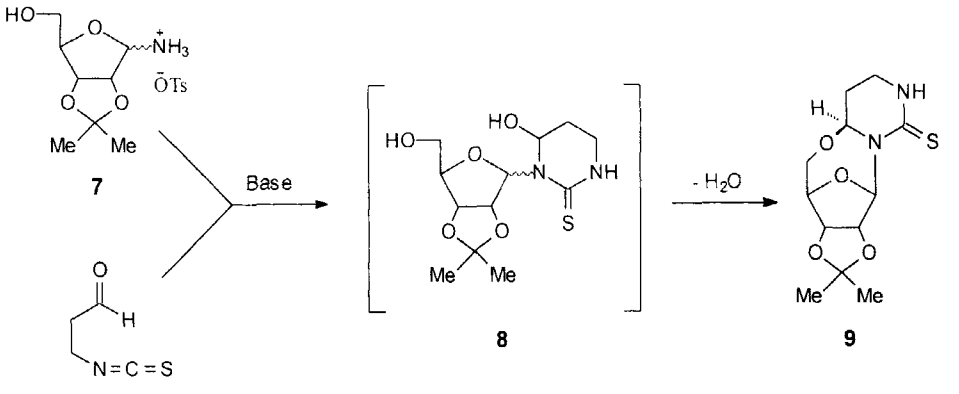
in sugar moiety. Earlier, we demonstrated that 4-hydroxyhexahydropyrimidine-2-thiones readily react with a variety of nucleophiles *e.c.*, alcohols and amines, to form products of substitution at the C6 of pyrimidine ring[11-14]. We hypothesised that for 1-glycosyl-6-hydroxyhexahydropyrimidine-2-thiones a similar reaction may proceed in an intramolecular fashion to give corresponding cyclonucleosides (Scheme 2). However, considering a number of hydroxy groups present in the sugar moiety, the specificity of the reaction was unpredictable. Very similarly, the stereochemical outcome of the substitution with respect to C6 of the pyrimidine ring remained unclear.

In this communication, we report the synthesis of novel cyclonucleosides with hydrogenated pyrimidine aglycones. The regio- and stereochemical course of their formation by the intramolecular dehydration of 6-hydroxy-1-(D-ribofuranosyl)-hexahydropyrimidine-2-thiones is clarified. X-Ray data obtained for the synthesised compounds is also discussed.

RESULTS AND DISCUSSION

In order to study the intramolecular cyclodehydration of 6-hydroxypyrimidine nucleosides, compound **9** was synthesised as a starting material from readily available **6**[17] and **7**[15,16].

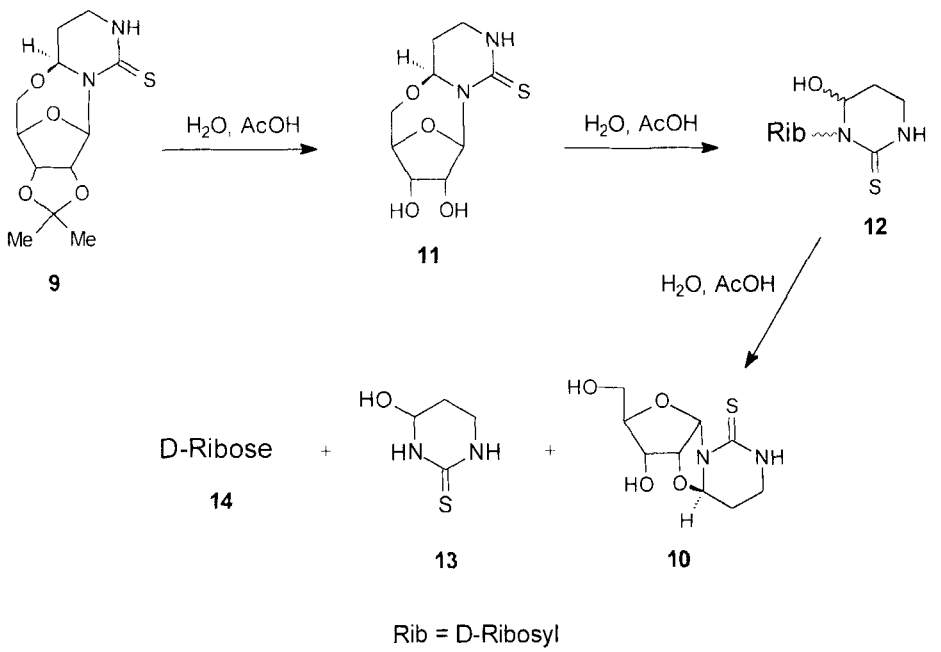
Scheme 3



In principle, **7** is known to exist in solution as a mixture of α- and β-anomers. In order to avoid formation of anomeric nucleosides, the reactions were carried out in

$CHCl_3$ where **7** has been reported to exist predominantly as the β-anomer (β/α: > 99:1)[16]. We found that **6** and **7** readily reacted in the presence of triethylamine. Expectedly, with the single hydroxy group at C5' available as a nucleophile in the intermediate **8**, intramolecular dehydration resulted in selective formation of crystalline β-cyclonucleoside **9** in 79 % yield (Scheme 3). Alternatively, **9** was prepared from **6** and **7** in pyridine (20 °C, 24 h) and isolated in 63 % yield by column chromatography. By both methods, **9** was obtained exclusively as an (S)-enantiomer with respect to C6, which was unambiguously established by a single crystal X-ray diffraction (see below).

Scheme 4



9 **11** **12** **14** **13** **10**

Next, the 2',3'-O-isopropylidene protection in **9** was removed to give **11** with two nucleophilic hydroxy groups available. This may, in principle, lead to a cascade of transformations if, under acidic conditions, formation of 6,5'-anhydro cycle was reversible. Indeed, upon prolonged treatment with AcOH (25% aq; 97 °C; 5 h), a novel 6,2'-anhydronucleoside, **10**, was obtained as a main product and isolated by column chromatography or recrystallization in 57 and 51 % yield, respectively (Scheme 4).

TABLE 1. Distribution of Products Formed from **9** under Treatment with 25% aq AcOH

Reaction time, h	Isolated yield, % (Molar Ratio by ^{1}H NMR, %)				
	9	**10**	**11**	**12**	**13**
1.2	25 (31)	43 (46)	16 (23)	3 (*a*)	3 (*a*)
1.6	20 (17)	47 (65)	13 (18)	8 (*a*)	6 (*a*)
2.75	*a* (7)	*a* (85)	*a* (8)	*a*	*a*
5.0	*a* (<1)	57 (>99)	*a* (<1)	*a*	12 (*a*)

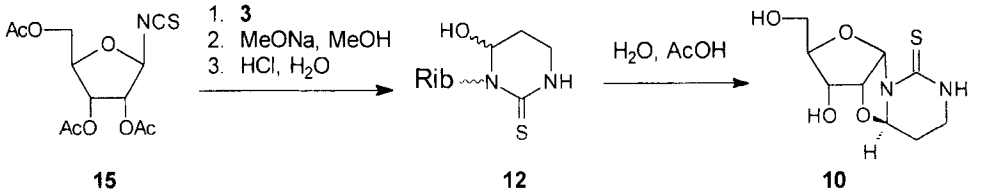
[a] not determined

Interestingly, **10** was formed exclusively as (R)-enantiomer with respect to C6. As side products, **13** (12 %) and **14**, both resulting from the glycosidic bond cleavage were also isolated from the reaction mixture by column chromatography.

In order to study the formation of possible intermediates, **9** was treated under the same conditions, and the reactions were stopped at different time points. The reaction mixtures were separated by silica gel chromatography. The isolated products, **9**, **10**, **11**, **12** and **13** are presented in Scheme 4. Additionally, the molar ratios of **9**, **10** and **11** were determined by ^{1}H NMR spectroscopy based on integral intensities of the anomeric proton signals (6.13-6.45 ppm in DMSO-d_6). The product distribution determined by both methods is summarised in Table 1. Analysis of the obtained data demonstrated that the ratio of **9–13** clearly depended on the reaction time. The data suggested that **11** was initially formed by cleavage of the 2',3'-O-isopropylidene protection in **9**. Subsequent cleavage of a C6-O-C5' bridge of **11** led to **12** which is an interconvertible mixture of isomers with respect to C6 and the sugar moiety[5]. Indeed, the ^{1}H NMR spectra of **12** in DMSO-d_6 showed four sets of 1'-H, NH and 6-H signals. For example, there are four doublets of the anomeric proton at δ 6.75, 6.71, 6.47, and 6.36 ppm ($J_{1',2'}$ = 3.2, 4.3, 9.5, and 9.1 Hz, respectively). Finally, the α-ribofuranose form of **12** underwent

intramolecular cyclization to give the final product, **10** (Scheme 4). These events were additionally complicated by the cleavage of glycosidic bond to form **13** and **14**.

Scheme 5



15 **12** **10**

To obtain further confirmation of the proposed reaction sequence, **12** was synthesised as a mixture of four isomers by independent route from **15** according to the reported procedure[5] (Scheme 5). When treated with 25 % aqueous AcOH (97 °C, 3.4 h), **12** formed a mixture where **10** was identified as a main product (80-85 %) by ^{1}H NMR. Following work-up and isolation gave **10** in 51 % yield. Similarly to the previous observations, **13** was formed as a side product that was identified by its ^{1}H NMR spectrum.

In summary, acid catalysed isomerization of **11** to form a novel 6,2'-anhydroriboside **10** was studied. The reaction path involved ring opening of **11** to give an intermediate **12** as a mixture of isomers. The α-ribofuranose form of **12** was finally dehydrated into **10**. The phenomenon was explained by reversible alkylation of the hydroxy functions of sugar moiety with C6 in pyrimidine ring serving as an electrophile.

X-RAY ANALYSIS

To obtain information about the three-dimensional molecular structure of **9** and **10**, the complete X-ray analysis of these substances was carried out.

Molecular structures of **9** and **10** are presented in Fig. **1a** and **b**, correspondingly. The C, N, and O atoms are shown by the 50 % probability thermal ellipsoids and H atoms by the spheres of an arbitrary radius.

The bond lengths and the bond angles in **9** and **10** well agree with each other and with other compounds containing similar structural fragments[18-24]. For this reason, only

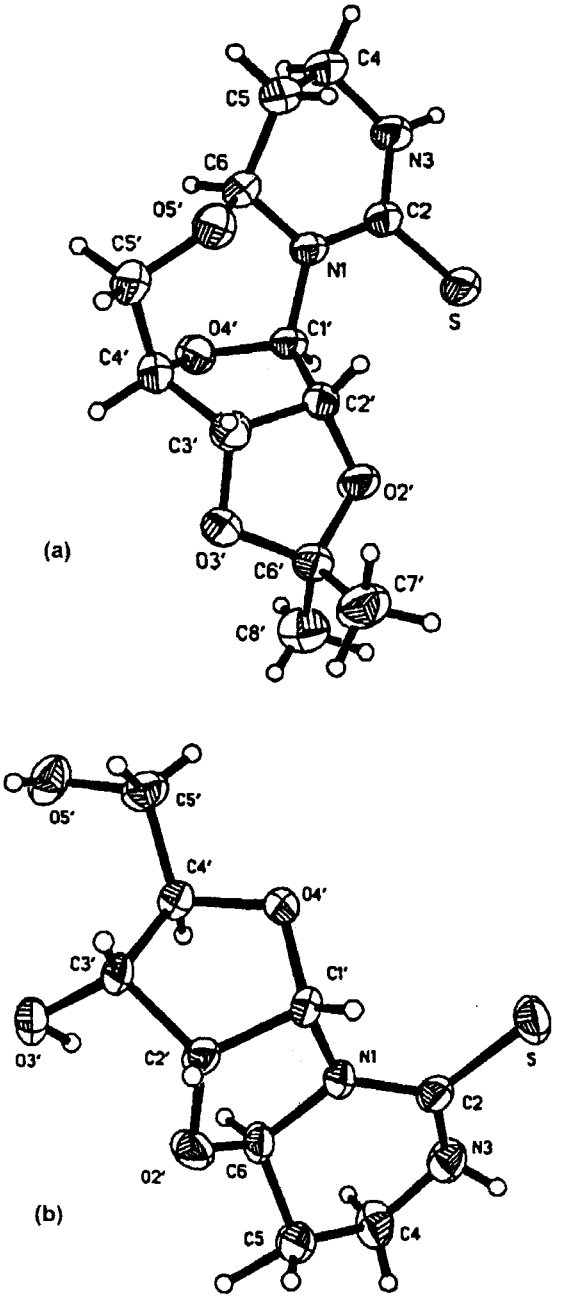


FIG. 1. The molecular structure of compounds **9 (a)** and **10 (b)**.

basic conformational and configurational characteristics of the studied compounds are analyzed below.

Expectedly, the hexahydropyrimidine rings of **9** and **10** were not flat. The atoms N1, C2, N3, C4, and S were in the same planes, whereas C5 and C6 were displaced from these planes to the direction opposite from O4′ by 0.784 and 0.221 Å in **9**, and by 0.778 and 0.109 Å in **10**, respectively. Atom O5′ of **9** was located pseudo-equatorially with respect to the heterocycle. This was confirmed by the following values of torsion angles: O5′–C6–C5–C4 = 167.3°, O5′–C6–N1–C2 = –133.7°, H6–C6–C5–C4 = –72.9°, and H6–C6–N1–C2 = 106.3°. The nucleoside **9** possessed the (S)-configuration relative to C6. Atom O2′ in **10** was also pseudo-equatorial. Relevant torsion angles were: O2′–C6–C5–C4 = –166.5°, O2′–C6–N1–C2 = 141.2°, H6–C6–C5–C4 = 69.5°, and H6–C6–N1–C2 = –94.7°. However, the configuration of **10** relative to the C6 was (R).

It should be noticed that due to the anomeric effect, the most stable conformations of 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones are those with axial orientation of hydroxy and alkoxy groups[11]. Unusual orientation of the substituents at the C6 positions in the studied cyclonucleosides may be explained by the presence of an anhydro cycle whose formation results in additional conformational rigidity.

Ribofuranose rings in **9** and **10** were in *twist* conformation.

Sugar conformation in **9** was *C4′- endo-O4′- exo*. Atoms C4′ and O4′ were located on the opposite sides of the plane of C1′, C2′, and C3′ at distances of 0.232 and 0.272 Å, respectively. The phase angle of pseudorotation **P** was equal to 254.8°, the degree of pucker Ψ_m was 34.6°. A similar sugar conformation was realized in two crystallographically independent molecules of 5′-deoxy-5′,6-epithio-5,6-dihydro-2′,3′-O-isopropylideneuridine[19]. The *O4′-exo* ribofuranose conformation was found for molecules of other cyclonucleoside, 6,5′-anhydro-4,5-dichloromethylene-6-hydroxy-1-(2′,3′-isopropylidene-β-D-ribofuranosyl)hexahydropyrimidine-2-one[20].

In **10**, where atoms O2′ and C6 were involved in cyclization, **P** = 61.4°, and Ψ_m = 28.5°, both in agreement with the sugar conformation *C4′-exo-O4′-endo*. Atom C4′ was displaced from the plane of atoms C1′, C2′, and C3′ by 0.345Å towards the base, whereas atom O4′ was shifted towards C5′ by 0.069 Å.

In comparison with natural nucleosides with $\Psi_m \sim 38°$ [25], the Ψ_m values of molecules **9** (34.6°) and **10** (28.5°) indicated a certain flattening of their furanose rings. It should be noticed that the presence of an additional bridge C6-O(S)-C5′ in nucleoside molecules containing a 2′,3′-isopropylidene fragment, usually results in a less pronounced sugar flattening. Thus, in 5-bromo-2′,3′-O-isopropylideneuridine[21], 5′-O-acetyl-2′,3′-isopropylideneuridine[22], and 2′,3′-O-methoxymethyleneuridine[23], the Ψ_m values are in the range of 16 - 23°, whereas in 5′-deoxy-5′,6-epithio-5,6-dihydro-2′,3′-O-isopropylideneuridine[19] and 6,5′-anhydro-4,5-dichloromethylene-6-hydroxy-1-(2′,3′-isopropylidene-β-D-ribofuranosyl)hexahydropyrimidine-2-one[20], as well as in the compound **9**, Ψ_m varies from 27 to 34°.

The mutual orientation of the sugar fragment and the base in **9** was described by the torsion angle χ (C2-N1-C1′-O4′) equal to −146.1°, which corresponded to the *anti* conformation of the nucleoside about N-glycoside bond. For α-anomer **10**, the angle χ = 92.0° was consistent with the *high-anti* conformation (torsion angle C6-N1-C1′-C2′ = 14.4°).

The seven-membered cycle in **9** demonstrated a *pseudochair* conformation. The atoms C6, N1, C1′, C4′, and C5′ were located in the same plane, whereas O5′ deviated from this plane by 0.750 Å towards C2′ and C3′ atoms, and O4′ deviated by 0.864 Å to the opposite direction. The base and seven-membered ring planes were positioned at the angle of 14.5° with respect to each other. The conformation of the seven-membered ring described above coincides with that of a similar ring in 6,5′-anhydro-4,5-dichloromethylene-6-hydroxy-1-(2′,3′-isopropylidene-β-D-ribofuranosyl)hexahydropyrimidine-2-one[20] and is probably characteristic of the like compounds.

The oxazolidine cycle in **10** had the *envelope* conformation. Atom C6 was shifted from the plane of N1, C1′, C2′, and O2′ atoms by 0.400 Å towards O4′. The planes of the base and the anhydrocycle were positioned at the angle of 23.8°.

Owing to the base-sugar cyclization specificity in **9**, the *gauche*$^+$ conformation about C4′ -C5′ bond was realized. The torsion angle γ (C3′-C4′-C5′-O5′) was 58.0°. The angle γ in **10** was equal to -70.3° and corresponded to *gauche*$^-$ conformation.

The dioxolane ring in **9** demonstrated a *twist* conformation - *O3′-endo-C6′-exo.* Atom O3′ deviated from the plane of C3′, C2′, and O2′ by 0.185 Å towards O4′, whereas

C6′ deviated by 0.283 Å to the opposite direction. A similar *twist* conformation of dioxolane cycles has been observed in a number of structures of dioxolan analogs of 2′,3′-dideoxynucleosides[24]. In **9**, the plane of C6′, C7′, and C8′ atoms of isopropylidene group was oriented nearly perpendicular to the planes of all cycles present in the molecule *i.e.*, furanose (92.2°), dioxolane (95.4°), seven-membered anhydrocycle (100.6°), and the base (92.9°).

CONCLUSION

Acid catalysed isomerization of **11** to form a novel 6,2'-anhydroriboside **10** was studied. The reaction path involved ring opening of **11** to give an intermediate **12** as a mixture of isomers. The α-ribofuranose form of **12** was finally dehydrated into **10**. The phenomenon was explained by reversible alkylation of the hydroxy functions of sugar moiety with C6 in pyrimidine ring serving as an electrophile. The reaction provides a convenient stereoselective synthetic route to novel, potentially biologically active cyclonucleosides. The results of X-ray analysis obtained for synthesised compounds confirm their structures and may provide a better understanding of their function in biological systems.

EXPERIMENTAL

Optical rotation was determined on a Perkin-Elmer 241 MC polarimeter for solutions in DMSO, water, or MeOH. IR spectra were recorded on a Shimadzu IR 435 spectrophotometer in nujol. UV-spectra were recorded on a Specord UV-VIS spectrophotometer in MeOH. The ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument at 250.13 MHz using DMSO-d_6 as a solvent. Chemical shifts are given in δ, ppm relative to TMS. The EI MS were obtained on a Varian MAT-112 spectrometer with direct injection of samples. The energy of ionizing electrons was 70 eV. The ionization chamber temperature was 180 °C. Thin layer chromatography (TLC) was performed on silica gel plates Silufol UV 254 (Czech Republic) or Kieselgel 60 F_{254} (Merck) in $CHCl_3$-MeOH (19:1, v/v) and $CHCl_3$-MeOH (9:1, v/v). The plates were visualized by exposing the plates to I_2 or with UV light. Column chromatography was carried out on silica gel 40-100 μm (Czech Republic).

Compounds **6**[17], **7**[15,16], and **12**[5] were prepared according to the reported procedures. Py was dried over KOH and then over BaO followed by distillation in vacuum. $CHCl_3$ was distilled over P_2O_5 before use.

(6S)-6,5'-anhydro-6-hydroxy-1-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-hexahydropyrimidine-2-thione (9). *Method A.* A solution of dry triethylamine (0.251 g, 2.51 mmol) in $CHCl_3$ (5 mL) was added to a suspension of **7** (0.865 g, 2.39 mmol) in dry $CHCl_3$ (7 mL) at 0 °C, followed by adding freshly distilled **6** (0.345 g, 2.99 mmol) in $CHCl_3$ (15 mL). The reaction mixture was kept at 0 °C for 24 h and evaporated in vacuum. The residue was treated with ice water (3 mL) and Et_2O (2 mL). The precipitate was filtered off, washed with cold water, Et_2O, and dried to give **9** (0.545 g, 79.4 %): m.p. 229-229.5 °C (MeOH); R_f 0.37 ($CHCl_3$–MeOH, 19:1); $[\alpha]_D^{20}$ -144.0°, $[\alpha]_{546}^{20}$ -174.5°, $[\alpha]_{436}^{20}$ -327.0°, $[\alpha]_{408}^{20}$ -409.9°, $[\alpha]_{366}^{20}$ -621.3°, $[\alpha]_{334}^{20}$ -1053.9°, $[\alpha]_{313}^{20}$ -2197.2° (c 1.4; DMSO); ^{1}H NMR (DMSO-d_6): δ 8.57 (1H, s, NH), 6.45 (1H, s, $J_{1',2'}$ = 0 Hz, 1'-H), 4.94 (1H, d.d, $J_{6,5a}$ = 7.0, $J_{6,5e}$ = 5.0 Hz, 6-H), 4.69 (1H, d, $J_{2',3'}$ = 6.0 Hz, 2'-H), 4.62 (1H, d, $J_{3',4'}$ = 0 Hz, 3'-H), 4.47 (1H, d, $J_{4',5'}$ = 0 Hz, 4'-H), 3.95 (1H, d, $J_{4',5''}$ = 2.3 Hz, 5'-H), 3.68 (1H, d.d, $J_{5',5''}$ = 12.6 Hz, 5''-H), 2.94-3.14 (2H, m, 4-H), 1.98-2.12 (1H, m, 5-H_e), 1.70-1.86 (1H, m, 5-H_a), 1.38 (3H, s, CH_3), 1.23 ppm (3H, s, CH_3); EI MS, m/z (abundance %): 286 (78), 271 (20), 228 (57), 171 (10), 132 (13), 117 (11), 116 (22), 115 (100), 113 (11), 103 (12), 97 (10), 83 (10), 72 (16), 69 (14), 68 (16), 59 (13), 58 (92), 57 (22), 56 (28), 43 (34), 41 (17); UV (MeOH), λ_{max} (lg ε): 250 nm (4.14); IR (nujol), ν_{max}: 3412, 3380 shoulder, 1526, 1267, 1218, 1181, 1112, 1060 cm^{-1}. Anal. Calcd. for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.78. Found: C, 50.50; H, 6.54; N, 9.58.

Method B. A solution of **6** (1.000 g, 8.68 mmol) and **7** (1.000 g; 2.77 mmol) in dry in Py (15 mL) was kept at r.t for 24 h and evaporated in vacuum. The residue was dissolved in a minimal amount of $CHCl_3$, applied to a silica gel column (1.8 × 12 cm), and eluted with $CHCl_3$ to yield **9** (0.500 g, 63.1 %).

(6R)-6,2'-anhydro-6-hydroxy-1-(α-D-ribofuranosyl)hexahydropyrimidine-2-thione (10). *Method A.* A solution of **9** (0.320 g, 1.12 mmol) in 25 % aq AcOH (6 mL) was heated at 97 °C for 5.0 h and evaporated in vacuum. The residue was evaporated

twice with MeOH and re-crystallised from MeOH (2 mL) to give **10** (0.140 g, 50.9 %): m.p. 217-217.5 °C (MeOH); $[\alpha]_D^{20}$ +269.2°, $[\alpha]_{546}^{20}$ +315.4°, $[\alpha]_{436}^{20}$ +561.5°, $[\alpha]_{408}^{20}$ +646.2°, $[\alpha]_{366}^{20}$ +876.9°, $[\alpha]_{334}^{20}$ +1138.5°, $[\alpha]_{313}^{20}$ +1353.8°, $[\alpha]_{302}^{20}$ +1430.8°, $[\alpha]_{297}^{20}$ +1476.9°, $[\alpha]_{289}^{20}$ +1707.7°, $[\alpha]_{280}^{20}$ +2753.8° (c 0.13; H_2O); $[\alpha]_D^{20}$ +222.4°, $[\alpha]_{546}^{20}$ +261.2°, $[\alpha]_{436}^{20}$ +431.9°, $[\alpha]_{408}^{20}$ +500.9°, $[\alpha]_{366}^{20}$ +619.0°, $[\alpha]_{334}^{20}$ +637.9°, $[\alpha]_{313}^{20}$ +90.5° (c 1.2; DMSO); R_f 0.13 ($CHCl_3$-MeOH, 7:1); ^{1}H NMR (DMSO-d_6): δ 8.55 (1H, s, NH), 6.34 (1H, d, $J_{1',2'}$ = 5.0 Hz, 1'-H), 5.17 (1H, d, $J_{3'\text{-OH},3'\text{-H}}$ = 6.5 Hz, 3'-OH), 5.14 (1H, d.d, $J_{6,5a}$ = 9.4, $J_{6,5e}$ = 4.4 Hz, 6-H), 4.76 (1H, t, $J_{5'\text{-OH},5'\text{-H}}$ = 5.1, $J_{5'\text{-OH},5''\text{-H}}$ = 6.2 Hz, 5'-OH), 4.49 (1H, d.d, $J_{2',3'}$ = 5.9 Hz, 2'-H), 3.77 (1H, d.t, $J_{3',4'}$ = 8.3 Hz, 3'-H), 3.62 (1H, d.d.d, $J_{4',5'}$ = 2.1 Hz, 5'-H), 3.57 (1H, d.d.d, $J_{4',5''}$ = 4.8 Hz, 4'-H), 3.37 (1H, d.d.d, $J_{5',5''}$ = 11.8 Hz, 5''-H), 3.09-3.21 (2H, m, 4-H), 2.28 (1H, m, 5-H$_e$), 1.44 ppm (1H, m, 5-H$_a$); EI MS, m/z (abundance %): 246 (16), 173 (5), 172 (50), 117 (5), 116 (7), 115 (100), 114 (5), 97 (5), 72 (9), 70 (7), 56 (15), 44 (6), 43 (6), 41 (6); UV (MeOH), λ_{max} (lg ε): 252 nm (4.17); IR (nujol), ν_{max}: 3409, 3265, 3162, 1541, 1499, 1314, 1230, 1119, 1092 cm^{-1}; Anal. Calcd. for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.37; S, 13.02. Found: C, 44.17; H, 5.94; N, 11.36; S, 12.83.

Method B. A solution of **12**[5] (92.8 mg, 0.35 mmol) in 25 % aqueous acetic acid (1.6 mL) was heated at 97 °C for 3.4 h and evaporated in vacuum. The residue was evaporated with dry acetonitrile (2 × 1 mL). The crude product (86.9 mg) was re-crystallised from MeOH (0.5 mL) to give **10** (44.2 mg, 51.1 %).

Transformation of 9 in 25 % aq AcOH. A solution of **9** (0.697 g, 2.43 mmol) in 25 % aq AcOH (12 mL) was heated at 97 °C for 1.2, 1.6, or 5.0 h and evaporated in vacuum. The residue was evaporated twice with acetone. The remaining solid was dissolved in Py (2 mL), applied on a silica gel column (1.8 × 30 cm) and eluted with a step gradient from 0 to 7 % MeOH in $CHCl_3$ (v/v). Depending on the reaction time, compounds **9**–**13** were isolated in yields listed in Table 1. The characteristics of **11**–**13** are presented below.

(6S)-6,5'-anhydro-6-hydroxy-1-(β-D-ribofuranosyl)hexahydropyrimidine-2-thione (11): m.p. 195-196 °C (MeOH); $[\alpha]_D^{20}$ -206.3° (c 0.67; MeOH); ^{1}H NMR

(DMSO-d_6): δ 8.65 (1H, s, NH), 6.13 (1H, s, $J_{1',2'}$ = 0 Hz, 1'-H), 5.15 (1H, d, $J_{2'\text{-OH},2'\text{-H}}$ = 5.5 Hz, 2'-OH), 5.01 (1H, t, $J_{6,5a}$ + $J_{6,5e}$ = 9.0 Hz, 6-H), ~5.01 (1H, d, $J_{3'\text{-OH},3'\text{-H}}$ ~ 6-7 Hz, 3'-OH overlapping with 6-H), 4.33 (1H, d, $J_{2',3'}$ = 5.9 Hz, 2'-H), 4.11 (1H, d.d, $J_{3',4'}$ = 2.5 Hz, 3'-H), 4.25 (1H, d.d, $J_{4',5'}$ = 0 Hz, 4'-H), 3.85 (1H, d, $J_{4',5''}$ = 2.0 Hz, 5'-H), 3.71 (1H, d.d, $J_{5',5''}$ = 12.4 Hz, 5''-H), 2.97-3.18 (2H, m, 4-H), 1.84-2.00 ppm (2H, m, 5-H); IR (nujol), ν_{max}: 3337, 1522, 1314, 1283, 1260, 1250, 1221, 1209, 1163, 1119, 1084 cm^{-1}. Anal. Calcd. for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.37. Found: C, 44.09; H, 5.66; N, 11.39.

6-Hydroxy-1-(D-ribosyl)hexahydropyrimidine-2-thione (12) was identical by TLC, IR, and ^{1}H NMR with an authentic sample prepared according to the reported procedure[5].

4-Hydroxyhexahydropyrimidine-2-thione (13) was identical by TLC, IR, and ^{1}H NMR with an authentic sample prepared according to the reported procedure[11].

X-Ray crystallography of 9 and 10. Crystals for X-ray analysis were obtained from saturated solutions of **9** and **10** in EtOH by slow evaporation of the solvent at room temperature.

Crystal data for the compound **9**: Crystals belonged to the space group P1, the unit cell parameters were: ***a*** = 5.970(1) Å, ***b*** =7.431(1) Å, ***c*** =7.774(2) Å, α = 87.66(2)°, β = 88.31(2)°, γ =76.03(2) °, V = 334.3(1) Å^3, Z = 1.

Crystal data for the compound **10**: Crystals belonged to the space group $P2_1$, the unit cell parameters were: ***a*** = 8.855(2) Å, ***b*** = 7.180(1) Å, ***c*** = 9.032(1) Å, α = γ = 90°, β = 111.58(2)°, V = 534.0(4) Å^3, Z = 2.

The cell dimensions and reflection intensities were determined using a CAD-4 diffractometer (Enraf-Nonius), Θ /2Θ scanning technique and the MoKα radiation with graphite monochromator. The experimental data were corrected for Lorentz and polarization factors. The intensities of 1675 crystallographically independent reflections with $I > 3\ \sigma(I)$ for compound **9** and 990 reflections for compound **10** were used in the structural studies.

TABLE 2. Atom coordinates (x10 ^{4}) and temperature factors *U eq* (Å^2 x10^2)

Atom	Compound **9**				Compound **10**			
	x	*y*	*z*	*U eq**	*x*	*y*	*z*	*U eq**
N1	3689(2)	1819(2)	5532(2)	35(1)	2232(3)	2670(4)	3316(3)	26(1)
C2	4778(3)	2860(2)	4482(2)	34(1)	2291(4)	3003(5)	4812(4)	27(1)
S	5000	5000	5000	44(1)	1549(1)	5000	5271(1)	41(1)
N3	5691(3)	2148(2)	3001(3)	46(1)	3000(4)	1718(6)	5882(4)	36(1)
C4	5669(5)	299(3)	2486(4)	56(1)	3564(5)	-90(7)	5573(4)	38(1)
C5	3413(5)	-101(3)	3092(3)	50(1)	2597(6)	-666(6)	3853(5)	35(1)
C6	3158(3)	77(2)	5013(3)	39(1)	2702(4)	898(6)	2795(4)	29(1)
O2'	537(3)	5041(2)	8619(2)	49(1)	1532(4)	646(4)	1225(3)	39(1)
O3'	-1047(2)	3037(2)	10198(2)	44(1)	2652(3)	1683(4)	-1038(3)	35(1)
O4'	3192(2)	819(2)	8407(2)	39(1)	2366(3)	5225(4)	1642(3)	26(1)
O5'	859(2)	103(2)	5496(2)	45(1)	4256(3)	5771(5)	-1268(4)	43(1)
C1'	3005(2)	2404(2)	7290(2)	31(1)	1383(4)	3821(5)	1933(3)	23(1)
C2'	527(2)	3571(2)	7493(2)	34(1)	985(4)	2418(5)	551(4)	26(1)
C3'	-746(3)	2297(2)	8517(3)	38(1)	1920(3)	3131(5)	-479(4)	24(1)
C4'	952(3)	407(2)	8571(3)	41(1)	3105(4)	4575(5)	552(4)	25(1)
C5'	626(4)	-801(2)	7132(3)	51(1)	3378(4)	6258(6)	-312(4)	37(1)
C6'	-1005(3)	4956(2)	10025(3)	38(1)	-	-	-	-
C7'	-3410(3)	6135(3)	9658(4)	52(1)	-	-	-	-
C8'	22(4)	5490(4)	11617(4)	55(1)	-	-	-	-

* Equivalent isotropic U defined as one third of the trace of the orthogonalised U(i,j) tensor

Both structures were solved by direct methods and refined using the full-matrix least-squares method (LSM) in the anisotropic approximation for non-hydrogen atoms. The hydrogen atom coordinates were determined from the difference Fourier syntheses and refined by LSM in the isotropic approximation. The final R factor values were: 2.7 % for structure **9**, and 3.5 % for structure **10**. The atomic coordinates for both structures are given in Table 2. All calculations were done with the SHELXTL-76 program package.

REFERENCES

1. Renis, H.E. *Antimicrob. Agents Chemother.*, **1978**, *13*, 613-617.
2. Skulnik, H.I. in *Chemistry and Biology of Nucleosides and Nucleotides*, Eds. Harmon, R., Robins, R., Townsend, L. Academic Press, New York, **1978**, 199-211.
3. Malspeis, L.; Desouza, J. *Proc. Amer. Assoc. Cancer Res.*, **1981**, *22*, 868.
4. Kusakabe, Y.; Nagatsu, J.; Shibuya, M.; Kawaguchi, O.; Hirose, Ch.; Shirato, Sh. *J. Antibiot.*, **1972**, *25*, 44-47.
5. Ignatova, L.A.; Shutalev, A.D.; Unkovskii, B.V.; Sinilova, N.G.; Duplishcheva, A.P. *Pharm. Chem. J.*, **1985**, *19*, 847-852. Engl. transl. from *Khim. - Farm. Zh.*, **1985**, 1447-1453.
6. Marquez, V.E.; Liu, P.S.; Kelley, J.A.; Driscoll, J.S.; McCormack, J.J. *J. Med. Chem.*, **1980**, *23*, 713-715.
7. Liu, P.S.; Marquez, V.E.; Driscoll, J.S.; Fuller, R.W.; McCormack, J.J. *J. Med. Chem.*, **1981**, *24*, 662-666.
8. Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *Chem. Heterocycl. Compd.*, **1984**, *20*, 201-203. Engl. transl. from *Khim. Geterotsikl. Soedin.*, **1982**, 825-829.
9. Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *Chem. Heterocycl. Compd.*, **1984**, *20*, 447-450. Engl. transl. from *Khim. Geterotsikl. Soedin.*, **1984**, 548-551.
10. Shutalev, A.D.; Ignatova, L.A.; Unkovskii, B.V. *USSR Inventor's Certificate,* No. 1,366,517 (Cl C 07H 19/06), 15 Sept 1987.
11. Ignatova, L.A.; Shutalev, A.D.; Shingareeva, A.G.; Dymova, S.F.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.*, **1985**, 260-266.
12. Ignatova, L.A.; Shutalev, A.D.; Pagaev, M.T.; Unkovskii, B.V. *Khim. Geterotsikl. Soedin.*, **1988**, 234-240.

13. Shutalev, A.D.; Ignatova, L.A. *Khim. Geterotsikl. Soedin.*, **1991**, 228-236.
14. Shutalev, A.D.; Pagaev, M.T.; Ignatova, L.A. *Khim. Geterotsikl. Soedin.*, **1994**, 1093-1104.
15. Cusack, N.J.; Shaw, G. *Chem. Commun.*, **1970**, 1114.
16. Cusack, N.J.; Hildick, B.J.; Robinson, D.H.; Rugg, P.W.; Shaw, G. *J. Chem. Soc. Perkin Trans. 1*, **1973**, 1720-1731.
17. Peretokin, A.V.; Shutalev, A.D.; Chupin, V.V.; Mergenova, A.M.; Ignatova, L.A.; Malina, Yu.F.; Unkovskii, B.V. *Zh. Org. Khim.*, **1985**, *21*, 1004-1011.
18. Dias, H.W.; Truter, M.R. *Acta Cryst.*, **1964**, *17*, 937-943.
19. Gautham, N.; Seshadri, T.P.; Viswamitra, M.A.; Salisbury, S.A.; Brown, D.M. *Acta Cryst.*, **1983**, *C39*, 1389-1392.
20. Marquez, V.E.; Rao, K.V.B.; Silverton, J.V.; Kelley, J.A. *J. Org. Chem.*, **1984**, *49*, 912-919.
21. Gautham, N.; Seshadri, T.P.; Viswamitra, M.A.; *Acta Cryst.*, **1983**, *C39*, 456-458.
22. Seshadri, T.P.; Gautham, N.; Viswamitra, M.A. *Acta Cryst.*, **1983**, *C39*, 1706-1708.
23. Kok, A.J.; Romers, C.; Leeuw, H.P.M.; Altona, C.; Boom, J.H. *J. Chem. Soc. Perkin Trans. 2*, **1977**, 487-493.
24. Bochkarev, A.V.; Efimtseva, E.V.; Mikhailov, S.N.; Gurskaya, G.V. *Crystallography*, **1994**, *39*, 635-640.
25. Altona, C.; Sundaralingam, M.J. *J. Amer. Chem. Soc.*, **1972**, *94*, 8205-8212.