2-(2′,3′-Dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one and 3-(2′,3′-Dihydroxypropyl)-5-amino-3*H*-1,3,4-thiadiazol-2-one [1]

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Dedicated to Professor Ernest E. Campaigne on the occasion of his 75th birthday

The synthesis of two new acyclic nucleoside analogs, 2-(2′,3′-dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one (**1**) and 3-(2′,3′-dihydroxypropyl)-5-amino-3*H*-1,3,4-thiadiazol-2-one (**2**), is reported. The first compound, **1**, was obtained by reaction of 3-chloro-1,2-propanediol with the sodium salt of 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**) in anhydrous dimethylformamide. Similarly, 5-amino-3*H*-1,3,4-thiadiazol-2-one (**4**) reacted with 3-chloro-1,2-propanediol to give **2**. The thiadiazole **4** was prepared by condensation-cyclization of hydrazothiodicarbonamide (**9**).

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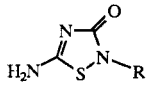
Introduction.

Over the past ten years or so, several groups of authors initiated an intensive search for effective antiviral agents represented by nucleoside analogs in which the sugar moiety is replaced by a hydroxylated acyclic side chain. A number of purine (adenine, guanine) and pyrimidine acyclonucleoside analogs have been synthesized [6-18]. However, until recently only a few acyclonucleoside analogs containing a five-membered ring heterocyclic system have been studied, *viz.*, thiazofurin [19], ribavirin [20], and pyrrole and imidazole derivatives [21-23].

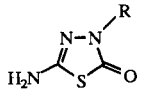
Within the framework of our continuing interest in the synthesis of novel potential antimetabolites of nucleic acid components which would possess cytostatic and/or antiviral activity [24-29], we have synthesized two new acyclonucleosides with a five-membered thiadiazole ring, **1** and **2**.

Results and Discussion.

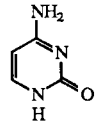
On the basis of the well-known analogy between a -CH = CH- group in benzenoid hydrocarbons and the bivalent sulfur, -S-, in their heterocyclic sulfur-containing counterparts (*e.g.*, thiophene is the π-isoelectronic analog of benzene) [30], 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**) is the analog of cytosine. Similarly, 5-amino-3*H*-1,3,4-thiadiazol-2-one (**4**) is the isomer of **3** and is also π-isoelectronic with cytosine (**5**).



1, R = $CH_2.CHOH.CH_2OH$
3, R = H



2, R = $CH_2.CHOH.CH_2OH$
4, R = H



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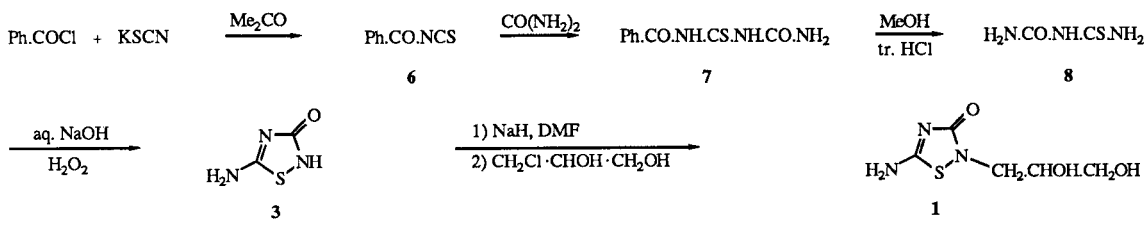
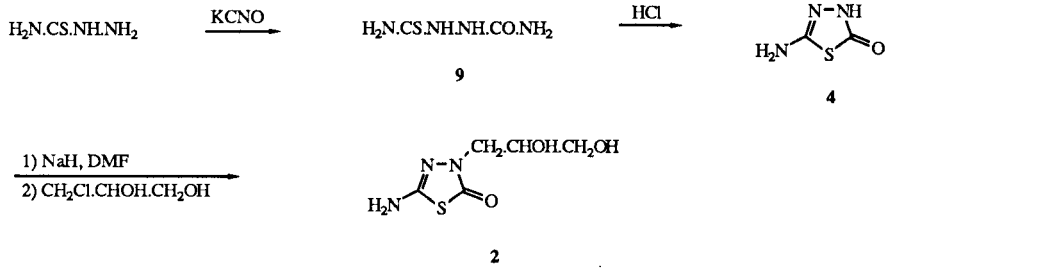
We have prepared the acyclic nucleoside analogs of **3** and **4**, *viz.*, 2-(2′,3′-dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one (**1**) and 3-(2′,3′-dihydroxypropyl)-5-amino-3*H*-1,3,4-thiadiazol-2-one (**2**).

The synthesis of 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**) and its derivative **1** is shown in Scheme 1. The starting materials for the synthesis of **3** were benzoyl chloride and potassium thiocyanate. Potassium thiocyanate was dissolved in warm acetone with difficulty - a larger volume of the solvent was needed than reported in the literature for sodium thiocyanate [31]. Benzoyl chloride was added and reacted with potassium thiocyanate to give benzoyl isothiocyanate (**6**) which upon condensation with urea yielded 1-benzoyl-2-thiobiuret (**7**) as a bright yellow solid [31]. The benzoyl group was removed by refluxing **7** in methanol with a trace of concentrated hydrochloric acid. This resulted in the formation of thiobiuret (**8**) in a 74% yield [31,32]. 5-Amino-2*H*-1,2,4-thiadiazol-3-one (**3**) [33] was then obtained in a 65% yield, using a modified procedure based on Revankar and Robins [34] (*cf.* also [35-39]). Finally, the 2-(2′,3′-dihydroxypropyl) derivative of **3** (**1**) was prepared from **3** by its conversion into a sodium salt with sodium hydride in anhydrous dimethylformamide, followed by condensation with 3-chloro-1,2-propanediol (40% yield). This is a procedure analogous to that described previously for other acyclic nucleoside analogs [40,41]. Interesting color changes were observed during this reaction (light yellow → light blue → dark blue → light yellow) while the temperature of the reaction mixture was increased from 50 to 85°. In order to achieve acceptable and reproducible yields, long reaction times (~24 hours) were necessary.

Scheme 1



Scheme 2



5-Amino-3*H*-1,3,4-thiadiazol-2-one (**4**) was prepared by condensation-cyclization of hydrazothiodicarbonamide (**9**) with concentrated hydrochloric acid [42] (see Scheme 2). In a procedure analogous to that described for the synthesis of **1**, reaction of **4** with 3-chloro-1,2-propanediol gave 3-(2′,3′-dihydroxypropyl)-5-amino-3*H*-1,3,4-thiadiazol-2-one (**2**) (30% yield). The color changes during this reaction were dark brown → red → orange red → light yellow, as the temperature of the reaction mixture rose from 50 to 85°.

The structures of the new compounds **1** and **2** were established on the basis of their elemental analysis and the nmr, uv, and ir spectra. Thus, the ^{1}H nmr spectra indicate the presence of a 1,2-propanediol unit at δ 3.2-3.6 ppm for compound **1** and at 3.3-3.8 ppm for compound **2**, and of an amino group at δ 7.9-8.2 ppm for compound **1** and 7.5-8.2 ppm for compound **2**. The uv spectra of compounds **1** and **2** show an intense absorption band at around 215-220 nm and a shoulder at about 245 nm, characteristic of the thiadiazole moiety. In the ir spectra, the hydroxyl group exhibits a strong band at 3400-3450 cm^{-1}, and the carboxyl group is indicated by another strong band at 1700-1740 cm^{-1}. The C=N ring bond shows a weak absorption band at 1600-1620 cm^{-1}. All the new compounds gave satisfactory elemental analyses for carbon, hydrogen, nitrogen, and sulfur.

In conclusion, we have developed improved procedures for the synthesis of 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**) and 5-amino-3*H*-1,3,4-thiadiazol-2-one (**4**). Also, we have prepared two new acyclonucleoside analogs, 2-(2′,3′-dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one (**1**) and 3-(2′,3′-dihydroxypropyl)-5-amino-3*H*-1,3,4-thiadiazol-2-one (**2**). The new compounds are expected to be biologically active.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The nmr spectra were recorded on a 60 MHz Varian EM-360 spectrometer using tetramethylsilane as the internal standard. The uv absorption spectra were obtained on a Perkin-Elmer 552 spectrophotometer. The ir spectra were measured with Perkin-Elmer 580B (with a Model 3500 Data Station) and Perkin-Elmer 710A spectrophotometers. The purity of all compounds was checked by thin-layer chromatography on silica gel 60-F-254 precoated plates and the spots were located in the uv light or by iodine vapor. Elemental microanalyses were carried out by the E + R Microanalytical Laboratory, Inc., Corona, NY. Most of the starting materials were purchased from Aldrich Chemical Company, Milwaukee, WI.

1-Benzoyl-2-thiobiuret (**7**) [31].

The procedure described in the literature was modified for a larger scale preparation and potassium rather than sodium thiocyanate was used. To a warm solution of potassium thiocyanate (48.0 g, 0.49 mole) in acetone (400 ml), benzoyl chloride (48 ml, 58.2 g, 0.41 mole) was added dropwise. Immediately upon the addition of benzoyl chloride, the solution became milky white and turned milky yellow when the addition had been completed. The mixture was stirred for 3.5 hours at 50°, and then it was left to cool to room temperature. The precipitated potassium chloride was filtered off with suction, and the amber filtrate was heated to 55° for 5 hours with urea (24.0 g, 0.40 mole). The resulting solution was cooled to room temperature and then placed in an ice bath for several hours. The solution was stirred periodically and the walls of the flask were scratched to induce crystallization. The

cold mixture was filtered to give 1-benzoyl-2-thiobiuret (**7**) (27.0 g, 30%) as a bright yellow solid, mp (crude product) 168-170°. Recrystallization from acetonitrile-methanol (10:1) afforded the pure product, mp 174-175° (lit [31] mp 175°); ^{1}H nmr (DMSO-d_6): δ 3.7 (s, 4H, NH_2 + 2 NH), 8.1-8.5 ppm (m, 5H, Ph); uv (methanol): λ max (log ε), 248 (4.28), 290 nm (4.17). In the next step, it is possible to use the crude product.

Thiobiuret (**8**) [31,32].

1-Benzoyl-2-thiobiuret (**7**, 11.0 g, 0.049 mole) was added to methanol (220 ml) containing 15 drops of concentrated hydrochloric acid and the solution was refluxed for 55 hours. The reaction mixture was cooled to room temperature and then evaporated under reduced pressure to dryness. The yellow residue was washed with hexane to remove the methyl benzoate and dried under reduced pressure. Recrystallization from water (charcoal) yielded thiobiuret as a yellowish-white powder (4.35 g, 75%); mp (crude product) 176-178°, after recrystallization from acetonitrile, mp 185-186° (lit [31] mp 189-193°); ^{1}H nmr (DMSO-d_6): δ 3.2 ppm (s, 4H, 2 NH_2), no NH peak observed; uv (methanol): λ max (log ε) 208 (4.10), 262 nm (4.15).

5-Amino-2*H*-1,2,4-thiadiazol-3-one (**3**) [34].

Thiobiuret (**8**, 5.0 g, 0.042 mole) was dissolved in 2*N* sodium hydroxide (32 ml). The cloudy yellow solution was cooled with ice and 30% hydrogen peroxide (6 ml) was added dropwise. After the addition had been completed, the solution was stirred for 2 hours at 0°. Then it was acidified to a *p*H 4.5 with 35% concentrated hydrochloric acid (3 ml). After the addition of about 0.8 ml of hydrochloric acid, the solution became milky white. The mixture was filtered and the crude product was recrystallized from boiling water to give 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**, 3.2 g, 65%), mp 219-221° dec (lit [34] mp 220-222° with dec); ^{1}H nmr (DMSO-d_6): δ 3.3-3.6 (m, 1H, OH), 7.9-8.3 ppm (m, 2H, NH_2); uv (aqueous hydrochloric acid, *p*H 1): λ max (log ε) 206 (3.86), 254 nm (3.84); uv (water, *p*H 7): λ max (log ε) 216 (4.01), 254 nm (3.81; ir (potassium bromide): ν 1150 (NH_2), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_2H_3N_3OS$: C, 20.51; H, 2.58; N, 35.88; S, 27.37. Found: C, 20.73; H, 2.59; N, 36.03; S, 27.19.

2-(2',3'-Dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one (**1**) (for the procedure, see [40,41]).

A mixture of 5-amino-2*H*-1,2,4-thiadiazol-3-one (**3**, 0.93 g, 0.0079 mole) and sodium hydride (0.32 g, 0.0133 mole) in anhydrous dimethylformamide (200 ml) was stirred at room temperature for 1 hour to give a milky solution of the sodium salt of **3**. Then 3-chloro-1,2-propanediol (0.55 g, 0.005 mole) was added and the mixture was heated to 80-85° with stirring for 24 hours.

A color change was observed during the reaction (light yellow → light blue → dark blue → light yellow). Thin-layer chromatography (tlc) was used to determine the completion of the reaction. The precipitated sodium chloride was filtered off and the filtrate was evaporated to dryness under reduced pressure. 2-(2',3'-Dihydroxypropyl)-5-amino-2*H*-1,2,4-thiadiazol-3-one (**1**) was obtained as a yellowish solid which was recrystallized from ethanol (0.60 g, 40%). The compound is very sensitive towards moisture; mp 214-216° dec; ^{1}H nmr (DMSO-d_6) [43]: δ 3.2-3.6 (m, 5H, 1'-CH_2, 2'-CH, 3'-CH_2), 4.1-4.5 (m, 2H, 2 OH), 7.9-8.2 ppm (m, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 220 (4.16), 245 nm (sh) (3.53); ir (potassium bromide): ν 1675 (NH_2), 1700 (C=O), 3400 cm^{-1} (OH).

Anal. Calcd. for $C_5H_9N_3O_3S$: C, 31.41; H, 4.74; N, 21.98; S, 16.77. Found: C, 31.84; H, 4.75; N, 21.48; S, 16.36.

5-Amino-3*H*-1,3,4-thiadiazol-2-one (**4**).

Thiosemicarbazide (5.0 g, 0.0549 mole) was dissolved in water (40 ml) and a solution of potassium cyanate (4.5 g, 0.055 mole) in water (15 ml) was added dropwise with stirring. Upon slow cooling to room temperature, white crystals of hydrazothiodicarbonamide (**9**) began to form. The mixture was filtered and the crude product was recrystallized from boiling water to give the pure product (3.5 g, 43%), mp 214-216° (lit [42] mp 218-220°); ^{1}H nmr (DMSO-d_6): δ 3.4 (s, 2H, $CONH_2$), 7.55 (s, 2H, $CSNH_2$), 8.05 (m, 1H, CONH), 9.15 ppm (m, 1H, CSNH).

5-Amino-3*H*-1,3,4-thiadiazol-2-one (**4**) was obtained in a low yield by heating of hydrazothiocarbonamide (**9**) with concentrated hydrochloric acid using the method described by Freund and Schander [42], yellow needles, mp 170-172° (lit [42,47] mp 172-174°, *cf.* also references [48,49]); ^{1}H nmr (DMSO-d_6): δ 8.1-8.5 (m, 1H, NH), 9.1-9.7 ppm (m, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 210 (4.10), 254 nm (3.83); ir (potassium bromide), ν 1690 (C=O), 1640 (NH_2), 1575 cm^{-1} (NH).

Anal. Calcd. for $C_2H_3N_3OS$: C, 20.51; H, 2.58; N, 35.88; S, 27.37. Found: C, 20.70; H, 2.56; N, 35.97; S, 27.52.

3-(2',3'-Dihydroxypropyl)-5-amino-1,3,4-thiadiazol-2-one (**2**).

5-Amino-3*H*-1,3,4-thiadiazol-2-one (**4**, 0.80 g, 0.0683 mole) was dissolved in anhydrous dimethylformamide (protected from moisture with a calcium chloride tube) and sodium hydride (0.20 g, 0.083 mole) was added. The mixture was stirred at room temperature for 1 hour to afford a milky solution of the sodium salt of **4**, and 3-chloro-1,2-propanediol (0.80 g, 0.072 mole) was added. Then the reaction mixture was stirred at 90-92° for 24 hours. After cooling, the precipitated sodium chloride was filtered off and the filtrate was concentrated under reduced pressure (at the end at 1 mm Hg). The remaining solid was dispersed in ethanol (80 ml) and filtered off to give 0.40 g (31%) of the hygroscopic product; mp 146-148° dec; ^{1}H nmr (DMSO-d_6): [43], δ 3.3-3.8 (m, 5H, 1'-CH_2, 2'-CH, 3'-CH_2), 4.1-4.3 (m, 2H, 2 OH), 7.5-8.2 ppm (m, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 215 (4.27), 245 nm (sh) (3.83); ir (potassium bromide): ν 1620 (NH_2), 1740 (C=O), 3450 cm^{-1} (OH).

Anal. Calcd. for $C_5H_9N_3O_3S$: C, 31.41; H, 4.74; N, 21.98; S, 16.77. Found: C, 31.74; H, 4.56; N, 21.56; S, 16.38.

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