Synthesis of Acyclic Nucleoside Analogs of 6-Substituted 2-Aminopurines and 2-Amino-8-azapurines [1]

Cyril Párkányi and Hui Liang Yuan

Department of Chemistry, Florida Atlantic University, P.O. Box 3091, Boca Raton, FL 33431-0991 [2]
and
Department of Chemistry, The University of Texas at El Paso, El Paso, TX 79968-0513

Received September 5, 1989

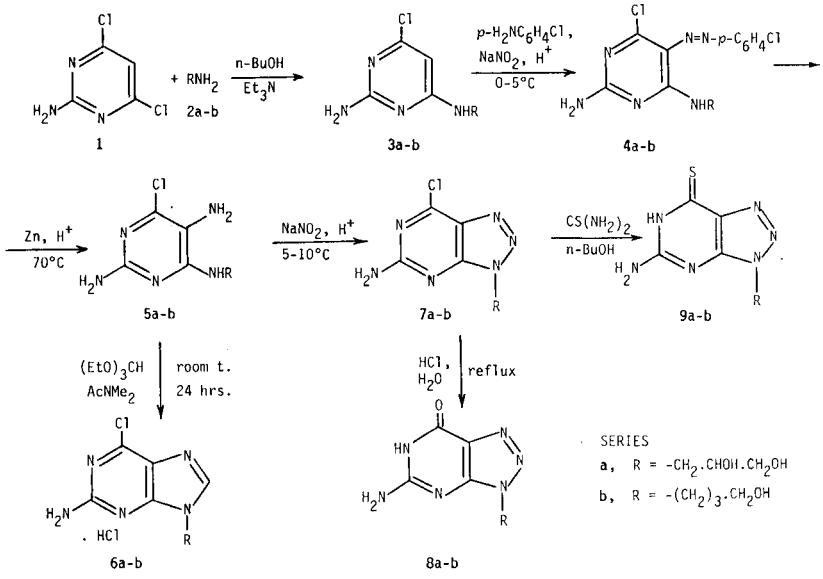
Several new acyclonucleoside purine and 8-azapurine analogs have been prepared from 2-amino-4,6-dichloropyrimidine (**1**) and 3-amino-1,2-propanediol (**2a**) and 4-amino-1-butanol (**2b**), respectively, as the starting materials. The new target compounds are: 2-amino-6-chloro-9-(2,3-dihydroxypropyl)purine (**6a**), 2-amino-6-chloro-9-(4-hydroxybutyl)purine (**6b**), 2-amino-6-chloro-9-(2,3-dihydroxypropyl)-8-azapurine (**7a**), 2-amino-6-chloro-9-(4-hydroxybutyl)-8-azapurine (**7b**), 9-(2,3-dihydroxypropyl)-8-azaguanine (**8a**), 9-(4-hydroxybutyl)-8-azaguanine (**8b**), 9-(2,3-dihydroxypropyl)-8-azathioguanine (**9a**), and 9-(4-hydroxybutyl)-8-azathioguanine (**9b**). Also, the requisite intermediate pyrimidine derivatives, 2,5-diamino-4-(2,3-dihydroxypropylamino)-6-chloropyrimidine (**5a**) and 2,5-diamino-4-(4-hydroxybutylamino)-6-chloropyrimidine (**5b**) are novel.

J. Heterocyclic Chem., **27**, 1409 (1990).

During the last few years, a great variety of acyclonucleoside analogs have been synthesized [3-15] and some of these compounds have been shown to possess significant antiviral activity. For example, 9-(2,3-dihydroxypropyl)adenine (DHPA) and 9-(2-hydroxyethoxymethyl)guanine (acyclovir, Zovirax®) have been reported to inhibit the replication of certain DNA and RNA viruses and to possess a selective activity against the Herpes Simplex I and II virus, respectively [16,17]. In connection with our systematic search for new anticancer and antiviral agents [18-24], we have become interested in the synthesis of 2-amino-6-substituted 8-azapurine 9-acyclonucleoside analogs with improved solubility in water and enhanced antiviral activity.

The starting materials for the synthesis were 2-amino-4,6-dichloropyrimidine (**1**), 3-amino-1,2-propanediol (**2a**), and 4-amino-1-butanol (**2b**). Condensation of **1** with **2a** and **2b** in refluxing 1-butanol in the presence of triethylamine by the method described in the literature [25-27] afforded 2-amino-4-(2,3-dihydroxypropylamino)-6-chloropyrimidine (**3a**) and 2-amino-4-(4-hydroxybutylamino)-6-chloropyrimidine (**3b**), respectively. The intermediate 5-(*p*-chlorophenyl)azo derivatives, **4a** and **4b**, were obtained in good yield (67% and 89%) by reaction of *p*-benzenediazonium chloride with **3a** and **3b**, using the method described by Shealy and co-workers [28-29]. Subsequent reduction of **4a** and **4b** with zinc in acetic acid afforded the requisite 2,5-diamino-4-(2,3-dihydroxypropylamino)-6-

Scheme 1



chloropyrimidine (**5a**) and 2,5-diamino-4-(4-hydroxybutylamino)-6-chloropyrimidine (**5b**), respectively. The new purines, 2-amino-6-chloro-9-(2,3-dihydroxypropyl)purine (**6a**) and 2-amino-6-chloro-9-(4-hydroxybutyl)purine (**6b**), respectively, were obtained by the acid-catalyzed condensation of **5a** and **5b** with triethyl orthoformate in dimethylacetamide [25,28,29]. The 2-amino-6-chloro-8-azapurine acyclonucleosides, *i.e.*, 2-amino-6-chloro-9-(2,3-dihydroxypropyl)-8-azapurine (**7a**) and 2-amino-6-chloro-9-(4-hydroxybutyl)-8-azapurine (**7b**) were prepared *via* diazotization of **5a** and **5b** with sodium nitrite in aqueous acetic acid. The acyclic nucleoside analogs of 8-azaguanine, 9-(2,3-dihydroxypropyl)-8-azaguanine (**8a**) and 9-(4-hydroxybutyl)-8-azaguanine (**8b**), were synthesized by treating **7a** and **7b** with aqueous hydrochloric acid. Finally, the corresponding 8-azathioguanine analogs, 9-(2,3-dihydroxypropyl)-8-azathioguanine (**9a**) and 9-(4-hydroxybutyl)-8-azathioguanine (**9b**), were obtained by reaction of **7a** and **7b** with thiourea in 1-butanol. All the above synthetic procedures are summarized in Scheme 1.

The structures of the new compounds were determined on the basis of their elemental microanalyses and spectral data which are in agreement with their proposed structures. Detailed nmr, uv, and ir spectra are given in the Experimental.

For example, the ir spectra of the compounds with a hydroxy group (hydroxy groups) exhibit a strong band at 3300-3500 cm^{-1}. The C=N ring bond shows a weak absorption at 1600-1650 cm^{-1}. The ir spectra are quite complex in the 2700-3500 cm^{-1} region due to the stretching frequencies of the hydroxy and amino groups involved in the formation of hydrogen bonds. In addition to the methylene group signals, the ^1H nmr spectra generally show the broad interchangeable signals at 4.50-5.35 ppm due to the presence of the hydroxy groups. In some compounds with only one hydroxy group present, the OH signals overlap with those from the CH_2-CH_2 adjacent to the hydroxy group (in dimethyl sulfoxide-d_6).

EXPERIMENTAL

Melting points were determined in capillary tubes heated in a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H nmr spectra were taken on Varian EM-360 (60 MHz) and IBM NR 200 AF (200 MHz) spectrometers using tetramethylsilane (TMS) as the internal standard. The electronic absorption spectra (uv) were obtained on a Perkin-Elmer Lambda 4C ultraviolet-visible spectrophotometer, with a Perkin-Elmer 7700 professional computer. Absorption maxima were determined at *p*H 1, 4, 7, and/or 13. The ir spectra were measured in potassium bromide disks on a Perkin-Elmer 580B infrared spectrophotometer with a Perkin-Elmer 3500 data station. The purity of all compounds was checked by thin-layer chromatography (tlc) on silica gel 60-F-254 precoated plates and the spots were located in the uv light or by iodine vapor. Elemental microanalyses were performed by Desert Analytics, Tucson, AZ. All solvents used were reagent grade. The following solvent systems were used as the mobile phases in tlc: I, ethyl acetate-acetone (1:1); II, acetonitrile-water (4:1); III, ethyl acetate; IV, chloroform-ethyl acetate (1:1).

2-Amino-4-(2,3-dihydroxypropylamino)-6-chloropyrimidine (**3a**) [25-27].

A mixture of 2-amino-4,6-dichloropyrimidine (**1**, 18.6 g, 0.113 mole), 3-amino-1,2-propanediol (**2a**, 10.4 g, 0.114 mole), and freshly distilled triethylamine (12.0 g, 0.119 mole) in 1-butanol (225 ml) was refluxed with stirring for 48 hours. Then the reaction mixture was evaporated under reduced pressure in order to remove the volatile materials, and the oily residue was dissolved in water (100 ml). After chilling, the white solid which had formed was filtered off with suction and washed three times with cold distilled water. The product, **3a**, was obtained in a good yield (21.8 g, 88%), mp 238-240°. It was recrystallized from water and dried under reduced pressure at 50° to afford an analytical sample, mp 240-242°; ^1H nmr (DMSO-d_6): δ 3.20-3.95 (m, 5H, $CH_2.CH.CH_2$), 4.80-5.25 (m, 2H, 2 OH), 6.20 (s, 1H, ArH), 6.82 (s, 2H, NH_2), 7.52 ppm (m, 1H, NH); uv (aqueous hydrochloric acid, *p*H 1): λ max (log ϵ) 215 (4.25), 237 (4.15), 276 (3.94), 286 sh (3.76), 316 nm (3.65); uv (water, *p*H 7): 211 (4.47), 239 (4.11), 286 nm (4.06); uv (aqueous sodium hydroxide, *p*H 13): 239 (4.05), 286 nm (4.07); ir (potassium bromide): strong and moderately strong bands, 600-4000 cm^{-1} region), ν 670, 796, 975, 1015, 1160, 1362, 1475, 1575 and 1650 (C=C and C=N), 2900-3200 (NH_2), 3350 cm^{-1} (OH); tlc: R_F, 0.55 (system I), 0.78 (II), 0.04 (III), 0.12 (IV).

Anal. Calcd. for $C_7H_{11}ClN_4O_2$: C, 38.46; H, 5.07; N, 25.63. Found: C, 38.91; H, 5.17; N, 25.40.

2-Amino-4-(4-hydroxybutylamino)-6-chloropyrimidine (**3b**).

A solution of 2-amino-4,6-dichloropyrimidine (**1**, 9.3 g, 0.057 mole), 4-amino-1-butanol (**2b**, 5.2 g, 0.058 mole), and triethylamine (6.0 g, 0.059 mole) in 1-butanol (130 ml) was heated under reflux for 48 hours. The volatile materials were removed under reduced pressure and the tan oily residue was dissolved in water (80 ml). After cooling, the white solid which had formed was filtered off with suction and washed three times with cold water, to give the product, **3b** (9.3 g, 76%), mp 137-138°. Recrystallization from water followed by drying at 50° under reduced pressure gave the analytically pure sample, mp 137-138°; ^1H nmr (DMSO-d_6): δ 1.35-1.85 (m, 4H, CH_2CH_2), 3.15-3.75 (m, 4H, CH_2CH_2OH), 4.50-4.72 (m, 1H, OH), 6.20 (s, 1H, ArH), 6.80 (s, 2H, NH_2), 7.45 ppm (m, 1H, NH); uv (aqueous hydrochloric acid, *p*H 1): λ max (log ϵ) 214 sh (4.35), 236 (4.05), 274 (3.95), 310 nm (3.25); uv (water, *p*H 7): 211 (4.35), 239 (4.01), 284 nm (3.96); ir (potassium bromide): ν 640, 790, 890, 920, 970, 1045, 1075, 1160, 1275, 1350, 1455, 1475, 1580 and 1650 (C=C and C=N), 2900-3180 (NH_2), 3370 cm^{-1} (OH); tlc: R_F, 0.74 (system I), 0.82 (II), 0.53 (III), 0.32 (IV).

Anal. Calcd. for $C_8H_{13}ClN_4O$: 44.35; H, 6.05; N, 25.86. Found: C, 44.25; H, 6.15; N, 25.60.

2-Amino-4-(2,3-dihydroxypropylamino)-5-(*p*-chlorophenylazo)-6-chloropyrimidine (**4a**) [28,29].

A cold solution of *p*-chlorobenzenediazonium chloride was prepared at 0-5° from *p*-chloroaniline (5.90 g, 0.046 mole), concentrated hydrochloric acid (12.8 ml), water (45 ml), and sodium nitrite (3.56 g, 0.052 mole) dissolved in water (40 ml). This cold solution was added dropwise during 20 minutes to a solution con-

taining **3a** (9.6 g, 0.044 mole), sodium acetate trihydrate (84 g), acetic acid (200 ml), and water (250 ml), and the resulting mixture was stirred at room temperature for 48 hours. The yellow crystalline precipitate was filtered off with suction, washed three times with cold water, and dried at 50° under reduced pressure, to give **4a** (10.6 g, 68%), mp 202-204°. This product was recrystallized from dimethylformamide-water (1:2), filtered off, washed with cold water, and dried *in vacuo* at 50° to give the pure compound (10.2 g, 96% recovery), mp 202-204°; ^{1}H nmr (DMSO-d_6): δ 3.45-3.85 (m, 5H, $CH_2.CH.CH_2$), 4.95-5.65 (m, 2H, 2 OH), 6.75 (s, 2H, NH_2), 7.85-8.30 ppm (m, 4H, C_6H_4); uv (aqueous hydrochloric acid, *p*H 4): λ max (log ϵ) 231 (4.20), 274 sh (3.85), 363 nm (4.15); ir (potassium bromide): ν 685, 797, 920, 1075, 1165, 1275, 1355, 1470, 1576, 1652, 2850-3200 (NH_2), 3450 cm^{-1} (OH); tlc: R_F, 0.70 (system I), 0.73 (II), 0.45 (III), 0.13 (IV).

Anal. Calcd. for $C_{13}H_{14}Cl_2N_6O_2$: C, 43.72; H, 3.95; N, 23.53. Found: C, 43.80; H, 3.88; N, 23.36.

2-Amino-4-(4-hydroxybutylamino)-5-(*p*-chlorophenylazo)-6-chloropyrimidine (**4b**).

A solution of **3b** (4.8 g, 0.222 mole) in acetic acid (105 ml) and water (100 ml), with sodium acetate trihydrate (42 g) in the solution, was cooled to 5-10° and a cold solution (5-10°) of *p*-chlorobenzenediazonium chloride [prepared from *p*-chloroaniline (3.2 g, 0.025 mole), concentrated hydrochloric acid (7.2 ml), water (25 ml), and a solution of sodium nitrite (1.9 g, 0.028 mole) in water (25 ml)] was added dropwise within 30 minutes. The mixture was stirred at room temperature for 48 hours, the yellow crystalline precipitate was filtered off with suction, washed three times with cold water, and dried at 50° under reduced pressure to give **4b** (7.0 g, 89%), mp 197-199°; ^{1}H nmr (DMSO-d_6): δ 1.55-1.82 (m, 4H, CH_2CH_2), 3.45-4.05 (m, 5H, CH_2CH_2OH and OH), 6.80 (s, 2H, NH_2), 7.85-8.40 ppm (m, 4H, C_6H_4); uv (aqueous hydrochloric acid, *p*H 4): λ (log ϵ) 230 (4.28), 274 sh (3.88), 367 nm (4.21); ir (potassium bromide): ν 795, 835, 1090, 1202, 1300, 1380, 1485, 1580, 1655, 2850-3490 cm^{-1} (NH_2, OH); tlc: R_F, 0.82 (system I), 0.79 (II), 0.55 (III), 0.13 (IV).

Anal. Calcd. for $C_{14}H_{16}Cl_2N_6O$: C, 47.34; H, 4.54; N, 23.66. Found: C, 47.48; H, 4.64; N, 23.22.

2,5-Diamino-4-(2,3-dihydroxypropylamino)-6-chloropyrimidine (**5a**).

To a suspension of **4a** (4.0 g, 0.011 mole) in ethanol (100 ml), water (90 ml) and acetic acid (10 ml) were added and the mixture was heated to 75° under nitrogen. Zinc dust (10.0 g) was added in small portions during 30 minutes and a light yellow solution was obtained. The vigorously stirred mixture was heated to 75° for 3 more hours and the completion of the reaction was checked by tlc. The solid phase was separated by filtration in the atmosphere of nitrogen, the residue was washed twice with ethanol, the filtrate and the washings were combined, and the solution was concentrated to a small volume under reduced pressure. The concentrated solution was extracted three times with ether to remove the unreacted *p*-chloroaniline and the aqueous layer was evaporated under reduced pressure. The residue was chromatographed on a silica column. Elution with dimethylformamide-methanol (1:1) afforded **5a** (1.80 g, 69%), suitable for the preparation of **6a** without further purification. A small portion was recrystallized from a mixture of dimethylformamide and methanol and the yellow crystals were dried at 50° under reduced pressure, mp 195-198° dec; ^{1}H nmr (DMSO-d_6): δ 3.55-3.95 (m, 5H, $CH_2.CH.CH_2$), 4.93-5.55 (m, 2H, 2 OH), 6.15 (s, 2H, NH_2), 6.95 (s, 2H, NH_2), 8.25 ppm (m, 1H, NH); uv (water, *p*H 7): λ max (log ϵ) 223 (4.24), 246 sh (4.28), 297 nm (4.08); ir (potassium bromide): ν 650, 793, 930, 1050, 1100, 1250, 1340, 1420, 1590, 1630, 3100-3200 (NH_2), 3390 cm^{-1} (OH); tlc: R_F, 0.20 (system I), 0.73 (II), 0.31 (III), 0.11 (IV).

Anal. Calcd. for $C_7H_{12}ClN_5O_2$: C, 35.99; H, 5.18; N, 29.98. Found: C, 35.93; H, 4.95; N, 30.28.

2,5-Diamino-4-(4-hydroxybutylamino)-6-chloropyrimidine (**5b**).

A suspension of **4b** (3.8 g, 0.011 mole) in ethanol (100 ml), water (100 ml), and acetic acid (10 ml) was heated to 75° under nitrogen and zinc dust (8.0 g) was added in small portions during 30 minutes. A light yellow solution resulted and the stirring was continued at 75° for an additional 4 hours. The solid material was removed by filtration, the filtrate combined with the washings was evaporated under reduced pressure, and the residue was chromtographed on a silica column. The column was eluted with ethyl acetate to remove the unreacted *p*-chloroaniline. Subsequent elution with dimethylformamide-methanol (1:1) afforded the title compound **5b** (1.5 g, 61%), mp 175-178° dec; ^{1}H nmr (DMSO-d_6): δ 1.75-1.95 (m, 4H, CH_2CH_2), 3.60-3.95 (m, 5H, CH_2CH_2OH and OH), 5.95 (s, 2H, NH_2), 6.95 ppm (s, 2H, NH_2); uv (water, *p*H 7): λ max (log ϵ) 223 (4.21), 247 sh (4.18), 300 nm (4.07); ir (potassium bromide): ν 620, 700, 960, 1040, 1420, 1460, 1550, 1625, 3100-3200 (NH_2), 3390 cm^{-1} (OH); tlc: R_F, 0.05 (system I), 0.31 (II), 0.07 (III), 0.05 (IV).

Anal. Calcd. for $C_8H_{14}ClN_5O$: C, 41.48; H, 6.09; N, 30.23. Found: C, 41.67; H, 5.98; N, 30.56.

2-Amino-6-chloro-9-(2,3-dihydroxypropyl)purine Hydrochloride (**6a**).

To a cold solution of **5a** (1.2 g, 0.051 mole) and dimethylacetamide (10 ml), freshly distilled triethyl orthoformate (10 ml) and concentrated hydrochloric acid (0.5 ml) were added, and the mixture was stirred overnight at room temperature. Then the solution was evaporated under reduced pressure, and the oily residue was dissolved in a mixture of chloroform (10 ml) and ether (10 ml). Hydrogen chloride was bubbled through the cooled solution until a white solid precipitated out. It was collected by filtration and dried under reduced pressure at room temperature, to give **6a** (1.35 g, 94%), mp 189-190°. Recrystallization from methanol-ether (1:2) afforded the pure product, mp 189-191°; ^{1}H nmr (DMSO-d_6): δ 3.45-3.85 (m, 5H, $CH_2.CH.CH_2$), 4.85-5.45 (m, 2H, 2 OH), 6.45 (s, 2H, NH_2), 7.95 ppm (s, 1H, purine CH); uv (water, *p*H 7): λ max (log ϵ) 224 (4.35), 250 sh (4.01), 315 nm (3.82); ir (potassium bromide): ν 680, 790, 1010, 1160, 1355, 1480, 1535, 1570, 1625, 2300-2550 (C=NH$^+$), 2900-3200 (NH_2, NH), 3400 cm^{-1} (OH); tlc: R_F, 0.35 (system I), 0.75 (II), 0.13 (III), 0.10 (IV).

Anal. Calcd. for $C_8H_{11}Cl_2N_5O_2$: C, 34.31; H, 3.96; N, 25.01. Found: C, 34.29; H, 3.52; N, 24.58.

2-Amino-6-chloro-9-(4-hydroxybutyl)purine Hydrochloride (**6b**).

Freshly distilled triethyl orthoformate (8 ml) and concentrated hydrochloric acid (0.5 ml) were added to a cold solution of **5b** (0.85 g, 0.0037 mole) in dimethylacetamide (8 ml). The mixture was stirred overnight at room temperature, then the solution was evaporated under reduced pressure, and the remaining oily residue was dissolved in chloroform (10 ml) and ether (10 ml). The solution was cooled and saturated with dry hydrogen

chloride gas. The white precipitate was filtered off and dried under reduced pressure at room temperature. Recrystallization from methanol-ether (1:2) afforded the hydrochloride **6b** (0.93 g, 91%), mp 145-147°; ^{1}H nmr (DMSO-d_6): δ 1.55-1.85 (m, 4H, CH_2CH_2), 3.45-4.15 (m, 5H, CH_2CH_2OH and OH), 6.55 (s, 2H, NH_2), 8.05 ppm (s, 1H, purine CH); uv (water, *p*H 7): λ max (log ε) 230 (4.23), 252 sh (3.95), 313 nm (3.85); ir (potassium bromide): ν 670, 730, 890, 1030, 1175, 1200, 1320, 1440, 1580, and 1620, (C=C and C=N), 2350-2600 (C=NH$^+$), 2800-3200 (NH_2, NH), 3400 cm^{-1} (OH); tlc: R_F, 0.45 (system I), 0.88 (II), 0.12 (III), 0.05 (IV).

Anal. Calcd. for $C_9H_{13}Cl_2N_5O$: C, 38.87; H, 4.71; N, 25.18. Found: C, 38.55; H, 4.48; N, 24.85.

2-Amino-6-chloro-9-(2,3-dihydroxypropyl)-8-azapurine (**7a**).

A solution of **5a** (1.1 g, 0.0047 mole) in water (30 ml) and acetic acid (8 ml) was cooled to 0-5° and a solution of sodium nitrite (0.35 g, 0.005 mole) in water (15 ml) was added dropwise. The mixture was stirred at 0-5° for 2 hours, and then the solution was concentrated to about a half of the original volume under reduced pressure and chilled (-15°). The precipitated **7a** was filtered off, washed with cold water, and dried under reduced pressure at 50°, 0.65 g (57%), mp 215-217° dec; ^{1}H nmr (DMSO-d_6): δ 3.45-3.95 (m, 5H, $CH_2.CH.CH_2$), 4.90-5.45 (m, 2H, 2 OH), 6.75-7.50 ppm (m, 2H, NH_2); uv (aqueous hydrochloric acid, *p*H 4): λ max (log ε) 223 (4.26), 246 sh (4.15), 307 nm (3.89); ir (potassium bromide): ν 680, 1010, 1040, 1060, 1200, 1340, 1420, 1640, 2900-3200 (NH_2), 3400 cm^{-1} (OH); tlc: R_F, 0.18 (system I), 0.49 (II), 0.11 (III), 0.10 (IV).

Anal. Calcd. for $C_7H_9ClN_6O_2$: C, 34.37; H, 3.71; N, 34.36. Found: C, 34.30; H, 4.10; N, 34.16.

2-Amino-6-chloro-9-(4-hydroxybutyl)-8-azapurine (**7b**).

A solution of **5b** (1.2 g, 0.0052 mole) in water (30 ml) and acetic acid (7.5 ml) was cooled to 0-5°, and a solution of sodium nitrite (0.5 g, 0.0073 mole) in water (15 ml) was added dropwise. The mixture was stirred for 3 hours, and then the solution was concentrated to about a half of its original volume under reduced pressure, and chilled. The crystalline **7b** was filtered off, washed twice with cold water, and dried under reduced pressure at 50°, 0.75 g (60%), mp 212-214° dec; ^{1}H nmr (DMSO-d_6): δ 1.65-1.92 (m, 4H, CH_2CH_2), 3.65-4.05 (m, 5H, CH_2CH_2OH and OH), 6.30 ppm (s, 2H, NH_2); uv (aqueous hydrochloric acid, *p*H 4): λ max (log ε) 225 (4.25), 247 sh (3.85), 307 nm (3.98); ir (potassium bromide): ν 680, 840, 940, 1030, 1055, 1240, 1330, 1400, 1625, 2950-3200 (NH_2), 3400 cm^{-1} (OH); tlc: R_F, 0.25 (system I), 0.55 (II), 0.10 (III), 0.06 (IV).

Anal. Calcd. for $C_8H_{11}ClN_6O$: C, 39.60; H, 4.57; N, 34.64. Found: C, 39.89; H, 4.23; N, 34.88.

9-(2,3-Dihydroxypropyl)-8-azaguanine (**8a**).

A solution of **7a** (0.105 g, 0.00043 mole) in 1*N* hydrochloric acid (5 ml) was heated under reflux for 3.5 hours. Then the mixture was treated with activated charcoal and filtered, the colorless filtrate was neutralized to *p*H 6.0 with 0.25*N* sodium carbonate, the crystalline precipitate was filtered off, washed three times with cold water, and dried under reduced pressure at 50°, to give **8a** (0.075 g, 77%), mp 258-262° dec; ^{1}H nmr (DMSO-d_6): δ 3.60-3.95 (m, 5H, $CH_2.CH.CH_2$), 4.85-5.35 (m, 2H, 2 OH), 6.40 ppm (s, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 225 (4.25), 246 sh (3.92), 278 nm (3.95); ir (potassium bromide): ν 790, 840, 1030, 1140, 1235, 1360, 1420, 1500, 1580, 1685, 1720, 3200-3280 (NH_2), 3400 cm^{-1} (OH); tlc: R_F, 0.35 (system I), 0.75 (II), 0.32 (III), 0.11 (IV).

Anal. Calcd. for $C_7H_{10}N_6O_3$: C, 37.17; H, 4.46; N, 37.15. Found: 37.53; H, 4.55; N, 36.86.

9-(4-Hydroxybutyl)-8-azaguanine (**8b**).

A solution of **7b** (0.077 g, 0.00032 mole) in 1*N* hydrochloric acid (5 ml) was heated under reflux for 4.5 hours and then neutralized to *p*H 6.0 with 0.25*N* sodium carbonate. The crystalline precipitate was filtered off, washed three times with cold water, and dried under reduced pressure at 50°; 0.055 g of **8b** (77%), mp 235-240° dec; ^{1}H nmr (DMSO-d_6): δ 1.60-1.95 (m, 4H, CH_2CH_2), 3.40-3.95 (m, 5H, CH_2CH_2OH and OH), 6.75 ppm (s, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 228 (4.23), 255 sh (4.02), 275 nm (3.75); ir (potassium bromide): ν 785, 940, 1020, 1100, 1270, 1350, 1590, 1640, 1740, 2920-3100 (NH_2), 3380 cm^{-1} (OH); tlc: R_F, 0.37 (system I), 0.78 (II), 0.35 (III), 0.12 (IV).

Anal. Calcd. for $C_8H_{12}N_6O_2$: C, 42.85; H, 5.39; N, 37.49. Found: C, 42.95; H, 5.49; N, 37.63.

9-(2,3-Dihydroxypropyl)-8-azathioguanine (**9a**).

A mixture of **7a** (0.115 g, 0.00047 mole) and thiourea (0.085 g, 0.0011 mole) in 1-butanol (10 ml) was heated under reflux for 8 hours. Then the reaction mixture was concentrated to about a half of the original volume under reduced pressure, chilled, and the yellow crystalline solid was separated by filtration, washed three times with cold water, and recrystallized from 1-propanol to give **9a** (0.075 g, 66%), mp 289-292°; ^{1}H nmr (DMSO-d_6): δ 3.45-3.85 (m, 5H, $CH_2.CH.CH_2$), 4.85-5.45 (m, 2H, 2 OH), 6.50 (m, 2H, NH_2), 10.50 ppm (s, 1H, NH); uv (water, *p*H 7): λ max (log ε) 233 (4.24), 265 (3.88), 315 nm (3.56); ir (potassium bromide): ν 840, 950, 1030, 1045, 1320, 1480, 1540, 1645, 2600, 2900-3200 (NH_2, NH), 3400 cm^{-1} (OH); tlc: R_F, 0.45 (system I), 0.80 (II), 0.42 (III), 0.18 (IV).

Anal. Calcd. for $C_7H_{10}N_6O_2S$: C, 34.71; H, 4.16; N, 34.69. Found: C, 34.27; H, 3.98; N, 34.48.

9-(4-Hydroxybutyl)-8-azathioguanine (**9b**).

A mixture of **7b** (0.105 g, 0.00043 mole) and thiourea (0.080 g, 0.001 mole) in 1-butanol (10 ml) was heated under reflux for 4 hours, then the reaction mixture was concentrated to about a half of the original volume under reduced pressure, chilled, and the light yellow crystalline product was filtered off, washed with cold water, and dried under reduced pressure at 50° to give **9b** (0.075 g, 73%), mp >300° dec; ^{1}H nmr (DMSO-d_6): δ 1.60-1.94 (m, 4H, CH_2CH_2), 3.65-4.05 (m, 5H, CH_2CH_2OH and OH), 6.95 ppm (s, 2H, NH_2); uv (water, *p*H 7): λ max (log ε) 234 (4.25), 258 (3.85), 305 nm (3.35); ir (potassium bromide): ν 895, 940, 1020, 1175, 1355, 1385, 1455, 1575, 1615, 2900-3200 (NH_2), 3450 cm^{-1} (OH); tlc: R_F, 0.42 (system I), 0.73 (II), 0.37 (III), 0.12 (IV).

Anal. Calcd. for $C_8H_{12}N_6OS$: C, 39.99; H, 5.03; N, 34.98. Found: C, 39.69; H, 4.98; N, 34.89.

Acknowledgements.

This work was supported by grants from the Elsa U. Pardee Foundation, Midland, MI, and the Robert A. Welch Foundation, Houston, TX (Grant AH-461). The authors wish to express their sincere thanks to Dr. Winston D. Lloyd for his help with the nmr spectra.

REFERENCES AND NOTES

[1] Presented, in part, at the 1987 Pacific Conference on Chemistry and Spectroscopy and the 23rd Western Regional Meeting of the American Chemical Society, Irvine, CA, October 28-30, 1987.

[2] Present address.

[3] G. B. Elion, P. A. Furman, J. A. Fyfe, P. De Miranda, L. Beauchamp and H. J. Schaeffer, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 5716 (1977).

[4] H. J. Schaeffer, L. Beauchamp, P. De Miranda, G. B. Elion, D. J. Bauer and P. Collins, *Nature (London)*, **272**, 583 (1978).

[5] E. De Clercq, J. Descamps, P. De Somer and A. Holý, *Science*, **200**, 563 (1978).

[6] E. De Clercq and P. F. Torrence, *J. Carbohydr., Nucleosides, Nucleotides*, **5**, 187 (1978).

[7] K. A. Watanabe, U. Reichman, K. Hirota and J. J. Fox, *J. Med. Chem.*, **22**, 21 (1979).

[8] E. De Clercq, J. Descamps, P. De Somer, P. J. Barr, A. S. Jones and R. T. Walker, *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 2947 (1979).

[9] E. De Clercq, *Trends Pharmacol. Sci.*, **3**, 492 (1982).

[10] K. K. Ogilvie, U. O. Cheriyan, B. K. Radatus, K. O. Smith, K. S. Galloway and W. L. Kennell, *Can. J. Chem.*, **60**, 3005 (1982).

[11] R. Vince, S. Daluge, H. Lee, W. M. Shannon, G. Arnett, T. W. Schafer, T. L. Nagabhushnan, P. Reichert and H. Tsai, *Science*, **221**, 1405 (1983).

[12] J. C. Martin, C. A. Dvorak, D. F. Smee, T. R. Matthews and J. P. H. Verheyden, *J. Med. Chem.*, **26**, 759 (1983).

[13] A. K. Field, M. E. Davies, C. De Witt, H. C. Perry, R. Liou, J. I. Germershausen, J. D. Karkas, W. T. Ashton, D. B. R. Johnston and R. L. Tolman, *Proc. Natl. Acad. Sci. U.S.A.*, **80**, 4139 (1983).

[14] A. Holý, A. Ludziša, I. Votruba, K. Šedivá and H. Pischel, *Collect. Czech. Chem. Commun.*, **50**, 393 (1985).

[15] C. K. Chu and S. J. Cutler, *J. Heterocyclic Chem.*, **23**, 289 (1986).

[16] E. De Clercq and A. Holý, *J. Med. Chem.*, **22**, 510 (1979).

[17] A. Holý, I. Votruba and E. De Clercq, *Collect. Czech. Chem. Commun.*, **50**, 245 (1985).

[18] J. Gut, J. Morávek, C. Párkányi, M. Prystaš, J. Škoda and F. Šorm, *Collect. Czech. Chem. Commun.*, **24**, 3154 (1959).

[19] J.Škoda, A. Čihák, J. Gut, M. Prystaš, A. Pískala, C. Párkányi and F. Šorm, *Collect. Czech. Chem. Commun.*, **27**, 1736 (1962).

[20] C. Párkányi, *Chem. Listy*, **56**, 652 (1962).

[21] C. Párkányi and F. Šorm, *Collect. Czech. Chem. Commun.*, **28**, 2491 (1963).

[22] C. Párkányi, N. S. Cho and G. S. Yoo, *J. Organometal. Chem.*, **342**, 1 (1988).

[23] C. Párkányi, H. L. Yuan, N. S. Cho, J.-H. J. Jaw, T. E. Woodhouse and T. L. Aung, *J. Heterocyclic Chem.*, **26**, 1331 (1989).

[24] N. S. Cho, K. Y. Song and C. Párkányi, *J. Heterocyclic Chem.*, **26**, 1807 (1989).

[25] H. J. Schaeffer, D. Vogel and R. Vince, *J. Med. Chem.*, **8**, 502 (1965).

[26] H. J. Schaeffer and P. S. Bhargava, *Biochemistry*, **4**, 71 (1965).

[27] L. Colla, R. Busson, E. De Clercq and H. Vanderhaeghe, *Eur. J. Med. Chem.*, **17**, 569 (1982).

[28] Y. F. Shealy, C. A. O'Dell, W. M. Shannon and G. Arnett, *J. Med. Chem.*, **27**, 1416 (1984).

[29] Y. F. Shealy, C. A. O'Dell and G. Arnett, *J. Med. Chem.*, **30**, 1090 (1987).