(±)-5'-Nor Ribofuranoside Carbocyclic Guanosine

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The synthesis of the guanine derivative (±)-2-amino-1,9-dihydro-9-[(1'α,2'β,3'β,4'α)-(2',3',4'-trihydroxy-1'-cyclopentyl]-6*H*-purin-6-one (**2**) is described. This compound is viewed as the carbocyclic ribofuranoside guanine nucleoside analogue lacking the 5'-methylene.

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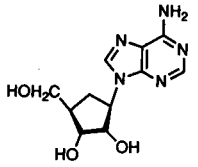
Purine and pyrimidine carbocyclic nucleosides [1] have become increasingly significant in the development of biological probes [2] and chemotherapeutic agents [3]. In the purine series, the naturally occurring carbocyclic adenosine (aristeromycin, **1**) [4,5] and several synthetic carbocyclic guanosines [6] have been shown to possess antiviral properties. Current studies [7,8] are focusing on the necessity that carbocyclic nucleosides possess a C-5' unit to elicit a biological response. In this direction, the synthesis of the (±)-5'-nor guanosine ribofuranoside derivative **2** has been accomplished.



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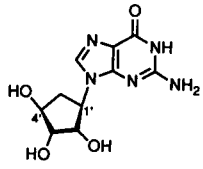

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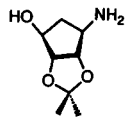

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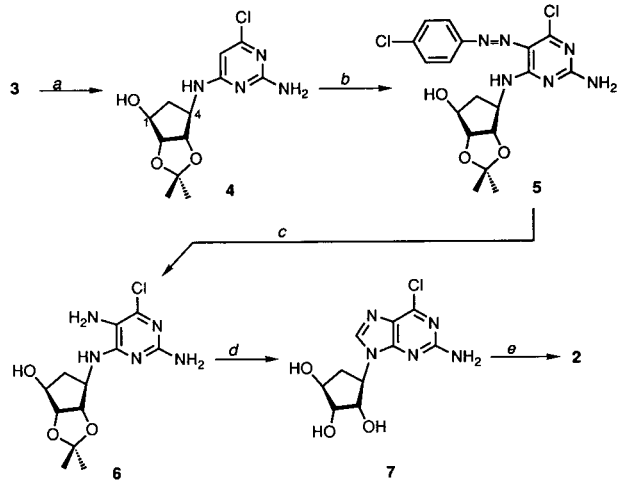
After considering several starting materials [5d,9,10] for the preparation of **2**, the 2,3-*O*-isopropylidene derivative of (±)-(1α,2β,3β,4α)-4-amino-1,2,3-cyclopentanetriol (**3**) [10] was chosen for use in the Scheme. Thus, reaction of **3** with 2-amino-4,6-dichloropyrimidine gave the 2,3-*O*-isopropylidene derivative of (±)-(1α,2β,3β,4α)-4-[(2-amino-6-chloropyrimidin-4-yl)amino]-1,2,3-cyclopentanetriol (**4**). Subsequent diazo coupling of **4** with 4-chlorobenzenediazonium chloride to **5** followed by reduction using zinc-acetic acid gave the diamine precursor **6**. Ring closure of **6** with diethoxymethyl acetate led to (±)-(1α,2β,3β,4α)-4-(2-amino-6-chloro-9*H*-purin-9-yl)-1,2,3-cyclopentanetriol (**7**). Hydrolysis of **7** in dilute hydrochloric acid produced the desired (±)-2-amino-1,9-dihydro-9-[(1'α,2'β,3'β,4'α)-(2',3',-4'-trihydroxy-1'-cyclopentyl)]-6*H*-purin-6-one (**2**).

Scheme



Reaction conditions: *a*, 2-amino-4,6-dichloropyrimidine; *b*, 4-chlorobenzenendiazonium chloride; *c*, zinc dust-acetic acid; *d*, (i) diethoxymethyl acetate; (ii) 0.5 N hydrochloric acid; *e*, 1 N hydrochloric acid

EXPERIMENTAL

Materials and Methods.

Melting points were recorded on a Mel-Temp capillary melting point apparatus and are uncorrected. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ. Reactions were monitored by thin layer chromatography (tlc) using 0.25 mm E. Merck Silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a Mineralight UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Davidson Chemical silca gel (60-200 mesh) or Aldrich silica gel (230-400 mesh, 60 Å) eluting with the indicated solvent system. Unless indicated otherwise, yields refer to chromatographically and spectroscopically (pmr and cmr) homogeneous materials.

The pmr and cmr spectra were recorded on a JEOL FX90Q spectrometer (operated at 90 MHz and 22.5 MHz, respectively) and a Bruker 360 AMX spectrometer (operated at 360 MHz and 90 MHz, respectively) in dimethyl sulfoxide-d_6 referenced to internal tetramethylsilane at 0.0 ppm. The spin multiplicities are indicated by the symbols s (singlet), d (doublet), and m (multiplet). It should be noted that, for the sake of assigning nmr peaks, the atoms of the cyclopentyl moiety in **2** are given prime designations with the position numbers following ribofuranosyl convention except that C-5' represents the endocyclic carbon that makes carbocyclic nucleosides unique. In compounds named as derivatives of

cyclopentanols, the standard cyclopentane position designations are given (see **4** of the Scheme) and the heterocyclic base is considered as a substituent.

(±)-(1α,2β,3β,4α)-4-[(2-Amino-6-chloropyrimidin-4-yl)amino]-2,-3-*O*-isopropylidene-1,2,3-cyclopentanetriol (**4**).

A mixture of the 2,3-*O*-isopropylidene derivative of (±)-(1α,2β,-3β,4α)-4-amino-1,2,3-cyclopentanetriol (**3**) [10] (1.65 g, 9.65 mmoles), 2-amino-4,6-dichloropyrimidine (2.37 g, 14.17 mmoles), and triethylamine (10 ml) in 1-butanol (50 ml) was refluxed under nitrogen for 2 days. The voltailes were removed under reduced pressure and the residue was then azeotroped with methanol. The material remaining after this treatment was purified by flash chromatography using methanol-methylene chloride (1:9) as the eluent; the solid thus obtained was recyrstallized from methylene chloride-hexane to yield **4** (2.72 g, 95%) as white crystals, mp 223.5-224-5°; pmr (dimethyl sulfoxide-d_6, 360 MHz): δ 1.19 and 1.33 (2s, 6 H, 2 x CH_3), 1.44-1.65 (m, 1 H, H-5), 2.04-2.17 (m, 1 H, H-5), 3.95-4.43 (m, 4 H, H-1, H-2, H-3, and H-4), 5.35 (broad s, 1 H, OH), 5.84 (broad s, 1 H, H-5 of pyrimidine), 6.42 (broad s, 2 H NH_2), 6.54 (broad s, 1 H, NH); cmr (dimethyl sulfoxide-d_6, 90 MHz): δ 24.01 and 26.39 (2 x CH_3), 35.94 (C-5), 55.58 (C-4), 75.48, 84.87, and 85.75 (C-1, C-2, and C-3), 93.08, 109.69, 157.47, 162.84, and 163.04 (C of isopropylidene and pyrimidine).

Anal. Calcd. for $C_{12}H_{17}ClN_4O_3$: C, 47.92; H, 5.69; N, 18.62. Found: C, 48.03; H, 5.77; N, 18.52.

(±)-2-Amino-1,9-dihydro-9-[(1′α,2′β,3′β,4′α)-(2′,3′,4′-trihydroxy-1′-cyclopentyl]-6*H*-purin-6-one (**2**).

A cold suspension of 4-chlorobenzenediazonium chloride was prepared by adding a solution of sodium nitrite (0.65 g, 9.5 mmoles) in water (5 ml) to a solution of 4-chloroaniline (1.15 g, 9 mmoles) dissolved in 12 *N* hydrochloric acid (5 ml) and water (15 ml) and cooled in an ice bath. The cold solution of 4-chlorobenzenediazonium chloride was added dropwise, with stirring, to a mixture of **4** (2.35 g, 7.8 mmoles), sodium acetate trihydrate (17 g), glacial acetic acid (40 ml) and water (40 ml) at room temperature. After stirring this mixture at room temperature for 18 hours, the reaction was found to be incomplete by tlc analysis. Therefore, additional 4-chlorobenzenediazonium chloride (prepared from sodium nitrite (0.325 g) and 4-chloroaniline (0.58 g), as described above) was slowly added to the mixture. The stirring was continued for a total of 40 hours. The reaction mixture was then cooled and the resulting yellow solid obtained by filtration, washed with cold water, and dried. The solid was recrystallized from methylene chloride-methanol to give (±)-(1α,2β,3β,4α)-4-{[2-amino-6-chloro-5-(4-chlorophenylazo)pyrimidin-4-yl]amino}-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol (**5**) as yellow crystals (3.155 g, 92%), mp 264-265° dec; pmr (dimethyl sulfoxide-d_6, 90 MHz): δ 1.21 and 1.35 (2s, 6 H, 2 x CH_3), 1.55-2.4 (m, 2 H, H-5), 3.15-4.95 (m, 5 H, H-1, H-2, H-3, H-4, and OH), 7.14-7.96 (m, 6 H, ArH and NH_2), 10.11 (d, 1 H, NH).

A mixture of **5** (2.16 g, 4.93 mmoles), zinc dust (3.14 g), glacial acetic acid (1.6 ml) in ethanol (80 ml) and water (80 ml) was refluxed under nitrogen until the yellow color of **5** disappeared (5 hours). The reaction mixture was filtered hot and the insoluble material was washed with hot ethanol. Evaporation of the combined filtrates under reduced pressure gave a residue that was, first, azeotroped with ethanol and, then, purified using flash chromatography with 3.5-5% methanol in methylene chloride as the eluent. This process gave pure (±)-(1α,2β,3β,4α)-4-[(2,5-diamino-6-chloropyrimidin-4-yl)amino]-2,3-*O*-isopropylidene-1,2,3-cyclopentanetriol (**6**) (1.2 g, 77%) as colorless crystals (from methanol-methylene chloride), mp 212-214°; pmr (dimethyl sulfoxide-d_6, 90 MHz): δ 1.21 and 1.35 (2s, 6 H, 2 x CH_3), 1.47-2.36 (m, 2 H, H-5), 3.97-4.51 (m, 4 H, H-1, H-2, H-3, and H-4), 5.42 (d, J = 2.6 Hz, 1 H, OH), 6.72 (broad s, 2 H, NH_2), 6.43 (d, 1 H, NH); cmr (dimethyl sulfoxide-d_6, 22.5 MHz): δ 24.01 and 26.40 (2 x CH_3), 35.61 (C-5), 56.08 (C-4), 75.86, 85.12, and 85.77 (C-1, C-2, and C-3), 109.50, 112.10, 144.77, 156.52, 156.90 (C of isopropylidene and pyrimidine).

A mixture of **6** (1.2 g, 3.8 mmoles) in diethoxymethyl acetate (30 ml) was stirred at room temperature for 1 hour. The reaction mixture was then stirred at 80-85° for 22 hours. The excess diethoxymethyl acetate was removed under reduced pressure and the residue was dissolved in 0.5 *N* hydrochloric acid in methanol (50 ml). This new reaction mixture was stirred for 30 minutes at room temperature and the solution evaporated under reduced pressure to yield a residue that was azeotroped with methanol. The resultant residue was dissolved in methanol and the *p*H adjusted to 7 by treating the solution with IRA 400 (basic) resin. The resin was removed by filtration and washed with methanol. The combined filtrates were evaporated under reduced pressure to produce a residue that was purified by column chromatography using methanol-methylene chloride (1:4) as eluent to give 300 mg of pure (±)-(1α,2β,3β,4β)-4-(2-amino-6-chloro-9*H*-purin-9-yl)-1,2,3-cyclopentanetriol (**7**) and 400 mg of mostly an uncyclized products (by pmr). This latter material was again subjected to the cyclization conditions described above to give, after similar workup, an additional 320 mg of **7** (total yield, 620 mg, 57%) that was recrystallized from chloroform-methanol, mp 166-168°; pmr (dimethyl sulfoxide-d_6, 360 MHz) δ 1.61-1.78 (m, 1 H, H-5), 2.50-2.68 (m, 1 H, H-5), 3.25-4.72 (m, 4 H, H-1, H-2, H-3, and H-4), 6.38 (broad s, 2 H, NH_2), 7.93 (s, 1 H, H-8 of purine).

Compound **7** (120 mg, 0.42 mmoles) was dissolved in 1 *N* hydrochloric acid (20 ml) and this solution was refluxed for 5 hours under nitrogen. The solvent was removed under reduced pressure and the residue then azeotroped with ethanol. The resultant white residue was dissolved in water (10 ml) and the new solution neutralized with 6 *N* aqueous sodium hydroxide solution (*p*H 7-8). Even though a precipitate formed immediately, the solution was refrigerated overnight. Following this, the solid material was obtained by filtration and then washed with cold water to give **2** (90 mg, 80%), mp >282° (after recrystallization from methanol-water); pmr (dimethyl sulfoxide-d_6, 360 MHz): δ 1.53-1.66 (m, 1 H, H-5′), 2.51-2.61 (m, 1 H, H-5′), 3.74 (broad s, 1 H, H-3′), 3.87 (broad s, 1 H, H-4′), 4.35-4.45 (m, 1 H, H-2′), 4.47-4.61 (m, 1 H, H-1′), 4.84 (d, J = 3.3 Hz, 1 H, C-3′ OH), 5.02 (d, J = 6.2 Hz, 1 H, C-2′ OH), 5.19 (d, J = 6.2 Hz, C-4′ OH), 6.44 (s, 2 H, NH_2), 7.77 (s, 1 H, H-8 of purine), 10.62 (s, 1 H, H-1 of purine); cmr (dimethyl sulfoxide-d_6, 90 MHz): δ 37.01 (C-5′), 57.21 (C-1′), 73.41, 75.28, and 76.55 (C-2′, C-3′, and C-4′), 116.57, 135.81, 151.29, 153.16, and 156.77 (C of purine).

Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.75\ H_2O$: C, 42.78; H, 5.20; N, 24.94. Found: C, 42.87; H, 5.08; N, 24.94.

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