Nucleoside Analogs. 4. Synthesis of 3′-Amino-3′-deoxyadenosine Analogs

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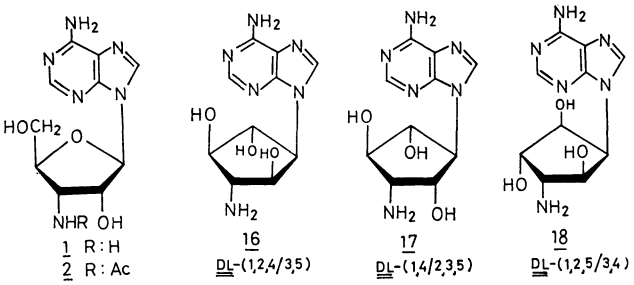
Three 9-(3-amino-2,4,5-trihydroxycyclopentyl)adenines and their *N*-acyl derivatives were prepared as carbocyclic analogs of 3′-amino and 3′-acetamido-3′-deoxyadenosine from the three diastereomers of diaminocyclopentanetriol and 4-amino-6-chloro-5-nitropyrimidine.

We have been working on a synthesis of nucleoside analogs, in which the ribofuranosyl moiety of adenosine is replaced by a cyclopentane ring stable against hydrolysis and enzymic action. In connection with the preceding paper,[1] we wish to report a synthesis of carbocyclic analogs of 3′-amino-3′-deoxyadenosine.

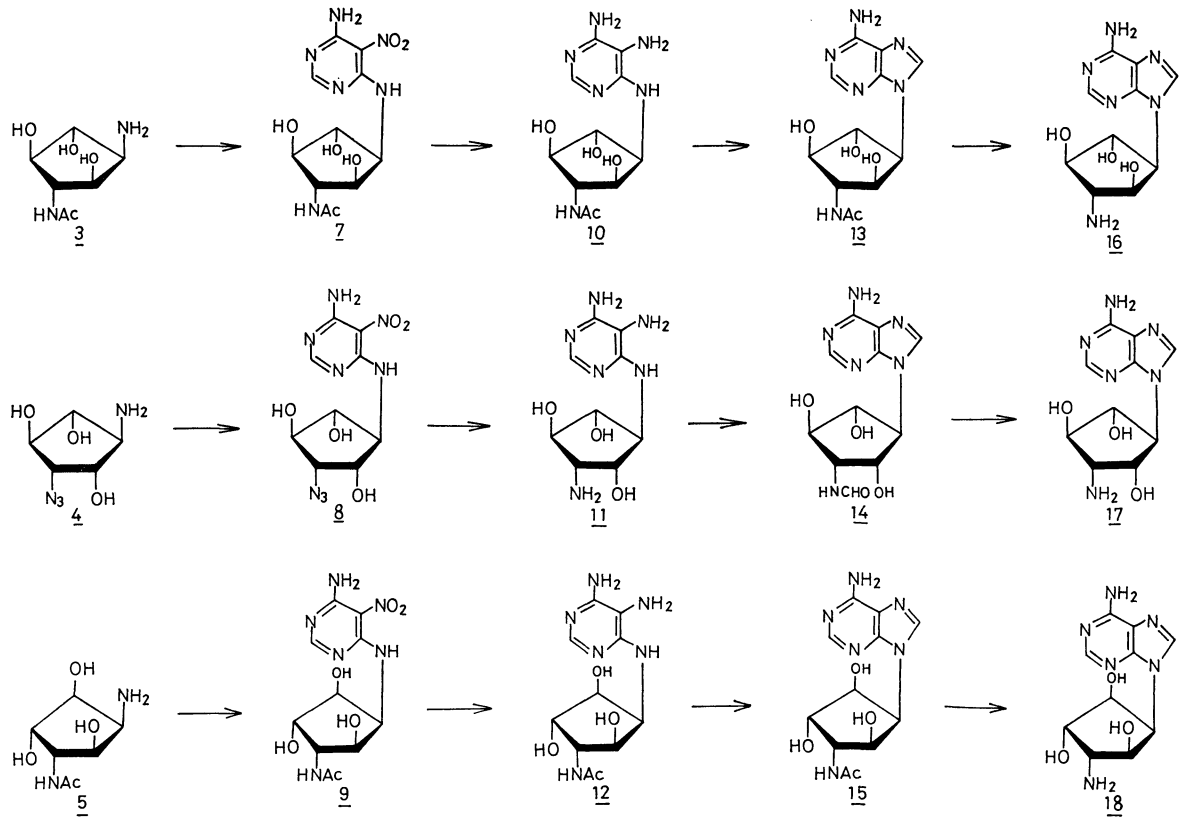
3′-Amino-3′-deoxyadenosine (**1**) has been found in a fermentation broth of *Helminthosporium*,[2] *Cordyceps militaris*,[3] and *Aspergillus nidulans*.[4] The compound has antitumor and antimitotic activity, inhibiting growth of *Cryptococcus neoformans* 4806 and *Candida albicans*.[4] 3′-Acetamido-3′-deoxyadenosine (**2**)[5] was found in a culture filtrate of *Helminthosporium* together with **1**, but inhibited growth of neither Ehrlich carcinoma nor of bacteria.[5]

The structural requirements in puromycin analogs for inhibition of protein synthesis were demonstrated by Daluge and Vince[6] in a synthesis of carbocyclic analogs of puromycin. They suggested that the ribofuranosyl ring can be replaced by the cyclopentyl ring without loss of activity, and that removal of the hydroxymethyl group is not detrimental to the activity, its removal being desirable for reducing toxicity.



Scheme 1.*

We were prompted to attempt the synthesis of a carbocyclic analog retaining the structural features suggested so far. We have prepared 9-(3-amino-2,4,5-trihydroxycyclopentyl)adenines (**16**, **17**, and **18**) and their *N*-acyl derivatives (**13**, **14**, and **15**) by the following reaction routes (Scheme 2).



Scheme 2.*

* Structures in Schemes 1 and 2 dipict only one enantiomer of the racemic form actually obtained in the present experiment.

Tri-*O*-acetyl-DL-(1,2,4/3,5)-5-acetamido-2-azido-1,3,4-cyclopentanetriol[7] was selectively *O*-deacetylated, and subsequently hydrogenated to give DL-(1,3,5/2,4)-2-acetamido-5-amino-1,3,4-cyclopentanetriol (**3**).

Hydrolysis of the starting material in 3 M hydrochloric acid, followed by removal of the chloride ion, gave 5-amino-2-azido-1,3,4-cyclopentanetriol (**4**). Another diastereomer: tri-*O*-acetyl-DL-(1,2,3/4,5)-5-acetamido-2-azido-1,3,4-cyclopentanetriol[7] was *O*-deacetylated, and subsequently hydrogenated catalytically to give DL-(1,4,5/2,3)-2-acetamido-5-amino-1,3,4-cyclopentanetriol (**5**).

Compounds **3**, **4**, and **5** were condensed with 4-amino-6-chloro-5-nitropyrimidine[8] (**6**) to give the corresponding pyrimidine derivatives (**7**), (**8**), and (**9**), respectively. Reduction of the nitro group, followed by ring closure of the respective pyrimidine derivatives (**10**), (**11**), and (**12**) with formamide, gave the corresponding 3′-*N*-acyl adenine derivatives (**13**), (**14**), and (**15**), respectively. Hydrolysis of **13**, **14**, and **15** in barium hydroxide solution yielded the corresponding adenine analogs (**16**), (**17**), and (**18**), respectively. These compounds showed no biological activity against HeLa S3 cell.

Experimental

Melting points were determined in capillary tubes in a liquid bath and are uncorrected. Solutions were evaporated under reduced pressure at 40—50 °C. TLC was performed on a silica gel plate (Wakogel B-10, Wako Pure Chemical Industries Ltd.). Elemental analyses were performed by Mr. Saburo Nakada to whom our thanks are due.

DL-(1,3,5/2,4)-2-Acetamido-5-amino-1,3,4-cyclopentanetriol (3). A 4.94 g portion of DL-1,3,4-tri-*O*-acetyl-(1,2,4/3,5)-5-acetamido-2-azido-1,3,4-cyclopentanetriol[7] was *O*-deacetylated in methanolic ammonia. The product was catalytically hydrogenated in 50% aqueous ethanol in the presence of Raney nickel to give 2.48 g of crude **3**, which was recrystallized from aqueous ethanol to give 0.98 g (36%) of pure **3**, mp 199—200 °C.

Found: C, 44.16; H, 7.39; N, 14.72%. Calcd for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.73%.

DL-(1,2,4/3,5)-5-Amino-2-azido-1,3,4-cyclopentanetriol (4). DL-1,3,4-tri-*O*-acetyl-(1,2,4/3,5)-5-acetamido-2-azido-1,3,4-cyclopentanetriol[7] (5.39 g) was hydrolyzed in 3 M hydrochloric acid (100 ml) at 100 °C for 3 h, and the solution was evaporated. The residue was dissolved in water and the solution was treated with Amberlite IRA-400 (OH^-) resin in a column. The effluent was evaporated and the residue was recrystallized from isopropyl alcohol to give 2.40 g (88%) of **4**, mp 115—116 °C.

Found: C, 34.73; H, 5.78: N, 32.02%. Calcd for $C_5H_{10}N_4O_3$: C, 34.48; H, 5.79; N, 32.17%.

DL-(1,4,5/2,3)-2-Acetamido-5-amino-1,3,4-cyclopentanetriol (5). DL-1,3,4-Tri-*O*-acetyl-(1,2,3/4,5)-5-acetamido-2-azido-1,3,4-cyclopentanetriol[7] (3.35 g) was *O*-deacetylated in methanolic ammonia to give 2.45 g of crude product. The product was triturated in ethanol to give 1.97 g (93%) of *O*-deacetylated derivative, mp 168—169 °C.

Found: C, 38.77; H, 5.74; N, 25.60%. Calcd for $C_7H_{12}N_4O_4$: C, 38.89; H, 5.60; N, 25.92%.

The above product (1.38 g) was catalytically hydrogenated in water (32 ml) overnight to give 1.17 g (97%) of crude **5**, which was recrystallized from ethanol to give an analytical sample, mp 175—176 °C (dec).

Found: C, 43.90; H, 7.36; N, 14.56%. Calcd for $C_7H_{14}N_2O_4$: C, 44.20; H, 7.42; N, 14.73%.

The hydrochloride melted at 194—195 °C.

Found: C, 37.29; H, 6.61; N, 12.13; Cl, 15.72%. Calcd for $C_7H_{15}N_2O_4Cl$: C, 37.09; H, 6.67; N, 12.36; Cl, 15.64%.

6-[DL-(1,2,4/3,5)-3-Acetamido-2,4,5-trihydroxycyclopentyl]-amino-4-amino-5-nitropyrimidine (7). A mixture of **3** (1.00 g), 4-amino-6-chloro-5-nitropyrimidine[8] (**6**) (1.10 g) and triethylamine (1 ml) was heated in 2-methoxyethanol (50 ml) at 90—95 °C for 1.5 h. After being cooled to ambient temperature, the resulting crystalline product was collected by filtration. The product was recrystallized from hot water and subsequently washed with warm ethanol to give 1.58 g (92%) of **7**, 275—285 °C (dec).

Found: C, 40.34; H 4.89; N, 25.72%. Calcd for $C_{11}H_{16}N_6O_6$; C, 40.25; H, 4.91; N, 25.60%.

4-Amino-6-[DL-(1,4/2,3,5)-3-azido-2,4,5-trihydroxycyclopentyl]-amino-5-nitropyrimidine (8). A mixture of **4** (1.00 g), 4-amino-6-chloro-5-nitropyrimidine[8] (1.10 g) and triethylamine (1 ml) was heated at 80 °C in 2-methoxyethanol (30 ml) for 1 h. The reaction mixture was evaporated and the residue was triturated with warm benzene. The residual solid was recrystallized from hot water to give 1.70 g (95%) of **8** as yellow crystals, mp 206—207 °C (dec).

Found: C, 34.68; H, 3.88; N, 35.66%. Calcd for $C_9H_{12}N_8O_5$: C, 34.62; H, 3.88; N, 35.89%.

6-[DL-(1,2,5/3,4)-3-Acetamido-2,4,5-trihydroxycyclopentyl]amino-4-amino-5-nitropyrimidine (9). A mixture of **5** (1.17 g), 4-amino-6-chloro-5-nitropyrimidine[8] (1.29 g) and triethylamine (2.4 ml) was heated in 2-methoxyethanol (59 ml) at 85 °C for 3 h. The reaction mixture was evaporated and the residue was triturated with warm ethanol to give 1.43 g (71%) of **9** as yellow crystals, mp 237—238 °C (dec).

Found: C, 40.31; H, 4.93; N, 25.28%. Calcd for $C_{11}H_{16}N_6O_6$: C, 40.25; H, 4.91; N, 25.60%.

6-[DL-(1,2,4/3,5)-3-Acetamido-2,4,5-trihydroxycyclopentyl]amino-4,5-diaminopyrimidine (10). Compound **7** was dissolved in hot water (80 ml) and to the resulting solution zinc powder (15 g) was added. The mixture was heated under reflux for 7.5 h, and filtered. The filtrate was evaporated and the residue was washed with ethanol to give 455 mg (100%) of **10**, which was acetylated in the usual way to give a hexa-*N*,*O*-acetyl derivative. The product was recrystallized from ethyl acetate–ethanol (1:1 v/v%) to give an analytical sample, mp 232—233 °C (dec).

Found: C, 49.69; H, 5.73; N, 16.68%. Calcd for $C_{21}H_{28}N_6O_9$: C, 49.60; H, 5.55; N, 16.53%.

6-[DL-(1,2,5/3,4)-3-Acetamido-2,4,5-trihydroxycyclopentyl]amino-4,5-diaminopyrimidine (12). Compound **9** (504 mg) was reduced with zinc powder in boiling water as in the preparation of **10**. The crude product was recrystallized from ethanol to give 402 mg (88%) of **12**. An analytically pure sample was obtained by further recrystallization from water as pale yellow crystals, mp 237—238 °C (dec).

Found: C, 44.40; H, 6.17; N, 27.84%. Calcd for $C_{11}H_{18}N_6O_4$: C, 44.29; H, 6.08; N, 28.17%.

9-[DL-(1,2,4/3,5)-3-Acetamido-2,4,5-trihydroxycyclopentyl]-adenine (13). Compound **10** was heated at 175—180 °C in formamide (10 ml) for 1.5 h, and evaporated. The residue was recrystallized from hot water (3 ml) to give 131 mg (37%) of **13** as colorless needles, mp 290—300 °C (dec).

UV: $\lambda_{max}^{0.1\ M\ HCl}$ 259 nm (ε=12400), $\lambda_{max}^{H_2O}$ 261 nm (ε=12900), $\lambda_{max}^{0.1\ M\ NaOH}$ 259 nm (ε=6450).

Acetylation of **13** in the usual way gave 9-[DL-(1,2,4/3,5)-3-acetamido-2,4,5-triacetoxycyclopentyl]-6-diacetylaminopurine, mp 201—203 °C.

Found: C, 50.90; H, 5.10; N, 16.13%. Calcd for $C_{22}H_{26}$-

N_6O_9: C, 50.96; H, 5.06; N, 16.21%.

*9-[DL-(1,4/2,3,5)-3-Formamido-2,4,5-trihydroxycyclopentyl]-adenine (**14**).* Compound **8** (600 mg) was hydrogenated in the presence of Raney nickel under hydrogen atmosphere (3.4 kg/cm^2) for 18 h in a Parr apparatus. After the catalyst had been filtered off, the filtrate was evaporated. The residue (484 mg) was heated at 170 °C for 1 h in formamide (20 ml) and subsequently evaporated. The residue was dissolved in hot water and decolorized with active charcoal. The solution was evaporated, and the residue was recrystallized from hot water to give 235 mg (42%) of **14**, mp 277—278 °C (dec).

Found: C, 44.64; H, 5.07; N, 28.77%. Calcd for $C_{11}H_{14}N_6O_4$: C, 44.90; H, 4.79; N, 28.56%.

*9-[DL-(1,2,5/3,4)-3-Acetamido-2,4,5-trihydroxycyclopentyl]-adenine (**15**).* Compound **12** was heated at 175 °C for 2 h in formamide (30 ml), and evaporated. The residue was decolorized with active charcoal in boiling water to give 381 mg (42%) of crude product. Recrystallization from hot water gave 318 mg (34%) of **15**, mp 278—280 °C (dec). **15** was acetylated in the usual way to give penta-*N,O*-acetyl derivative. The product was recrystallized from ethyl acetate to give an analytical pure sample, mp 219—220 °C (dec).

Found: C, 50.15; H, 4.99; N, 17.72%. Calcd for $C_{20}H_{24}N_6O_8$: C, 50.42; H, 5.08; N, 17.64%.

*9-[DL-(1,2,4/3,5)-3-Amino-2,4,5-trihydroxycyclopentyl]adenine (**16**).* Compound **13** (150 mg) was heated at 85 °C for 3 h in a barium hydroxide [$Ba(OH)_2 \cdot 8H_2O$, 300 mg] solution (water, 23 ml). Carbon dioxide was bubbled into the solution and the resulting precipitate was filtered off. The filtrate was evaporated to a small volume and the residue was allowed to stand in a refrigerator to give 114 mg (88%) of crystals. The product was recrystallized from hot water to give an analytical sample of **16**, mp 280—290 °C (dec).

Found: C, 45.09; H, 5.34; N, 31.19%. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.30; N, 31.56%.

UV: $\lambda_{max}^{0.1\,M\,HCl}$ 259 nm (ε=14200), $\lambda_{max}^{H_2O}$ 260 nm (ε=12400), $\lambda_{max}^{0.1\,M\,NaOH}$ 261 nm (ε=6700).

*9-[DL-(1,4/2,3,5)-3-Amino-2,4,5-trihydroxycyclopentyl]adenine (**17**).* Compound **14** (230 mg) was treated with Dowex IX-2 (OH^-) (5 ml) in water (180 ml) at 50 °C for 3 h with agitation. After the resin had been filtered off, the solution was evaporated. The residue was recrystallized from hot water to give 176 mg (85%) of **17**, mp 255—256 °C (dec).

Found: C, 44.81; H, 5.25; N, 30.99%. Calcd for $C_{10}H_{14}N_6O_3$: C, 45.11; H, 5.30; N, 31.56%.

UV: $\lambda_{max}^{0.1\,M\,HCl}$ 258 nm (δ=15000), $\lambda_{max}^{H_2O}$ 260 nm (ε=16000), $\lambda_{max}^{0.1\,M\,NaOH}$ 261 nm (ε=16000).

The hydrochloride melts at 250 °C (dec).

Found: C, 39.49; H, 4.97; N, 27.49; Cl, 11.75%. Calcd for $C_{10}H_{15}N_6O_3Cl$: C, 39.68; H, 4.99; N, 27.76; Cl, 11.71%.

*9-[DL-(1,2,5/3,4)-3-Amino-2,4,5-trihydroxycyclopentyl]adenine (**18**).* Compound **15** (200 mg) was hydrolyzed by treating in the barium hydroxide solution for 6 h as in the preparation of **16** to give 105 mg (61%) of **18**, mp 264—266 °C (dec).

Found: C, 44.69; H, 5.25; N, 30.69%. Calcd for $C_{10}H_{14}N_6O_3 \cdot 1/4\ H_2O$: C, 44.36; H, 5.40; N, 31.04%.

UV: $\lambda_{max}^{0.1\,M\,HCl}$ 258 nm (ε=14300), $\lambda_{max}^{H_2O}$ 259 nm (ε=14600), $\lambda_{max}^{0.1\,M\,NaOH}$ 259 nm (ε=14500).

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