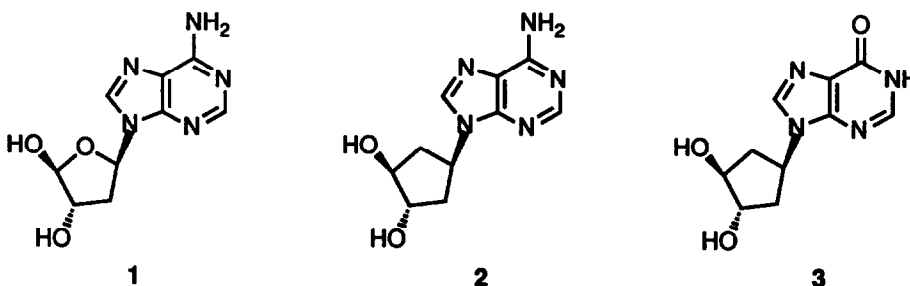


THE SYNTHESIS OF TWO 2'-DEOXY CARBOCYCLIC PURINE NUCLEOSIDES LACKING THE 5'-METHYLENE

Masakazu Koga and Stewart W. Schneller*
Department of Chemistry, University of South Florida
Tampa, Florida 33620-5250

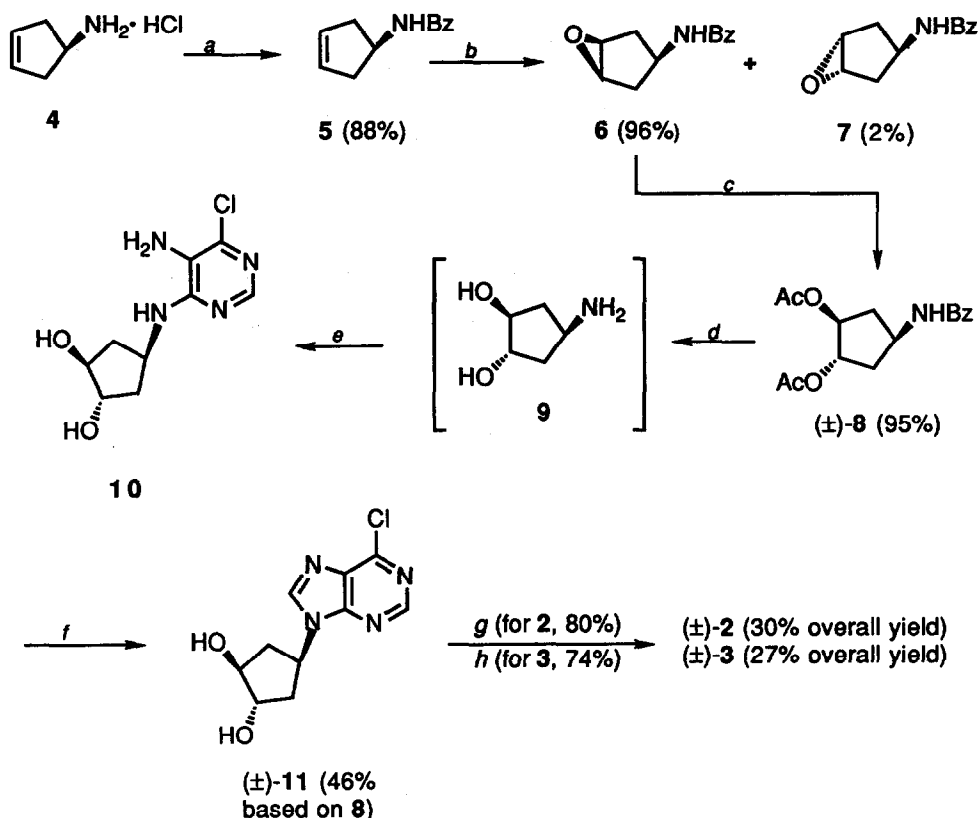
Summary: The synthesis of the adenine derivative ($\pm$)-(1 α ,2 β ,4 α)-4-(6-amino-9H-purin-9-yl)-1,2-cyclopentanediol (**2**) and its hypoxanthine analogue (**3**) as carbocyclic nucleosides lacking the 5'-methylene is described in 7 steps from 3-cyclopenten-1-ylamine hydrochloride (**4**) in an overall yield of 30% for **2** and 27% for **3**.

Motivated by the desire to enlighten nucleic acid structure and function and to develop biologically active agents derived therefrom, numerous analogues of the naturally occurring nucleosides and nucleotides have been prepared. However, missing from these studies is an analysis of the biochemical necessity of the 5'-methylene moiety of the ribofuranosyl unit. To conduct such an analysis, it would have been necessary to work with derivatives, such as the adenine compound **1**, that are hemiacetals and likely to be part of a mixture also containing the C-4' epimer and open chain forms. This situation can be overcome by the carbocyclic analogues (for example, **2** and **3**) in which the hydroxyl center of interest is merely a secondary alcohol. This report describes the synthesis of **2** and **3**, the former of which can also be viewed as the 5'-nor 2'-deoxy derivative of the carbocyclic nucleoside aristeromycin.¹



A review of the literature² indicated that 3-cyclopenten-1-ylamine hydrochloride (**4**)³ would be a useful starting material. Thus, benzylation of **4** (Scheme) yielded N-(3-cyclopenten-1-yl)benzamide (**5**,^{4,5} mp 126 °C from CHCl₃-hexane). Oxidation of **5** using *m*-chloroperoxybenzoic acid yielded (1 α ,3 β ,5 α)-N-(6-oxabicyclo[3.1.0]hex-3-yl)benzamide (**6**,^{4,6} mp 84 °C from CHCl₃-hexane) and (1 α ,3 α ,5 α)-N-(6-oxabicyclo[3.1.0]hex-3-yl)benzamide (**7**,^{4,7} mp 153 °C from CHCl₃-hexane). The diastereomers **6** and **7** were distinguished by comparing their ¹H NMR data for the benzamide NH and the epoxide protons: the NH region for **6** (δ 7.3-7.7 ppm) is shielded by the *cis*-epoxide oxygen relative to the NH in **7** (δ 8.31 ppm) whereas the epoxide protons in **7** (δ 3.54 ppm) are shielded by the *cis*-nitrogen when compared to the epoxide protons in **6** (δ 3.57 ppm).

Scheme



Reaction conditions: *a*, BzCl/pyridine/Et₃N in CHCl₃; *b*, *m*-chloroperoxybenzoic acid in CHCl₃, room temp.; *c*, (i) 2% aq. H₂SO₄, room temp. then neutralize; (ii) Ac₂O/pyridine, room temp; *d*, 6N HCl, reflux; *e*, 5-amino-4,6-dichloropyrimidine in 1-BuOH containing Et₃N, reflux; *f*, (EtO)₃CH and conc. HCl, reflux; *g*, NH₃ in MeOH, 100 °C, 48 h; *h*, 1N HCl, reflux

Ring opening of 6 with dilute sulfuric acid followed by acetylation of the resultant *trans*-vicinal diol gave (±)-(1 α ,3 α ,4 β)-N-[3,4-bis(acetyloxy)cyclopentyl]benzamide (8,^{4,8} mp 95 °C from hexane). Hydrolysis of 8 to (1 α ,2 β ,4 α)-4-amino-1,2-cyclopentanediol (9, oil). Compound 9, which was not fully characterized, was reacted with 5-amino-4,6-dichloropyrimidine to yield (±)-(1 α ,2 β ,4 α)-4-[(5-amino-6-chloro-4-pyrimidin-2-yl)amino]-1,2-cyclopentanediol (10,⁹ mp 189 °C from CHCl₃-MeOH-EtOAc) that was converted into (±)-(1 α ,2 β ,4 α)-4-(6-chloro-9H-purin-9-yl)-1,2-cyclopentanediol (11,^{4,10} mp 202 °C from MeOH) with triethyl orthoformate. Ammonolysis of 11 gave the desired (±)-(1 α ,2 β ,4 α)-4-(6-amino-9H-purin-9-yl)-1,2-cyclopentanediol (2,^{4,11} mp 211 °C from MeOH).

Reaction of 11 with dilute hydrochloric acid produced the hypoxanthine analogue (±)-(1 α ,3 α ,4 β)-9-(3,4-dihydroxycyclopentyl)-1,9-dihydro-6H-purin-6-one (3,^{4,12} mp 283 °C from H₂O-MeOH).

Acknowledgments. We are appreciate the assistance of Ms. Linda Morgan in the synthesis of 4.

References and Notes

1. See, for example, Yoshikawa, M.; Okaichi, Y.; Cha, B.C.; Kitagawa, I. *Chem Pharm. Bull.* **1989**, *37*, 2555.
2. (a) Murdock, K.C.; Angier, R.B. *J. Am. Chem. Soc.* **1962**, *84*, 3748. (b) Murdock, K.C.; Angier, R.B. *J. Org. Chem.* **1962**, *27*, 3317.
3. Murdock, K.C.; Angier, R.B. *J. Org. Chem.* **1962**, *27*, 2395.
4. Satisfactory microanalytical data was obtained for this compound.
5. The spectral data¹³ for **5** is as follows: IR (Nujol, cm⁻¹) 3300 (NH), 1630 (C=O), 1575, 1550 and 1540 (C=C); ¹H NMR (DMSO-d₆, ppm) δ 2.2-2.9 (m, 4 H, H-2' and H-5'), 4.4-4.8 (m, 1 H, H-1'), 5.73 (s, 2 H, H-3' and H-4'), 7.3-7.6 and 7.8-8.0 (m, 5 H, H of phenyl), 8.52 (d, 1 H, J=7 Hz, NH); ¹³C NMR (DMSO-d₆, ppm) δ 39.17 (C-2' and C-5'), 49.19 (C-1'), 127.42, 128.18, 131.05, and 134.73 (C of phenyl), 129.10 (C-3' and C-4'), 166.21 (C=O).
6. The spectral data¹³ for **6** is as follows: IR (Nujol, cm⁻¹) 3400 (NH), 1660 (C=O), 1575, 1530, and 1520 (C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.9-2.2 (m, 4 H, H-2' and H-4'), 3.57 (s, 2 H, H-1' and H-5'), 4.2-4.5 (m, 1 H, H-3'), 7.3-7.7 (m, 4 H, NH and H-3, H-4, and H-5 of phenyl), 7.7-8.0 (m, 2 H, H-2 and H-6 of phenyl); ¹³C NMR (DMSO-d₆, ppm) δ 34.94 (C-2' and C-4'), 46.48 (C-3'), 56.94 (C-1' and C-5'), 127.09, 128.23, 131.05, and 134.62 (C of phenyl), 165.01 (C=O).
7. The spectral data¹³ for **7** is as follows: IR (Nujol, cm⁻¹) 3285 (NH), 1630 (C=O), 1575 and 1555 (C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.5-1.9 and 2.2-2.5 (m, 4 H, H-2' and H-4'), 3.54 (s, 2 H, H-1' and H-5'), 3.9-4.2 (m, 1 H, H-3'), 7.3-7.6 (m, 3 H, H-3, H-4, and H-5 of phenyl), 7.7-7.9 (m, 2 H, H-2 and H-6 of phenyl), 8.31 (d, J=8 Hz, 1 H, NH); ¹³C NMR (DMSO-d₆, ppm) δ 33.21 (C-2' and C-4'), 44.85 (C-3'), 55.04 (C-1' and C-5'), 127.31, 128.28, 131.15, and 134.57 (C of phenyl), 166.04 (C=O).
8. The spectral data¹³ for **8** is as follows: IR (Nujol, cm⁻¹) 3370 (NH), 1735 (C=O of acetyl), 1635 (C=O of benzoyl), 1580 and 1515 (C=C); ¹H NMR (DMSO-d₆, ppm) δ 2.04 (s, 6 H, 2 x CH₃) overlapped by 1.5-2.7 (m, 4 H, H-2' and H-5'), 4.3-4.6 (m, 1 H, H-1'), 4.9-5.3 (m, 2 H, H-3' and H-4'), 7.2-7.5 (m, 3 H, H-3, H-4, and H-5 of phenyl), 7.6-7.9 (m, 2 H, H-2 and H-6 of phenyl), 8.52 (d, J=7 Hz, 1 H, NH); ¹³C NMR (DMSO-d₆, ppm) δ 20.80 (2 x CH₃), 36.24 (C-2' and C-5'), 46.97 (C-1'), 76.93 (C-3' and C-4'), 127.36, 128.23, 131.21, and 134.46 (C of phenyl), 166.15 (C=O of benzoyl), 169.78 (C=O of acetyl).
9. The spectral data¹³ for **10** is as follows: IR (Nujol, cm⁻¹) 3400-3100 (NH and OH), 1650 and 1580 (C=N and C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.1-2.6 (m, 4 H, H-3 and H-5), 3.8-4.0 (m, 2 H, H-1 and H-2), 4.4-4.8 (m, 1 H, H-4), 4.75 and 4.88 (2 d, J=3 Hz, 2 H, 1-OH and 2-OH), 5.08 (s, 2 H, NH₂), 6.74 (d, J=7 Hz, 1 H, NH), 8.06 (s, 1 H, H-2 of pyrimidine); ¹³C NMR (DMSO-d₆, ppm) δ 38.95 (C-3 and C-5), 48.92 (C-4), 76.82 (C-1 and C-2), 123.41, 136.79, 145.78, and 151.63 (C of pyrimidine).
10. The spectral data¹³ for **11** is as follows: IR (Nujol, cm⁻¹) 3345 (OH), 1595 and 1560 (C=N and C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.8-2.8 (m, 4 H, H-3 and H-5), 4.0-4.2 (m, 2 H, H-1 and H-2), 5.0-5.5 (m, 3 H, H-4, 1-OH, and 2-OH), 8.79 (br s, 2 H, H-2 and H-8 of purine); ¹³C NMR (DMSO-d₆, ppm) δ 38.95 and 39.38 (C-3 and C-5), 52.71 (C-4), 76.49 and 76.71 (C-1 and C-2), 131.10, 146.22, 148.98, 151.25, and 151.69 (C of purine).

11. The spectral data¹³ for 2 is as follows: IR (Nujol, cm⁻¹) 3340 and 3165 (NH and OH), 1660, 1595, and 1575 (C=N and C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.8-2.8 (m, 4 H, H-3 and H-5), 4.0-4.2 (m, 2 H, H-1 and H-2), 4.9-5.6 (m, 3 H, H-4, 1-OH, and 2-OH), 7.35 (br s, 2 H, NH₂), 8.21 (br s, 2 H, H-2 and H-8 of purine); ¹³C NMR (DMSO-d₆, ppm) δ 39.17 and 39.33 (C-3 and C-5), 51.95 (C-4), 76.66 and 76.98 (C-1 and C-2), 119.24, 139.99, 149.14, 152.23, and 156.18 (C of purine).
12. The spectral data¹³ for 3 is as follows: IR (Nujol, cm⁻¹) 3220-3430 (NH and OH), 1680 (C=O), 1595, 1550, and 1515 (C=N and C=C); ¹H NMR (DMSO-d₆, ppm) δ 1.7-2.8 (m, 4 H, H-2' and H-5'), 3.8-4.2 (m, 2 H, H-3' and H-4'), 4.8-5.3 (m, 3 H, H-1', 3'-OH, and 4'-OH), 8.09 and 8.2 (2 s, 2 H, H-2 and H-8 of purine), 12.31 (br s, 1 H, NH of purine); ¹³C NMR (DMSO-d₆, ppm) δ 39.44 and 39.76 (C-2' and C-5'), 52.06 (C-1'), 76.55 and 76.82 (C-3' and C-4'), 124.17, 138.96, 145.46, 148.22, and 156.83 (C of purine).
13. Refer to the compound name in the narrative to determine atom numbering for spectra assignments.

(Received in USA 3 July 1990)