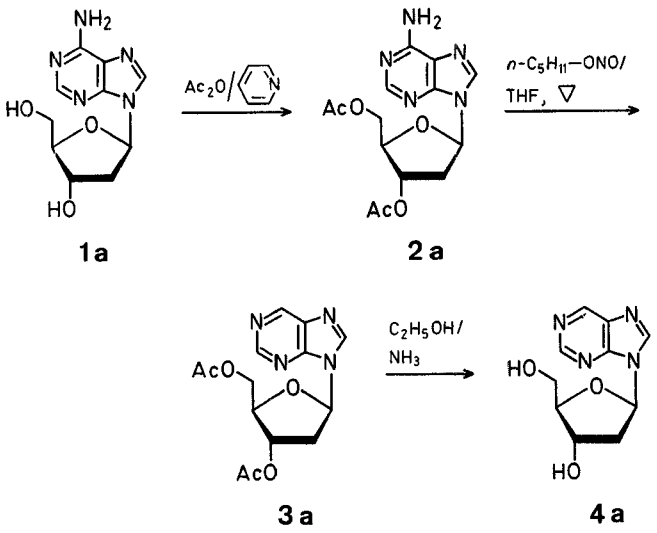

diazotization procedure in non-hydroxylic organic solvents requires that the nucleoside hydroxy groups are protected to avoid cross nitrite ester formation and also to enhance solubility. The protected (acetylated) nucleosides **2** were deaminated on heating with *n*-pentyl nitrite in dry tetrahydrofuran under nitrogen. The yields for the deaminations varied between 46 and 81 % (Table 1). The optimum temperature for

Table 1. Steps and Product Yields in the Reductive Deamination of Nucleosides

Starting Compound	Yields [%] for			Final Product
	acetylation	deamination	deacetylation	
1a	74	64	71	**4a**
1b	72	75	83	**4b**
1c	94	51	74	**4c**
1d	86	46	72	**4d**
1e	72	81	90	**4e**

Reductive Deamination of Aminopurine Nucleosides

Vasu NAIR,* Stanley D. CHAMBERLAIN

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, U.S.A.

The reductive deamination of adenosine analogs provides a direct route to purine nucleosides. Some of these uncommon nucleosides have been found to have interesting enzymatic and biological properties. For example, 9-(β-D-ribofuranosyl)-9*H*-purine (**4b**; nebularine) is an antibiotic, which is a strong competitive inhibitor of adenosine deaminase[1,2,3]. It has been studied as an antileukemic agent in combination chemotherapy[4]. 7-Deazanebularine (**4d**) inhibits cellular and viral nucleic acid synthesis and is cytotoxic to mammalian cells[5,6]. Other deaminated nucleosides also have been reported to exhibit biological activity[7,8,9]. We have reported recently[10] that when protected adenosine is treated thermally with *n*-pentyl nitrite in tetrahydrofuran, the corresponding reductively deaminated product, nebularine is formed. The reaction apparently proceeds through the intermediacy of purinyl radicals which abstract hydrogen atoms from solvent molecules. This paper reports the improvement of this synthetic procedure and its application to the direct synthesis of a number of nucleoside antimetabolites.

The starting compounds for these reductive deaminations were obtained commercially with the exception of 8-azaadenosine (**1e**) which was prepared by a reported method[11]. The

Table 2. Physical Data for Compounds **4a–e**

Product	m.p. [°C] (Lit.m.p.[°C])	M.S. *m/e* (relative intensity %)	U.V. (H_2O) λ_{max} (ε)	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]	^{13}C-N.M.R. (DMSO-d_6) δ [ppm]
4a	180–182° (181–182°)[14]	236 (M^+, 1.1); 219 (1.6); 206 (5.7); 163 (2.3); 159 (5.0); 149 (42.6); 135 (4.4); 121 (100); 120 (26.2); 119 (12.4); 93 (16.5); 66 (8.8)	264 (7450)	2.37 (m, 1 H); 2.78 (m, 1 H); 3.53 (m, 1 H); 3.63 (m, 1 H); 3.89 (q, 1 H, J = 7.8 Hz, 4.4 Hz); 4.45 (m, 1 H); 4.99 (t, 1 H, J = 5.6 Hz); 5.37 (d, 1 H, J = 3.9 Hz); 6.49 (t, 1 H, J = 6.7 Hz); 8.82 (s, 1 H); 8.95 (s, 1 H); 9.18 (s, 1 H)	39.4; 61.6; 70.6; 83.6; 88.0; 134.2; 145.2; 148.0; 150.6; 151.9
4b	178–179° (181–182°)[12]	252 (M^+, 0.5); 235 (2.6); 222 (2.8); 175 (4.4); 163 (24.6); 159 (1.4); 149 (90.7); 134 (4.4); 133 (8.7); 121 (100); 120 (12.9); 119 (4.4); 93 (5.5); 66 (1.3)	262 (6690)	3.65 (d, 1 H, J = 11.7 Hz); 3.74 (d, 1 H, J = 11.7 Hz); 4.04 (d, 1 H, J = 3.7 Hz); 4.24 (t, 1 H, J = 4.0 Hz); 4.68 (t, 1 H, J = 5.2 Hz); 5.14 (br. s, 1 H); 5.30 (br. s, 1 H); 5.87 (br. s, 1 H); 6.11 (d, 1 H, J = 5.6 Hz); 8.87 (s, 1 H); 8.99 (s, 1 H); 9.22 (s, 1 H)	61.3; 70.4; 73.8; 85.8; 87.7; 134.2; 145.4; 148.2; 151.0; 152.1
4c	253–254° (242–243°)[15]	236 (3.1); 222 (0.6); 175 (1.3); 165 (15.7); 149 (100); 134 (3.0); 133 (7.5); 121 (74.6); 120 (20.9); 119 (1.7); 93 (5.3); 66 (100)	262 (7220)	3.16 (d, 1 H, J = 4.2 Hz); 3.68 (s, 2 H); 3.82 (s, 1 H); 4.17 (d, 1 H, J = 4.2 Hz); 4.24 (s, 1 H); 5.10 (s, 1 H); 5.57 (d, 1 H, J = 3.1 Hz); 5.66 (s, 1 H); 6.42 (d, 1 H, J = 4.4 Hz); 8.67 (s, 1 H); 8.94 (s, 1 H); 9.17 (s, 1 H)	60.7; 74.8; 75.7; 83.7; 84.4; 133.5; 146.0; 147.6; 151.0; 151.9
4d	118–119° (117°)[16]	251 (M^+, 2.5); 234 (0.8); 221 (2.8); 174 (3.3); 162 (16.7); 158 (1.3); 148 (100); 133 (7.0); 132 (13.0); 120 (58); 119 (95.5); 118 (2.8); 92 (9.8); 65 (1.5)	270 (3500)	3.57 (d, 1 H, J = 11.1 Hz); 3.62 (d, 1 H, J = 11.1 Hz); 3.94 (d, 1 H, J = 3.2 Hz); 4.14 (s, 1 H); 4.45 (s, 1 H); 5.09 (br. s, 1 H); 5.18 (br. s, 1 H); 5.37 (br. s, 1 H); 6.23 (d, 1 H, J = 6.0 Hz); 6.72 (d, 1 H, J = 3.4 Hz); 7.87 (d, 1 H, J = 3.4 Hz); 8.81 (s, 1 H); 9.03 (s, 1 H)	61.5; 70.5; 73.9; 85.1; 86.6; 100.3; 119.1; 127.6; 149.4; 150.5; 150.8
4e	101–102° (101°)[17]	253 (M^+, 4.6); 223 (2.4); 175 (2.8); 165 (5.0); 159 (4.7); 149 (44.9); 135 (9.2); 122 (6.4); 121 (11.3); 120 (11.9); 97 (36.6); 85 (57.0); 71 (88.1); 57 (100)	262 (5860)	3.60 (m, 2 H); 4.04 (m, 1 H); 4.39 (t, 1 H, J = 3.8 Hz); 4.96 (t, 1 H, J = 5.2 Hz); 6.36 (d, 1 H, J = 4.6 Hz); 9.31 (s, 1 H); 9.83 (s, 1 H)	61.6; 70.6; 73.1; 86.2; 89.7; 135.5; 148.6; 152.1; 156.3

these reactions was 50 °C. Other hydrogen atom donors were also tried but proved inferior to tetrahydrofuran although dimethylformamide gave lower but acceptable yields.

The deacetylation of the deaminated compounds **3** to the purine nucleosides **4** required a modification of the literature procedure as low yields are often reported for this reaction[12,13]. Our modified procedure and work-up conditions gave yields of 70–90% (Table 1).

Indentification of the final products were made by U.V., mass spectral, and N.M.R. data, and by comparison of physical data available in the literature on these compounds. The high-field ^{1}H- and ^{13}C-N.M.R. data reported in Table 2 represent the most complete compilation of N.M.R. data for these compounds.

In summary, the reductive deamination procedure described in this paper has proved to be an excellent and direct route for the synthesis of purine nucleosides from their more readily available 6-amino precursors. This method has generality and can be utilized for the synthesis of a wide variety of biologically active nucleosides.

Melting points, determined on a Thomas Hoover capillary melting point apparatus, are uncorrected. N.M.R. spectra were recorded on a Bruker WM 360 spectrometer. U.V. spectra were taken on a Cary 219 spectrophotometer. Mass spectra at 70 eV were obtained on a Hewlett Packard 5985B GC-mass spectrometer.

Acetylation Reaction 1 → 2; General Procedure:
A mixture of nucleoside **1** (0.5 mmol), acetic anhydride (6 mmol), and dry pyridine (5 ml) is stirred at 0 °C for 1 h protected by a calcium chloride drying tube. The mixture is then stirred at 25 °C for

5 h. Ethanol (1 ml) is added and stirring is continued for 45 min. The solvent is then removed in vacuo (< 50 °C). The residue is repeatedly taken up in ethanol and evaporated until all of the pyridine is removed. The remaining clear oil is taken up in dichloromethane and chromatographed on preparative layer silica gel plates with methanol/dichloromethane (1 : 9) as the developing solvent.

Deamination Reaction 2 → 3; General Procedure:
A solution of the acetylated nucleoside **2** (0.5 mmol), dry, distilled *n*-pentyl nitrite (0.5 ml, 3.7 mmol), and dry tetrahydrofuran is stirred at 50 °C under nitrogen for 24 h. An additional aliquot of *n*-pentyl nitrite (0.5 ml) is added each day for two more days. The solvent is then removed and the oily residue is taken up in a methanol/dichloromethane mixture and chromatographed on silica gel plates with methanol/dichloromethane (1 : 9) as the eluting solvent. The products have R_f values just greater than the starting materials. The deaminated material is normally dried on a vacuum pump and used in the deacetylation reaction.

Deacetylation Reaction 3 → 4; General Procedure:
Absolute ethanol is cooled to ice/salt bath temperatures and saturated with ammonia over a period of 0.5 h. The acetylated nucleoside **3** is then dissolved in a minimum amount of absolute ethanol and added to the saturated solution. After standing for one day at room temperature, the mixture is re-saturated with ammonia and allowed to react for one more day. Removal of the solvent in vacuo is followed by repeatedly taking up the residue in methanol and rotoevaporating off the methanol. To ensure complete removal of acetamide the residue is placed in a sublimation apparatus at 30 °C for 12 h. The products are crystallized finally from methanol/ether.

This research was supported by a grant (BC-350) from the American Cancer Society.

Received: October 6, 1983

[1] J.G. Cory, R.J. Suhadolnik, *Biochemistry* **4**, 1729 (1965).
[2] R.J. Suhadolnik, *Nucleoside Antibiotics* Wiley, New York, **1970**, p. 264.
[3] R. Wolfenden, J. Kaufman, J.B. Macon, *Biochemistry* **8**, 2412 (1969).
[4] T.P. Lynch, J.H. Paran, A.R.P. Paterson, *Cancer Res.* **41**, 560 (1981).
[5] B. Brdar, E. Reich, *J. Biol. Chem.* **247**, 725 (1972).
[6] D.C. Ward, E. Reich, *J. Biol. Chem.* **247**, 705 (1972).
[7] D.A. Carson et al., *Proc. Natl. Acad. Sci. U.S.A.* **77**, 6865 (1980).
[8] C.M. Smith, G. Zombor, J.F. Henderson, *Cancer Treatment Report* **60**, 1567 (1976).
[9] T.H. Haskell, *Ann. N. Y. Acad. Sci.* **284**, 81 (1977).
[10] V. Nair, S.G. Richardson, *J. Org. Chem.* **45**, 3969 (1980).
[11] J.A. Montgomery, H.J. Thomas, S.J. Clayton, *J. Heterocyclic Chem.* **7**, 215 (1970).
[12] G.B. Brown, V.S. Weliky, *J. Biol. Chem.* **204**, 1019 (1953).
[13] J.A. Montgomery, K. Hewson in *Synthetic Procedures in Nucleic Acid Chemistry*, Vol. 1, W.W. Zorbach, R.S. Tipson, Eds., Interscience, New York, **1968**, p. 180.
[14] M.J. Robins, R.K. Robins, *J. Am. Chem. Soc.* **87**, 4934 (1965).
[15] E.J. Reist, A. Benitez, L. Goodman, B.R. Baker, W.W. Lee, *J. Org. Chem.* **27**, 3274 (1962).
[16] J.F. Gerster, B. Carpenter, R.K. Robins, L.B. Townsend, *J. Med. Chem.* **10**, 326 (1967).
[17] W. Hutzenlaub, R.L. Tolman, R.K. Robins, *J. Med. Chem.* **15**, 879 (1972).