Modification of Nucleic Acid Bases via Radical Intermediates: Synthesis of Dihalogenated Purine Nucleosides[1]

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New and improved preparations of structurally modified nucleic acid bases and their corresponding nucleosides are important goals in synthetic organic chemistry because of the potential utility of these compounds as synthetic precursors, in chemotherapeutic studies, and as biochemical probes in the investigation of specific enzyme-catalyzed reactions[2]. This is particularly true for halogenated nucleosides. For example, dihalopurine ribosides, such as 2,6-dichloro-9β-D-ribofuranosylpurine, are valuable synthetic precursors to 2-chloroadenosine[3,4], and a wide variety of derivatives. Some of these compounds have shown biological activity as coronary vasodilators[3], inhibitors of blood platelet aggregation[5], antihypertensives[6], and antilipemic/hypocholesterolemic agents[7,8].

We have reported recently that thermal and adjunctive photolytic homolysis of 6-diazonium salts (or the corresponding azo forms) of 9-substituted adenines in non-hydroxylic media apparently produce purinyl radical intermediates. These radicals can abstract hydrogen or halogen atoms from appropriate solvent molecules[9,10]. This paper reports on the utilization of transient neutral purinyl radicals for the synthesis of 2,6-dihalogenated nucleosides.

The starting material for these conversions was the 2-amino-6-chloro nucleoside **(2)** prepared easily from 2′,3′,5′-tri-*O*-acetylguanosine[11] by treatment with phosphoryl chloride and *N,N*-diethylaniline[12]. When **2** was heated in tetrachloromethane in the presence of *n*-pentyl nitrite for 24 h, the 2,6-dichloro nucleoside **4** was obtained in 66% yield as a white crystalline product identical chromatographically and spectrally to authentic **4** prepared in 44% yield by established literature methods[13] (see also Refs.[14,15]). Extension of this reaction to the 2-bromo-6-chloro nucleoside **5**[3,15] was carried out by heating **2** in tribromomethane in the presence of *n*-pentyl nitrite for 8 h. Compound **5** was isolated in 55% yield. The 2-iodo-6-chlororibofuranosylpurine **(6)** is a new dihalogenated nucleoside. It can be prepared in excellent yields (83%) as a crystalline solid by warming **2** in diiodomethane and *n*-pentyl nitrite for 1 h.

The purin-2-yl radical **3** presumably is generated as the transient species in these conversions from the thermal homolysis of the 2-diazonium salt/2-azo compound intermediate. This purinyl radical abstracts halogen atoms from solvent molecules. No competition of hydrogen with halogen abstraction was observed in the preparation of the 2-bromo- and 2-iodo-substituted nucleosides, where tribromomethane and diio-

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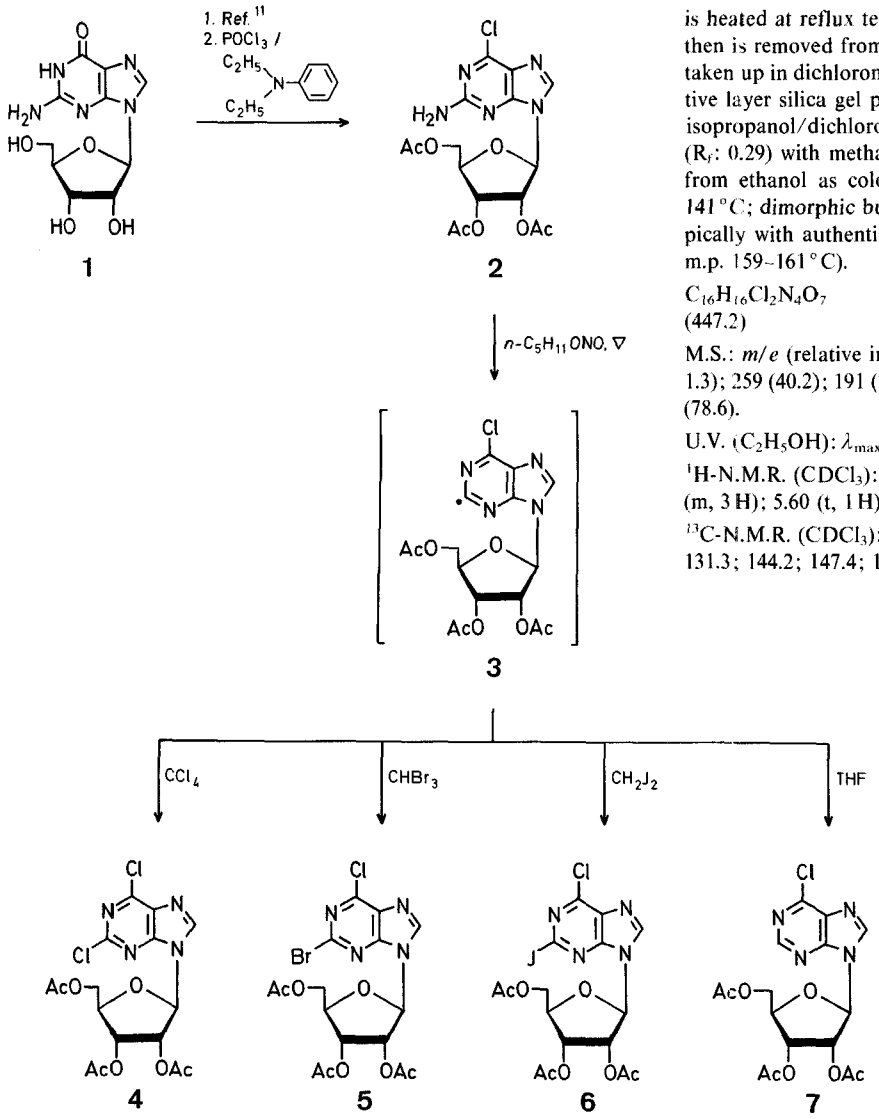

domethane, respectively, were used as solvents. This is expected from the differences in bond energies between C—H (406 kJ/mol; 97 kcal/mol) and C—Br (276 kJ/mol; 66 kcal/mol) or C—J (218 kJ/mol; 52 kcal/mol). As expected, when the reaction was carried out in tetrahydrofuran as solvent, reductive deamination to 6-chloronebularine (**7**)[10] occurred.

In summary, this work provides a useful approach to the synthesis of dihalogenated purine nucleosides using simple, readily available reagents. The yields are good to excellent. Neither hydrolytic deamination, hydrolysis of halogen, nor sugar cleavage are significant side reactions under these mild, non-aqueous, non-acidic reaction conditions. The high cost and limited availability of 2,6-dihalogenated purines, and the yield and selectivity of base-sugar coupling methods suggests that specific transformations using natural nucleosides is the best approach for the synthesis of halogenated nucleosides.

Melting points, determined on a Thomas-Hoover capillary melting-point apparatus, are uncorrected. N.M.R. spectra were recorded on JEOL FX90Q and Bruker HX90E pulse Fourier transform spectrometers. 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.

2,6-Dichloro-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (4):
A mixture of compound **2**[11,12] (0.293 g, 0.685 mmol), dry, distilled *n*-pentyl nitrite (1.53 ml, 11.4 mmol), and dry tetrachloromethane (30 ml) is heated at reflux temperatures under nitrogen for 24 h. The solvent then is removed from the yellow solution and the resulting residue is taken up in dichloromethane (3 ml) and chromatographed on preparative layer silica gel plates. The plates are developed twice with 1:50 isopropanol/dichloromethane. Elution of the only significant band (R_f: 0.29) with methanol/dichloromethane gives **4** which crystallizes from ethanol as colorless needles; yield: 0.201 g (66%); m.p. 139–141 °C; dimorphic but identical chromatographically and spectroscopically with authentic **4** prepared by the literature method[13] (Ref.[13], m.p. 159–161 °C).

$C_{16}H_{16}Cl_2N_4O_7$	calc.	C 42.97	H 3.61	N 12.53
(447.2)	found	43.2	3.5	12.3

M.S.: *m/e* (relative intensity) = 448 ($^{35}Cl^{37}ClM^+$, 0.4); 446 ($^{35}Cl_2M^+$, 1.3); 259 (40.2); 191 (7.1); 190 (2.7); 189 (10.9); 188 (2.8); 139 (100); 97 (78.6).

U.V. (C_2H_5OH): λ_{max} = 213 (ε = 20000); 252 (5400); 273.5 nm (8300).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.09 (s, 3H); 2.14 (s, 3H); 2.17 (s, 3H); 4.43 (m, 3H); 5.60 (t, 1H); 5.82 (t, 1H); 6.23 (d, 1H); 8.34 ppm (s, 1H).

^{13}C-N.M.R. ($CDCl_3$): δ = 20.3; 20.5; 20.7; 62.9; 70.5; 73.2; 80.8; 86.6; 131.3; 144.2; 147.4; 152.2; 153.3; 169.4; 169.6; 170.2 ppm.

2-Bromo-6-chloro-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (5):
A mixture of compound **2** (0.165 g, 0.385 mmol), *n*-pentyl nitrite (0.87 ml, 6.44 mmol), and tribromomethane (10 ml) is heated under nitrogen at 85 °C for 8 h. Work-up, separation, and crystallization as described for **4** gives **5** as white crystals; yield: 0.102 g (55%); m.p. 155–156 °C (Ref.[3], m.p. 153–154 °C).

$C_{16}H_{16}BrClN_4O_7$	calc.	C 39.08	H 3.28	N 11.40
(491.7)	found	39.3	3.4	11.3

M.S.: *m/e* (relative intensity) = 494 ($^{81}Br^{37}ClM^+$, 0.2); 492 ($^{79}Br^{37}ClM^+$ and $^{81}Br^{35}ClM^+$, 0.4); 490 ($^{79}Br^{35}ClM^+$, 0.4); 259 (53.5); 235 (11.0); 234 (3.3); 233 (9.2); 232 (2.2); 139 (100.0); 97 (67.0).

U.V. (CH_3OH): λ_{max} = 216 (ε = 21800); 254 (5200); 275 nm (8600).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.10 (s, 3H); 2.13 (s, 3H); 2.17 (s, 1H); 4.44 (m, 3H); 5.65 (t, 1H); 5.82 (t, 1H); 6.24 (d, 1H); 8.34 ppm (s, 1H).

^{13}C-N.M.R. ($CDCl_3$): δ = 20.4; 20.5; 20.8; 63.0; 70.6; 73.3; 80.8; 86.7; 131.7; 143.4; 144.0; 151.8; 152.5; 169.5; 169.6; 170.3 ppm.

2-Iodo-6-chloro-9β-(2′,3′,5′-tri-*O*-acetyl)-D-ribofuranosylpurine (6):
A mixture of compound **2** (0.303 g, 0.709 mmol), *n*-pentyl nitrite (1.91 ml, 14.2 mmol), and diiodomethane (5 ml) is heated at 85 °C for 1 h. Work-up, separation, and crystallization as described for **4** gives **6** as hygroscopic, white crystals; yield: 0.318 g (83%); m.p. 181–183 °C.

$C_{16}H_{16}ClJN_4O_7 \cdot 1.5H_2O$	calc.	C 33.97	H 3.39	N 9.90
(538.7)	found	34.2	3.2	9.6

M.S.: *m/e* (relative intensity) = 540 ($^{37}ClM^+$, 1.0); 538 ($^{35}ClM^+$, 2.1); 283 (6.6); 282 (2.3); 281 (15.3); 280 (2.3); 259 (68.7); 139 (100.0); 97 (75.6).

U.V. (CH_3OH): λ_{max} = 222.5 (ε = 21200); 258 (6600); 281 nm (9300).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.11$ (s, 3H); 2.13 (s, 3H); 2.18 (s, 3H); 4.43 (m, 3H); 5.65 (t, 1H); 5.81 (t, 1H); 6.23 (d, 1H); 8.27 ppm (s, 1H).

^{13}C-N.M.R. ($CDCl_3$): $\delta = 20.4$; 20.5; 20.8; 62.9; 70.5; 73.3; 80.8; 86.7; 116.9; 132.2; 143.4; 150.7; 151.9; 169.4; 169.5; 170.2 ppm.

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