Purine Nucleosides. XXIX. The Synthesis of 2′-Deoxy-L-adenosine and 2′-Deoxy-L-guanosine and Their α Anomers[1a]

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The synthesis of 6-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-deoxy-L-adenosine) (**9**) and its α anomer **8** has been accomplished by the first reported fusion of a 1-*O*-methyl-2-deoxy sugar derivative. Fusion of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**1**) and 2,6-dichloropurine (**2**) gave 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**3** and **4**, respectively). Selective amination at position 6 with concurrent deblocking, followed by hydrogenolysis of the 2-chloro function, gave the desired L enantiomers **8** and **9**. The α and β anomers of **1** were separated and individually fused with **2**. The α anomer gave higher total yields of nucleosides (**3** plus **4**) and gave a higher proportion of β nucleoside **4**. Fusion of 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**5**) and 2-fluoro-6-benzyloxypurine (**10**) followed by treatment with alcoholic ammonia and hydrogenolysis of the 6-benzyloxy group gave 2-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-deoxy-L-guanosine, **15**) and its α anomer **12**. These 2′ deoxynucleosides obey Hudson's isorotation rule and the "triplet"–"quartet" ^{1}H nmr anomeric proton splitting patterns for β and α anomers, respectively.

The synthesis of L-adenosine[2] and DL-adenosine[3] represent the first attempts to prepare ribonucleosides for biological and physical investigation of enantiomorphic nucleic acid components. During the course of this work,[4] a report of the preparation of L-thymidine appeared.[5]

We now wish to report the synthesis of 2′-deoxy-α- and -β-L-adenosines and -guanosines, which are the first examples of enantiomorphs of the natural purine deoxynucleosides of DNA. The polymerization of the β anomers of these L isomers into DNA-like fragments would provide exciting information[6] concerning helical structure and properties. The finding that 6-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**8**) acts as a substrate for adenosine deaminase[7] suggests the potential biological activity of stereoisomers of deoxynucleosides, a possibility borne out in the case of the selectively toxic 2-amino-9-(2-deoxy-α-D-*erythro*-pentofuranosyl)purine-6-thione (2′-deoxy-α-thioguanosine).[8]

Success of the fusion[9] procedure for purine deoxynucleoside synthesis[10,11] suggested application of this method to the 2′-deoxy-L isomers. The preparation of 2-deoxy-L-*erythro*-pentose (2-deoxy-L-ribose) was effected according to the procedure of Vargha and Kuszman[12] (for the D enantiomer) from 3,5-di-*O*-acetyl-L-arabinal.[13] The method of Hoffer[14] was used to convert the free 2-deoxy-L-*erythro*-pentose into 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**1**).

The 1-*O*-methyl sugar **1** (Scheme I) was fused directly with 2,6-dichloropurine (**2**) to give the anomeric 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**3** and **4**, respectively), which were resolved into pure anomers by alumina column chromatography and fractional crystallization. Treatment of these anomeric nucleosides with alcoholic ammonia gave 6-amino-2-chloro-9-(2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**6** and **7**, respectively). These anomerically pure intermediates were catalytically hydrogenated to give 6-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-deoxy-L-adenosine, **9**) and 6-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**8**).

This sequence represents the first reported use of a 1-*O*-methyl-2-deoxy sugar derivative in the fusion synthesis of deoxynucleosides. The α and β anomers of **1** were resolved by fractional crystallization and were individually subjected to fusion with 2,6-dichloropurine (**2**). Dichloroacetic acid catalyzed fusion of **1** (β anomer) and **2** at 140° for 5 min gave a 15% isolated yield of the blocked nucleosides **3** (63%) and **4** (37%). Identical fusion of **1** (α anomer) and **2** gave a 45% isolated yield of **3** (29%) and **4** (71%). Similar fusion of the anomeric mixture of **1** with **2** gave a 25% yield of **3** (41%) and **4** (59%). These results indicate that 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose is structurally more suitable for the fusion reaction and also leads to the predominant formation of β nucleoside **4** by overall inversion at C-1.

The α- and β-L-2′-deoxyadenosines (**8** and **9**, respectively) were found to exhibit identical uv, ir, and ^{1}H nmr spectra with their corresponding D enantiomers[10,15] and essentially equal and opposite optical rotations (and circular dichroism spectra[16]).

For the synthesis of the anomeric L-2′-deoxyguanosines, a recently developed method for guanine nucleoside synthesis[11] was employed. The anomeric mixture of **1** was hydrolyzed with dilute acid to give 3,5-di-*O*-*p*-toluyl-2-deoxy-L-*ethythro*-pentose, which was acetylated

(1) (a) This research was supported by Grant CA-08109 from the National Cancer Institute of the National Institutes of Health. (b) To whom correspondence should be addressed: Department of Chemistry, the University of Alberta, Edmonton 7, Canada:

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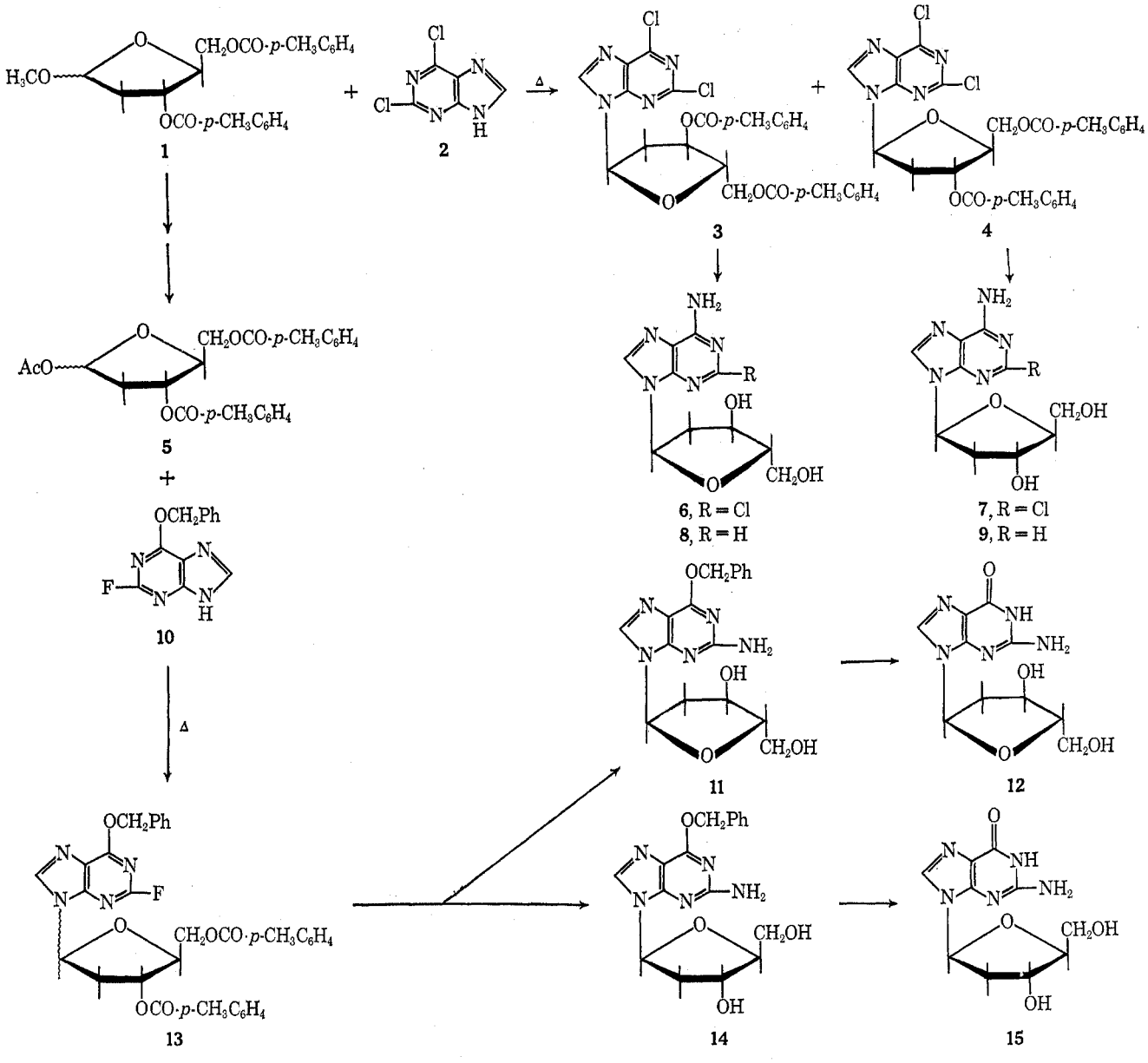
SCHEME I



to give 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose[5] (**5**) as a sirupy mixture. Fusion of **5** (*ca.* 50:50 α/β by nmr) with 2-fluoro-6-benzyloxypurine[11] (**10**) gave at least a 14% yield of the anomeric nucleoside **13**. This intermediate was verified by uv and tlc and was then treated directly with alcoholic ammonia. The resulting 2-amino-6-benzyloxy-9-(2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (**11** and **14**, respectively) were resolved by chromatography on Dowex 1-X2 (OH^-).[11,17] The observed ratio of α/β anomers in this case was *ca.* 2:1, which is in contrast with the predominance of β anomer in the fusion of **1** and **2**. As in the case of the D enantiomers,[11] **11** (α anomer) crystallized and was completely characterized. Hydrogenation of the anomerically pure intermediates **14** and **11** over palladium gave 2-amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-deoxy-L-guanosine, **15**) and 2-amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purin-6-one (**12**).

Again these products were characterized and their structures were confirmed by comparison with the corresponding D enantiomers.[11] It is of interest to note that (as expected) the H_1' proton of these L-2′ deoxynucleosides obey the same "triplet"–"quartet" splitting patterns for β and α anomers, respectively, as observed with a number of previously observed[10,11] D-2′ deoxynucleosides.

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Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. Nmr spectra were determined on a Varian A-60 instrument with tetramethylsilane or sodium 5,5-dimethyl-5-silapentanesulfonate as internal standard. Uv spectra were determined on a Beckman DK-2 instrument. Hydrogenations were effected using a Parr hydrogenation apparatus at specified hydrogen gas pressure. Evaporations were accomplished using a Büchler rotating evaporator under reduced pressure (aspirator) unless specified otherwise. Thin layer chromatography (tlc) was run on glass plates coated with SilicAR-7GF (Mallinckrodt Chemical Works) using the upper phase of EtOAc–*n*-PrOH–H_2O (4:1:2) unless otherwise specified.

1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (1).—To 280 ml of H_2O was added 10 g (0.048 mol) of 2-deoxy-L-*erythro*-pentose anilide,[5] 10 ml of benzaldehyde, and 1 g of benzoic acid. This mixture was stirred for 17 hr at room tempeature and then extracted with three 100-ml portions of Et_2O. The resulting aqueous solution was evaporated to dryness at a temperature less

than 30° and EtOH was added to the residue. This solution was evaporated to dryness and this procedure was repeated twice with absolute EtOH and twice with absolute MeOH. The resulting 2-deoxy-L-*erythro*-pentose was dissolved in 100 ml of absolute MeOH and treated with MeOH–HCl followed by *p*-toluyl chloride according to the procedure of Hoffer.[14] The resulting 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (**1**) was dissolved in 20 ml of absolute EtOH and cooled at 0°. Three crops of crystalline sugar (5.2 g, 4.2 g, and 2.9 g, respectively, total yield 67%) were obtained. Several recrystallizations of the first crop from EtOH gave colorless needles of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose (α anomer of **1**): mp 83–84°; $[\alpha]^{27}D$ −135.2° (*c* 0.9, $CHCl_3$); nmr ($CDCl_3$) δ 3.40 (s, 3, OCH_3-1) [lit.[18] (for the D enantiomer) mp 82–83°; $[\alpha]^{20}D$ +130° (*c* 0.67, $CHCl_3$)].

Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.76; H, 6.25. Found: C, 68.48; H, 6.21.

Several recrystallizations of the third crop of crystalline **1** gave needles of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose (β anomer of **1**): mp 78–78.5°; $[\alpha]^{27}D$ +7.7° (*c* 1.7, $CHCl_3$); nmr ($CDCl_3$) δ 3.32 (s, 3, OCH_3-1) [lit.[18] (for the D enantiomer) mp 76.5–78°; $[\alpha]^{20}D$ −8.1° (*c* 2.5, $CHCl_3$)].

Anal. Found: C, 68.95; H, 6.37.

2,6-Dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α- and -β-L-*erythro*-pentofuranosyl)purines (3 and 4). A. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose (α Anomer of 1).—A finely powdered mixture of 1.87 g (0.0049 mol) of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranose and 0.93 g (0.0049 mol) of 2,6-dichloropurine (**2**) was heated in an oil bath at 143° for 6 min. Dichloroacetic acid (2 drops) was added and fusion was continued for 5 min at 143° *in vacuo* (aspirator). The clear melt was cooled to about 100° and dissolved in EtOAc. This solution was washed with two 50-ml portions of cold, saturated, aqueous $NaHCO_3$ and 50 ml of cold H_2O, dried (Na_2SO_4), and filtered. The filtrate was evaporated to a gum and this material was treated twice with EtOH and evaporated. The residue was dissolved in 5 ml of benzene and this solution was applied to a neutral alumina column (90 g). The column was washed with 1000 ml of benzene and elution was begun with EtOAc–PhH (2:8). The fractions (100 ml) were evaporated to dryness and evaluated by uv and tlc. Fractions 1 and 2 contained 0.33 g of sugar **1**; fractions 3–9 contained the blocked nucleosides and were fractionally recrystallized individually from EtOH to give 0.35 g (13%) of **3** (α anomer) and 0.84 g (32%) of **4** (β anomer), total yield 1.19 g (45%). Pure 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**3**) was obtained, mp 140–142°, uv max (EtOH) 241 mμ (ε 35,800) and 272.5 (11,500).

Anal. Calcd for $C_{26}H_{22}O_5N_4Cl_2$: C, 57.68; H, 4.06; N, 10.35. Found: C, 57.72; H, 4.06; N, 10.37.

Pure 2,6-dichloro-9-(3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranosyl)purine (**4**) was obtained, mp 154–156°, uv max (EtOH) 240.5 mμ (ε 35,500) and 272.5 (11,300).

Anal. Found: C, 57.55; H, 4.21; N, 10.45.

B. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose (β Anomer of 1).—Fusion of 1.67 g (0.00435 mol) of 1-*O*-methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-β-L-*erythro*-pentofuranose and 0.83 g (0.0044 mol) of 2,6-dichloropurine (**2**) according to procedure A above gave 0.22 g (9.3%) of **3** (α anomer) and 0.13 g (5.5%) of **4** (β anomer), total yield 14.8%.

C. From 1-*O*-Methyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose (1).—Fusion of 2.7 g (0.007 mol) of the crystalline anomeric mixture **1** with 1.3 g (0.0069 mol) of 2,6-dichloropurine (**2**) according to procedure A above gave 0.38 g (10%) of **3** (α anomer) and 0.55 g (15%) of **4** (β anomer), total yield 25%.

6-Amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (8).—To a solution of 100 ml of methanol saturated with ammonia at room temperature was added 1.47 g (0.0027 mol) of **3** and the suspension was stirred at room temperature for 3 days with periodic addition of ammonia gas to saturation. The resulting solution was heated on the steam bath for 30 min and then evaporated to dryness. The residue was treated with 100 ml of H_2O and this was washed with three 100-ml portions of Et_2O. The aqueous solution of 6-amino-2-chloro-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**6**) had uv absorption and tlc mobility identical with those of the corresponding D enantiomer[10] and was hydrogenated without further purification.

(18) D. L. MacDonald and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **84**, 1262 (1962).

The above aqueous solution was diluted to 150 ml with H_2O and 15 ml of concentrated, aqueous NH_3 was added. The resulting solution was hydrogenated at 40 psi for 8 hr in the presence of 1 g of 10% Pd–C. This mixture was filtered and the filtrate was evaporated with a water bath at less than 25°. The residue was dissolved in 1.5 ml of H_2O, cooled at 0° for 16 hr, and filtered to give 0.21 g (31%) of **8**. A second crop, 0.11 g, raised the yield to 47%. Recrystallization of this material from H_2O gave **8** as needles: mp 204–204.5°; $[\alpha]^{22}D$ −70.8° (*c* 1.0, H_2O) [lit.[15] (for the D enantiomer) $[\alpha]^{29}D$ +68.2° (H_2O)]; uv max (pH 1) 257 mμ (ε 16,000), (pH 11) 259 mμ (ε 16,400); nmr (D_2O) δ 6.42 ("q," 1, $J_{1'-2',2''}$ = 3.3 and 7.5 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.91; H, 5.38; N, 27.96.

6-Amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (2′-Deoxy-L-adenosine, 9).—Treatment of 1.19 g (0.0022 mol) of **4** with methanolic ammonia followed by hydrogenation under the identical conditions described above for the α anomer (**3** → **8**) gave 0.21 g (38%) of pure, crystalline **9**: mp 184–185°; $[\alpha]^{23}D$ +23.2° (*c* 1, H_2O) [lit.[15] (for the D enantiomer) $[\alpha]^{30}D$ −24.0° (H_2O)]; uv max (pH 1) 257 mμ (ε 15,400); (pH 11) 260 mμ (ε 15,800); nmr (D_2O) δ 6.42 ("t," 1, $J_{1'-2',2''}$ = 7.0 Hz, H_1').

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.72; H, 5.43; N, 28.00.

2-Amino-6-benzyloxy-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)-purine (11) and 2-Amino-6-benzyloxy-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (14).—A well-stirred mixture of 4.22 g (0.017 mol) of finely powdered 2-fluoro-6-benzyloxypurine[11] (**10**) and 7.82 g (0.019 mol) of sirupy 1-*O*-acetyl-3,5-di-*O*-*p*-toluyl-2-deoxy-L-*erythro*-pentofuranose[5] (**5**) was placed in an oil bath preheated to 155°. Dichloroacetic acid (7 drops) was added with stirring and the mixture was stirred for 8 min at 155°, at which time a clear, amber melt had formed. An aspirator was connected and fusion *in vacuo* was continued for 17 min. The melt was cooled to *ca.* 100° and dissolved in EtOAc. This solution was washed with two 50-ml portions of ice-cold, saturated, aqueous Na_2CO_3 solution, 50 ml of ice–H_2O, and 50 ml of saturated aqueous NaCl solution, and dried (Na_2SO_4). This mixture was filtered using a Norit–Celite bed and the filtrate was evaporated to a heavy sirup. MeOH was added and evaporated and this was repeated twice. The sirup was dissolved in 25 ml of MeOH, treated with 200 ml of MeOH presaturated with NH_3 at −10°, and heated at 85° for 4 hr in a steel bomb. The solution was cooled, 17 ml of 1 *N* NaOH was added, and the solution was evaporated to dryness. The residue was treated with 100 ml of EtOAc and 40 ml of H_2O and the separated aqueous layer was extracted with three 50-ml portions of EtOAc. The combined organic phase was washed with 30 ml of saturated aqueous NaCl, dried (Na_2SO_4), filtered, and evaporated to *ca.* 20 ml. This solution was applied to a column (2 × 20 in.) of silica gel, the column was washed with 800 ml of $CHCl_3$ to remove *p*-toluamide and methyl *p*-toluate, and the nucleoside material was eluted with EtOH. The EtOH fractions were evaporated to dryness, the residue was dissolved in 9 ml of 1,2-dimethoxyethane (glyme), and 11 ml of H_2O was added. This solution was applied to a column (1 × 35 in., 500 ml) of Dowex 1-X2 (OH^-) 200–400 mesh[17] packed in glyme–H_2O (45:55).[11] Elution was effected with the same solvent mixture and 10-ml fractions were collected. Fractions 1–72 were discarded. Fractions 73–89 were pooled and evaporated to dryness to yield crude 2-amino-6-benzyloxy-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purine (**11**). This material was recrystallized from *i*-PrOH using seed crystals of the D enantiomer to give 0.1 g (1.6% overall yield from **10**) of fine needle clusters: mp 97–99° [lit.[11] (for the D enantiomer) mp 158–160°]; uv max (pH 1) 287 mμ (ε 12,500), (pH 11) 280 mμ (ε 12,000) and 249 (10,000), (MeOH) 282 mμ (ε 12,500) and 249 (10,900); nmr (DMSO-d_6) δ 6.23 ("q," 1, $J_{1'-2',2''}$ = 3.0 and 7.5 Hz, H_1').

Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.33; H, 5.21; N, 19.59.

Fractions 90–97 contained both anomers and were discarded.

Fractions 98–130 were pooled and evaporated to dryness to give crude 2-amino-6-benzyloxy-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purine (**14**), which was hydrogenated without further purification. The tlc migrations of **11** and **14** were identical with those of their D enantiomers,[11] R_{14}/R_{11} = 1.1.

2-Amino-9-(2-deoxy-α-L-*erythro*-pentofuranosyl)purin-6-one (12).—The combined filtrates from crystallization of **11** were evaporated to dryness, dissolved in 25 ml of EtOH and 50 ml of H_2O, and hydrogenated for 17 hr at 46 psi with 0.12 g of 5%

Pd-C. The mixture was filtered using Celite and the filtrate was evaporated to dryness. The white crystalline solid was recrystallized from 6 ml of H_2O to give 0.36 g (7.3% overall yield from **10**) of **12** hemihydrate: $[\alpha]^{26}D$ −103° (*c* 1.1, DMF) [lit.[11] (for the D enantiomer) $[\alpha]^{26}D$ +102.4° (*c* 0.99, DMF)]; uv max (pH 1) 253 mμ (ε 12,700) and 274 sh (8800), (pH 11) 258–265 mμ (br, ε 12,000), (MeOH) 253 mμ (ε 14,500); nmr (DMSO-d_6–D_2O) δ 6.13 ("q," 1, $J_{1'-2',2''}$ = 3.5 and 7.5 Hz, H_1'), (DMSO-d_6) δ 3.41 (s, 1, $\frac{1}{2}H_2O$ of hydration).

Anal. Calcd for $C_{10}H_{18}N_5O_4 \cdot \frac{1}{2}H_2O$: C, 43.47; H, 5.11; N, 25.35. Found: C, 43.51; H, 4.78; N, 25.37.

2-Amino-9-(2-deoxy-β-L-*erythro*-pentofuranosyl)purin-6-one (2′-Deoxy-L-guanosine, 15).—The entire crude sample of **14** was dissolved in 20 ml of EtOH and 40 ml of H_2O and hydrogenated at 47 psi for 15 hr in the presence of 0.09 g of 5% Pd-C. This mixture was treated as in the preparation of **12** above to yield 0.19 g (3.9% overall yield from **10**) of crystalline **15** monohydrate: $[\alpha]^{26}D$ +20.5° (*c* 1, DMF) [lit.[11] [for the D enantiomer) $[\alpha]^{26}D$ −20.3° (*c* 1.2, DMF)]; uv max (pH 1) 254 mμ (ε 12,900) and 275 sh (8900), (pH 11) 259–266 mμ (br, ε 12,000), (MeOH) 254 mμ (ε 14,700); nmr (DMSO-d_6–D_2O) δ 6.18 ("t," 1, $J_{1'-2',2''}$ = 7 Hz, H_1'), nmr (DMSO-d_6) δ 3.46 (s, 2, H_2O of hydration).

Anal. Calcd for $C_{10}H_{18}N_5O_4 \cdot H_2O$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.97; H, 5.24; N, 24.53.

The anomers **12** and **15** exhibited identical tlc mobility with their D enantiomer,[11] R_{15}/R_{12} = 1.2.

Registry No.—α anomer of **1**, 22837-36-1; β anomer of **1**, 22837-37-2; **3**, 22837-38-3; **4**, 22837-39-4; **8**, 17015-19-9; **9**, 14365-45-8; **11**, 22837-42-9; **12**, 22837-43-0; **15**, 22837-44-1.

The Hydrolysis of Cyclic Vinyl Ethers. An ^{18}O Study of the Hydrolysis of 2-Alkyl-2,3,4,5,6,7-hexahydrobenzofurans[1]

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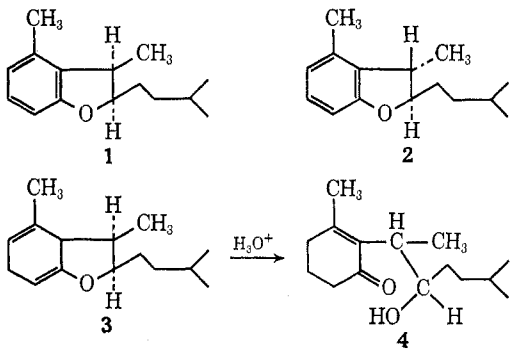
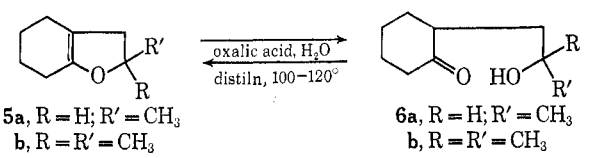
The hydrolysis of the ^{18}O-labeled cyclic vinyl ethers, 2-methyl-2,3,4,5,6,7-hexahydrobenzofuran (**5a**) and the corresponding 2,2-dimethyl compound (**5b**), followed by recyclization, leads to no loss of the ^{18}O label, within experimental error of the mass spectrometric analysis. The cracking patterns for these vinyl ethers and of 2-(2′-methoxypropyl)cyclohexanone (**8**) have been determined. The labeling experiments rule out a free carbonium ion intermediate in the hydrolysis of **5b**, where a tertiary carbonium ion could be formed; they also show that stereochemistry would be preserved around the oxygen–C-2 bond of compounds like **5a** and **5b** during acid hydrolysis.

Earlier papers[2] have reported experiments on the preparation of 2,3-dihydrobenzofurans as possible intermediates for syntheses in the fumagillin series. One of the sequences planned involved a Birch reduction[2c,3] of the 2,3-dialkyl-2,3-dihydrobenzofuran, such as **1**, followed by hydrolysis of the resulting tetrahydrobenzofuran **3**; both **1** and the corresponding *trans* compound **2** were prepared, their configurations were established, and both were reduced with lithium and liquid ammonia and then hydrolyzed.[2,3] It is obviously



necessary to know whether in the hydrolysis of the vinyl ether **3** (and the related *trans* compound) there has been cleavage of the oxygen–C-2 bond in **3**, and hence any possibility of change in the configuration of the carbon carrying the hydroxyl group in **4**.

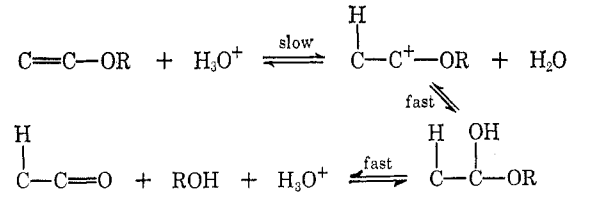
The present study shows by ^{18}O labeling studies that there is no oxygen–C-2 cleavage in compound **5a**, where C-2 carries one alkyl group, and also none in compound **5b**, where C-2 is a tertiary carbon, carrying two methyl groups.



5a, R = H; R′ = CH_3
b, R = R′ = CH_3

6a, R = H; R′ = CH_3
b, R = R′ = CH_3

Earlier studies on the mechanism of hydrolysis of acetals and of open-chain vinyl ethers have shown that, in $H_2{}^{18}O$, none of the label appears in the alcohol formed,[4] and therefore the hydrolysis does not involve cleavage of the O–R bond. Kinetic studies[5,6] and solvent isotope[6] effects indicate that the slow step is the transfer of a proton to the unsaturated carbon β to the oxygen atom, to form the resonance-stabilized carbo-



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