Synthesis of 2′-Deoxytubercidin, 2′-Deoxyadenosine, and Related 2′-Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure

Zygmunt Kazimierczuk,† Howard B. Cottam, Ganapathi R. Revankar, and Roland K. Robins*

Contribution from the Cancer Research Center, Department of Chemistry, Brigham Young University, Provo, Utah 84602. *Received January 9, 1984. Revised Manuscript Received April 19, 1984*

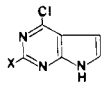
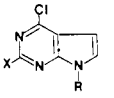
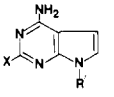
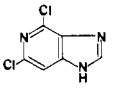
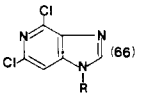
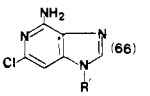
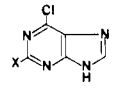
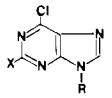
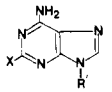
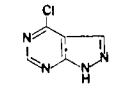
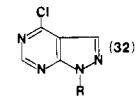
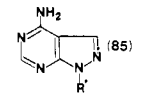
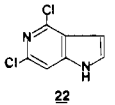
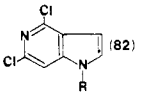
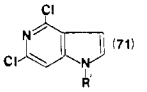
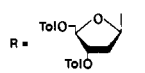
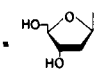
Abstract: A general and stereospecific synthesis has been developed for the direct preparation of 2′-deoxy-β-D-ribofuranosylpurine analogues including 2′-deoxyadenosine derivatives. The reaction of the sodium salt of 4-chloropyrrolo[2,3-*d*]pyrimidine (**4**) or 2,4-dichloropyrrolo[2,3-*d*]pyrimidine (**1**) with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (**25**) provided the corresponding *N*-1,2′-deoxy-β-D-ribofuranosyl blocked derivatives (**5** and **2**) which, on ammonolysis, gave 2′-deoxytubercidin (**6**) and 2-chloro-2′-deoxytubercidin (**3**), respectively, in good yield. This glycosylation also readily proceeds in the presence of a 2-methylthio group. Application of this glycosylation procedure to 4,6-dichloroimidazo[4,5-*c*]pyridine (**10**), 6-chloropurine (**16**), 2,6-dichloropurine (**13**), and 4-chloropyrazolo[3,4-*d*]pyrimidine (**19**) gave 2-chloro-2′-deoxy-3-deazaadenosine (**12**), 2′-deoxyadenosine (**18**), 2-chloro-2′-deoxyadenosine (**15**), and 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazolo-[3,4-*d*]pyrimidine (**21**), respectively. Similarly, glycosylation and ammonolysis of 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine (**22**) gave 4,6-dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[3,2-*c*]pyridine (**24**). This stereospecific attachment of the 2-deoxy-β-D-ribofuranosyl moiety appears to be due to a Walden inversion at the C-1 carbon of **25**.

A simple and stereospecific synthesis has now been developed for the direct preparation of 2′-deoxyadenosine derivatives and related analogues. This procedure appears to be of general utility and overcomes many of the limitations found in earlier glycosylation procedures. Derivatives of 2′-deoxyadenosine are of considerable current interest due to the potent antitumor effects of 2-chloro-2′-deoxyadenosine (**15**)[1-4] and 2-bromo-2′-deoxyadenosine.[4] Montgomery has recently found[4] that **15**, given on a frequent schedule, results in 60% survivors of mice injected with L1210 leukemia.

Prior glycosylation procedures introducing the 2-deoxy-β-D-ribofuranosyl (2-deoxy-β-D-*erythro*-pentofuranosyl) moiety into an aglycon reported from our laboratory[5-8] and by others[9-12] invariably provide anomeric mixtures as well as positional isomers which result in very low yields of the desired 2′-deoxynucleoside. In view of these difficulties, a four-step deoxygenation procedure using phenoxythiocarbonylation[13-15] or imidazolylthiocarbonylation[16,17] of the 2′-hydroxy group of the corresponding 3′, 5′-protected β-D-ribonucleoside has recently been developed to provide the requisite 2′-deoxynucleoside. These latter procedures, however, require the availability of the preformed ribonucleoside and unfortunately are not applicable in the presence of haloheterocyclic derivatives,[18] which are most useful for further nucleophilic displacement. We have recently employed the sodium salt of 4,6-dichloro-2-(methylthio)pyrrolo[2,3-*d*]pyrimidine and 1-bromo-2,3,5-tri-*O*-benzoyl-D-ribofuranose in dioxane to give a 68% yield of 4,6-dichloro-2-(methylthio)-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine.[19] Application of this simple single phase sodium salt glycosylation procedure to the synthesis of 2′-deoxynucleosides of chloropurines and related chloropurine analogues is the subject of the present report.

In the present work we elected to use chloroheterocyclic derivatives for glycosylation studies to obtain the corresponding glycosyl intermediates, which could readily be converted into the desired 2′-deoxyadenosine analogues and related derivatives by direct nucleophilic displacement. Treatment of pyrrolo[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione[20] with $POCl_3$ in the presence of *N*,*N*-dimethylaniline gave 2,4-dichloropyrrolo[2,3-*d*]pyrimidine (**1**). The sodium salt of **1**, produced in situ by NaH in acetonitrile, was treated with 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose[21] (**25**) at 50 °C. A clean reaction mixture was obtained, and the product was purified on a silica gel column to give 2,4-dichloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-

Table I. Condensation of the Sodium Salt of Various Chloropurines and Chloropurine Analogues with 1-Chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose (25)

starting heterocycle	intermediate (% yield)	final product (% yield)
 1, X = Cl; 4, X = H; 7, X = SCH_3	 2, X = Cl (60); 5, X = H (71); 8, X = SCH_3 (66)	 3, X = Cl (61); 6, X = H (85); 9, X = SCH_3 (72)
 10	 (66) 11	 (66) 12
 13, X = Cl; 16, X = H	 14, X = Cl (59); 17, X = H (59)	 15, X = Cl (71); 18, X = H (78)
 19	 (32) 20	 (85) 21
 22	 (82) 23	 (71) 24
	R = 	R′ = 

† On leave from the Faculty of Biophysics, University of Warsaw, Poland.

(1) Plunkett, W.; Nowak, B. J.; Robins, R. K. *Proc. Am. Assoc. Cancer Res.* **1980**, *71*, 302.

0002-7863/84/1506-6379$01.50/0

pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**2**) in 60% yield. When **2** was treated with methanolic ammonia at 100 °C for 12 h, deprotection of the sugar with concomitant nucleophilic displacement of the 4-chloro function to an amino group occurred to give 2-chloro-4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2-chloro-2′-deoxytubercidin, **3**). Dehalogenation of **3** with Pd/C in a hydrogen atmosphere readily provided 4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′-deoxytubercidin, **6**). 2′-Deoxytubercidin (**6**) was also prepared in good yield by the direct glycosylation of the sodium salt of 4-chloropyrrolo[2,3-*d*]pyrimidine[22] (**4**) with **25** to obtain 4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**5**), followed by ammonolysis.

This glycosylation was also found to proceed with equal ease in the presence of a methylthio group. Thus, the glycosylation of the sodium salt of 2-(methylthio)-4-chloropyrrolo[2,3-*d*]pyrimidine[23] (**7**) with **25** in acetonitrile gave a 66% yield of 2-(methylthio)-4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**8**). Ammonolysis of **8** readily gave 2-(methylthio)-4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**9**). Dethiation of **9** by treatment with Raney nickel furnished yet another route to 2′-deoxytubercidin (**6**), which in all cases was found to be identical with 2′-deoxytubercidin previously reported.[24,25]

The anomeric configuration of the isolated pyrrolo[2,3-*d*]pyrimidine 2′-deoxynucleosides was assigned by ^{1}H NMR spectroscopy. The pattern of the anomeric proton signal was identical with that published for 2′-deoxytubercidin,[25] as well as for other 2′-deoxyribonucleosides.[6] Since the starting 1-chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranose[21] has the α-configuration[26] in the solid state, the exclusive formation of the blocked 2′-deoxy-β-nucleosides in the present study is viewed to be due to a direct Walden inversion (S_N2) at the C_1 carbon by the anionic heterocyclic nitrogen.

This type of direct glycosylation via the sodium salt of a preformed pyrrolo[2,3-*d*]pyrimidine in acetonitrile appears to be considerably superior to previously reported glycosylations of this ring system,[27-30] including phase-transfer procedures.[31,32] Our synthesis of 2′-deoxytubercidin provides a unique simple total synthesis starting with a requisite heterocycle which appears to be superior to published multistep procedures[14,25] requiring first the corresponding ribonucleoside as in the recently described six-step synthesis of 2′-deoxysangivamycin[33] from toyocamycin. In view of the current interest in the new pyrrolo[2,3-*d*]pyrimidine nucleoside antibiotics cadequomycin[34-37] and dapiramicin,[38-40] the presently described procedure should provide a direct route to the synthesis of 2′-deoxycadeguomycin and the 2′-deoxy-β-D-ribofuranosyl derivative of dapiramicin.

This general synthetic procedure has been found to be applicable equally well to the preparation of 3-deazapurine 2′-deoxynucleosides. The following represents the direct preparation of the previously unknown 4-amino-6-chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*c*]pyridine (**12**). Treatment of the sodium salt of 4,6-dichloroimidazo[4,5-*c*]pyridine[41] (**10**) with **25** in acetonitrile in an inert atmosphere gave crystalline 4,6-dichloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*c*]pyridine (**11**). Ammonolysis of **11** with $MeOH/NH_3$ at elevated temperature and pressure gave **12**. The UV absorption spectrum of **12** was very similar to that of 4-amino-6-chloro-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine[42] and together with the observed triplet for the anomeric proton in the ^{1}H NMR spectrum established the site of glycosylation in **12** as N-1 and the anomeric configuration as β.

In the purine series, reaction of the protected deoxychloro sugar **25** with the sodium salt of 6-chloropurine[43] (**16**) gave a mixture of two nucleosidic products. After silica gel column chromatography, a 59% yield of 6-chloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (**17**) and the corresponding N-7 glycosyl isomer in 11% yield were obtained. Subsequent treatment of **17** with $MeOH/NH_3$ at 100 °C for 12 h resulted in the deprotection of the glycon moiety with concomitant nucleophilic displacement of the 6-chloro function to give 6-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (**18**), identical with an authentic sample of 2′-deoxyadenosine.[44] A similar glycosylation of the sodium salt of 2,6-dichloropurine[43] (**13**) with **25** gave a mixture of 2,6-dichloro-9-(2-deoxy-3,5-di-

(2) Results from the National Cancer Institute on 2-chloro-2′-deoxyadenosine (NSC 105014), submitted from our laboratory, show a T/C (treated/control) of 192 at 25 mg/kg daily dose against L1210 leukemia in mice.

(3) Carson, D. A.; Wasson, D. B.; Kaye, J.; Ullman, B.; Martin, D. W., Jr.; Robins, R. K.; Montgomery, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 6865.
(4) Montgomery, J. A. *Cancer Res.* **1982**, *42*, 3911.
(5) Robins, M. J.; Bowles, W. A.; Robins, R. K. *J. Am. Chem. Soc.* **1964**, *86*, 1251.
(6) Robins, M. J.; Robins, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 4934.
(7) Robins, M. J.; Robins, R. K. *J. Org. Chem.* **1969**, *34*, 2160.
(8) Witkowski, J. T.; Fuertes, M.; Cook, P. D.; Robins, R. K. *J. Carbohydr. Nucleosides, Nucleotides* **1975**, *2*, 1.
(9) For a review of the synthesis of 2′-deoxynucleoside, see: (a) Goodman, L. In "Basic Principles in Nucleic Acid Chemistry"; Ts'o, P. O. P., Ed.; Academic Press: New York, 1974; Vol. I, pp 93–208. (b) Moffatt, J. G. In "Nucleoside Analogues: Chemistry, Biology, and Medical Applications"; Walker, R. T., De Clercq, E., Eckstein, F., Eds.; Plenum Press: New York, 1979; pp 71–164.
(10) Mian, A. M.; Khwaja, T. A. *J. Med. Chem.* **1983**, *26*, 286.
(11) Christensen, L. F.; Broom, A. D.; Robins, M. J.; Bloch, A. *J. Med. Chem.* **1972**, *15*, 735.
(12) Wright, G. E.; Dudycz, L. W. *J. Med. Chem.* **1984**, *27*, 175.
(13) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
(14) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.
(15) Lessor, R. A.; Leonard, N. J. *J. Org. Chem.* **1981**, *46*, 4300.
(16) Pankiewicz, K.; Matsuda, A.; Watanabe, K. A. *J. Org. Chem.* **1982**, *47*, 485.
(17) Fukukawa, K.; Ueda, T.; Hirano, T. *Chem. Pharm. Bull.* **1983**, *31*, 1842.
(18) Montgomery, J. A. In "Nucleosides, Nucleotides, and their Biological Applications"; Rideout, J. L.; Henry, D. W., Beacham III, L. M.; Eds.; Academic Press: New York, 1983; pp 19–46.
(19) Kazimierczuk, Z.; Revankar, G. R.; Robins, R. K. *Nucleic Acids Res.* **1984**, *12*, 1179.
(20) West, R. A.; Ledich, K.; Hitchings, G. H. British Patent 812 366 1959; *Chem. Abstr.* **1960**, *54*, 5921.
(21) Hoffer, M. *Chem. Ber.* **1960**, *93*, 2777.
(22) Davoll, J. *J. Chem. Soc.* **1960**, *131*.
(23) Noell, C. W.; Robins, R. K. *J. Heterocycl. Chem.* **1964**, *1*, 34.
(24) Seela, F.; Kehne, A. *Liebigs Ann. Chem.* **1983**, *876*.
(25) Robins, M. J.; Muhs, W. H. *J. Chem. Soc., Chem. Commun.* **1976**, *269*.
(26) Bhattacharya, A. K.; Ness, R. K.; Fletcher, H. G., Jr. *J. Org. Chem.* **1963**, *28*, 428.
(27) Tolman, R. L.; Robins, R. K.; Townsend, L. B. *J. Heterocycl. Chem.* **1967**, *4*, 230.
(28) Tolman, R. L.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1969**, *91*, 2102.
(29) Tolman, R. L.; Tolman, G. L.; Robins, R. K.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 799.
(30) Townsend, L. B.; Tolman, R. L.; Robins, R. K.; Milne, G. H. *J. Heterocycl. Chem.* **1976**, *13*, 1363.
(31) Seela, F.; Winkeler, H.-D. *Carbohydr. Res.* **1983**, *118*, 29.
(32) Winkeler, H.-D.; Seela, F. *J. Org. Chem.* **1983**, *48*, 3119.
(33) Maruyama, T.; Wotring, L. L.; Townsend, L. B. *J. Med. Chem.* **1983**, *26*, 25.
(34) Tanaka, N.; Wu, R. T.; Okabe, T.; Yamashita, H.; Shimazu, A.; Nishimura, T. *J. Antibiot.* **1982**, *35*, 272.
(35) Wu, R. T.; Okabe, T.; Namibiot. **1982**, *35*, 279.
(36) Kondo, T.; Goto, T.; Okabe, T.; Tanaka, N. *Tetrahedron Lett.* **1983**, *24*, 3647.
(37) Beylin, V. G.; Kawasaki, A. M.; Cheng, C. S.; Townsend, L. B. *Tetrahedron Lett.* **1983**, *24*, 4793.
(38) Shomura, T.; Nishizawa, N.; Iwata, M.; Yoshida, J.; Ito, M.; Amano, S.; Koyama, M.; Kojima, M.; Inouye, S. *J. Antibiot.* **1983**, *36*, 1300.
(39) Nishizawa, N.; Kondo, Y.; Koyama, M.; Omoto, S.; Iwata, M.; Tsuruoka, T.; Inouye, S. *J. Antibiot.* **1984**, *37*, 1.
(40) Seto, H.; Otake, N.; Koyama, M.; Ogino, H.; Kodama, Y.; Nishizawa, N.; Tsuruoka, T.; Inouye, S. *Tetrahedron Lett.* **1983**, *24*, 495.
(41) Rousseau, R. J.; Robins, R. K. *J. Heterocycl. Chem.* **1965**, *2*, 196.
(42) May, J. A., Jr.; Townsend, L. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 125.
(43) Beaman, A. G.; Robins, R K. *J. Appl. Chem.* **1962**, *12*, 432.
(44) Ness, R. K. In "Synthetic Procedures in Nucleic Acid Chemistry"; Zorbach, W. W., Tipson, R. S., Eds.; Interscience: New York, **1968**; Vol. I, pp 183–187.

O-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (**14**), 59% yield, and the corresponding N-7 glycosyl isomer (13% yield) which were separated on a silica gel column using toluene:acetone gradient. Further ammonolysis of **14** with $MeOH/NH_3$ at 100 °C for 5 h readily gave the desired 2-chloro-2′-deoxyadenosine[11] (**15**) in 71% yield.

Although the enzymatic synthesis of 4-amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**21**) has been documented,[45] there is, until the present work, no report of a suitable chemical synthesis of **21**. Application of the sodium salt glycosylation procedure to 4-chloropyrazolo[3,4-*d*]pyrimidine[46] (**19**) gave 4-chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrazolo[3,4-*d*]pyrimidine (**20**) as the major product in 32% yield, along with a minor amount of the N-2 positional isomer. Treatment of **20** with $MeOH/NH_3$ at room temperature gave **21** in 85% yield. Compound **21** was found to be identical in all respects with the nucleoside prepared enzymatically.[45]

The versatility of this stereospecific glycosylation procedure has also been demonstrated with pyrrolo[3,2-*c*]pyridine (3,7-dideazapurine) ring system containing electronegative substituents. When the sodium salt of 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine[47] (**22**) was allowed to react with **25** in acetonitrile in an inert atmosphere, 4,6-dichloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[3,2-*c*]pyridine (**23**) was formed exclusively in 82% yield. Further treatment of **23** with $MeOH/NH_3$ at elevated temperature and pressure gave a good yield of 4,6-dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[3,2-*c*]pyridine (**24**). The ^1H NMR spectrum of **24** displayed a triplet for the anomeric proton centered at δ 6.41 (peak width 13.31 Hz) indicating the β configuration. The essentially identical UV absorption spectra of **22** and **24** indicated the site of glycosylation in **24** to be N-1.

Selective nucleophilic displacement of the 4-chlorine atom of **24** and the stereospecific attachment of the 2-deoxy-β-D-ribofuranosyl moiety to other hetereocycles by this simple sodium salt procedure are presently under further investigation in our laboratory.

Experimental Section

General Procedures. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H NMR) spectra were determined at 90 MHz with a JEOL FX 90Q spectrometer. The chemical-shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Ultraviolet spectra (UV; sh = shoulder) were recorded on a Cary Model 15 spectrophotometer. Elemental analyses were performed by Robertson Labs, Florham Park, NJ. Evaporations were carried out under reduced pressure with the bath temperature below 30 °C.

2,4-Dichloropyrrolo[2,3-*d*]pyrimidine (1). A mixture of dry pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione[20] (8.0 g, 53 mmol), phosphorus oxychloride (80 mL), and freshly distilled *N*,*N*-dimethylaniline (18 mL) was heated under reflux for 2.5 h. The reaction mixture was evaporated to one-third the volume and poured with stirring onto crushed ice (~350 g). The aqueous solution was brought to pH 2–3 with concentrated NH_4OH and extracted with $CHCl_3$ (3 × 200 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to an oil. The oil was purified on a silica gel column (3 × 40 cm) with successively toluene, toluene–$CHCl_3$ (1:1), and $CHCl_3$ to obtain the pure product which, on crystallization (toluene), gave 0.08 g (8.0%) of analytical sample: mp 249 °C; UV λ_{max} (MeOH) 227 nm (ε 30 400), 290 (4200); ^1H NMR (Me_2SO-d_6) δ 6.70 (d, 1, C_5H), 7.80 (d, 1, C_6H). Anal. Calcd for $C_6H_3Cl_2N_3$ (188.01): C, 38.33; H, 1.60; N, 22.35; Cl, 37.71. Found: C, 38.31; H, 1.81; N, 22.15; Cl, 37.42.

2,4-Dichloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2). To a suspension of **1** (0.62 g, 3.3 mmol) in dry CH_3CN (25 mL) was added sodium hydride (50% in oil, 0.17 g, 3.6 mmol) and the mixture was stirred at room temperature under a nitrogen atmosphere for 30 min. 1-Chloro-2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-*erythro*-pentofuranose[21] (**25**, 1.28 g, 3.3 mmol) was added portionwise with stirring. The reaction mixture was stirred at 50 °C for 2 h before it was filtered to remove a small amount of insoluble material. Evaporation of the filtrate gave an oily residue, which was purified on an open-bed silica gel column (2.5 × 40 cm) using toluene:acetone (9:1, v/v) as the solvent. The homogeneous product was crystallized from EtOH to give 1.08 g (60%) of **2** as needles: mp 164–165 °C; ^1H NMR (Me_2SO-d_6) δ 2.38 and 2.42 (2 s, 6, 2 CH_3), 6.74 (t + d, 2, $C_1'H$ and C_5H), 7.32 and 7.96 (m, 9, 2 Ph and C_6H). Anal. Calcd for $C_{27}H_{23}Cl_2N_3O_5$ (540.4): C, 60.00; H, 4.29; N, 7.78. Found: C, 60.06; H, 4.33; N, 7.92.

2-Chloro-4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2-Chloro-2′-deoxytubercidin, 3). A solution of **2** (0.94 g, 1.74 mmol) in methanolic ammonia (saturated at 0 °C, 15 mL) was heated in a steel bomb at 100 °C for 12 h, and the mixture was evaporated to dryness. The residue was dissolved in MeOH (25 mL) and adsorbed onto silica gel (~25 g). Coevaporation with MeOH (3 × 50 mL) gave a dry residue, which was placed on top of a silica gel column (2 × 40 cm). The column was eluted with $CHCl_3$–MeOH gradient. The title compound was eluted at 15% methanolic chloroform and crystallized from water to yield 0.30 g (61%): mp 205 °C; UV λ_{max} (pH 1) 229 nm (ε 18 500), 276 (10 100); UV λ_{max} (pH 7 and 12) 274 nm (ε 10 700); ^1H NMR (Me_2SO-d_6) δ 6.40 (t, 1, $C_1'H$, peak width 14 Hz), 6.60 (d, 1, J = 4.0 Hz, C_5H), 7.36 (d, 1, J = 4.0 Hz, C_6H), 7.50 (br, s, 2, NH_2), and other sugar protons. Anal. Calcd for $C_{11}H_{13}ClN_4O_3$ (284.7): C, 46.41; H, 4.60; N, 19.68. Found: C, 46.34; H, 4.69; N, 19.62.

4-Amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (2′-Deoxytubercidin, (6). Method A. To a solution of **3** (0.57 g, 2 mmol) in 80% aqueous 1-propanol (50 mL) containing K_2CO_3 (0.10 g) was added Pd/C (10%, 50 mg) and the mixture was hydrogenated at 2 atm for 2 h. The mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness. Crystallization of the residue from water gave 0.45 g (90%) of 2′-deoxytubercidin: mp 218 °C [lit.[24] mp 216 °C and all other physicochemical properties of **6** are identical with those for 2′-deoxytubercidin previously reported.

Method B. To a solution of **9** (0.59 g, 2 mmol) in 1-propanol (50 mL) was added Raney nickel (W-4, wet weight 4 g) and the mixture was heated under reflux for 5 h. After cooling to room temperature, the mixture was filtered through a Celite pad and the filtrate evaporated to dryness. The residue was crystallized from water to give 0.35 g (70%): mp 218 °C, which was identical in every detail with the 2′-deoxytubercidin **6** prepared by method A.

Method C. In the same manner as for **2**, 4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**5**) was prepared by using 4-chloropyrrolo[2,3-*d*]pyrimidine[22] (**4**, 1.22 g, 8 mmol), NaH (50% in oil, 0.40 g, 8.3 mmol), **25** (3.1 g, 8 mmol), and CH_3CN (50 mL) to yield 2.9 g (71%): mp 118 °C; ^1H NMR (Me_2SO-d_6) δ 6.80 (d + t, overlap, 2, C_5H and $C_1'H$), 7.36 and 7.96 (m, 9, 2 Ph and C_6H), 8.70 (s, 1, C_2H). Anal. Calcd for $C_{27}H_{24}ClN_3O_5$ (505.9): C, 64.10; H, 4.78; N, 8.31. Found: C, 63.95; H, 4.80; N, 8.19.

A solution of **5** (0.20 g, 0.75 mmol) and $MeOH/NH_3$ (saturated at 0 °C, 12 mL) was heated at 120 °C for 12 h and then evaporated to dryness. The residue was dissolved in water (50 mL), adsorbed on Dowex 1-X8 (OH^-) column (1 × 10 cm) and eluted with water (200 mL), followed by H_2O–MeOH (3:1, v/v, 300 mL) gave 2′-deoxytubercidin, 0.16 g (85%), mp 217–218 °C, and was identical in every detail with **6** prepared by method A.

2-(Methylthio)-4-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[2,3*d*]pyrimidine (8). In the same manner as for **2**, the title compound was prepared by using 2-(methylthio)-4-chloropyrrolo[2,3-*d*]pyrimidine[23] (**7**, 0.60 g, 3 mmol), NaH (50% in oil, 0.16 g, 3.3 mmol), CH_3CN (25 mL), and **25** (1.18 g, 3 mmol). Purification on a silica gel column (2 × 30 cm) with toluene–acetone (95:5, v/v) gave crystalline (from EtOH) compound, 1.10 g (66%): mp 118 °C; ^1H NMR (Me_2SO-d_6) δ 2.36 and 2.40 (2 s, 6, 2 CH_3), 6.66 and 6.74 (t + d, 2, $C_1'H$ and C_5H), 7.35 and 7.90 (m, 9, 2 Ph and C_6H). Anal. Calcd for $C_{28}H_{26}ClN_3O_5S$ (552.05): C, 60.92; H, 4.75; N, 7.61. Found: C, 61.16; H, 4.96; N, 7.43.

2-(Methylthio)-4-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-pyrrolo[2,3-*d*]pyrimidine (9). A solution of **8** (2.50 g, 4.5 mmol) in methanolic ammonia (saturated at 0 °C, 50 mL) was heated in a steel bomb at 100 °C for 12 h, and the resulting solution was evaporated to dryness. The residue was purified on a silica gel column (3 × 40 cm) with MeOH–$CHCl_3$ (1:6) as the solvent. Crystallization of the homogeneous product from MeOH gave the title compound, 0.97 g (72%): mp 233–234 °C (lit.[24] mp 233 °C); UV λ_{max} (pH 1) 226 nm (ε 21 300), 280 (14 000); UV λ_{max} (pH 7 and 12) 236 nm (ε 23 100), 282 (14 200) [lit.[24] UV λ_{max} (MeOH) 234 (ε 25 700), 281 (15 000)].

4,6-Dichloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*c*]pyridine (11). In the same manner as for **2**, the title compound was prepared by using 4,6-dichloroimidazo[4,5-*c*]-pyridine[41] (**10**, 0.61 g, 3.2 mmol), NaH (50% in oil, 0.17 g, 3.5 mmol),

(45) Stout, M. G.; Hoard, D. E.; Holman, M. J.; Wu. E. S.; Siegel, J. M. *Methods Carbohydr. Chem.* **1976**, *7*, 19.
(46) Robins, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 784.
(47) Schneller, S. W.; Hosmane, R. S. *J. Heterocycl. Chem.* **1978**, *15*, 325.

CH_3CN (25 mL) and **25** (1.38 g, 3.5 mmol). Purification on a silica gel column (4 × 40 cm) with toluene–acetone (95:5, v/v) gave crystalline (from EtOH) product, 1.15 g (66%): mp 165–167 °C; ^1H NMR (Me_2SO-d_6) δ 2.40 and 2.44 (2 s, 6, 2 CH_3), 6.68 (t, 1, $C_1'H$, peak width 14.0 Hz), 7.38 and 7.96 (m, 9, 2 Ph and C_7H), 8.84 (s, 1, C_2H). Anal. Calcd for $C_{27}H_{23}Cl_2N_3O_5$ (540.4): C, 60.00; H, 4.29; N, 7.78. Found: C, 60.25; H, 4.50; N, 7.59.

4-Amino-6-chloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)imidazo[4,5-*c*]pyridine (12). Ammonolysis of **11** (1.30 g, 2.4 mmol) with $MeOH/NH_3$ (50 mL) at 135–140 °C for 25 h in the same manner as described for **3** gave the title compound. Crystallization from water gave analytical sample, 0.45 g (66%): mp 186–187 °C; UV λ_{max} (pH 1) 266 nm (ε19 300), 285 (sh) (13 400); UV λ_{max} (pH 7 and 12) 271 nm (ε 20 600); ^1H NMR (Me_2SO-d_6) δ 6.22 (t, 1, $C_1'H$, peak width 13.0 Hz), 6.66 (s, 2, NH_2), 6.97 (s, C_7H), 8.30 (s, 1, C_2H), and other sugar protons. Anal. Calcd for $C_{11}H_{13}ClN_4O_3$ (284.7): C, 46.41; H, 4.60; N, 19.68. Found: C, 46.40; H, 4.80; N, 19.53.

2,6-Dichloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (14). A mixture of 2,6-dichloropurine[43] (**13**, 0.95 g, 5 mmol) and sodium hydride (50% in oil, 0.25 g, 5.2 mmol) in anhydrous CH_3CN (35 mL) was stirred at ambient temperature under a nitrogen atmosphere for 30 min. Dry, powdered **25** (1.95 g, 5 mmol) was added portionwise with stirring, during 20 min, and stirring was continued for further 15 h. A small amount of insoluble material was removed by filtration. Evaporation of the solvent gave an oil residue, which was purified on a silica gel column (5 × 60 cm) with toluene–acetone (9:1, v/v) as the solvent. The following two nucleosides were isolated in the order listed; the title compound (**14**) was crystallized from EtOH to yield 1.60 g (59%): mp 159–162 °C [lit.[11] mp 155–157 °C].

The N-7 glycosyl isomer 2,6-dichloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine was isolated and crystallized from EtOH to yield 0.35 g (13%): mp 141–143 °C; ^1H NMR (Me_2SO-d_6) δ 6.88 (t, 1, $C_1'H$, peak width 14.5 Hz), 7.36 and 7.90 (m, 8, Ph), 9.28 (s, 1, C_8H). Anal. Calcd for $C_{26}H_{22}Cl_2N_4O_5$ (541.4): C, 57.68; H, 4.09; N, 10.35. Found: C, 57.55; H, 4.00; N, 10.36.

2-Chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (15). A solution of **14** (2.50 g, 4.6 mmol) in CH_3OH/NH_3 (saturated at 0 °C, 60 mL) was heated at 100 °C for 5 h, and the mixture was evaporated to dryness. The residue was purified on a silica gel column (5 × 40 cm) with $CHCl_3$–MeOH (8:2, v/v) as the solvent. Crystallization of the homogeneous solid from EtOH gave 0.87 g (71%) of analytically pure title compound: mp 220 °C (softens), resolidifies, turns brown, does not melt below 300 °C [lit.[11] mp 210–215 °C (softens) and then solidifies and turns brown].

6-Chloro-9-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine (17). In the same manner as for **14**, reaction of the sodium salt of 6-chloropurine[43] (**16**, 0.77 g, 5 mmol and 50% NaH in oil, 0.25 g, 5.2 mmol) with **25** (2.0 g, 5.15 mmol) in CH_3CN (50 mL) gave 1.51 g (59%) of crystalline (from EtOH) **17**: mp 107–109 °C; ^1H NMR (Me_2SO-d_6) δ 6.76 (t, 1, $C_1'H$, peak width 14.0 Hz), 7.36 and 7.94 (m, 8, Ph), 8.80 (s, 1, C_2H), 9.00 (s, 1, C_8H). Anal. Calcd for $C_{26}H_{23}ClN_4O_5$ (506.9): C, 61.60; H, 4.57; N, 11.05. Found: C, 61.73; H, 4.72; N, 11.03.

The N-7 glycosyl isomer 6-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine was isolated and crystallized from EtOH to yield 0.29 g (11%): mp 152–153 °C; ^1H NMR (Me_2SO-d_6) δ 6.96 (t, 1, $C_1'H$, peak width 14.5 Hz), 7.36 and 7.94 (m, 8, Ph), 8.94 (s, 1, C_2H), 9.26 (s, 1, C_8H). Anal. Calcd for $C_{26}H_{23}ClN_4O_5$ (506.9): C, 61.60; H, 4.57; N, 11.05. Found: C, 61.55; H, 4.49; N, 11.05.

6-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (2′-Deoxyadenosine, 18). A solution of **17** (1.01 g, 2 mmol) in $MeOH/NH_3$ (18 mL) was heated at 100 °C for 12 h and then evaporated to dryness. The aqueous solution of the residue was extracted with $CHCl_3$ (2 × 25 mL), followed by ether (2 × 25 mL), and then evaporated to dryness. The residue was crystallized from water to yield 0.41 g (78%): mp 186–189 °C [lit.[44] mp 187–189 °C, and all other physico-chemical properties of **18** are identical with 2′-deoxyadenosine reported in literature].

4-Chloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrazolo[3,4-*d*]pyrimidine (20). In the same manner as for **2**, the title compound was prepared by using 4-chloropyrazolo[3,4-*d*]pyrimidine[46] (**19**, 1.54 g, 10 mmol), NaH (50% in oil, 0.57 g, 12 mmol) dioxane (100 mL), and **25** (3.9 g, 10 mmol). Purification of the product on a Kieselgel-60 (230–400 mesh) flash column (2.4 × 25 cm) with hexane–ether (4:1, v/v) gave crystalline analytical sample, 1.62 g (32%): mp 130–132 °C; UV λ_{max} (MeOH) 240 nm (ε 17 600); ^1H NMR ($CDCl_3$) δ 2.40 and 2.44 (2 s, 6, 2 CH_3), 6.98 (t, 1, $C_1'H$, peak width 14.0 Hz), 7.27 and 7.96 (m, 8, Ph), 8.16 (s, 1, C_6H), 8.78 (s, 1, C_3H). Anal. Calcd for $C_{26}H_{23}ClN_4O_5$ (506.9): C, 61.60; H, 4.57; N, 11.05; Cl, 6.99. Found: C, 61.49; H, 4.66; N, 10.86; Cl, 7.27.

4-Amino-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrazolo[3,4-*d*]pyrimidine (21). In the same manner as for **18**, compound **21** was prepared by using **20** (0.25 g, 0.49 mmol) and $MeOH/NH_3$ (35 mL). After crystallization from aqueous ethanol gave 0.10 g (85%): mp 240–242 °C [lit.[45] mp 245–246 °C, and was identical in all respects with **21** prepared enzymatically].

4,6-Dichloro-1-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrrolo[3,2-*c*]pyridine (23). In the same manner as for **2**, the title compound was prepared by using 4,6-dichloro-1*H*-pyrrolo[3,2-*c*]pyridine[47] (**22**, 0.40 g, 2.15 mmol), NaH (50% in oil, 0.10 g, 2.4 mmol), CH_3CN (100 mL), and **25** (0.84 g, 2.15 mmol). Purification of the product on a Kieselgel-60 (230–400 mesh) flash column with toluene–EtOAc (7:1, v/v) gave 0.95 g (82%) as colorless foam: UV λ_{max} (EtOH) 227 nm (ε 80 200), 240 (54 100), 274 (14 100); ^1H NMR ($CDCl_3$) δ 2.43 and 2.46 (2 s, 6, 2 CH_3), 6.34 (t, 1, $C_1'H$, peak width 14.3 Hz), 6.60 (d, 1, J = 4.5 Hz, C_3H), 7.30 (m, 6, Ph, C_2H and C_7H), 7.94 (m, 4, Ph). Anal. Calcd for $C_{28}H_{24}Cl_2N_2O_5$ (539.4): C, 62.34; H, 4.48; N, 5.19. Found: C, 62.07; H, 4.53; N, 4.98.

4,6-Dichloro-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrrolo[3,2-*c*]pyridine (24). Compound **23** (0.80 g, 1.5 mmol) was combined with methanolic ammonia (50 mL, saturated at 0 °C) and heated in a steel bomb at 135–150 °C for 20 h. The reaction mixture was evaporated to dryness and the residue was purified on a Kieselgel-60 (230–400 mesh) flash column with CH_2Cl_2–MeOH (14:1, v/v) to obtain 0.32 g (71%) of title compound, which was crystallized from aqueous ethanol as colorless needles: mp 173 °C (softens at 110 °C); UV λ_{max} (pH 1, 7 and 11) 224 nm, (ε 29 300), 274 (5600), 289 (sh) (3600); ^1H NMR (Me_2SO-d_6) δ 6.41 (t, 1, $C_1'H$, peak width 13.31 Hz), 6.67 (d, 1, J = 3.38 Hz, C_3H), 7.88 (d, 1, J = 3.61 Hz, C_2H), 7.95 (s, 1, C_7H), and other sugar protons. Anal. Calcd for $C_{12}H_{12}Cl_2N_2O_3$ (303.1): C, 47.55; H, 3.99; N, 9.24; Cl, 23.39. Found: C, 47.63; H, 4.11; N, 9.06; Cl, 23.18.

Acknowledgment. This investigation was supported by Grant No. R01 AI 15324-04, awarded by the National Cancer Institute, DHEW.

Registry No. 1, 90213-66-4; **2**, 91713-42-7; **3**, 91741-81-0; **4**, 3680-69-1; **5**, 91713-43-8; **6**, 60129-59-1; **7**, 57564-94-0; **8**, 91713-44-9; **9**, 86402-13-3; **10**, 2589-12-0; **11**, 91713-45-0; **12**, 91741-82-1; **13**, 5451-40-1; **14**, 38925-80-3; **15**, 4291-63-8; **16**, 87-42-3; **17**, 91713-46-1; **18**, 958-09-8; **19**, 5399-92-8; **20**, 91713-47-2; **21**, 17318-21-7; **22**, 67139-79-1; **23**, 91713-48-3; **24**, 91713-49-4; **25**, 4330-21-6; pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione, 39929-79-8; 2,6-dichloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)pyrine, 91713-50-7; 6-chloro-7-(2-deoxy-3,5-di-*O*-*p*-toluoyl-β-D-*erythro*-pentofuranosyl)purine, 91713-51-8.