9-Deazapurine Nucleosides. The Synthesis of Certain *N*-5-2'-Deoxy-β-D-*erythro*pentofuranosyl and *N*-5-β-D-Arabinofuranosylpyrrolo[3,2-*d*]pyrimidines

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Received October 22, 1986

A number of 2,4-disubstituted pyrrolo[3,2-*d*]pyrimidine *N*-5 nucleosides were prepared by the direct glycosylation of the sodium salt of 2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**3**) using 1-chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*pentofuranose (**1**) and 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**11**). The resulting *N*-5 glycosides, 2,4-dichloro-5-(2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidine (**4**) and 2,4-dichloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**12**), served as versatile key intermediates from which the *N*-7 glycosyl analogs of the naturally occurring purine nucleosides adenosine, inosine and guanosine were synthesized. Thus, treatment of **4** with methanolic ammonia followed by dehalogenation provided the adenosine analog, 4-amino-5-(2-deoxy*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**6**). Reaction of **4** with sodium hydroxide followed by dehalogenation afforded the inosine analog, 5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**9**). Treatment of **4** with sodium hydroxide followed by methanolic ammonia gave the guanosine analog, 2-amino-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**10**). The preparation of the same analogs in the β-D-arabinonucleoside series was achieved by the same general procedures as those employed for the corresponding 2'-deoxy-β-D-ribonucleoside analogs except that, in all but one case, debenzylation of the sugar protecting groups was accomplished with cyclohexene-palladium hydroxide on carbon, providing 4-amino-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**18**). Structural characterization of the 2'-deoxyribonucleoside analogs was based on uv and proton nmr while that of the arabinonucleosides was confirmed by single-crystal X-ray analysis of **15a**. The stereospecific attachment of the 2-deoxy-β-D-ribofuranosyl and β-D-arabinofuranosyl moieties appears to be due to a Walden inversion at the C_1 carbon by the anionic heterocyclic nitrogen (S_N2 mechanism).

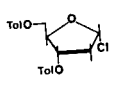
J. Heterocyclic Chem., **24**, 821 (1987).

Recently we reported [1,2] the development of a general and stereospecific synthesis for the direct preparation of 2'-deoxy-β-D-ribofuranosylpurines and purine analogs by the condensation of the requisite sodium salt of various chloropurines and related analogs with 1-chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*pentofuranose (**1**). Among the purine analogs successfully glycosylated were derivatives of two fused pyrrole ring systems, pyrrolo-[2,3-*d*]-pyrimidine and pyrrolo[3,2-*c*]pyridine. The application of this simple single phase sodium salt glycosylation procedure has been extended to the synthesis of 2'-deoxy-β-D-ribofuranosyl (2'-deoxy-β-D-*erythro*pentofuranosyl) and β-D-arabinofuranosylnucleosides of the pyrrolo-[3,2-*d*]pyrimidine (9-deazapurine) system and is the subject of the present report.

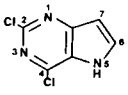
Although the synthesis of the pyrrolo[3,2-*d*]pyrimidine *C*-nucleosides, 9-deazainosine [3], 9-deazaadenosine [4,5], and 9-deazaguanosine [5,6] has been reported, the preparation of the corresponding *N*-5 nucleosides of this ring system is not documented in the literature. Attachment of a carbohydrate moiety to the pyrrole nitrogen of this ring system thus constitutes the chemical synthesis of nucleosides which are isosteric with 7-glycosylpurines.

In the present work we elected to use a heterocycle for the glycosylation studies which subsequently could be readily converted into various desired 2,4-disubstituted nucleosides by direct nucleophilic substitutions. 2,4-Dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**2**) [7] served as the starting material for these studies and was prepared by treatment of the monosodium salt of 5*H*-pyrrolo[3,2-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**3**) [7] with phenylphosphonic dichloride at 170-180° for 3 hours thus providing **2** in 78% yield- a considerable improvement over reported procedures [7] wherein **2** was prepared in 32% and 56% yields using phosphorus chloride-dimethylaniline and pyrophosphoryl chloride, respectively. Glycosylation of the sodium salt of **2** using the 2-deoxy-α-chloro sugar, **1** [8], afforded an 84% yield of 2,4-dichloro-5-(2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**4**) (Scheme I). This key dichloro intermediate, **4**, served as the versatile nucleoside starting material from which the 7-glycosyl analogs of the naturally occurring

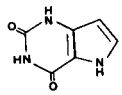
purine nucleosides adenosine, inosine and guanosine in the 2′-deoxy series were obtained. Thus, treatment of **4** with methanolic ammonia for 12 hours at 100° gave 4-amino-2-chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**5**) in 72% yield. Dehalogenation of **5** with palladium on carbon in a hydrogen atmosphere provided an excellent yield of 4-amino-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**6**).



1



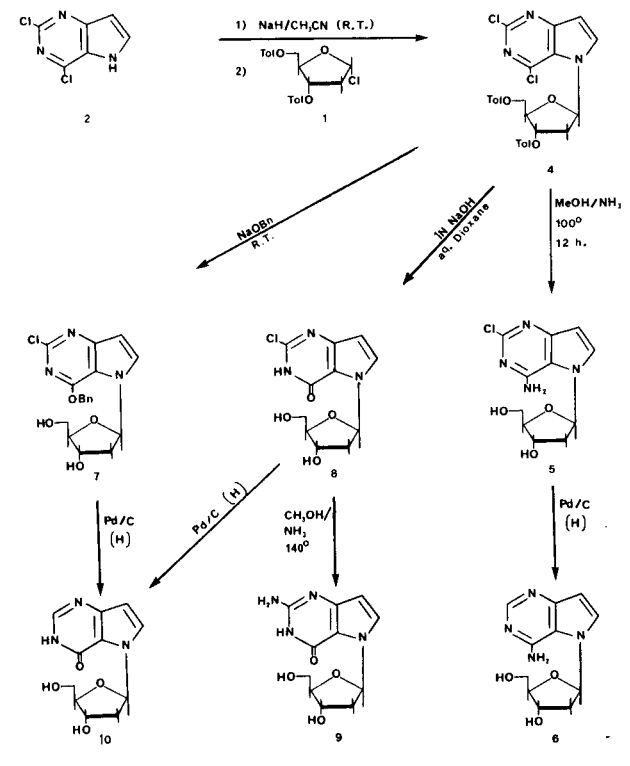
2



3

When **4** was treated with sodium benzyloxide in benzyl alcohol at room temperature an 80% yield of 4-benzyloxy-2-chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**7**) was obtained. Treatment of **7** with palladium on carbon in a hydrogen atmosphere provided simultaneous debenzylation with dehalogenation to yield 5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidin-4(3*H*)-one (**9**). Treatment of **4** with boiling aqueous sodium hydroxide/dioxane gave 2-chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**8**) which, upon reaction with Pd/C in a hydrogen atmosphere, provided a second route to the synthesis of **9**. Reaction of **8** with methanolic ammonia at 140° for 12 hours provided a 64% yield of 2-amino-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**10**).

Scheme I



The anomeric configuration of the isolated 2′-deoxynucleosides was assigned by ^{1}H nmr spectroscopy, wherein the β anomers exhibited the characteristic pseudo-triplet for the anomeric proton. This pattern has been observed for the anomeric proton of other 2′-deoxy-β-D-ribonucleosides [9,10] including fused pyrrole ring systems [1,2]. The uv spectra of nucleosides **6** and **9** were very similar to the spectra of the corresponding heterocyclic bases, the spectra of which have been reported [7], thus supporting the assignment of the site of glycosylation as *N*-5 rather than *N*-1 or *N*-3.

The preparation of the corresponding β-D-arabinofuranosylnucleosides was accomplished in the same general manner as that of the 2′-deoxyribofuranosylnucleosides. Compound **2** was glycosylated by the sodium salt procedure using 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**11**) [11] to provide 2,4-dichloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**12**) in 81% yield. Treatment of **12** with methanolic ammonia gave a good yield of the benzyl-blocked nucleoside, **13**, which was concomitantly debenzylated and dehalogenated with cyclohexene-20% palladium on carbon [12] to afford 4-amino-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**14**). When **12** was treated with boiling aqueous sodium hydroxide/dioxane, the benzyl-protected intermediate, 2-chloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**15**), was obtained in 87% yield. Compound **15** was deprotected using cyclohexene-20% palladium on carbon [12] with concomitant dehalogenation to give 5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**16**). Finally, treatment of **15** with methanolic ammonia at 140° yielded the intermediate **17** which was deblocked to yield 2-amino-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**18**).

The site of glycosylation for the arabinonucleoside series was assigned as *N*-5 based on uv spectral comparisons of compounds **14** and **16** with those of the corresponding heterocyclic bases [7]. The assignment of the anomeric configuration for the arabinofuranosylnucleosides was established as β by single-crystal X-ray analysis of 2-chloro-5-(β-D-arabinofuranosyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidin-4(3*H*)-one (**15a**).

X-Ray Crystallographic Study.

Compound **15a** was prepared by treatment of **15** with boron trichloride to remove the benzyl protecting groups and then was allowed to crystallize slowly from acetonitrile to yield suitable crystals for X-ray analysis. A crystal (0.43 x 0.25 x 0.20 mm) was cut from a feather-shaped lobe of a sea-urchin-like cluster and mounted on an Enraf-Nonius CAD4 automated diffractometer. Ni filtered Cu K_α (λ = 1.5418 Å) radiation was employed. The compound crystallizes with two molecules per asymmetric unit in space

group $P2_1$ of the monoclinic system with lattice parameters, obtained from a least-squares refinement of the setting angles of 25 reflections ($50.24° \leq 2\theta \leq 55.46°$), of $a = 13.953(2)$, $b = 5.3747(6)$, $c = 16.834(2)$ Å, $\beta = 99.257(10)°$ and $V = 1246.0(3)$ Å^3. A total of 2978 reflections were measured ($3° \leq 2\theta \leq 152°$) and merged to give 2879 unique reflections with $R_{int} = 0.015$. The data were corrected for absorption ($\mu = 30.006$ cm^{-1}, transmission factor range: 0.425 - 0.634), Lorentz and polarization effects. Cell parameters and data were measured at 295 K.

The 22 atoms of the two independent base rings were obtained from MULTAN82 [13]; the remaining 18 non-hydrogen atoms were found in successive electron density difference maps. All hydrogen atoms were located in a difference map. Non-hydrogen atoms were refined anisotropically while hydrogen atoms were refined isotropically. Least-squares refinement (SHELX76 [14]) was carried out in two blocks, composed of one complete molecule each, until the shift/error ratio was less than 0.02, at which point $R = 0.0307$, $wR = 0.0473$ and $S = 1.87$ for 457 parameters and 2798 reflections having $F \geq 4\sigma_F$. The refined extinction parameter was 1.04×10^{-6}. The largest peak in the final difference map was 0.30 e/Å^3. The function minimized was $\Sigma w(|F_o|-|F_c|)^2$ where $w = 1/(\sigma_F^2 + 0.00040F^2)$. The data were reduced with the SDP-Plus package [15]. Scattering factors and anomalous dispersion corrections were taken from the International Tables [16].

Atomic coordinates are given in Table 1; bond lengths and bond angles are given in Table 2. Figure 1 is a perspective ORTEPII [17] drawing of the two crystallographically distinct molecules of **15a**. The β anomeric configuration is confirmed. The molecules have different conformations. Molecule A is $C_{1'}$ *exo*-$C_{2'}$ *endo* ($_1T^2$ form) with phase of pseudorotation of 140.2° and amplitude of pucker (τ_m) of 43.8° whereas B is $C_{2'}$ *endo*-$C_{3'}$ *exo* ($_3T^2$ form) with phase of 184.2° and τ_m of 36.3° [18]. The C(5')-O(5') side chain of A is gauche-gauche while in B it is gauche-*trans*. The base rings are planar within experimental error and the dihedral angles between the fused rings in each molecule are 1.52(8)° for A and 0.99(11)° for B. The glycosidic torsion angles [O(1')-C(1')-N(1)-C(2)] are 53.1(3)° for A and 10.2(3)° for B. The side-chain conformation in A allows the formation of an intramolecular hydrogen bond O(2')-H(2'O)··O(5'). Hydrogen bonding is summarized in Table 3. The N(6)→O(10)B and N(6)B→O(10) hydrogen bonds produce the dimeric asymmetric unit.

Table 1

Atomic positions in fractional coordinates and U_{eq} [a] for non-hydrogen atoms in **15a**

Atom	x/a	y/b	z/c	U_{eq}
Cl	1.00212(5)	.7106(2)	.19957(4)	.0625(3)
N(1)	.83169(13)	.1383(4)	.42895(11)	.0318(5)
C(2)	.9094(2)	−.0172(5)	.45260(14)	.0370(7)
C(3)	.9834(2)	.0325(5)	.41048(14)	.0371(7)
N(4)	1.00066(13)	.3588(5)	.30616(12)	.0387(6)
C(5)	.9520(2)	.5361(6)	.26806(13)	.0385(7)
N(6)	.85975(13)	.6032(5)	.27379(11)	.0333(5)
C(7)	.80334(14)	.4880(4)	.32484(11)	.0289(6)
C(8)	.85688(14)	.2978(5)	.37152(11)	.0283(5)
C(9)	.95116(15)	.2354(5)	.35946(12)	.0329(6)
O(10)	.71802(11)	.5537(4)	.32262(9)	.0374(5)
C(1')	.7490(2)	.1677(4)	.47014(12)	.0292(6)
C(2')	.6865(2)	−.0633(5)	.47656(13)	.0348(6)
C(3')	.6332(2)	.0162(5)	.54530(14)	.0354(7)
C(4')	.7094(2)	.1764(5)	.59863(13)	.0331(6)
C(5')	.7541(2)	.0554(7)	.67661(14)	.0433(8)
O(1')	.78600(12)	.2244(4)	.55250(9)	.0323(4)
O(2')	.7414(2)	−.2805(4)	.49750(12)	.0459(6)
O(3')	.54867(13)	.1613(5)	.51849(13)	.0511(7)
O(5')	.79181(13)	−.1848(5)	.66382(11)	.0457(6)
ClB	.48293(5)	−.1328(2)	.28945(5)	.0625(3)
N(1)B	.68821(12)	.4387(4)	.08331(10)	.0277(5)
C(2)B	.6141(2)	.5928(5)	.05118(14)	.0343(6)
C(3)B	.5322(2)	.5399(5)	.08401(14)	.0365(7)
N(4)B	.50068(13)	.2174(5)	.18584(11)	.0376(6)
C(5)B	.5453(2)	.0407(6)	.22798(13)	.0377(7)
N(6)B	.63868(13)	−.0293(5)	.23024(11)	.0352(6)
C(7)B	.70079(15)	.0869(5)	.18470(12)	.0306(6)
C(8)B	.65414(14)	.2816(5)	.13685(12)	.0280(5)
C(9)B	.55702(14)	.3432(5)	.13810(12)	.0310(6)
O(10)B	.78600(11)	.0157(4)	.18930(10)	.0398(5)
C(1')B	.78321(14)	.4198(4)	.05626(11)	.0251(5)
C(2')B	.79425(14)	.1785(4)	.01031(13)	.0272(6)
C(3')B	.85837(13)	.2647(4)	−.05046(13)	.0274(6)
C(4')B	.82079(14)	.5265(4)	−.07042(12)	.0269(5)
C(5')B	.7382(2)	.5347(5)	−.14181(14)	.0368(7)
O(1')B	.79037(12)	.6173(3)	.00197(9)	.0305(5)
O(2')B	.70141(11)	.1071(4)	−.02913(11)	.0341(5)
O(3')B	.95797(11)	.2851(4)	−.01330(11)	.0366(5)
O(5')B	.70262(13)	.7824(4)	−.15214(11)	.0364(5)

a $U_{eq} = \frac{1}{3}\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* A_{ij}$, where A_{ij} is the dot product of the i^{th} and j^{th} direct-space unit-cell vectors.

The mechanism of glycosylation of **2** using 1-chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**11**) appears to be similar to that involving 1-chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*pentofuranose (**1**) in that only *N*-5 β-nucleosides are formed in both cases. This observation would indicate that glycosylation occurs by S_N2, that is, by a Walden inversion at the anomeric carbon atom by the nucleophilic fused pyrrole anion. While this S_N2-type glycosylation is now well-documented [1,2] in the 2'-deoxyribonucleoside series involving fused pyrroles, its application to the synthesis of arabinonucleosides of such pyrrole systems has not, until now, been reported [19]. Inasmuch as both halogenosugars, **1** [11] and **11** [20], have been assigned as α-anomers and only β-nucleoside products were observed for both glycosylation reactions, it is evident that significant anomerization of the α-chlorosugars did not take place under these conditions before these reactions were complete.

Table 2

Bond lengths (Å) and bond angles (°) in **15a**

1	2	3	A 1 - 2	B 1 - 2	A 1-2-3	B 1-2-3
C(2)	N(1)	C(8)	1.375(3)	1.366(3)	107.6(2)	108.2(2)
C(8)	N(1)	C(1')	1.379(3)	1.373(3)	125.5(2)	125.7(2)
C(1')	N(1)	C(2)	1.447(3)	1.472(3)	125.4(2)	125.5(2)
C(3)	C(2)	N(1)	1.369(4)	1.375(3)	110.9(2)	109.9(2)
C(9)	C(3)	C(2)	1.415(4)	1.401(4)	105.8(2)	106.4(2)
C(9)	N(4)	C(5)	1.385(3)	1.386(3)	113.6(2)	114.3(2)
N(4)	C(5)	Cl	1.280(4)	1.284(4)	120.1(2)	118.9(2)
Cl	C(5)	N(6)	1.719(3)	1.727(3)	113.3(2)	114.1(2)
N(6)	C(5)	N(4)	1.354(3)	1.350(3)	126.5(2)	126.9(2)
C(7)	N(6)	C(5)	1.399(3)	1.393(3)	124.1(2)	122.8(2)
C(8)	C(7)	O(10)	1.424(3)	1.413(3)	129.6(2)	127.8(2)
C(8)	C(7)	N(6)			111.0(2)	112.0(2)
O(10)	C(7)	N(6)	1.236(3)	1.238(3)	119.3(2)	120.2(2)
C(9)	C(8)	N(1)	1.403(3)	1.397(3)	107.7(2)	107.6(2)
C(9)	C(8)	C(7)			120.8(2)	121.7(2)
N(1)	C(8)	C(7)			131.5(2)	130.7(2)
C(3)	C(9)	N(4)			128.2(2)	129.8(2)
C(3)	C(9)	C(8)			108.0(2)	107.9(2)
N(4)	C(9)	C(8)			123.8(2)	122.3(2)
C(2')	C(1')	O(1')	1.529(4)	1.529(3)	103.0(2)	106.6(2)
C(2')	C(1')	N(1)			116.9(2)	112.6(2)
O(1')	C(1')	N(1)	1.431(3)	1.414(3)	107.2(2)	108.0(2)
C(3')	C(2')	O(2')	1.533(4)	1.534(3)	110.6(2)	111.0(2)
C(3')	C(2')	C(1')			100.3(2)	101.4(2)
O(2')	C(2')	C(1')	1.408(3)	1.409(2)	113.4(2)	108.0(2)
C(4')	C(3')	O(3')	1.539(3)	1.519(3)	109.7(2)	107.6(2)
C(4')	C(3')	C(2')			102.8(2)	102.1(2)
O(3')	C(3')	C(2')	1.424(3)	1.433(2)	113.0(2)	111.1(2)
C(5')	C(4')	O(1')	1.506(3)	1.525(3)	107.9(2)	111.7(2)
C(5')	C(4')	C(3')			114.6(2)	113.0(2)
O(1')	C(4')	C(3')	1.441(3)	1.438(3)	106.7(2)	105.4(2)
O(5')	C(5')	C(4')	1.422(4)	1.421(3)	111.8(2)	109.1(2)
C(1')	O(1')	C(4')			107.5(2)	110.7(2)

Table 3.
Hydrogen bonding for **15a**

D - H ··· A			Symmetry of A relative to D	d(D··A) (Å)	d(H··A) (Å)	∠ (D-H··A) (°)
N(6)	H(6)	O(10)B	x, 1+y, z	2.744(3)	1.96(3)	178(3)
O(2')	H(2'0)	O(5')	x, y, z	2.823(3)	1.88(4)	171(4)
O(3')	H(3'0)	O(3')	1-x, y-.5, 1-z	3.031(3)	2.15(7)	148(5)
O(5')	H(5'0)	N(4)	2-x, y-.5, 1-z	2.868(3)	1.85(4)	173(4)
N(6)B	H(6)B	O(10)	x, y-1, z	2.849(3)	2.03(3)	178(3)
O(2')B	H(2'0)B	O(5')B	x, y-1, z	2.710(3)	1.89(4)	157(4)
O(3')B	H(3'0)B	O(3')B	2-x, y-.5, -z	2.938(3)	2.08(5)	164(4)
O(5')B	H(5'0)B	N(4)B	1-x, y+.5, -z	2.824(2)	2.10(5)	167(6)

EXPERIMENTAL

General Procedures.

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H nmr) spectra were determined at 300.1 MHz with an IBM NR300AF 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 Beckman DU-50 spectrophotometer. Elemental analyses were performed by Robertson Labs, Florham Park, NJ. Evaporations were carried out under reduced pressure with the bath temperature below 40°. Thin layer chromatography (tlc) was run on silica gel 60 F-254 plates (EM Reagents). E. Merck silica gel (230-400 mesh) was used for flash column chromatography.

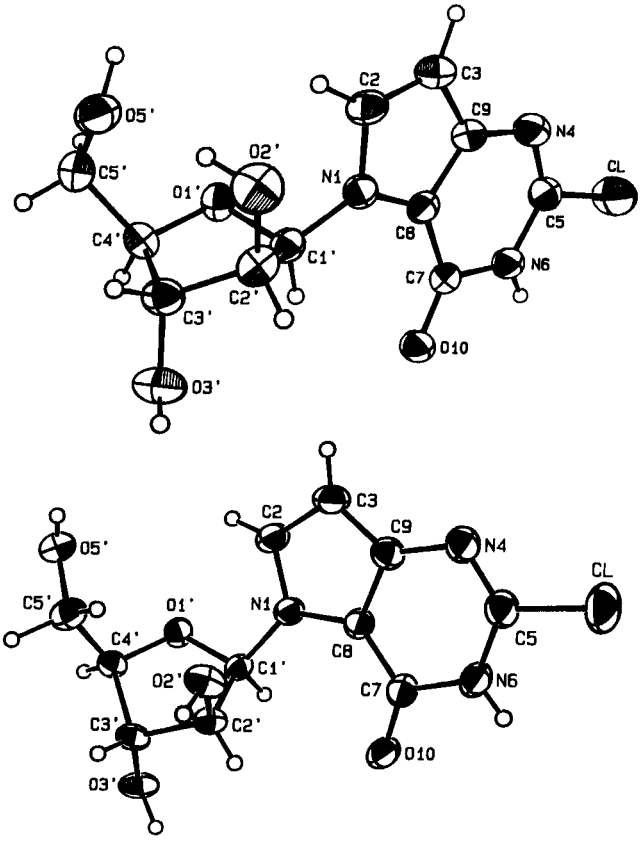
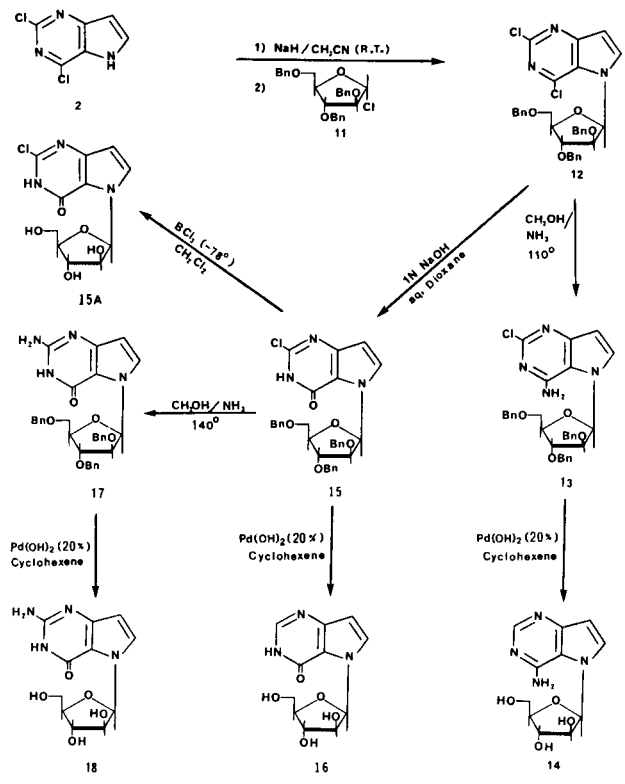


Figure 1. Perspective ORTEPII drawings of (a) molecule A and (b) molecule B. Thermal ellipsoids are at the 50% probability level.

Scheme II



5H-Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione Sodium Salt.

5*H*-Pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione [21] (**3**, 6.04 g, 40 mmoles) was dissolved in warm aqueous sodium hydroxide (40 ml, 1 *N*). The solution was concentrated to one-fourth the original volume and cooled on ice. The solid which separated was filtered and recrystallized from a small amount of water to give 5.1 g (73%) of the monosodium salt of **3**, mp >360°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 6.99 (d, J = 1.98 Hz, 1H, C_6H), 5.72 (d, J = 1.98 Hz, 1H, C_7H).

Anal. Calcd. for $C_5H_4N_3O_2Na\cdot1.25H_2O$: C, 36.83; H, 3.34; N, 21.48. Found: C, 36.43; H, 3.26; N, 22.08.

2,4-Dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**2**).

The dry sodium salt of 5*H*-pyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (2.0 g, 11.6 mmoles) was suspended in phenylphosphonic dichloride (12 g, 61.5 mmoles) and the mixture was heated at 170-180° for 3 hours. The reaction mixture was poured while still hot onto crushed ice (about 250 g) with stirring. The resulting aqueous solution was extracted with ethyl acetate (2 x 200 ml) and the organic layer was washed with saturated aqueous sodium bicarbonate (1 x 300 ml) and dried (sodium sulfate). Evaporation of the solvent and recrystallization of the residue from toluene provided 1.7 g (78%) of **2**, mp 222-223° (lit [7] 224°); uv (methanol): λ max 224 nm (ε 30,900), 279 (7,800); ^{1}H nmr (dimethylsulfoxide-d_6): δ 12.77 (s, 1H, NH), 8.11 (d, J = 3.15 Hz, 1H, C_6H), 6.73 (d, J = 3.15, 1H, C_7H).

Anal. Calcd. for $C_6H_3Cl_2N_3$: C, 38.33; H, 1.61; N, 22.35; Cl, 37.71. Found: C, 38.40; H, 1.76; N, 22.19; Cl, 37.54.

2,4-Dichloro-5-(2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*pentofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**4**).

To a solution of 2,4-dichloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**2**, 5.0 g, 26.6 mmoles) in dry acetonitrile (400 ml) was added sodium hydride (1.2 g, 29.3 mmoles, 60% in oil) and the mixture was stirred at room temperature for 30 minutes. 1-Chloro-2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*pentofuranose [8] (**1**, 10.3 g, 26.6 mmoles) was then added and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered and the filtrate evaporated to dryness to yield an oily residue which was purified by flash column chromatography using petroleum ether-ethyl acetate (4:1, v/v) to obtain, after crystallization from the same solvent, 12.0 g (84%) of **4**, mp 126°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.45 (d, J = 3.46 Hz, 1H, C_6H), 7.93-7.29 (4d, 8H, toluoyl aromatic protons), 7.03 (t, 1H, C_1H, peak width 13.09 Hz), 6.85 (d, J = 3.46 Hz, 1H, C_7H), and other sugar protons.

Anal. Calcd. for $C_{27}H_{23}Cl_2N_3O_5$: C, 60.01; H, 4.29; N, 7.77; Cl, 13.12. Found: C, 59.84; H, 4.30; N, 7.79; Cl, 13.37.

4-Amino-2-chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidine (**5**).

A solution of **4** (4.0 g, 7.4 mmoles) in methanolic ammonia (50 ml, saturated at 0°) was heated in a steel bomb at 100° for 12 hours and then the mixture was evaporated to dryness. The solid residue was triturated with ethyl acetate and filtered. Recrystallization from water gave 1.5 g (72%) of **5** as colorless crystals: mp 191°; uv (*p*H 1): λ max 213 nm (ε 6,300), 241 (4,700), 278 (5,000); uv (*p*H 7,11): λ max 236 nm (ε 8,500), 283 (3,400); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.79 (d, J = 3.29 Hz, 1H, C_6H), 7.21 (s, 2H, NH_2, exchangeable), 6.34 (d, J = 3.29 Hz, 1H, C_7H), 6.24 (pseudo q, 1H, C_1H, peak width 13.45 Hz), and other sugar protons.

Anal. Calcd. for $C_{11}H_{13}ClN_4O_5$: C, 43.64; H, 4.99; N, 18.51; Cl, 11.73. Found: C, 43.80; H, 5.07; N, 18.51; Cl, 12.09.

4-Amino-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidine (**6**).

To a solution of **5** (0.5 g, 1.8 mmoles) in 50% aqueous ethanol (50 ml) was added palladium on carbon (60 mg of 10%) and the mixture was hydrogenated at 20 psi for 6 hours at room temperature. The mixture was filtered through a Celite pad and the filtrate was evaporated to dryness. Crystallization of the solid residue from ethanol gave 0.4 g (95%) of **6**, mp 211°; uv (*p*H 1): λ max 230 nm (ε 12,000), 266 (12,300); uv (*p*H 7): λ max 225 nm (ε 14,700), 270 (8,100); uv (*p*H 11): λ max 225 nm (ε 15,900), 272 (7,600); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.58 (s, 1H, C_2H), 8.53 (s, 2H, NH_2, exchangeable), 8.12 (d, J = 3.29 Hz, 1H, C_6H), 6.58 (d, J = 3.29 Hz, 1H, C_7H), 6.41 (t, 1H, C_1H, peak width 12.76 Hz), and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_3\cdot2H_2O$: C, 46.14; H, 6.34; N, 19.57. Found: C, 46.20; H, 6.36; N, 19.27.

4-Benzyloxy-2-chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**7**).

Compound **4** (4.0 g, 7.4 mmoles) was added in small portions to a solution of sodium benzyloxide in benzyl alcohol (made by dissolving 0.68 g, 29.6 mmoles of sodium in 50 ml dry benzyl alcohol) at room temperature. The gelatinous mass obtained after stirring for 30 minutes was suspended in water (100 ml) and extracted with ethyl acetate (3 x 100 ml), dried over sodium sulfate and excess ethyl acetate was evaporated. The residual benzyl alcohol was removed under high vacuum and the semi-solid residue was crystallized from toluene to give 2.2 g (80%) of **7** as a colorless solid, mp 88-90°; uv (*p*H 1,7): λ max 232 nm (ε 25,300), 277 (10,100); uv (*p*H 11): λ max 229 nm (ε 31,900), 269 (8,200); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.15 (d, J = 3.21 Hz, 1H, C_6H), 7.56-7.36 (m, 5H, benzyl aromatic protons), 6.65 (t, 1H, C_1H, peak width 12.49 Hz), 6.63 (d, J = 3.21 Hz, 1H, C_7H), 5.60 (s, 2H, CH_2 of benzyl), and other sugar protons.

Anal. Calcd. for $C_{18}H_{18}ClN_3O_4\cdot\frac{1}{4}C_7H_8$: C, 59.47; H, 5.02; N, 10.53; Cl, 8.90. Found: C, 59.15; H, 5.28; N, 10.68; Cl, 8.93.

2-Chloro-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidin-4(3*H*)-one (**8**).

A solution of **4** (1.9 g, 3.5 mmoles) in dioxane (18 ml, peroxide free) was added dropwise over 15 minutes to boiling aqueous sodium hydroxide (2 *N*, 18 ml). After addition, the mixture was refluxed 2 hours, cooled and neutralized with glacial acetic acid. The precipitated solid was collected by filtration and recrystallized from ethanol to yield 0.60 g (60%); mp 225° dec; uv (*p*H 1): λ max 235 nm (ε 42,800), 267 (16,500); uv (*p*H 7): λ max 232 nm (ε 39,800), 269 (14,600); uv (*p*H 11): λ max 231 nm (ε 38,500), 272 (13,600); ^{1}H nmr (dimethylsulfoxide-d_6): δ 13.00 (b, 1H, N_3H), 7.84 (d, J = 3.00 Hz, 1H, C_6H), 6.89 (t, 1H, C_1H, peak width 13.51 Hz), 6.42 (d, J = 3.00 Hz, 1H, C_7H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_4$: C, 46.23; H, 4.20; N, 14.71; Cl, 12.43. Found: C, 46.16; H, 4.38; N, 14.43; Cl, 12.36.

5-(2-Deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**9**).

From **7**.

Compound **7** (1.0 g, 2.7 mmoles) was dissolved in 50% aqueous ethanol (50 ml) and palladium on carbon (0.1 g of 10%) was added. The mixture was hydrogenated at 20 psi for 8 hours at room temperature. The mixture was filtered through a Celite pad and the filtrate evaporated to dryness. Crystallization of the residue from dioxane/ethanol (1:1, v/v) gave 0.5 g (75%) of **9** mp 201-202°; uv (*p*H 1): λ max 230 nm (ε 19,500), 252 sh (9,300); uv (*p*H 7): λ max 223 nm (ε 19,800), 257 (8,700); uv (*p*H 11): λ max 221 nm (ε 19,600), 264 (8,100); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.62 (s, 1H, C_2H), 8.13 (d, J = 3.90 Hz, 1H, C_6H), 7.09 (t, 1H, C_1H), 6.72 (d, J = 3.90 Hz, 1H, C_7H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{13}N_3O_4\cdot2H_2O$: C, 45.99; H, 5.97; N, 14.63. Found: C, 45.83; H, 5.93; N, 14.69.

From **8**.

Compound **8** (1.0 g, 3.6 mmoles) was treated with palladium on carbon (0.1 g of 10%) exactly as described for compound **7** above to yield 0.7 g (80%) of **9**. This product was found to be identical in all respects to that prepared from **7** above.

2-Amino-5-(2-deoxy-β-D-*erythro*pentofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin4(3*H*)-one (**10**).

A solution of **8** (1.0 g, 3.6 mmoles) in methanolic ammonia (25 ml, saturated at 0°) was heated in a steel bomb at 140° for 12 hours and the mixture was evaporated to dryness. The residual solid was purified by flash silica gel column chromatography using chloroform-methanol (8:1, v/v) to yield 0.6 g (64%) of **10** as colorless needles after crystallization from ethanol, mp 195-197°; uv (*p*H 1): λ max 226 nm (ε 13,200), 260 (10,400); uv (*p*H 7): λ max 223 nm (ε 16,700), 254 (7,600), 282 sh (6,000); uv (*p*H 11): λ max 220 nm (ε 16,000), 282 (5,700); ^{1}H nmr (dimethylsulfoxide-d_6): δ 11.99 (s, 1H, N_3H), 7.53 (d, J = 3.00 Hz, 1H, C_6H), 6.70 (t, 1H, C_1H), 6.28 (s, 2H, NH_2, exchangeable), 6.00 (d, J = 3.00 Hz, 1H, C_7H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_4 \cdot H_2O$: C, 46.43; H, 5.63; N, 19.71. Found: C, 46.03; H, 5.39; N, 19.40.

2,4-Dichloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidine (**12**).

To a solution of **2** (4.7 g, 25 mmoles) in dry acetonitrile (400 ml) was added sodium hydride (1.2 g, 30 mmoles, 60% in oil) and the mixture was stirred at room temperature for 30 minutes. 1-Chloro-2,3,5-tri-*O*-benzyl-α-D-arabinofuranose (**11**, prepared from 15.7 g, 27.5 mmoles, of 1-*O*-(*p*-nitrobenzoyl)-2,3,5-tri-*O*-benzyl-D-arabinofuranose [11]) in dry acetonitrile (100 ml) was added to the reaction mixture and stirring was continued for 6 hours. The mixture was filtered and the filtrate evaporated to dryness. The residual syrup was purified by flash silica gel column chromatography using petroleum ether-ethyl acetate (6:1, v/v) to give **12** as a colorless syrup, yield 12.0 g (81%); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.14 (d, J = 3.41 Hz, 1H, C_6H), 7.38-7.05 (2m, 15H, benzyl aromatic protons), 6.86 (d, J = 5.13 Hz, 1H, C_1H), 6.71 (d, J = 3.41 Hz, 1H, C_7H), 4.65, 4.54 and 4.42 (3s, 6H, $3CH_2$ of benzyls), and other sugar protons.

Anal. Calcd. for $C_{32}H_{29}Cl_2N_3O_4$: C, 65.09; H, 4.95; N, 7.12; Cl, 12.00. Found: C, 65.15; H, 5.01; N, 6.94; Cl, 11.98.

4-Amino-2-chloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidine (**13**).

A solution of **12** (5.9 g, 10 mmoles) in methanolic ammonia (60 ml, saturated at 0°) was heated in a steel bomb at 110° for 12 hours. The methanolic ammonia was evaporated and the residue was purified by flash silica gel column chromatography using chloroform-acetone (6:1, v/v) to yield 4.3 g (75%) of **13** as a colorless syrup; ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.76 (d, J = 3.35 Hz, 1H, C_6H), 7.37-7.18 (2m, 15H, benzyl aromatic protons), 6.83 (d, J = 5.04 Hz, 1H, C_1H), 6.39 (d, J = 3.35 Hz, 1H, C_7H), 4.56, 4.53 and 4.22 (3s, 6H, $3CH_2$ of benzyls), and other sugar protons.

Anal. Calcd for $C_{32}H_{31}ClN_4O_4$: C, 67.31; H, 5.43; N, 9.81; Cl, 6.22. Found: C, 67.09; H, 5.44; N, 9.66; Cl, 6.38.

4-Amino-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidine (**14**).

To a solution of **13** (2.0 g, 3.5 mmoles) in absolute ethanol (50 ml) was added cyclohexene (50 ml) and palladium hydroxide on carbon (0.5 g of 20%). The mixture was heated under reflux for 12 hour and then filtered through a Celite pad. The filtrate was evaporated to dryness and the residue was purified by flash silica gel column chromatography using chloroform-methanol (4:1, v/v) to give 0.7 g (75%) of **14**; mp 242-244°; uv (*p*H 1): λ max 238 nm (ε 12,400), 264 sh (5,600); uv (*p*H 7): λ max 232 nm (ε 12,800), 264 (4,900); uv (*p*H 11): λ max 229 nm (ε 12,400), 275 (4,500); ^{1}H nmr (dimethylsulfoxide-d_6): δ 8.09 (s, 1H, C_2H), 7.85 (d, J = 3.11 Hz, 1H, C_6H), 6.66 (s, 2H, NH_2, exchangeable), 6.36 (d, J = 3.11 Hz, 1H, C_7H), 6.26 (d, J = 4.77 Hz, 1H, C_1H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_4 \cdot H_2O$: C, 46.47; H, 5.63; N, 19.71. Found: C, 46.56; H, 5.38; N, 19.58.

2-Chloro-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo-[3,2-*d*]pyrimidin-4(3*H*)-one (**15**).

A solution of **12** (3.2 g, 5.4 mmoles) in dioxane (30 ml, peroxide-free) was added dropwise to a boiling aqueous 2 *N* sodium hydroxide solution (30 ml). After addition was complete, the mixture was refluxed an additional 3 hours, cooled and neutralized with glacial acetic acid. The resulting solution was extracted with ethyl acetate (3 x 300 ml), the extract dried over sodium sulfate and evaporated to furnish a pale-yellow syrup. Purification by flash silica gel column chromatography using chloroform-acetone (7:1, v/v) gave 2.7 g (87%) of **15** as a colorless syrup; ^{1}H nmr (dimethylsulfoxide-d_6): δ 13.00 (s, 1H, NH), 7.61 (d, J = 3.11 Hz, C_6H), 7.35-6.89 (3m, 15H, benzyl aromatic protons), 6.96 (d, J = 5.13 Hz, C_1H), 6.35 (d, J = 3.11 Hz, 1H, C_7H), 4.61, 4.59 and 4.53 (3s, 6H, $3CH_2$ of benzyls), and other sugar protons.

Anal. Calcd. for $C_{32}H_{30}ClN_3O_5$: C, 67.19; H, 5.25; N, 7.35; Cl, 6.21. Found: C, 66.94; H, 5.46; N, 7.15; Cl, 6.23.

2-Chloro-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**15a**).

To a solution of **15** (2.8 g, 5 mmoles) in dry dichloromethane (75 ml) at −78° was added boron trichloride (62.5 ml, 1*M* in dichloromethane). The reaction mixture was stirred at this temperature for 2 hours and then at −40° for an additional 2 hours. A mixture of methanol-dichloromethane (125 ml, 1:1) was added and stirring was continued at room temperature for 30 minutes. The mixture was then neutralized with ammonium hydroxide and filtered to remove inorganic salts. The filtrate was evaporated to dryness under reduced pressure and the residue (2.0 g) was purified by flash silica gel chromatography using dichloromethane-methanol (5:1, v/v) to yield **15a** (0.9 g, 60%) after crystallization from acetonitrile: mp 185-187°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 12.93 (b, 1H, N_3H, exchangeable), 7.70 (d, 1H, J = 3.12 Hz, C_6H), 6.76 (d, 1H, J = 4.83 Hz, C_1H), 6.36 (d, 1H, J = 3.12 Hz, C_7H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_5$: C, 43.79; H, 4.01; N, 13.93; Cl, 11.75. Found: C, 43.52; H, 4.70; N, 14.01; Cl, 11.70.

5-β-D-Arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**16**).

To a solution of **15** (2.0 g, 3.5 mmoles) in 100% ethanol (75 ml) was added cyclohexene (75 ml) and palladium hydroxide on carbon (0.4 g of 20%) and the mixture was refluxed for 6 hours. After filtration of the reaction mixture through a Celite pad, the filtrate was evaporated to dryness and the residue purified by flash silica gel column chromatography using chloroform-methanol (6:1, v/v) to give hygroscopic colorless crystals, yield 0.5 g (54%); mp 210-212°; uv (*p*H 1): λ max 230 nm (ε 17,900), 254 sh (8,900); uv (*p*H 7): λ max 223 nm (ε 17,600), 257 (8,000); uv (*p*H 11): λ max 221 nm (ε 17,400), 263 (7,200); ^{1}H nmr (dimethylsulfoxide-d_6): δ 11.98 (s, 1H, NH, exchangeable), 7.79 (s, 1H, C_2H), 7.67 (d, J = 3.00 Hz, 1H, C_6H), 6.85 (d, J = 4.50 Hz, 1H, C_1H), 6.37 (d, J = 3.00 Hz, 1H, C_7H), and other sugar protons.

Anal. Calcd. for $C_{11}H_{13}N_3O_5 \cdot \frac{1}{4}H_2O$: C, 48.61; H, 5.00; N, 15.46. Found: C, 48.38; H, 4.79; N, 15.12.

2-Amino-5-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5*H*-pyrrolo[3,2-*d*]-pyrimidin-4(3*H*)-one (**17**).

A solution of **15** (2.0 g, 3.5 mmoles) in methanolic ammonia (saturated at 0°) was heated at 140° for 12 hours in a steel bomb. The methanolic ammonia was evaporated and the residue purified by flash chromatography on silica gel using chloroform-methanol (10:1, v/v) to yield 1.5 g (78%) of colorless crystalline solid, mp 142-144°; ^{1}H nmr (dimethylsulfoxide-d_6): δ 10.61 (s, 1H, NH, exchangeable), 7.37-6.92 (3m, 15H, benzyl aromatic protons), 7.36 (d, J = 3.00 Hz, 1H, C_6H), 6.93 (d, J = 4.80 Hz, 1H, C_1H), 5.98 (d, J = 3.00 Hz, 1H, C_7H), 5.86 (s, 2H, NH_2, exchangeable), and other sugar protons.

Anal. Calcd. for $C_{32}H_{32}N_4O_5$: C, 69.56; H, 5.80; N, 10.14. Found: C, 69.47; H, 5.95; N, 9.91.

2-Amino-5-β-D-arabinofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4(3*H*)-one (**18**).

To a solution of **17** (1.2 g, 2.6 mmoles) in 100% ethanol (75 ml) was added cyclohexene (75 ml) and palladium hydroxide on carbon (0.3 g of 20%) and the mixture was refluxed for 12 hours. The mixture was then filtered through a Celite pad and the filtrate evaporated to dryness. The residue was flash chromatographed on silica gel using chloroform-methanol (7:1, v/v) and crystallized from ethanol to yield 0.5 g (75%) of a

colorless solid; mp 212-214°; uv (*p*H 1): λ max 227 nm (ε 18,400), 261 (14,500); uv (*p*H 7): λ max 224 nm (ε 19,500), 256 (9,100), 281 sh (7,000); uv (*p*H 11): λ max 221 nm sh (ε 18,900), 281 (6,800); ^{1}H nmr (dimethylsulfoxide-d_6): δ 10.63 (s, 1H, NH, exchangeable), 7.42 (d, J = 3.00 Hz, 1H, C_6H), 6.71 (d, J = 3.30 Hz, 1H, C_1H), 5.94 (d, J = 3.00 Hz, 1H, C_7H), 5.90 (s, 2H, NH_2, exchangeable), and other sugar protons.

Anal. Calcd. for $C_{11}H_{14}N_4O_5 \cdot 0.5H_2O$: C, 45.36; H, 5.19; N, 19.24. Found: C, 45.15; H, 5.25; N, 19.25.

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