2'-DEOXY-3,7-DIDEAZANEUBLARINE AND 2'-DEOXY-3,7-DIDEAZAINOSINE: 
SYNTHESIS OF PYRROLO[3,2-c]PYRIDINE 8-D-2'-DEOXYRIBOFURANOSIDES 
BY SOLID-LIQUID PHASE-TRANSFER GLYCOSYLATION

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Abstract — 1-(2-Deoxy-8-D-erythro-pentofuranosyl)-1H-pyrrolo- 
[3,2-c]pyridine (2'-deoxy-3,7-dideazanebularine, 1) and 1-(2-deoxy-8-D- 
erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridin-4(5H)-one 
(2'-deoxy-3,7-dideazainosine, 2a) have been synthesized by regio- and 
diastereospecific solid-liquid phase-transfer glycosylation. Employing the 
cryptand TDA-1, solid KOH, and an aprotic solvent the nucleoside 6 was 
formed in almost quantitative yield. It was converted into compounds 2b or 
3b by selective displacement of the 4-chloro group. Compounds 1, 2a, or 3c 
were obtained after catalytic hydrogenation. The nucleoside 2a is 
extremely stable under acidic as well as under alkaline conditions. 
Compound 1 is strongly fluorescent.

Recently, we have reported the stereoselective synthesis of pyrrolo[2,3-d]pyrimi-
dine 8-D-2'-deoxyribonucléosides via solid-liquid phase-transfer glycosylation 
1,2. This technique is extremely useful for glycosylation reactions carried out 
with the halogenose 5 containing alkaline labile protecting groups. 
As we were interested in the synthesis of pyrrolo[3,2-c]pyridine 2'-deoxyribonu-
cleosides we have applied this technique for the preparation of 2'-deoxy-3,7-dide-
azanebularine (1) and 2'-deoxy-3,7-dideazainosine (2a). As 2'-deoxy-7-deazanebu-
larine 3 exhibits a strong fluorescence in aqueous solution, similar properties 
were expected from compound 1. On the other hand the inosine analogue 2a should 
show ambiguous base pairing with dG, dA, and dT within a DNA-duplex as it has been 
reported from corresponding purine and pyrrolo[2,3-d]pyrimidine nucleosides 4,5.
When we began our studies only a few 3,7-dideazapurines were known. The only described 2'-deoxyribonucleoside containing a 3,7-dideazapurine system was the dichloro nucleoside. Its protected precursor was obtained in 82% yield from the anion of the nucleobase with sodium hydride. We have carried out glycosylation of compound with the halogenose in the presence of the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) and a fivefold excess of solid powdered KOH. The cryptand TDA-1 chelates monovalent ions. It shows a great complexing affinity for ionic compounds containing large polarizable anions e.g. nucleobase anions. An excess of KOH was used to ensure that traces of water and hydrochloric acid formed during glycosylation were removed. Otherwise the cryptand will be protonated at its nitrogen and loose its ability to bind cations. The reaction was carried out in acetonitrile at room temperature and was complete within 30 min. Compound was isolated after chromatographic purification in 90% yield (¹³C-nmr data see table).

From compound the nucleoside (mp 180°C) was obtained by deprotection either with 1N sodium methoxide (71% yield) or ammonia in methanolic solution. Catalytic hydrogenation (10% Pd on charcoal, MeOH-ammonia) furnished 2'-deoxy-3,7-dideazanebularine (1). It was purified from inorganic salt by chromatography on an Amberlite XAD resin (MeOH-H₂O) and was crystallized from water (mp 175-176°C).
Table 13C-nmr Chemical Shifts of Pyrrolo[3,2-c]pyridine 2'-Deoxyribofuranosides a,b)

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N/O-CH₃ 53.6 | 52.8 | 33.3 | 

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a) Spectra were measured in (Me)₂SO-d₆. b) Assignment was made on the basis of gated-decoupled spectra. c) Signal superimposed by solvent signals. d) Tentative assignment.

(water) , uv \( \lambda_{max} \) (0.1 N aq. HCl) 224, 274 nm. Anal. Calcd. for 

\( C_{12}H_{14}N_{2}O_{3} \): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.55; H, 6.12; N, 12.02.

As compound 3a is a useful intermediate for the synthesis of other pyrrolo[3,2-c]-pyridine nucleosides we considered nucleophilic displacement of halogen substituents. Although it has been reported that nucleophilic displacement reactions on the nucleobase 4a occurs only with great difficulty ⁹ it was accomplished if anion formation at the nucleobase was avoided. This was studied on compound 4b which was obtained by phase-transfer methylation of 4a with MeI [mp 149-150°C (MeOH) , uv \( \lambda_{max} \) (MeOH), 279 nm. Anal. Calcd. for \( C_{8}H_{6}Cl_{2}N_{2} \): C, 47.79; H, 3.01; N, 13.94; Cl, 35.27. Found: C, 47.56; H, 3.15; N, 14.14; Cl, 35.23].
We were also able to displace the 4-chloro group of 3a selectively either with 1 N sodium methoxide in methanol (40 h heating) or with 2 N aq. NaOH–1,4-dioxane (30 h heating). After purification of the reaction products by hydrophobic chromatography on an Amberlite XAD resin (water, MeOH) the methoxynucleoside 3b as well as compound 2b were obtained as colorless crystals.

Compound 3b [uv $\lambda_{\text{max}}$ (MeOH) 271, 280 nm. Anal. Calcd. for C$_{13}$H$_{15}$ClN$_2$O$_4$: C, 52.27; H, 5.06; Cl, 11.87; N, 9.38. Found: C, 52.24; H, 5.14; Cl, 12.05; N, 9.46]. Compound 2b [mp 242–243 °C (water), uv $\lambda_{\text{max}}$ (MeOH) 270, 292 nm. Anal. Calcd. for C$_{12}$H$_{13}$ClN$_2$O$_4$: C, 50.63; H, 4.60; Cl, 12.45; N, 9.84. Found: C, 50.79; H, 4.74; Cl, 12.69; N, 9.80].

The chloro substituent of 3b was removed by catalytic hydrogenation as described for 3a to yield the nucleosides 3c [mp 147–148°C (water), uv $\lambda_{\text{max}}$ (MeOH) 262 nm. Anal. Calcd. for C$_{13}$H$_{16}$N$_2$O$_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.09; H, 6.07; N, 10.65].

By the same route the chlorine of 2b was removed to give 2'-deoxy-3,7-dideazainosine (2a) [mp 229 – 230°C (water), uv $\lambda_{\text{max}}$ (MeOH) 264 nm. Anal. Calcd. for C$_{12}$H$_{14}$N$_2$O$_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.64; H, 5.74; N, 11.06].

The strong alkaline reaction conditions employed during nucleophilic displacement reactions at compound 3a showed that the pyrrolo[3,2-c]pyridine 2'-deoxyribofuranosides 2a or 3c are not sensitive against strong bases neither at the aglycone nor at the sugar moiety. Treatment of 2a with 0.5 N HCl at room temperature also indicated that the N-glycosyl bond is stable under acidic condition, whereas 2'-deoxynosine was readily hydrolyzed $(t/2 = 21$ min). These properties are similar to pyrrolo[2,3-d]pyrimidine 2'-deoxyribofuranosides but different from purine 2'-deoxyribonucleosides. Compound 1 exhibits a strong fluorescence in aqueous solution (emission : 415 nm, excitation 268 nm).

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

13. The $^1$H-nmr spectra were recorded in (Me)$_2$SO-d$_6$ solution, the chemical shifts (δ, ppm) are the following:
   1: 2.23 (m, 2'-H$_b$), 2.29 (m, 2'-H$_a$), 3.55 (m, 5'-H$_2$), 3.85 (m, 4'-H), 4.38 (m, 3'-H), 4.99 (5'-OH, broad), 5.37 (3'-OH, broad), 6.42 (pseudo t (pt), 1'-H), 6.66 (d, J = 3 Hz, 3 H), 7.62 (d, J = 6 Hz, 7-H), 7.71 (d, J = 3 Hz, 2-H), 8.21 (d, J = 6 Hz, 6-H), 8.23 (s, 4-H).
   2a: 2.22 (m, 2'-H$_b$), 2.40 (m, 2'-H$_a$), 3.52 (m, 5'-H$_2$), 3.81 (m, 4'-H), 4.32 (m, 3'-H), 4.93 (t, J = 5.4 Hz, 5'-OH), 5.30 (d, J = 4.3 Hz, 3'-OH, broad), 6.21 (pt, 1'-H), 6.54 (d, J = 3 Hz, 3-H), 6.62 (d, J = 7.3 Hz, 7-H), 7.03 (d, broad, J = 7.3 Hz, 6-H), 7.34 (d, J = 3 Hz, 2-H), 10.87 (s, broad, NH).
   2b: 2.22 (m, 2'-H$_b$), 2.38 (m, 2'-H$_a$), 3.53 (m, 5'-H$_2$), 3.80 (m, 4'-H), 4.33 (m, 3'-H), 4.96 (5'-OH, broad), 5.20 (3'-OH, broad), 6.21 (pt, 1'-H), 6.54 (d, J = 3 Hz, 3-H), 6.96 (s, 7-H), 7.38 (d, J = 3 Hz, 2-H), 11.81 (NH, broad).
   3a: 2.28 (m, 2'-H$_b$), 2.43 (m, 2'-H$_a$), 3.56 (m, 5'-H$_2$), 3.85 (m, 4'-H), 18.31 (s, N).
4.38 (m, 3'-H), 5.02 (t, J = 5.2 Hz, 5'-OH), 5.34 (d, J = 4.1 Hz, 3'-OH),
6.42 (pt, 1'-H), 6.67 (d, J = 3 Hz, 3-H), 7.89 (d, J = 3 Hz, 2-H),
7.96 (s, 7-H).

3b: 2.25 (m, 2'-H<sub>b</sub>), 2.42 (m, 2'-H<sub>a</sub>), 3.54 (m, 5'-H<sub>2</sub>), 3.82 (m,
4'-H), 3.96 (s, OCH<sub>3</sub>), 4.35 (m, 3'-H), 4.96 (t, J = 5.3 Hz, 5'-OH),
5.30 (d, J = 4.2 Hz, 3'-OH), 6.34 (pt, 1'-H), 6.57 (d, J = 3 Hz, 3-H),
7.45 (s, 7-H), 7.60 (d, J = 3 Hz, 2-H).

3c: 2.23 (m, 2'-H<sub>b</sub>), 2.47 (m, 2'-H<sub>a</sub>), 3.53 (m, 5'-H<sub>2</sub>), 3.83 (m,
4'-H), 3.95 (s, OCH<sub>3</sub>), 4.35 (m, 3'-H), 4.95 (t, J = 5.4 Hz, 5'-OH),
5.33 (d, J = 4.2 Hz, 3'-OH), 6.35 (pt, 1'-H), 6.55 (d, J = 3 Hz, 3-H),
7.27 (d, J = 6.0 Hz, 7-H), 7.56 (d, J = 3 Hz, 2-H), 7.76 (d, J = 6.0
Hz, 6-H).

4b: 3.91 (s, CH<sub>3</sub>), 6.65 (dd, J = 0.8 and 3.3 Hz, 3-H), 7.67 (d, J =
3.3 Hz, 2-H), 7.81 (d, J = 0.8 Hz, 7-H).

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