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

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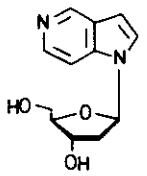
Abstract ——— 1-(2-Deoxy-ß-D-erythro-pentofuranosyl)-1H-pyrrolo-[3,2-c]pyridine (2'-deoxy-3,7-dideazanebularine, 1) and 1-(2-deoxy-ß-D-erythro-pentofuranosyl)-1H-pyrrolo[3,2-c]pyridin-4(5H)-one (2'-deoxy-3,7-dideazainosine, 2a) have been synthesized by regio- and diastereospecific solid-liquid phase-transfer 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]pyrimidine ß-D-2'-deoxyribofuranosides 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'-deoxyribonucleosides we have applied this technique for the preparation of 2'-deoxy-3,7-dideazanebularine (1) and 2'-deoxy-3,7-dideazainosine (2a). As 2'-deoxy-7-deazanebularine [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].



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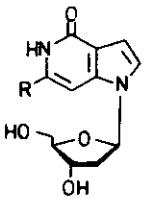
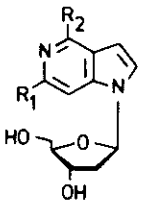
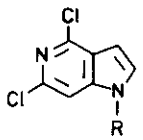


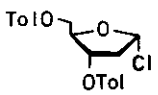
2a, R = H
2b R = Cl



3a: R_1 and R_2 = Cl
3b: R_1 = Cl; R_2 = OCH_3
3c: R_1 = H; R_2 = OCH_3



4a: R = H
b: R = CH_3



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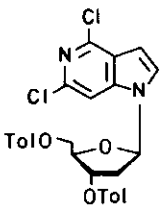

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When we began our studies only a few 3,7-dideazapurines were known [6,7]. The only described 2'-deoxyribonucleoside containing a 3,7-dideazapurine system was the dichloro nucleoside 3a [8]. Its protected precursor 6 was obtained in 82 % yield from the anion of the nucleobase 4a [9] which was generated with sodium hydride [8]. We have carried out glycosylation of compound 4a with the halogenose 5 [10] in the presence of the cryptand tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1) [11] 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 6 was isolated after chromatographic purification in 90 % yield (^{13}C-nmr data see table).

From compound 6 [8] the nucleoside 3a [8] (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-H_2O) and was crystallized from water [mp 175-176°C

Table ^{13}C-nmr Chemical Shifts of Pyrrolo[3,2-c]pyridine 2'-Deoxyribofuranosides [a,b]

	1	2a	2b	3a	3b	3c	4a	4b	6
C-2	126.9	122.0	123.2	129.7	126.0	124.8	129.4	133.6	129.7
C-3	101.7 [d]	104.6	104.1	101.3	100.5	100.4	100.2	99.9	102.0
C-3a	125.5	115.9	114.0	123.1	111.4	112.2	122.5	122.5	123.1
C-4	143.3 [d]	159.6	158.7	140.4	156.1	157.8	140.2	140.3	140.6
C-6	140.6	127.8	129.1	139.7	138.8	137.8	138.9	139.1	140.0
C-7	105.9 [d]	93.8	94.9	106.1	100.8	101.7	106.3	105.4	106.1
C-7a	139.2	139.0	139.2	142.0	142.5	141.2	142.2	142.8	142.4
N/O-CH_3					53.6	52.8		33.3	
C-1'	84.6	84.8	85.0	85.5	85.1	84.9			81.7
C-2'	[c]	[c]	40.5	40.6	[c]	40.0			36.8
C-3'	70.8	70.7	70.6	70.5	70.6	70.8			74.9
C-4'	87.3	87.4	87.4	87.6	87.4	87.3			85.6
C-5'	61.9	61.8	61.7	61.5	61.7	61.8			64.2

[a] Spectra were measured in $(Me)_2SO$-d_6. [b] Assignment was made on the basis of gated-decoupled spectra. [c] Signal superimposed by solvent signals. [d] Tentative assignment.

(water) , uv λ_{max}(0.1 N aq. HCl) 224, 274 nm. Anal. Calcd. for $C_{12}H_{14}N_2O_3$: 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 λ_{max} (MeOH), 279 nm. Anal. Calcd. for $C_8H_6Cl_2N_2$: 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 λ_{max} (MeOH) 271, 280 nm. Anal. Calcd. for $C_{13}H_{15}ClN_2O_4$: 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 λ_{max} (MeOH) 270, 292 nm. Anal. Calcd. for $C_{12}H_{13}ClN_2O_4$: 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 λ_{max} (MeOH) 262 nm. Anal. Calcd. for $C_{13}H_{16}N_2O_4$: 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 λ_{max} (MeOH) 264 nm. Anal. Calcd. for $C_{12}H_{14}N_2O_4$: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-glycosylic bond is stable under acidic condition, whereas 2'-deoxyinosine was readily hydrolized (t/2 = 21 min). These properties are similar to pyrrolo[2,3-d]pyrimidine 2'-deoxyribofuranosides [12] but different from purine 2'-deoxyribonucleosides. Compound 1 exhibits a strong fluorescence in aqueous solution (emission : 415 nm, excitation 268 nm).

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12. F. Seela and H. Driller, Nucleic Acids Res., 1985, 13, 911.
13. The ^{1}H-nmr spectra were recorded in $(Me)_2SO$-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), 5.32 (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), 5.29 (3'-OH, broad), 6.22 (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),

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_b), 2.42 (m, 2'-H_a), 3.54 (m, 5'-H_2), 3.82 (m, 4'-H), 3.96 (s, OCH_3), 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_b), 2.47 (m, 2'-H_a), 3.53 (m, 5'-H_2), 3.83 (m, 4'-H), 3.95 (s, OCH_3), 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_3), 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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