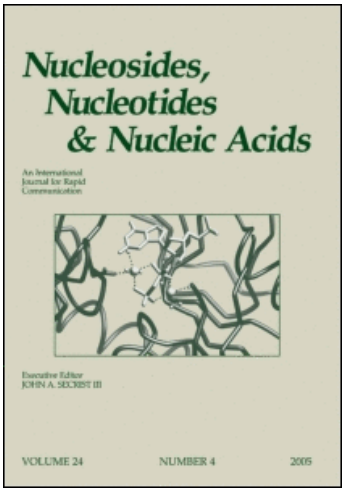


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

7-Carbapurine Ribofuranosides: Synthesis by Solid-Liquid Phase-Transfer Glycosylation and ^{15}N-NMR Spectra

F. Seela[a]; H. Rosemeyer[a]; A. Biesewig[a]; T. Jorgens[a]
[a] Laboratorium für Organische und Bioorganische Chemie, Universität Osnabrück, Osnabrück, Bundesrepublik Deutschland

To cite this Article Seela, F. , Rosemeyer, H. , Biesewig, A. and Jorgens, T.(1988) '7-Carbapurine Ribofuranosides: Synthesis by Solid-Liquid Phase-Transfer Glycosylation and ^{15}N-NMR Spectra', Nucleosides, Nucleotides and Nucleic Acids, 7: 5, 581 — 584
To link to this Article: DOI: 10.1080/07328318808056289
URL: http://dx.doi.org/10.1080/07328318808056289

NUCLEOSIDES & NUCLEOTIDES, 7(5&6), 581-584 (1988)

7-CARBAPURINE RIBOFURANOSIDES: SYNTHESIS BY SOLID-LIQUID PHASE-TRANSFER GLYCOSYLATION AND ^{15}N-NMR SPECTRA

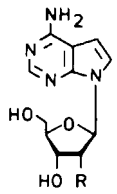
F. Seela*, H. Rosemeyer, A. Biesewig, and T. Jürgens

Laboratorium für Organische und Bioorganische Chemie, Universität Osnabrück, Barbarastr. 7, D-4500 Osnabrück, Bundesrepublik Deutschland

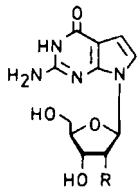
Abstract: The synthesis of pyrrolo[2,3-d]pyrimidine ribofuranosides by solid-liquid phase-transfer glycosylation is described and ^{15}N NMR spectra of 7-carbapurine nucleosides are reported.

The first efficient synthesis of a pyrrolo[2,3-d]pyrimidine ribofuranoside employing pyrrolyl anions has been carried out by T. Goto [1]. In 1983 the synthesis of 7-carbaguanosine (2a) by liquid-liquid phase transfer glycosylation [2] has been reported by our laboratory. Recently, the halogenose 6 [3] was used for stereoselective synthesis of compounds 7a and 7b employing sodium hydride as condensation reagent [4]. We have applied phase-transfer conditions for glycosylation of 5a or 5b with the halogenose 6 and have obtained anomerically pure β-D-ribofuranosides in yields of 65% (7a) and 68% (7b), respectively.

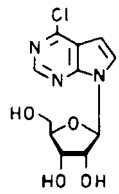
For glycosylation of compounds 5a or 5b the anions were generated in MeCN with an excess of solid KOH in the presence of 0.02 equivalents of TDA-1 [6,7]. To this solution the in-situ reaction mixture of an equimolar amount of the halogenose 6 was added at room temperature under stirring. The glycosylation products 7a or 7b were isolated after 20 h reaction time at room temperature by chromatographic work-up. Deprotec-



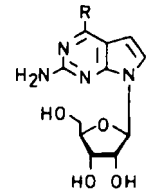
1a : R = OH
1b : R = H



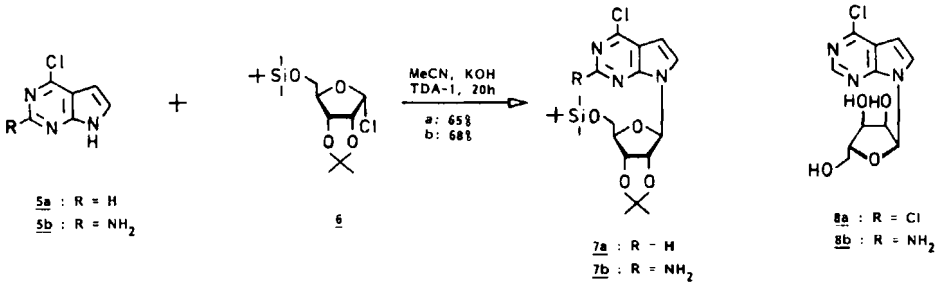
2a : R = OH
2b : R = H



3



4a : R = Cl 4c : R = NH_2
4b : R = OCH_3 4d : R = H



tion of 7a or 7b (aq.CF_3CO_2H) yielded the chloro nucleosides 3 or 4a.

Compound 3 was treated with aq. ammonia to give tubercidin (1a) in 82% yield [6]. The derivative 4a was subjected to displacement reactions with several nucleophiles. Treatment with sodium methoxide afforded 4b (76 %), which was transformed into crystalline 2a [2] upon heating with 1 N NaOH in almost quantitative yield. Replacement of the 4-chloro substituent by an amino group with aqueous NH_3 gave 4c (83%). Catalytic hydrogenation (Pd/C) removed the 4-chloro substituent to yield 4d (50%), a compound exhibiting strong fluorescence.

The β-anomer of 6 was also prepared [3] and employed during glycosylation of 5a. Anomerically pure α-nucleoside 8a was obtained exclusively after removal of protecting groups and was subsequently converted into α-tubercidin (8b). As glycosylation proceeds with a yield of 46% without resulting in β-anomers, this route is now the most promising reaction to obtain pure α-nucleosides. ^{13}C-NMR data are summarized in table 1.

TABLE 1. ^{13}C-NMR Data[a] of Pyrrolo[2,3-d]pyrimidine Ribofuranosides[b]

	2a	3	4a	4b	4c	4d	7a	7b	8a
C-2	152.6	150.6	159.5	159.5	159.4	160.0	150.6	159.5	150.3
C-4	158.7	150.8	151.2	163.0	157.6	150.8	150.7	151.5	150.4
C-4a	100.1	117.4	109.0	97.3	96.5	111.3	117.6	108.9	117.0
C-5	102.3	99.8	99.9	99.1	100.1	100.7	99.9	100.1	98.3
C-6	117.3	128.7	123.4	120.0	118.4	122.7	129.2	124.1	131.7
C-7a	151.2	151.3	154.4	154.9	152.7	153.5	151.0	153.6	151.1
C-1′	86.0	87.3	86.1	86.2	86.8	85.6	89.7	88.6	84.0
C-2′	73.7	74.4	73.7	73.5	73.3	73.5	80.9	80.8	71.0
C-3′	70.6	70.6	70.7	70.7	70.8	70.7	83.9	83.6	70.7
C-4′	84.5	85.5	84.9	84.7	84.7	84.7	86.1	86.0	85.0
C-5′	61.7	61.5	61.7	61.8	62.0	61.8	63.3	63.5	61.6

a) δ-values rel. to TMS; b) in [D_6]DMSO

TABLE 2. ^{15}N NMR Chemical Shifts [a,b] and Coupling Constants (<J(N,H)>)[c] of Pyrrolo[2,3-d]pyrimidine Nucleosides and Congeners

Compds	N-3[N-1]	N-1[N-3]	[N-7]	N-7[N-9]	NH_2
[Ado]	-145.0 (17)	-158.3 (16)	-140.0 (12)	-211.4 (9)	-299.3(89)
1a	-150.5 (15;3)	-157.9 (15)		-227.0 (8)	-298.3(89)
1b	-150.3 (18)	-157.8 (15)		-223.8 (10)	-298.4(89)
2b	-218.1 (90)	-212.6 (3)		-222.6 (9)	-309.7(89)
3	-112.1 (16)	-134.2 (15)		-222.8 (9)	
4a	-147.5 (3)	-184.0 (3)		-229.1 (9)	-299.5(89)
8a	-113.1 (16)	-134.7 (15)		-222.7 (9)	

a) in $[D_6]$DMSO; b) δ-values are relative to external CH_3NO_2 (0 ppm) containing 5% of $[D_6]$DMSO; c) <J(N,H)> (Hz) in parenthesis are taken from INEPT spectra; d) purine numbering in brackets.

From the structure of 7-carbapurine nucleosides it is apparent that the protonation sites of these molecules may be different from those of the parent purines. As ^{15}N-NMR spectroscopy on compounds with naturally occuring isotop pattern is the method of choice to study these phenomena we measured the spectra of compounds 1b and 2b in the presence and absence of CF_3CO_2H. Table 2 shows for the first time ^{15}N-NMR spectra of pyrrolo[2,3-d]pyrimidine nucleosides.

Compared to adenosine the ^{15}N-NMR spectrum of tubercidin (1a) shows an upfield shift of the signal of the glycosylic nitrogen (15.6 ppm). The signals of the pyrimidine nitrogens of 1a were assigned unequivocally as only N-3 shows a ^2J(N-3;H-2) and a ^3J(N-3;NH_2) coupling.

Changing to 2′-deoxytubercidin (1b) only N-7 undergoes a slight downfield shift (3.2 ppm) demonstrating the electron-donating effect of 2′-OH. Compared with 7-carba-2′-deoxyadenosine (1b) the 2-amino group of 2b shifts the N-1/N-3 signals upfield. Nevertheless, their assignment is unequivocal due to the ^1J(N,H) coupling of N-3 to H-3. The chemical shift of N-7 of 1b and 2b varies only unsignificantly (Δδ = 1.2 ppm) showing that the electron density of the pyrimidine moiety does not affect the electronic state of the pyrrol nitrogen. Moreover, almost identical N-7 chemical shifts are observed for the anomeric ribofuranosides 3 and 8a which seems to be typical for anomeric nucleosides. Measurement of the ^{15}N-NMR spectra of 7-carba-2′-deoxyadenosine (1b) and -guanosine (2b) in the presence of 0.5 eq. of CF_3CO_2H shows significant upfield shifts of either N-3 (1b, 51 ppm) or N-1 (2b, 25 ppm) while δ-values of the other nitrogen atoms remain almost unaffected. This identifies N-3 (1b; pK 5.5) and N-1 (2b; pK 1.4) as protonation sites.

REFERENCES AND NOTES

1 Kondo T., Ohgi T., and Goto T. (1977) Agric. Biol. Chem. 41, 1501.
2 Seela F. and Hasselmann D. (1981) Chem. Ber. 114, 3395-3402.
3 Wilcox C. S. and Otoski R. M. (1986) Tetrahedron Lett. 27, 1011-1014.
4 Ramasamy K., Imamura N., Robins R. K., and Revankar G. R. (1987) Tetrahedron Lett. 28, 5701-5110.
5 Seela F., Westermann B., and Bindig U. (1988) J. Chem. Soc. (London) Perkin 1, in the press.
6 Gerster J. F., Carpenter B., Robins R. K., and Townsend L.B. (1967) J. Med. Chem. 10, 326-331.
7 Data of compds. 3 : mp 160-162°C, UV λ_{max} (MeOH) 273 nm (ε 4.800).
4a:mp 170-72°C (H_2O/MeOH); UV λ_{max} (MeOH) 317, 259 nm (ε 5.600, 4.950). ^{1}H-NMR ([D_6]DMSO) δ 7.39 (d, J = 3.9 Hz, 6-H), 6.71 (s, NH_2), 6.37 (d, J = 3.9 Hz, 5-H), 6.00 (d, J = 6.3 Hz, 1′-H), 5.30, 5.10 (d, J = 6.2, 4.5 Hz, 2′,3′-OH), 4.99 (t, J = 5.4 Hz, 5′-OH), 4.31 (m, 2′-H), 4.05 (m, 3′-H), 3.85 (m, 4′-H), 3.55 (m, 5′-H); Anal. calc. for $C_{11}H_{13}N_4O_4Cl$: C, 43.94; H, 4.36; N, 18.63. Found: C, 44.13; H, 4.52; N, 18.45.
4b:mp 168°C (2-PrOH/EtAc); UV λ_{max} (MeOH) 260, 286 nm (ε 8.600, 6.700); Anal. calc. for $C_{12}H_{16}N_4O_5$: C, 48.65; H, 5.44; N, 18.91. Found: C, 48.94;H, 5.51; N, 18.61.
4c:UV λ_{max} (MeOH) 285, 264 nm. Anal. calc. for $C_{11}H_{15}N_5O_4$: C, 49.97; H, 5.38. Found: C, 46.82; H, 5.50.
4d:mp 162-64°C (H_2O); UV λ_{max} (MeOH) 256,315 nm (ε 4.200, 5.100); Anal.calc. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: C, 49.81; H, 5.39; N 20.98.
7a:UV λ_{max}(MeOH) 272 nm (ε 4.800). ^{1}H-NMR ($CDCl_3$) δ 8.68 (s, 2-H), 7.90 (d, J = 3.7 Hz, 6-H), 6.75 (d, J = 3.7 Hz, 5-H), 6.35 (d, J = 2.6 Hz, 1′-H), 5.28 (m, J = 3.6 Hz, 2′-H), 4.94 (m, J = 3.1 Hz, 3′-H), 4.21 (m, J = 3.3 Hz, 4′-H), 3.77 (m, 5′-H), 1.33, 1.55 (2s, 2 CH_3), 0.80 (s, CH_3-t.Bu), 0.03 (s, $Si(CH_3)_2$). Anal. calc. for $C_{20}H_{30}ClN_3O_4Si$: C, 54.59; H, 6.87; N, 9.55. Found: C, 54.50; H, 6.82; N, 9.43.
7b:UV λ_{max} (MeOH) 317, 258, 235 nm (ε 4.800, 4.100, 22.000). ^{1}H-NMR ($CDCl_3$) δ 7.12 (d, J = 3.8 Hz, 6-H), 6.40 (d, J = 3.8 Hz, 5-H), 6.23 (d, J = 2.9 Hz, 1′-H), 4.9 (m, 2′-H, 3′-H, NH_2), 4.25 (m, J = 3.3 Hz, 4′-H), 3.80 (m, 5′-H), 1.37, 1.62 (2s, 2 CH_3), 0.90 (s, CH_3-t.Bu), 0.05 (s, $Si(CH_3)_2$). Anal. calc. for $C_{20}H_{31}ClN_4Si$: C, 52.79; H, 6.87; N, 12.31. Found: C, 52.97; H, 6.99; N, 12.18.
8a:mp 182-84°C, UV λ_{max} (MeOH) 274 nm (ε 4.500); ^{1}H-NMR ($(Me)_2SO$-d_6) δ 8.64 (s, 2-H), 8.00 (d, J = 3.8 Hz, 6-H), 6.65 (d, J = 3.8 Hz, 5-H), 6.60 (d, J = 5.3 Hz, 1′-H), 5.35, 5.32 (d, J = 5.9, 5.1 Hz, 2′,3′-OH), 4.89 (t, J = 5.5 Hz, 5′-OH), 4.38 (m, 2′-H), 4.16 (m, 3′-H/4′-H), 5.56 (m, 5′-H); Anal. calc. for $C_{11}H_{12}N_3O_4Cl$: C, 46.25; H, 4.23; N,14.71. Found: C, 46.33; H, 4.39; N, 14.72.