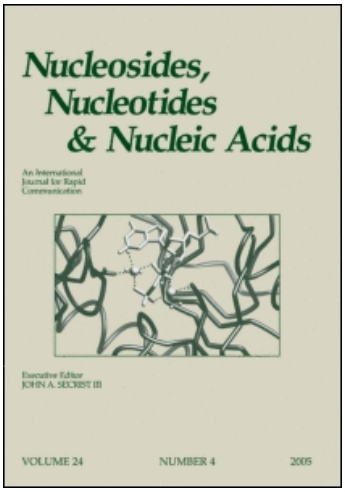


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 2-Alkyl-3-hydroxy-4-pyridinone-ribonucleosides, Potential Oral Iron Chelators

Gang Liu[a]; Fred W. Bruenger[a]; Amy M. Barrios[a]; Scott C. Miller[a]
[a] Division of Radiobiology, School of Medicine, University of Utah, Salt Lake City, UT, U.S.A.

To cite this Article Liu, Gang , Bruenger, Fred W. , Barrios, Amy M. and Miller, Scott C.(1995) 'Synthesis of 2-Alkyl-3-hydroxy-4-pyridinone-ribonucleosides, Potential Oral Iron Chelators', Nucleosides, Nucleotides and Nucleic Acids, 14: 9, 1901 — 1904
To link to this Article: DOI: 10.1080/15257779508010712
URL: http://dx.doi.org/10.1080/15257779508010712

NUCLEOSIDES & NUCLEOTIDES, 14(9&10), 1901-1904 (1995)

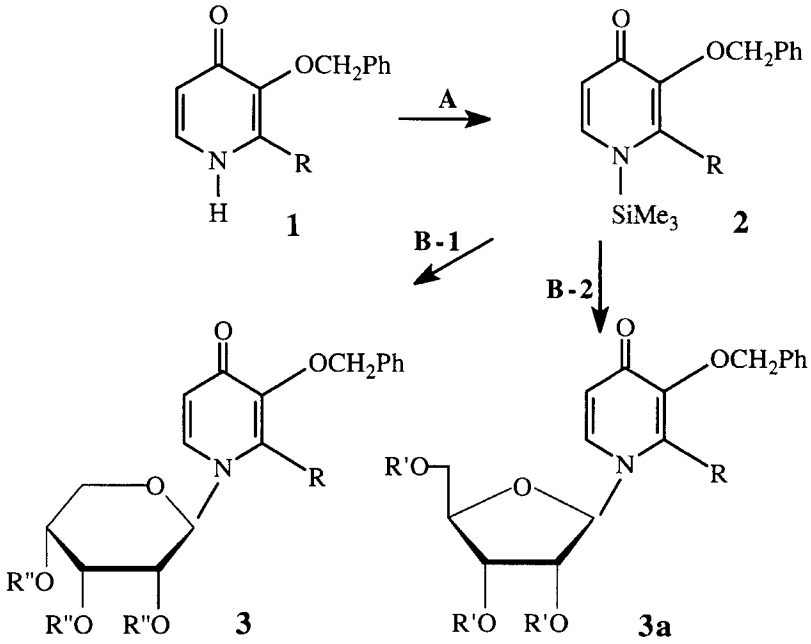
SYNTHESIS OF 2-ALKYL-3-HYDROXY-4-PYRIDINONE-RIBONUCLEOSIDES, POTENTIAL ORAL IRON CHELATORS

Gang Liu, Fred W. Bruenger, Amy M. Barrios and Scott C. Miller*

Division of Radiobiology, School of Medicine, University of Utah, Bldg 585,
Salt Lake City, UT 84112, U.S.A.

Abstract: Several ribonucleosides, named 2-alkyl-3-hydroxy-1-(β-D-ribofuranosyl or pyranosyl)-4-pyridinones, were synthesized in good yield. The method provides a useful means to obtain α-ketohydroxypyridin derivatives with different sugar moieties that, if used as drugs, might enhance their absorption from the intestine and certain other desirable pharmacological properties.

The 2-alkyl-3-hydroxy-4-pyridinones and some of their derivatives are powerful transition metal chelators. They are characterized by high chemical stability and by high affinity and specificity for iron (III) [1]. This property renders them potentially useful as drugs for the removal of physiological iron overloads that occur in several million humans. The pyridinones can be especially useful if they are effective when given orally. The status of oral iron chelators and the prospect for future research has been reviewed by Porter [1,2]. Lipophilic N-substituted alkyl derivatives that are absorbed from the intestine, have been developed and are now under investigation [3]. However, most of these proved to be toxic [4]. In order to improve the pharmacological properties, we have designed 2-alkyl-3-hydroxy-4-pyridinone derivatives with a sugar moiety as a carrier attached to the N atom instead of alkyl groups. It is anticipated that the sugar moiety imparts less toxicity to the pyridinone than the alkyl group while, at the same time, the sugar maintained penetration of the intestine and permeation of cell membranes. Aspects of the intestinal permeability of some simple carbohydrate compounds have been reviewed by Travis and Menzies [5]. The synthesis of such compounds has been reported [6], but their pharmacological properties have not been extensively explored. There is a notable exception, as a 3-hydroxy-4-



R=Me or Et; R'=Bz; R"=Ac.

A: Me_3SiCl, $Me_3SiNHSiMe_3$

B-1: $SnCl_4$, $ClCH_2CH_2Cl$ and 1,2,3,4-tetra-O-acetyl-ß-D-ribopyranose

B-2: $SnCl_4$, $ClCH_2CH_2Cl$ and 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose

Scheme 1

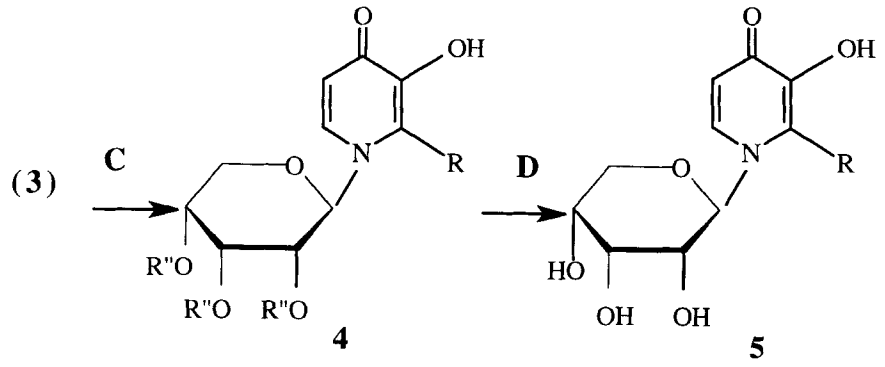
pyridinone ribofuranosyl nucleoside was tested as a potential anti tumor agent [6]. However, the yields for the synthesis of this compound were very low.

Here we report an efficient way to synthesize furanose or pyranose substituted 2-alkyl-3-hydroxy-4-pyridinones in good yield and under mild conditions by employing a method similar to the Hilbert-Johnson reaction and its extension by Niedballa and Vorbrüggen [7]. This reaction was followed by hydrogenation and deprotection of the benzyl group and removal of the benzoyl- or acetyl groups from the nucleoside by standard methods.

Experimental

The overall reaction is described in Schemes 1 and 2.

First, 2-alkyl-3-hydroxy-4-pyridinone **1**, in which the hydroxyl group had been protected by a benzyl group in order to silylate at the N-position only, was refluxed under N_2 for 2



C: H_2 Pd/C, Aqueous MeOH with acetic acid

D: Ammonia-MeOH solution

Scheme 2

hrs with hexamethyldisilazane containing about 10% of trimethylchlorosilane as a catalyst. After evaporation of the solvent, the residue **2** was redissolved in 1,2-dichloroethane, and 1-O-acetyl-2,3,5-tri-O-benzoyl-ß -D-furanose (or 1,2,3,4-tetra-O-acetyl-ß-D-ribopyranose) and $SnCl_4$ or trimethylsilyltrifluoromethane-sulfonate (catalyst) were added. The resulting mixture was stirred at room temperature for 4 hr. and was then treated with an aqueous solution of saturated sodium bicarbonate. After removing the bicarbonate solution, the organic phase was dried with sodium sulfate and the solvent evaporated. The products **3** and **3a** were isolated by silica gel chromatography in good yield (96% and 89%, respectively). Compounds **3** and **3a** now contain two types of protection groups, the benzyl group on the pyridinone which requires acid hydrolysis, and the acetyl - or benzoyl groups on the sugar moiety which requires alkaline hydrolysis. To produce Compound **4**, the benzyl group was removed first in acidic aqueous methanol and H_2 Pd/C (Reaction C). Then, the hydroxyl groups of the sugar moiety were deprotected by alkaline hydrolysis in an NH_3-MeOH medium (Reaction D). Compound **5** was obtained in pure form after crystallization from a 1:1 solution of $CHCl_3$/MeOH.

The analogous reaction was carried out with **3a** (not shown in the scheme). The structures of the newly synthesized compounds have been established according to their ^1H NMR, 2D ^1H NMR, MS data, UV-Visible spectral data and elemental analysis. The data for the pyranoside **5** are as follows: m. p. 248-250 ^0C; ^1H NMR (DMSO -d_6) δ 7.65 (1H, d, 6-H), 6.14 (1H, d, 5-H), 5.28 (1H, d, 1'-H), 3.97-3.50 (5H, m, 2' to 5'-H), 2.30 (3H, s, 2-CH_3); UV (20 mM TRIS HCl, pH=7,54) λ_{max}= 283nm (ε 1.54 x 10^4), λ_{max}= 217nm

(ε 1.86 x 10^4); Mass (m/z) 258 (M+H, 100%); $C_{11}H_{15}NO_6$ (257.2), calculated: C = 51.36%, H = 5.88%, N = 5.44%; found: C = 51.10%, H = 5.80%, N = 5.74%. Data obtained for the furanoside **5** are: ^{1}H NMR (DMSO -d_6) δ 8.00 (1H, d, 6-H), 6.17 (1H, d, 5-H), 5.63 (1H, d, 1'-H), 3.99-3.33 (5H, m, 2' to 5'-H), 2.34 (3H, s, 2-CH_3); UV (20 mM TRIS HCl, pH=7,54) λ_{max}= 283nm (ε 1.46 x 10^4), λ_{max}= 218nm (ε 1.92 x 10^4); Mass (m/z) 258 (M+H). Upon reaction with Fe^{3+}, strong absorption in the visible range was obtained: furanoside **5**; λ_{max} = 457nm (ε 4.48 x 10^3); pyranoside **5**; λ_{max} =458nm (ε 5.06 x 10^3). Both compounds form 3 : 1 complexes with iron. More complete data about their complex formation and pharmacological properties will be published elsewhere,

Summary

We have described an easy and useful method of synthesizing sugar derivatives of hydroxylpyridinone. These compounds are potentially useful for the removal of iron from overloaded biosystems by oral administration. We see little difficulty in applying the overall scheme as a general route for synthesizing other hydroxypyridinone nucleosides. Some other compounds of this new nucleoside and its application will be reported elsewhere.

Acknowledgement: This research was supported by Grant CA 47659 from the National Cancer Institute.

References

1. Porter, J. B., *Eur. J. Haematol* . **1989**, 43, 271-285.
2. Porter, J. B., Hider, R. C. and Huehns, E. R., *Seminars in Hematology*. **1990**, 27, 95-100.
3 Hider, R. C., Singh, S., Porter, J. B. and Huehns, E. R., In *Annals of the New York Academy of Science*, Bank, A. Ed.; New York Academy of Science: New York, Vol. 612, **1990**, 327-338.
4. Singh, S., Hider, R. C., In *Free Radical Damage and its Control*, Rice-Evans, C. A., Burdon, R. H. Eds.; Elsevier Science B. V., **1994**, 189-216.
5. Travis, S., Menzies, I., *Clinical Science*. **1992**, 82, 471-488.
6. Mao, D. T., Driscoll, J. S. and Marquez, V. E., *J. Med. Chem.* **1984**, 27, 160-164.
7. Niedballa, U., Vorbrüggen, H., *Angew. Chem. Internat. Edition.* **1970**, 9, 461.

Received December 29, 1994
Accepted August 9, 1995