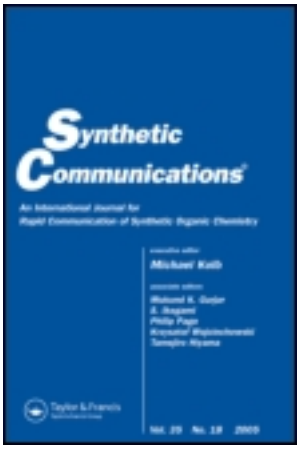

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Efficient Synthesis of N-[(2-Hydroxyethoxy)methyl]-2-alkyl-3-hydroxy-4-pyridinone by a Modified Hilbert-Johnson Reaction

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EFFICIENT SYNTHESIS OF N-[(2-HYDROXYETHOXY) METHYL]-2-ALKYL-3-HYDROXY-4-PYRIDINONE BY A MODIFIED HILBERT-JOHNSON REACTION

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Abstract: Ethyleneglycol derivatives of 2-methyl (and ethyl)-3-hydroxy-4-pyridinone were synthesized by a modified Hilbert-Johnson reaction. The synthesis proceedes by reaction of O-protected 2-alkyl-3-hydroxy-4-pyridinone with hexamethyldisilazane in the presence of chlorotrimethylsilane followed by trimethylsilyl trifluoromethanesulfonate catalized alkylation with benzyloxy-ethoxymethylchloride in dichloroethane and deprotection by hydrogenation. The overall yield was 87%. This method provides a useful way to produce oligo- or polyethyleneglycol substituted hydroxypyridinones.

Introduction: The 2-alkyl-3-hydroxy-4-pyridinones are powerful chelators that are characterized by a high affinity and specificity for iron. Because of this property, they are being investigated for the removal of physiological iron overload in humans. However, absorption of this potential drug from the intestine is poor. In order to improve the absorption from the gut and to facilitate oral application, several substituted pyridinones have been or are being tested [1]. These efforts have been only marginally successful and the search for different derivatives with more desirable phamacological properties is still continuing. As part of this effort, we have designed and synthesized several new N-substituted-2-alkyl-3-hydroxy-4-pyridinones. Here we report an efficient synthesis of N substituted

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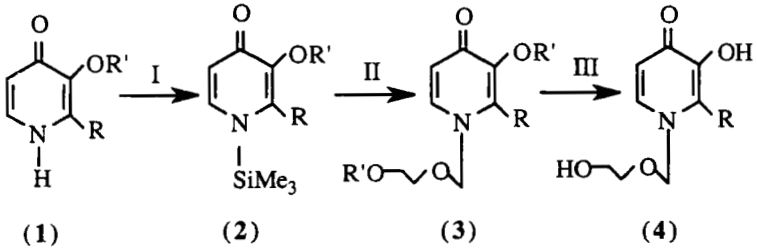
hydroxypyridinones with a glycosidic linkage using a Hilbert-Johnson type reaction as modified by Niedballa and Vorbrueggen [2]. The method appears to be generally applicable for the synthesis of hydroxypyridinones substituted by other oligo- or polyethylene glycols which seem to impart a higher bioavailability from the gastrointestinal tract in man [3].

For synthesizing the title compound, 3-benzyloxyl-2-alkyl-4-pyridinone was first silylated under reflux for 2 hrs with hexamethyldisilazane in the presence of a catalytic amount of chlorotrimethylsilane and then alkylated at room temperature with benzyloxyethoxymethylchloride [4] in 1,2-dichloroethane and trimethylsilyl trifluoromethanesulfonate as a catalyst as shown below.

Scheme



R=Me (a), Et (b); R'=CH_2Ph.

I=Hexamethyldisilazane, chlorotrimethylsilane.

II=Benzyloxyethoxymethylchloride, trimethylsilyl trifluoromethanesulfonate in 1,2-dichloroethane.

III=H_2, Pd/C, AcOH in 95% EtOH.

The C-N bond formation is, basically, a Friedel-Crafts type reaction and a corresponding catalyst should favor the reaction. $SnCl_4$ has been used earlier as a catalyst to alkylate the nitrogen in heterocyclic rings with O-protected

hydroxyethoxymethylhalogen, but possibly due to the instability of the starting materials in the presence of $SnCl_4$, the yield was only between 50-60% [5,6]. Use of the weaker catalyst trimethylsilyl trifluoromethanesulfonate avoided this problem and facilitated the product separation after the alkylating reaction [6,7,8]. After shaking the reaction mixture with an ice cold aqueous solution of saturated $NaHCO_3$, then drying with Na_2SO_4 and evaporating, the residue was purified in excellent yield by chromatography. Both benzyl protection groups were removed by hydrogenation in the presence of Pd/C in acidic solution. The new compounds were characterized by proton NMR, Mass spectra and elemental analysis. The final products form complexes with iron as determined by the absorption at λ_{max} between 450-460 nm which is the characteristic absorption of the parent pyridinone-iron complexes.

Experimental: Chemicals used in the experiment were of analytical grade or better. Melting points of newly synthesized compounds were determined on a Fisher-Johns melting point apparatus without correction. ^1H NMR spectra were recorded at 200 MHz with an IBM NR 200 spectrometer. Mass spectra were recorded on a VG ANALYTICAL 70-SEQ instrument. UV-vis spectra were recorded on a Beckman DU-64. Column chromatography was performed with Aldrich silica gel (70-230 mesh). Thin layer chromatography (TLC) was done on Sigma acid-washed silica gel with a 254 nm fluorescent indicator on polyester plates. All elemental analyses were carried out by Desert Analytic Organic Microanalysis Inc.

N-Benzyloxyethoxymethyl-3-benzyloxyl-2-methyl-4-pyridinone (3a). 3-Benzyloxyl-2-methyl-4-pyridinone (**1a**) (1.016 g, 4.72 x 10^{-3} mol) in hexamethyldisilazane (20 ml) with chlorotrimethylsilane (0.72 ml) as a catalyst was

refluxed under N_2 for 2 hrs. After evaporation of the solvent in vacuo, the residue **2a** was redissolved in 1,2-dichloroethane (40 ml). Benzyloxyethoxymethylchloride (1.042 g, 5.19 x 10^{-3} mol) was added, followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate under N_2 atomsphere. The resulting mixture was stirred at r. t. for 24 hrs. After this. the reaction mixture was washed with ice cold saturated aqueous $NaHCO_3$ (2 x 50 ml) and saline (50 ml). The organic phase was dried with Na_2SO_4. After removing the solvent by evaporation under vacuum, the residue was purified by silica gel chromatography, first using MeOH/$CHCl_3$ (1: 30 v/v), then MeOH/$CHCl_3$ (1: 20 v/v) as eluants. After removal of solvents, a pale yellow oily product was obtained (yield: 95%). TLC (in MeOH/$CHCl_3$, 1: 20 v/v) R_f=0.34. ^{1}H NMR ($CDCl_3$): δ 7.47 - 7.26 (11H, m, H6 and aromatic H), 6.62 (1H, d, H5), 5.26 (2H, s, 1'- CH_2), 5.20 (2H, s, Ph-CH_2-pyridinone), 4.52 (2H, s, Ph-CH_2-O-), 3.59 (4H, s, -O-CH_2CH_2-O-), 2.22 (3H, s, -CH_3). MS (m/z 379.44); 380.18 (M+1. 100%). Anal. Calcd. for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.28; H, 6.51; N, 3.66.

N-Benzyloxyethoxymethyl-3-benzyloxyl-2-ethyl-4-pyridinone (3b). This compound was synthesized as described above for **3a** except using 3-Benzyloxyl-2-ethyl-4-pyridinone (**1b**) (1.019 g, 4.43 x 10^{-3} mol) and benzyloxyethoxymethylchloride (0.98 g, 4.87 x 10^{-3} mol). Yield 96%. TLC (in MeOH/$CHCl_3$, 1: 20 v/v) R_f=0.40. ^{1}H NMR ($CDCl_3$): δ 7.49-7.27 (11H, m, H6 and aromatic H), 6.64 (1H, d, H5), 5.30 (2H, s, 1'- CH_2), 5.26 (2H, s, Ph-CH_2-pyridinone), 4.52 (2H, s, Ph-CH_2-O-), 3.62 (4H, s, -O-CH_2CH_2-O-), 2.72 (2H, q, -$\underline{CH_2}CH_3$), 1.06 (3H, t, CH_3). MS (m/z 393.47); 394.24 (M+1, 100%). Anal. Calcd. for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.07; H, 6.74; N, 3.53.

N-Hydroxyethoxymethyl-3-hydroxyl-2-methyl-4-pyridinone (4a). The two benzyl protecting groups were removed by hydrogenation of **3a** (1.42 g, 3.73

x 10^{-3} mol) over Pd/C catalyst (0.28 g) in 95% EtOH (45 ml) with glacial acetic acid (1.8 ml). The mixture was stirred at r. t. for 24 hrs. After filtration the solvent was evaporated under vacuum to dryness. The residue was recrystallized from ether/MeOH and then ethyl acetate/MeOH and colorless crystals were obtained (yield: 93%). TLC (in MeOH/$CHCl_3$, 1: 4 v/v) R_f=0.35. m.p. 123-5 °C. ^1H NMR (DMSO-d_6): δ 7.68 (1H, d, H6), 6.08 (1H. d, H5), 5.31 (2H, s, 1'- CH_2), 3.44-3.15 (4H, m, -O-CH_2CH_2-O-), 2.30 (3H, s, CH_3). MS (m/z 199.20); 200.05 (M+1, 100%), 126.16 (13%). Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.12; H, 6.60; N, 6.89.

2-Ethyl-N-hydroxyethoxymethyl-3-hydroxyl-4-pyridinone (4b). **3b** was hydrogenated catalytically over Pd/C catalyst (0.22 g) in 95% EtOH (35 ml) using glacial acetic acid (1.4 ml) to remove the two benzyl protecting groups. The procedure was as described above for **4a**. Yield 91%. TLC (in MeOH/$CHCl_3$, 1: 4 v/v) R_f=0.42. m.p. 113-5 °C. ^1H NMR (DMSO-d_6): δ 7.94 (1H, d, H6), 6.53 (1H, d, H5), 5.50 (2H, s, 1'- CH_2), 3.48-3.16 (4H, m, -O-CH_2CH_2-O-), 2.87 (2H, q, -CH_2CH_3), 1.16 (3H, t, CH_3). MS (m/z 213.23); 214.05 (M+1, 100%), 140.10 (9%). Anal. Calcd. for $C_{10}H_{15}NO_4$ x H_2O: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.78; H, 6.87; N, 5.79.

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References

1. Hider, R. C., Porter, J. B. and Singh, S., *The Development of Iron Chelators for Clinical Use*; Bergeron, R. J. and Brittenham, G. M. Eds.; CRC Press, Inc.: Florida, 1994; pp. 354-371.
2. Niedballa, U. and Vorbrueggen, H., *J. Org. Chem.* **1974**, *39*, 3668-3671.

3. Maxton, D. G., Bjarnason, I., Reynolds, A. P., Catt, S. D., Peters, T. J. and Menzies, I. S., *Clin. Sci.* **1986**, *71*, 71-80.

4. Schaeffer, H. J., Gurwara, S., Vince, R., and Bittner. S., *J. Med. Chem.* **1971**, *14*, 367-369.

5. Robins, M. J. and Hatfield, P. W., *Can. J. Chem.*, **1982**, *60*, 547-553.

6. Mao, D. T., Driscoll, J. S. and Marquez, V. E., *J. Med. Chem.* **1984**, *27*, 160-164.

7. Maruenda, H. and Johnson, F., *J. Med. Chem.* **1995**, *38*, 2145-2151.

8. Vorbrueggen, H. and Krolikiewicz, K., *Angew. Chem.* Internat. Edit. **1975**, *14*, 421-422.

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