Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: G. Liu , S. C. Miller & F. W. Bruenger (1995) Synthesis of Lipophilic 3-Hydroxy-2-methyl-4-pyridinone Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:20, 3247-3253, DOI: 10.1080/00397919508015476

To link to this article: http://dx.doi.org/10.1080/00397919508015476

SYNTHETIC COMMUNICATIONS, 25(20), 3247-3253 (1995)

SYNTHESIS OF LIPOPHILIC 3-HYDROXY-2-METHYL- 4-PYRIDINONE DERIVATIVES

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ABSTRACT: Hydrophilic 2- hydroxy-3-methyl-4-pyridinone derivatives were acylated with either long chain acid chlorides or with 1,3,5-benzenetricarbonyl trichloride. The products are either partially lipophilic, bidentatate or hexadentate chelators that form strong 3:1 and 1:1 complexes, respectively, with Fe (III).

Introduction

The 2-alkyl-3-hydroxy-4-pyridinones are powerful chelators with a high affinity for iron. Because of this property and because of their relatively low toxicity, they are being tested for the treatment of iron overload diseases. They are bidentate and require three molecules of the pyridinone to satisfy the full coordination sphere of iron. However, most of these compounds are only marginally lipophilic and have to be administered parenterally because of their poor absorption from the intestine. It appears reasonable to improve their pharmacological activities by a) increasing the lipophilic properties and b) by

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constructing a hexadentate pyridinone derivative in which the donors are spaced around an iron atom similar to the arrangement found in the corresponding 3:1 chelates. Attempts have been made to accomplish both of these goals by either replacing the original, small 2- alkyl group by a slightly longer chain or by adding an alkyl group in the 1-N position and by condensing three bidentate into one hexadentate molecule (Dobbin [1], Streater [2]). It was shown that these changes increased the iron removal efficiency. However, this also tended to increase the toxicity. Thus, there is substantial room for further improvement. Our own experience with other compounds is that a considerably longer alkyl chain is necessary to direct the drug to the liver, the dominant iron storage organ and that such long chains did not impart a significant toxicity (Bruenger, [3] Miller [4]). The increased molecular size in our previous experiments did not diminish the drug efficacy. Consequently we have synthesized three bidentate, N-substituted pyridinones with longer chain substitutents and also a tripodal, hexadentate pyridinone in which the functional groups are expected to be less constrained than in previously reported tripodals. The synthesis of these compounds is described.

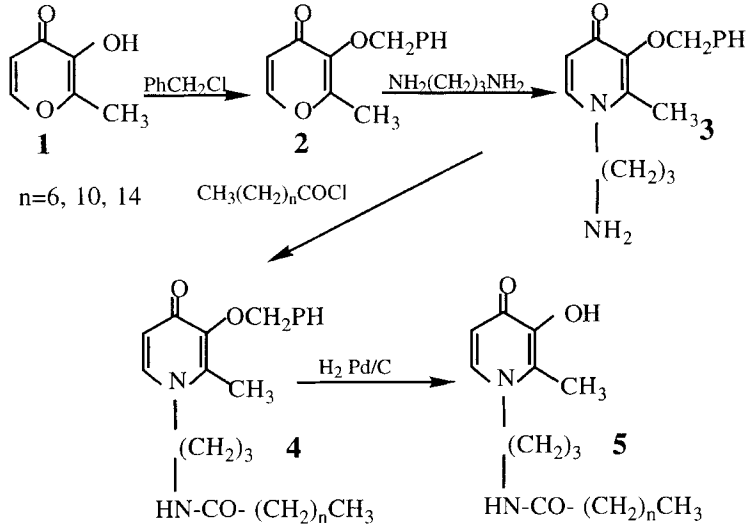
Experimental:

Chemicals used were of analytical grade or better. Melting points of newly synthesized compounds were determined on a Reichert Hot Stage apparatus without correction. ^{1}H NMR spectra were obtained at 200 MHz with an IBM NR 200 spectrometer. IR spectra were recorded as KBr discs on a Beckman 2100 spectroscope. UV-VIS spectra were recorded on a Beckman DU-64 spectrophotometer. Mass spectra were recorded on a VG ANALYTICAL 70- SEQ instrument by positive ion bombardment using 1-thioglycerol as the matrix. Elemental analyses were carried out by Desert Analytics Organic Microanalysis Inc. Detailed analytical information is presented only for key intermediates and final compounds.

a) Long chain, lipophilic 1-N-(3-hydroxy-2-methyl-4-pyridinone) derivatives:

General Procedure: The synthesis of the lipophilic, bidentate hydroxy pyridinones proceeded in four steps: 1) Protection of the hydroxyl group of the parent compound, 2) conversion to the 1-(γ-aminopropyl) pyridinone, 3)

attachment of the long chain lipohilic group by an acylation reaction and 4) deprotection by catalytic hydrogenation. These steps are outlined in scheme 1 .



Scheme 1

Synthesis of the alkylated γ– aminopropylpyridinone derivatives: Starting with 2-methyl-3-hydroxypyrone (1), the OH group was first protected using a standard benzylchloride etherification method to form 2-alkyl-3-benzyloxy-4-pyrone (**2**) in 94% yield. 1-(γ-Aminopropyl)-3-benzyloxy-2-methyl-4-pyridinone (**3**) was synthesized at room temperature by reaction of equimolar quantities of 2 and 1,3-diaminopropane in a 3/2 mixture of H_2O/EtOH. After a reaction time of 1 week, solvents and residual amine were evaporated in vacuo. The residue was dissolved in $CHCl_3$, washed 3 times with H_2O and dried with Na_2SO_4. After removing the $CHCl_3$, MeOH was added and the pH was adjusted to pH=1 with HCl. After cooling, the precipitated amine salt was filtered, washed with ether, dried under vacuum and purified by crystallization from MeOH and ether, yield=71% . Compound 3 was identified by elemental analysis, ^{1}H NMR, and IR. $C_{16}H_{20}N_2O_2$ x 2HCl: calculated: C=55.65; H=6.42 and N=8.12; found: C=55.40; H=6.26 and N=8.35. m.p.: 188 ^oC·

Using triethylamine as a proton scavenger, compound 3 was acylated in THF with a 20% excess of the appropriate $CH_3(CH_2)_nCOCl$ (n=6, 10, 14) at room temperature for 24 hours. The precipitated triethylamine salt was filtered off and washed with THF. From the combined filtrate, THF was removed under vacuum, and the product was isolated and purified by silica gel chromatography using $CHCl_3$/MeOH (95v/5v) as the eluant. Yield = 92% -93% of compound (**4**).The stuctures of the three respective 3-benzyloxy-2-methyl-1-(γ-$CH_3(CH_2)_n$ amidopropyl)-4-pyridinones were identified by ^1H NMR (spectra not given). The benzyloxy protection group was then removed by catalytic (Pd/C) hydrogenation in ethanol-acetic acid for 24 hours. After filtering off the Pd/C and evaporation of the solvent, compounds [5(a-c)] were obtained in 84% (n=6), 80% (n=10) and 86% (n=14) yield, respectively, as a white powder. NMR data for the three compounds are given in Table 1 below.

TABLE 1, NMR-DATA FOR COMPOUNDS 5 (a-c)
(^1H NMR, MeOH-d_4)

	1H,d, 6-H	1H,d, 5-H	2H,t, α- CH_2 prop.	2H,t, γ- CH_2 prop.	3H,s, (2) CH_3	2H,t, α- CH_2, acyt.	2H,m, β,- CH_2 prop.	2H,m, β- CH_2, acyt.	(2n-4) H, b, CH_2, acyt.	3H,t, term. CH_3, acyt.
n=6	7.62	6.38	4.05	3.23	2.42	2.18	1.93	1.60	1.31	0.89
n=10	8.13	7.03	4.35	3.26	2.61	2.19	2.02	1.60	1.28	0.89
n=14	7.62	6.39	4.05	3.24	2.42	2.18	1.93	1.59	1.27	0.89

In addition, the following analytical data were obtained: 1-(γ-octanoylamidopropyl) -3-hydroxy-2-methyl-4-pyridinone **5a)**. UV (80% MeOH with water) λ_{max} 284 nm, ε 1.5 x10^4 MS (M/E): 309, (Cal. 308.41); m. p. <40^0 C; Results of Elem. Anal.: calcd. for $C_{17}H_{28}N_2O_3$ x CH_3OH: C=63.5; H=9.47; N=8.23; Found: C=63.21;H=8.9; N=8.57.

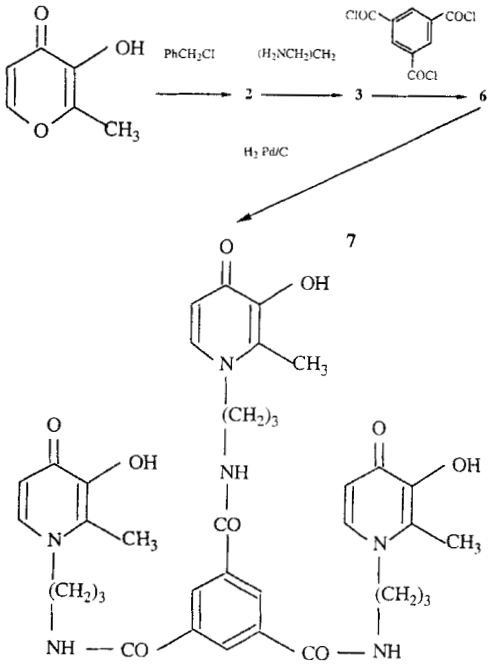
1-(γ-dodecanoylamidopropyl)-3-hydroxy-2-methyl-4-pyridinone **5b)**. UV (80% MeOH with water) λ_{max} 284 nm, ε=1.41 x 10^4; MS (M/E): 365 (Calc. 364.5); m. p. 117-119^0 C. Results of Elem. Anal.: calc. for $C_{21}H_{36}N_2O_3$ x $2H_2O$: C=62.97; H=10.07; N=7.0. Found: C=62.84; H=9.77; N=6.84.

1-(γ-hexadecanoylamidopropyl)-3-hydroxy-2-methyl-4-pyridinone **5c)**, UV (80% MeOH with water) λ_{max} 284 nm, ε=1.45 x 10^4; MS (M/E)=421 (Calc. 420,62);

m. p. 90-92^0 C. Results of Elem. Anal.: calc. for $C_{25}H_{44}N_2O_3$: C=71.38; H=10.54; N=6.66. Found: C=71.40; H=10.64; N=6.43.

b) Hexadentate, tripodal 1, 3, 5,-tris {[γ-(3-hydroxy-2-methyl-4- pyridinon-1-yl) propyl]carbamido}benzene (7).

General Procedure: The synthesis of the hexadentate, tripodal pyridinone derivative proceeded analogous to that of the lipophilic derivatives with the first two steps being identical to those of scheme 1. In the next step, three equivalents of compound 3 were acylated with one equivalent of 1, 3, 5-benzenetricarbonyl chloride and the tripodal derivative with the benzenetricarbonyl as the common cap for the three pyridinone legs was formed, compound (**6**). The last step again was the deprotection of the pyridinone hydroxyl. The overall synthesis is outlined in scheme 2.



Scheme 2

Synthesis of the tripodal compound: Compound 3 and benzenetricarbonyl chloride were mixed in a 3/1 molar ratio in N, N-dimethyl acetamide / triethylamine (10 / 1) and stirred for 20 hrs at 95-110 ^{0}C. The product was filtered to remove the Et_3N x HCl and evaporated to dryness under vacuum. The residue was extracted with hot MeOH which also was removed under vacuum. Then the residue was washed sequentially with dilute aq NaOH and with water. The residue was crystallized from MeOH / ether. 1,3,5-Tris{[γ-(3-Benzyloxy-2-methyl-4-pyridin-1-yl)propyl] - carbamido}benzene (6) was filtered off and recrystallized from CH_3CN / MeOH. ^{1}H NMR (MeOH-d_4), 8.31 ppm (3H, s, benzene ring H), 7.81 ppm (3H, d, 6-H), 7.38-7.28 ppm (15H, m, benzene ring H in protection group), 6.52 ppm (3H, d, 5-H), 5.03 ppm (6H, s, benzylic CH_2), 4.11 ppm (6H, t, γ propylenic CH_2), 3.46 ppm (6H, m, α propylenic CH_2), 2.23 ppm (9H, s, 2 position CH_3), 2.02 ppm (6H, m, β propylenic CH_2). MS (M/E): 974, (Cal. 973.10). m.p. 138-140^0 C. Results of Elem. Anal. calcd. for $C_{57}H_{60}N_6O_9$ x $3H_2O$: C=66.65; H=6.48; N=8.18. Found: C=66.49; H=6.08; N=7.91.

Compound 6 was catalytically hydrogenated as described for the corresponding bidentate compound. The final product, 1,3,5-tris{[γ-(3-hydroxy-2-methyl-4-pyridin-1-yl)propyl]carbamido}benzene (7), was obtained in 90% yield as a white powder, ^{1}H NMR (MeOH-d_4), 8.38 ppm (3H, s, benzene ring H), 7,77 ppm (3H, d, 6-H), 6.49 ppm (3H, d, 5-H), 4.22 ppm (6H, t, γ propylenic CH_2), 3.51 ppm (6H, m, α propylenic CH_2), 2.48 ppm (9H, s, 2 position CH_3), 2.12 ppm (6H, m, β propylenic CH_2); UV (20mmol Tris buffer, MeOH 1 /1) λ_{max} 282 nm, $\varepsilon = 4.57 \times 10^4$; MS (M / E)$^+$: 703.5, (Calcd. 702.75); m.p. 166-8^0 C. Results of Elem. Anal. calcd. for $C_{36}H_{42}N_6O_9x3H_2O$: C=57.13; H=6.39; N=11.11. Found: C=57.26; H=5.92; N=10.39.

Summary:

We have described the synthesis in good yield of 1-N lipophilic, bidentate 3-hydroxy-4-pyridinone derivatives and the synthesis of a tripodal, hexadentate 3-hydroxy-4-pyridinone by applying an acylating reaction. The synthetic pathway appears to provide a simple, general method of synthesis for this type of pyridinone derivative. The products form strong 3:1 and 1:1 complexes, respectively, with Fe(III) which makes them potentially useful as bioactive iron chelators that can be applied pharmacologically for the oral treatment of endogenous iron overload.

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

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(Received in the USA 16 March 1995)