Synthesis of 2,6-Diformyl-3-hydroxypyridine Bis[*N*-methyl-*N*-(2′-pyridyl)hydrazone]: A Pentadentate *N,N,N,N,N* Ligand for the Preparation of Chelating Resins

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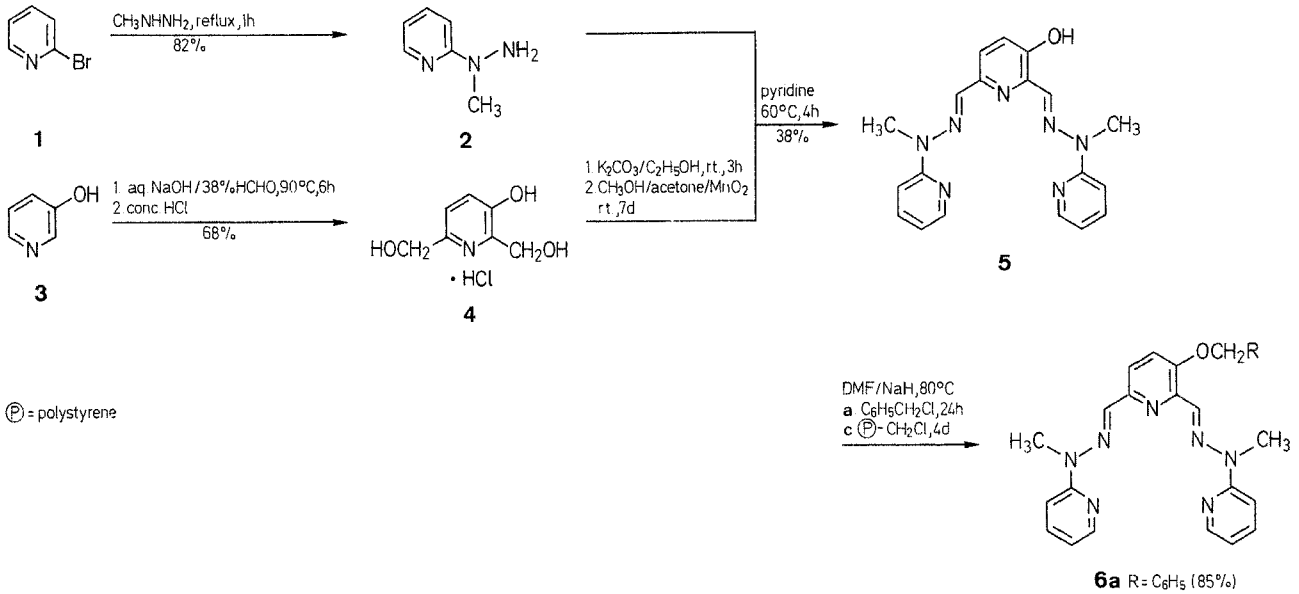
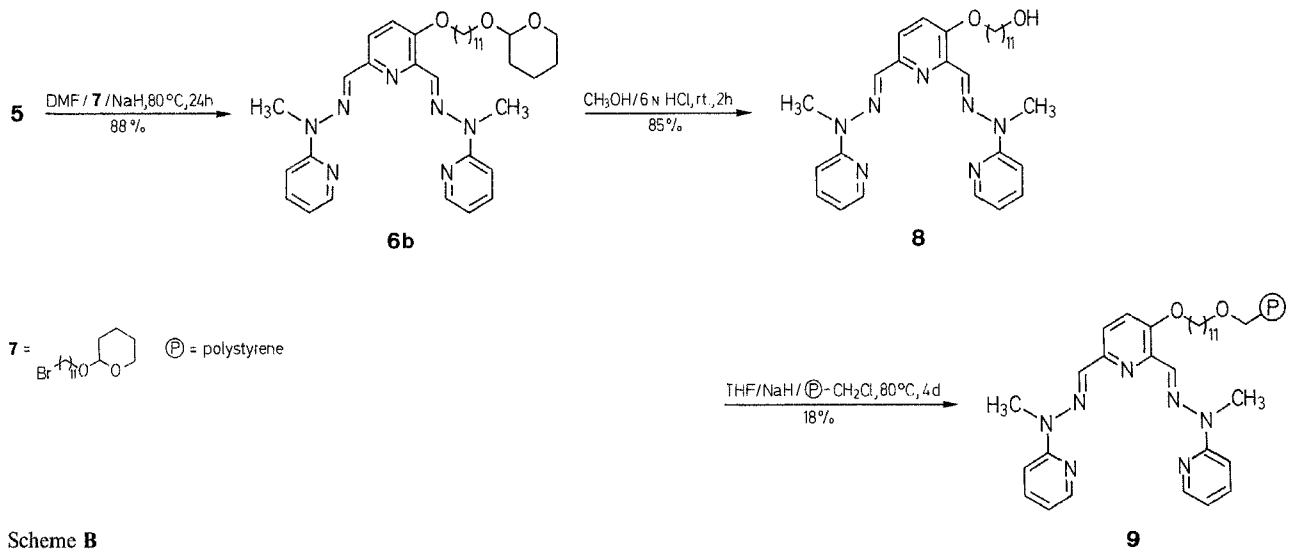
The synthesis of 2,6-diformyl-3-hydroxypyridine bis[*N*-methyl-*N*-(2′-pyridyl)hydrazone] as a versatile intermediate with a reactive hydroxyl group, which can be bonded to lipophilic chains and/or to polymeric supports, is reported.

The use of polymer-supported chelating agents for the selective removal of metal ions from aqueous solutions represents an important analytical and industrial endeavor.[1]

The synthesis of a chelating resin can be achieved either by attachment of an appropriate complexing agent to a polymeric matrix or by polymerization of a suitable chelating monomer.[2] Both approaches would lead to an effective chelating polymer if the ligating behaviour of the chelating group in the polymeric matrix is similar to that of the active group in the monomeric system.



Scheme A



Scheme B

It has been suggested that higly selective behaviour could be expected of a polymeric system that contained a polydentate chelating group capable of forming a stable 1:1 complex with a particular metal ion and much less stable complexes with others.[3,4] Following this approach, we anchored a pentadentate chelating ligand of known selectivity[5] to a chloromethylated cross-linked polystyrene.

We report here the synthesis of 2,6-diformyl-3-hydroxylpyridine bis[*N*-methyl-*N*-(2'-pyridyl)hydrazone] (**5**), in which the presence of the hydroxy group affords a simple way to bind the ligand to any functionalized molecule. In addition, the covalent attachment of **5** either directly or through a 11-C atom linear alkyl chain to chloromethylated polystyrene 1% crosslinked with divinylbenzene is described (Scheme **A** and Scheme **B**).

The synthetic approach to the target molecules **5** and **8** utilizes *N*-methyl-*N*-(2-pyridyl)-hydrazine **2** and 2,6-bis(hydroxymethyl)-3-hydroxypyridine hydrochloride **4** as key reagents. Thus an efficient synthetic route to these intermediates was a necessary prerequisite. The previously reported hydrazine derivative **2**[6] was more conveniently prepared, in 82% yield, by refluxing 2-bromopyridine **1** in *N*-methylhydrazine, followed by work-up and purification *via* column chromatography.

Although the dihydroxymethyl derivative **4** is a known compound,[7] an improved procedure to its preparation was developed. Thus **4** was obtained (68% yield) by treatment of 3-hydroxypyridine **3** with 38% formaldehyde in aqueous sodium hydroxide. Neutralization of the hydrochloride **4** with anhydrous potassium carbonate in ethanol, gave the free base which, in turn, was oxidized with commercially available manganese dioxide.[8] The oxidative treatment proved to be a troublesome step, due mainly to the limited solubility of 2,6-bis(hydroxymethyl)-3-hydroxypyridine in the solvents usually employed in manganese dioxide oxidations. Methanol/acetone (1:4) was found to be a suitable solvent mixture for the transformation of the free base of **4** to the corresponding dialdehyde at room temperature. This was reacted directly with hydrazine **2** to provide the bis-hydrazone **5**, in 38% overall yield from **4**. Spectroscopic characterization by ^{1}H-NMR of **5** was not possible owing to its very low solubility in organic solvents at room temperature. A suitable solubility was achieved by converting compound **5** into the benzyl ether derivative **6a**, ^{1}H-NMR data of which confirmed the proposed structure.

Condensation of **5** with the tetrahydropyranylether of 1-bromoundecanol produced the tetrahydropyranyl protected intermediate **6b** (88% purified yield), from which the tetrahy-

dropyranyl protecting group was removed with 6 normal hydrochloric acid/methanol to give the desired 11-hydroxyundecyl pentadentate ligand **8** in 85% yield.

Finally, the etherification of chloromethyl polystyrene with **5** and **8** was performed in the presence of sodium hydride in dimethylformamide or tetrahydrofuran, respectively. The degree of functionalization of **6c** and **9** was found 81% and 18% respectively, as determined by nitrogen elemental analysis. This large difference could arise from the absence of a suitable phase-transfer catalyst, i.e. a crown ether, which, as reported,[9] makes the etherification of chloromethylated polystyrene with long alkyl chains more efficient. Tests of selective complexation of the resins are now in progress.

N-Methyl-N-(2-pyridyl)hydrazine (2):
A mixture of methylhydrazine (50 mL) and 2-bromopyridine (**1**; 10.0 g, 63.3 mmol) is refluxed with stirring under argon for 1 h. After cooling, excess methylhydrazine is removed *in vacuo* and the residue partitioned between a 10% Na_2CO_3 solution (25 mL) and ethyl acetate (200 mL). The organic layer is washed with saturated NaCl solution, dried (Na_2SO_4) and then evaporated to give an oil which is column chromatographed on silica gel eluting with chloroform; yield: 6.4 g (82%); b.p. 87 °C/2 mm (Lit.[6] b.p. 68 °C/0.5 mm).

IR (KBr): ν = 3315 (m, broad), 3190 (m, broad), 1594 (s), 1558 (m), 1480 (s), 1435 (s), 770 cm^{-1} (s).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.14 (s, 3H); 4.02 (s, 2H); 6.50 (m, 1H); 6.87 (d, 1H, J = 8.5 Hz); 7.32 (m, 1H); 8.09 (br d, 1H).

2,6-Bis(hydroxymethyl)-3-hydroxypyridine Hydrochloride (4):
Four portions (20 mL each) of 38% formaldehyde are added in 90 min intervals to a stirred solution of NaOH (10.0 g, 0.25 mol) and 3-hydroxypyridine (**3**; 23.8 g, 0.25 mol) in water (100 mL) at 90 °C. After 90 min from the last addition, the mixture is cooled to room temperature, neutralized with acetic acid (15 mL) and evaporated to dryness, and the residue is taken up in DMF (200 mL). The resulting suspension, after filtration, is acidified with concentrated HCl (25 mL) and then evaporated *in vacuo*. The residue is taken up in methanol (150 mL) and treated with activated charcoal followed by filtration. After evaporation of the solvent the residue is crystallized from *n*-propyl alcohol. The crystalline product is collected, dried and recrystallized from methanol/acetone; yield: 32.6 g (68%); m.p. 144–146 °C (Lit.[7] 143–146 °C).

$C_7H_{10}ClNO_3$	calc.	C 43.88	H 5.26	N 7.31	Cl 18.50
(191.2)	found	43.67	5.23	7.21	18.55

IR (KBr): ν = 3500–2500 (s, broad), 1623 (ms), 1540 (s), 1050 (s), 840 cm^{-1} (s).

^{1}H-NMR (DMSO-d_6/TMS): δ = 4.75 (s, 4H); 5.11 (br s, 3H, D_2O exchange); 7.71 (d, 1H, J = 8.6 Hz); 8.01 (d, 1H, J = 8.6 Hz).

2,6-Diformyl-3-hydroxypyridine Bis[N-methyl-N-(2'-pyridyl)hydrazone] (5):
To a solution of **4** (5.0 g, 26 mmol) in absolute ethanol (100 mL), is added anhydrous K_2CO_3, followed by two drops of water. After 3 h of stirring at room temperature, the mixture is filtered and evaporated to give a highly viscous oil which is dissolved in methanol/acetone (2:8, 150 mL). Manganese dioxide (35 g) is added and the resulting suspension stirred at room temperature for 7 d, after which it is filtered on celite. The filtrate is concentrated nearly to dryness, and the resulting wet solid product dried at 25 °C under vacuum overnight. The residue is taken up in pyridine (100 mL), and to the resulting solution is added *N*-methyl-*N*-(2-pyridyl)hydrazine (**2**; 4.8 g, 39 mmol) followed by pyridinium *p*-toluenesulfonate[10] (0.628 g, 2.5 mmol). The mixture is maintained at 60 °C for 4 h and, after cooling, the crude product obtained is filtered off and recrystallized from pyridine; yield: 3.6 g (38%); m.p. 284–285 °C.

$C_{19}H_{19}N_7O$	calc.	C 63.14	H 5.30	N 27.13
(361.4)	found	63.15	5.30	27.20

IR (KBr): ν = 3005 (w), 2920 (br. w), 1589 (vs), 1559 (s), 1433 (vs), 1377 (s), 1288 (s), 1214 (s), 1129 (vs), 1000 (ms), 980 (ms), 766 cm^{-1} (vs).

3-(Benzyloxy)-2,6-diformylpyridine Bis[N-methyl-N-(2'-pyridyl)hydrazone] (6a):
A solution of benzyl chloride (253 mg, 2 mmol) in anhydrous DMF (30 mL) is added dropwise over 1 h to a stirred suspension of **5** (361 mg, 1 mmol) and sodium hydride (80 mg, 2 mmol; 60% dispersion) in anhydrous DMF at 80 °C under argon. After 24 h, the bulk of the solvent is evaporated and the residue partitioned between CH_2Cl_2 (50 mL) and water (30 mL). The organic layer is washed with 5% Na_2CO_3 solution (2 × 30 mL) and water (2 × 30 mL), dried (Na_2SO_4) and evaporated. The product is recrystallized from ethanol; yield: 385 mg (85%); m.p. 165–166 °C.

$C_{26}H_{25}N_7O$	calc.	C 69.16	H 5.58	N 21.71
(451.5)	found	68.53	5.53	21.54

IR (KBr): ν = 3055 (w), 3005 (w), 2920 (br. w), 1592 (vs), 1562 (s), 1434 (vs), 1370 (s), 1258 (m), 1215 (s), 1123 (vs), 982 (ms), 765 (m), 698 cm^{-1} (m).

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.70 (s, 6H); 5.21 (s, 2H); 6.78 (m, 2H); 7.29–8.24 (m, 15H).

2,6-Diformyl-3-[11-(tetrahydro-2-pyranyloxyundecyloxy]pyridine Bis[N-methyl-N-(2'-pyridyl)hydrazone] (6b):
The title compound is prepared from **5** (1.81 g, 5 mmol) and **7** (2.18 g, 6.5 mmol) as described for **6a**; the product crystallizes from ethanol; yield: 2.72 g (88%; m.p. 89–91 °C.

$C_{35}H_{49}N_7O_3$	calc.	C 68.26	H 8.02	N 15.92
(615.8)	found	67.97	8.13	15.87

IR (KBr): ν = 2940 (s), 2920 (s), 2850 (s), 1590 (vs), 1562 (vs), 1433 (vs), 1371 (s), 1265 (s), 1213 (s), 1120 (vs), 1030 (m), 982 (ms), 769 cm^{-1} (s).

^{1}H-NMR (CD_2Cl_2/TMS): δ = 1.10–1.99 (m, 24H); 3.32–3.82 (m, 4H); 3.69 (s, 6H); 4.10 (t, 2H, J = 6.2 Hz); 4.53 (s, 1H); 6.80 (m, 2H); 7.25–8.25 (m, 10H).

Polymer-Supported Pentadentate Ligand (6c):
To a stirred solution of **5** (517 mg, 1.43 mmol) in anhydrous DMF (120 mL) at 80 °C under an argon atmosphere is added sodium hydride (114 mg, 2.86 mmol; 60% dispersion) followed by chloromethyl polystyrene (1% cross-linked with divinylbenzene, containing 1.3 mmol chlorine/g; 1 g, 1.3 mmol). The mixture is allowed to react for 4 d, after which it is filtered. The polymer is washed successively with hot DMF, water, methanol, CH_2Cl_2, Et_2O and then dried at 65 °C under reduced pressure for 4 h. Elemental analysis for nitrogen (calc. 8.92; found 7.27) indicates a 81% yield of binding.

1-Bromo-11-(tetrahydro-2-pyranyloxy)undecane (7):
A solution of 11-bromo-1-undecanol (5.0 g, 20 mmol), dihydropyran (2.5 g, 30 mmol) and pyridinium-*p*-toluensulfonate[10] (0.502 g, 2 mmol) in dry CH_2Cl_2 (50 mL) is stirred at room temperature for 18 h. After washing with 5% Na_2CO_3 solution and water, the organic phase is dried (Na_2SO_4) and then concentrated to dryness. The residual yellow brown oil is chromatographed on silical gel, eluting with 10% ethyl acetate/cyclohexane to give **7** as a clear colorless oil; yield: 5.2 g (78%).

IR (KBr): ν = 2922 (vs), 2850 (s), 1132 (m), 1118 (m), 1030 cm^{-1} (s).

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.92–2.02 (m, 24H); 3.30–3.79 (m, 6H); 4.56 (s, 1H).

2,6-Diformyl-3-(11-hydroxyundecyloxy)pyridine Bis[N-methyl-N-(2-pyridyl)hydrazone] (8):
A solution of **6b** (1.85 g, 3 mmol) in methanol (16 mL) and 6 normal HCl (4 mL) is stirred at room temperature for 2 h. Then the mixture is neutralized with Na_2CO_3 and extracted with CH_2Cl_2 (200 mL). The organic phase is washed with water, dried (Na_2SO_4) and concentrated to a small volume. The product crystallizes on addition of Et_2O; yield 1.36 g (85%); m.p. 116.5–117.5 °C.

$C_{30}H_{41}N_7O_2$	calc.	C 67.77	H 7.77	N 18.44
(531.7)	found	67.34	7.85	18.22

IR (KBr): ν = 2920 (ms), 2850 (m), 1590 (vs), 1562 (s), 1434 (vs), 1371 (s), 1267 (s), 1213 (s), 1122 (vs), 1117 (vs), 988 (s), 772 (m), 762 cm^{-1} (ms).

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.20–2.03 (m, 18H + 1H D_2O exchange); 3.62 (t, 2H, J = 6.4 Hz); 3.72 (s, 6H); 4.10 (t, 2H, J = 6.2 Hz); 6.80 (m, 2H); 7.22–8.26 (m, 10H).

Polymer-Supported Pentadentate Ligand (9):
The resin is prepared as above described for **6c** by reaction of **8** (800 mg, 1.5 mmol) with chloromethyl polystyrene (1% cross-linked with divinylbenzene containing 1.3 mmol chlorine/g; 1 g; 1.3 mmol) using THF instead of DMF as solvent.

Elemental analysis for nitrogen (calc. 7.74, found 1.38) indicates a 18% yield of binding.

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(2) Mathur, N.K., Narang, C.K., Williams, R.E. *Polymers as Aids in Organic Chemistry*, Academic Press, New York, 1980.
(3) Millar, J.R. *Chem. Ind. (London)* **1957**, 606.
(4) Blasius, E., Brozio, B. in: *Chelates in Analytical Chemistry*, Flaschka, H.A., Barnard, A.J., (eds.), Marcel Dekker Inc., New York, 1967, p. 49.
(5) Marangoni, G., unpublished results.
(6) Palazzo, G., Baiocchi, L. *Ann. Chim. (Rome)* **1965**, *55*, 935.
(7) Stempel, A., Buzzi, E.C. *J. Am. Chem. Soc.* **1949**, *71*, 2969.
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(10) Miyashita, N., Yoshikoshi, A., Grieco, P.A. *J. Org. Chem.* **1977**, *42*, 3772.

Errata:

– Baldo, M. A., Chessa, G., Marangoni, G., Pitteri, B. *Synthesis* **1987**, 720. On p. 722, line 6, "degree of functionalization" should read "yield of binding". On the same page in the preparation of bis-hydrazone **5**, line 8, "solid product" should read "oil".

– Singh, L. W., Ila, H., Junjappa, H. *Synthesis* **1988**, 89. On p. 90 in the ^{1}H-NMR data for dioxime **4**, line 2, "N_2" should read "NH_2".

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- Singh, L.W., Ila, H., Junjappa, H. *Synthesis* **1988**, 89. On p. 90 in the ^{1}H-NMR data for dioxime **4**, line 2, "N_2" should read "NH_2".

- Burger, K., Hübl, D., Geith, K. *Synthesis* **1988**, 194. On p. 196 in the table, for entries **4l**, **4m**, and **4n**, Y = O, and *Nu* = Cl, Br, and C_6H_5, respectively.

- Tolstikov, A.G., Khakhalina, N.V., Spirikhin, L.V. *Synthesis* **1988**, 221. In the title and abstract, benzyl esters should read benzyl ethers.

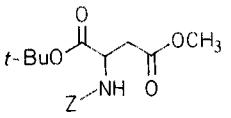
- Gupta, A.K., Ila, H., Junjappa, H. *Synthesis* **1988**, 284. Compounds **4** are 1,6-dioxo-1,2,3,6-tetrahydropyrano[3,4-*c*]pyrroles; compounds **9** are 1,6-dioxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[3,4-*c*]pyridines.

- Keshavarz-K., M., Cox, S.D., Angus, R.O., Jr., Wudl, F. *Synthesis* **1988**, 641. On p. 642 the IR spectra shown in Figures 2 and 3 should be interchanged.

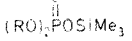
- Rodriguez, J., Waegell, B. *Synthesis* **1988**, 534. On p. 535, the first line of the general procedure should read: "DMAP (0.92 g, 7.5 mmol) and then α,β-unsaturated aldehyde **1** (0.1 mol)..."

- Zbiral, E., Drescher, M. *Synthesis* **1988**, 735. On p. 738 in the last procedure, the name for compounds **14** should read: (5-Oxo-5,6-dihydroimidazo[1,2-*c*]pyrimidin-3-yl)methylphosphonsäuren.

- Valerio, R.M., Alewood, P.F., Johns, R.B. *Synthesis* **1988**, 786. On p. 787 formula **2** should be:



Also on p. 787 in the reaction of **5** in the scheme on the right side, the reagent should be:



- Garrigues, B., Mulliez, M. *Synthesis* **1988**, 810. The title should read: Salts of *N*-(Sulfoalkyl)ureas and -thioureas.

- Yokoyama, M., Watanabe, S., Seki, T. *Synthesis* **1988**, 879. On p. 880 the name of compound **3a** in the first procedure should be azido(2-benzyloxyethoxy)methane.