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Synthesis of 4-Aminomethyl-5-ethoxy-3-[(4-vinyl)benzyloxy]pyridine and Its Polymeric Derivatives Planned as Selective Inhibitors of Enzymes

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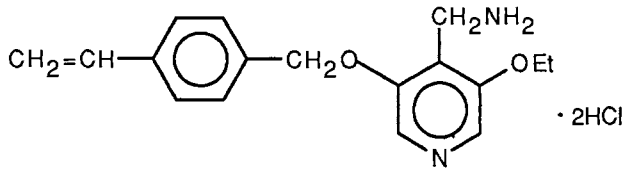
The synthesis of the new monomer 4-aminomethyl-5-ethoxy-3-[(4-vinyl)-benzyloxy]pyridine and its hydrochloride derivative together with their radical homo- and copolymerization to afford the first examples of macromolecular systems planned as selective inhibitors of copper-containing amine oxidases are described.

The insertion of biologically active molecules into water soluble or insoluble polymeric supports through covalent bonding has proved very effective for various purposes as the elucidation of the action mechanism of drugs, hormones, neurotransmitters[1] or the isolation of receptors, cells and natural biopolymers.[1,2]

During our study on the selective inhibition of copper-containing amine oxidases, an enzyme family that catalyzes the oxidative deamination of primary amines,[3] we were able to devise and develop new inhibitors of benzylamine oxidase highly selective with respect to other members of the same family such as diamine oxidase and lysyloxidase. Of the numerous inhibitors prepared, the 3,5-dialkoxy-4-aminomethylpyridine derivatives showed the best selectivity together with the lowest toxicity.[4]

We want to report now the synthesis of the new pyridine monomer **1** also in the form of its free base **5** and the preparation of their polymers and copolymers with comonomers of different hydrophilicity as first examples of macromolecular systems designed for the selective inhibition of amine oxidases, potentially useful as target polymeric drugs or insoluble supports for enzyme separation purposes.



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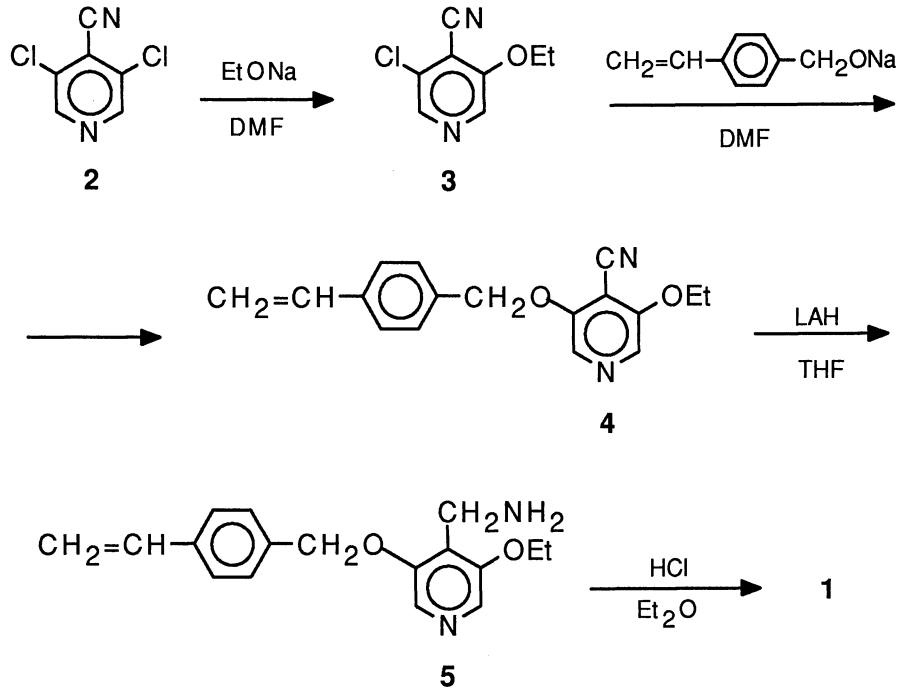
The 3,5-dichloro-4-pyridinecarbonitrile,[5] obtainable from 3,5-dichloropyridine, is a very useful reagent previously prepared and advantageously used by some of us in the synthesis of various symmetric or unsymmetric 3,5-disubstituted-4-aminomethylpyridines, which in the present work has fully confirmed its preparative value. It smoothly reacts with nucleophiles allowing the substitution of one or both the chlorine atoms, so it has been transformed[5] into 3-chloro-5-ethoxy-4-pyridinecarbonitrile **3** by slow addition of stoichiometric sodium ethoxide, starting a sequence of reactions (Scheme 1) which affords the monomer 4-aminomethyl-5-ethoxy-3-[(4-vinyl)benzyloxy]pyridine **5** and its dihydrochloride **1**.



Scheme 1.

The reaction of **3** with the sodium alcoholate obtained from NaH and 4-hydroxymethylstyrene,[6] besides the desired 5-ethoxy-3-[(4-vinyl)benzyloxy]-4-pyridinecarbonitrile **4**,[7] produces variable percentages of 3,5-bis[(4-vinyl)benzyloxy]-4-pyridinecarbonitrile[8] depending on the reaction conditions, in accordance with some literature findings which show alkoxy group displacement in alkoxypyridines[9] and alkoxy 3-nitropyridines.[10]

The reduction of the nitrile **4** without modification of the vinyl group, performed with lithium aluminum hydride which is known to reduce the cyano function in cyanopyridines,[11] afforded moderate yields of **5**,[12] but it cannot be excluded that an optimization of the reaction time and separation procedure could improve them.

Monomer **5** and its hydrochloride **1**,[13] whose structures are fully confirmed by IR and ^{1}H-NMR spectra, are stable compounds storable at low temperatures for long periods. For what concerns the ^{1}H-NMR assignment of the positions of the protons 2 and 6 in the new pyridine derivatives, homonuclear NOE experiments were performed by saturating the methylene signals.

Monomer **1** was radically homo- and copolymerized[14] at 50 °C with *N,N*-dimethylacrylamide, *N*-acryloylmorpholine[15] and *N*-(4-vinylbenzoyl)morpholine[16] in DMF/water obtaining conversion yields in the range 14-82% after 21-23 h, starting from 24-31 mole percent of **1** in the feed. The polymers and copolymers resulted in air-stable yellow powders, soluble in polar solvents such as methanol, DMF, water and insoluble in benzene, ether, acetone. The copolymers with the morpholine comonomers were also soluble in chloroform and dichloromethane.

The free base **5** was radically homo- and copolymerized at 70 °C with the same comonomers using dioxane as solvent and 1% by weight of 2,2'-azobis(2-methylproprionitrile) as initiator. Starting from 30 mole percent of **5** in the feed, conversion yields in the range 32-62% were obtained after 21-23 h. The polymers and copolymers resulted in air-stable white powders soluble in dichloromethane, chloroform, dioxane, methanol, DMF, swellable in water and insoluble in petrol, ether, benzene.

The IR spectra of the prepared polymeric materials confirmed the presence of the expected monomeric units (see Table 1) and evidenced a lack of absorption of the vinyl group in the 995-905 cm^{-1} region in accordance with a vinyl type polymerization reaction. The band in the interval 1422-1432 cm^{-1} characteristic of monomer **5** and its precursor **4**, which are in form of free base, is also found in the IR spectra of its homopolymer and copolymer with *N,N*-dimethylacrylamide, but is "covered" by an intense absorption deriving from morpholine units in the copolymers with *N*-acryloylmorpholine and *N*-(4-vinylbenzoyl)morpholine.

Copolymers of **1**, more than those of **5**, owing to their facile solubility in water were considered good models for biological tests, so the best selections have been addressed to kinetic studies in vitro with enzymes.

Table 1. Typical IR absorption bands of the prepared polymers

Polymer	υ/cm^{-1}
Homopolymer **1**	1528, 840, 815, 615 (pyridine)
Copolymer **1**/DMMA[a)]	1602 (amide), 1530, 840, 815, 615 (pyridine)
Copolymer **1**/NAM[b)]	1605 (amide), 1530, 840, 815, 615 (pyridine)
Copolymer **1**/NVBM[c)]	1600 (amide), 1530, 838, 815(sh), 615 (pyridine)
Homopolymer **5**	1557, 1422, 844, 818 (pyridine)
Copolymer **5**/DMMA	1605 (amide), 1557, 1422, 842, 818 (pyridine)
Copolymer **5**/NAM	1620 (amide), 1558, 842, 822 (pyridine)
Copolymer **5**/NVBM	1615 (amide), 1557, 839, 820 (sh) (pyridine)

a) DMAA = *N,N*-dimethylacrylamide; b) NAM = *N*-acryloylmorpholine; c) NVBM = *N*-(4-vinylbenzoyl)morpholine

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7) **4** : [Yield 74%. Mp 101-102 °C (cyclohexane); IR (KBr) 2230 (CN), 1550, 1432, 850 and 825 (pyridine), 993 and 905 cm^{-1} (vinyl). ^{1}H-NMR ($CDCl_3$): δ = 1.51 (t; CH_3), 4.26 (q; OCH_2Me), 5.28 (dd; vinyl H_{cis}), 5.29 (s; OCH_2Ph), 5.77 (dd; vinyl H_{trans}), 6.71 (dd; vinyl H), 7.39-7.46 (m; aromatic CH), 8.07 (s; pyridine H6), 8.10 (s; pyridine H2); J= 7.0 Hz, J_{cis}= 10.9 Hz, J_{trans}= 17.6 Hz, J_{gem}= 0.8 Hz]. Found : C, 72.70; H, 5.73; N, 10.09%; Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N 9.99%.

8) 3,5-Bis[(4-vinyl)benzyloxy]-4-pyridinecarbonitrile : [yield 10%. Mp 132-134°C (dichloromethane/ether); IR (KBr) 2230 (CN), 1550, 1428, 840 and 825 (pyridine), 990 and 920 cm^{-1} (vinyl). ^{1}H-NMR ($CDCl_3$): δ = 5.29 (dd; vinyl H_{cis}), 5.30 (s; OCH_2Ph); 5.78 (dd; vinyl H_{trans}), 6.72 (dd; vinyl H), 7.38-7.46 (m; aromatic CH), 8.11 (s; pyridine CH); J_{cis}= 10.8 Hz, J_{trans}= 17.6 Hz, J_{gem}= 0.8 Hz]. Found: C, 77.71; H, 5.44; N 7.81%; Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60%.

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12) **5** : [Oil chromatographed on a Merck silica gel column (Φ = 3 cm h = 40 cm, 230-400 mesh) using a mixture ether/methanol saturated with gaseous ammonia 99/1 as eluent; yield 30%. IR (film) 1556, 1422, 842 and 822(pyridine), 985 and 905 cm^{-1}(m, vinyl). ^{1}H-NMR ($CDCl_3$) : δ = 1.45 (t; CH_3), 3.94 (s; CH_2N), 4.15 (q; OCH_2Me), 5.16 (s; OCH_2Ph), 5.27 (d, vinyl H_{cis}), 5.76 (d; vinyl H_{trans}), 6.72 (dd; vinyl H), 7.41 (m; aromatic CH), 7.97 (s; pyridine H6), 8.03 (s; pyridine H2)].

13) **1** : [Yield 67%. Mp 169-180 °C (dec., ethanol/ether). IR (KBr) 3410 (broad; NH^+), 1528 842, 825 and 613(pyridine), 990 and 920 cm^{-1} (w; vinyl). ^{1}H-NMR (CD_3OD) : δ = 1.55 (t; CH_3), 4.34 (s; CH_2N), 4.40 (q; OCH_2Me), 5.28(dd; vinyl H_{cis}), 5.43 (s; OCH_2Ph), 5.83 (dd; vinyl H_{trans}), 6.76 (dd; vinyl H), 7.52 (m; aromatic CH), 8.49(s; pyridine H6), 8.54(s; pyridine H2). J= 7.0 Hz, J_{cis}= 10.9 Hz, J_{trans}= 17.6 Hz, J_{gem}= 0.9 Hz]. (357.279) Found: C, 57.13; H, 6.34; N, 7.77; Cl, 19.92%; Calcd for $C_{17}H_{22}Cl_2N_2O_2$: C 57.15; H, 6.21; N, 7.84; Cl 19.79%.

15) J. Parrod and J. Elles, *J. Polym. Sci.*, **29**, 411 (1958).

14) Using ammonium persulfate 10% by weight as initiator and a mixture DMF/water 1/1.5 as solvent.

16) Obtained from 4-vinylbenzoyl chloride (A. Hirao, Y. Ishino, and S. Nakahama, *Macromolecules,* **21**, 561 (1988)) and excess of morpholine : [Yield 42%. Mp 56 °C. IR (KBr) 1610 (CO), 1002 and 902 cm^{-1} (vinyl). ^{1}H-NMR ($CDCl_3$) : δ = 3.30-4.10 (broad, CH_2), 5.33 (dd; vinyl H_{cis}), 5.81 (dd; vinyl H_{trans}), 6.72 (q; vinyl H), 7.36-7.47 (m; aromatic CH). J_{cis}=10.9 Hz, J_{trans}=17.6 Hz, J_{gem}=0.7 Hz].

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