

## 3,5-DICHLORO-4-PYRIDINECARBONITRILE AS A KEY REAGENT IN A SYNTHESIS OF COPPER CONTAINING AMINE OXIDASE INHIBITORS

Vincenzo Bertini,<sup>1\*</sup> Francesco Lucchesini,<sup>1</sup> Marco Pocci,<sup>1</sup> and Angela De Munno<sup>2</sup>

<sup>1</sup>Istituto di Analisi e Tecnologie Farmaceutiche ed Alimentari, Università di Genova,  
Via Brigata Salerno, I-16147 Genova, Italy

<sup>2</sup>Dipartimento di Chimica e Chimica Industriale, Università di Pisa  
Via Risorgimento 35, I-56126 Pisa, Italy

**Abstract** - Various synthetic approaches to 3,4,5-trifunctionalized pyridine derivatives useful as benzylamine oxidase inhibitors are extensively explored. Fully satisfactory preparations of the inhibitors 3,5-diethoxy-4-aminomethylpyridine (**4**), 3,5-bis(3-hydroxypropoxy)-4-aminomethylpyridine (**11**), 3,5-bis(4-hydroxybutoxy)-4-aminomethylpyridine (**12**) and 3-ethoxy-5-phenylmethoxy-4-aminomethylpyridine (**16**), all in the form of dihydrochloride salt, using 3,5-dichloro-4-pyridinecarbonitrile as key precursor, are reported.

## INTRODUCTION

Our previous researches on the selective inhibition of enzymes pertaining to the class of copper containing amine oxidases, which catalyze in nature probably with the same mechanism the oxidative deamination of different primary amines, allowed us to devise and develop new inhibitors<sup>1</sup> of benzylamine oxidase structurally derived from benzylamine or 4-aminomethylpyridine, characterized by absence of denaturing effect and high selectivity with respect to other enzymes of the same class such as diamine oxidase and lysyloxidase. The pyridine inhibitors showed the best selectivity and the lowest toxicity, and 3,5-diethoxy-4-aminomethylpyridine, known<sup>2</sup> as B24, is suitable also for oral administration in *in vivo* experiments.

Owing to the increasing interest for such inhibitors we now report their synthesis (compounds **4**, **11**, **12**, **16**) together with some original findings on the pyridine chemistry brought to light during our work in achieving satisfactory synthetic procedures for their multigram preparation.

3,4,5-Trifunctionalized pyridines are often hard to prepare and not frequently encountered in the literature as also recent reviews show,<sup>3,4,5</sup> nevertheless hydrogen-lithium exchange reactions soon appeared to us to have good synthetic potentialities, as confirmed later by numerous reports on the subject. The hypothesis of obtaining the desired pyridine inhibitors through lithiation of 3,5-dialkoxy- or 3,5-dichloropyridine stems from the following relevant literature findings:

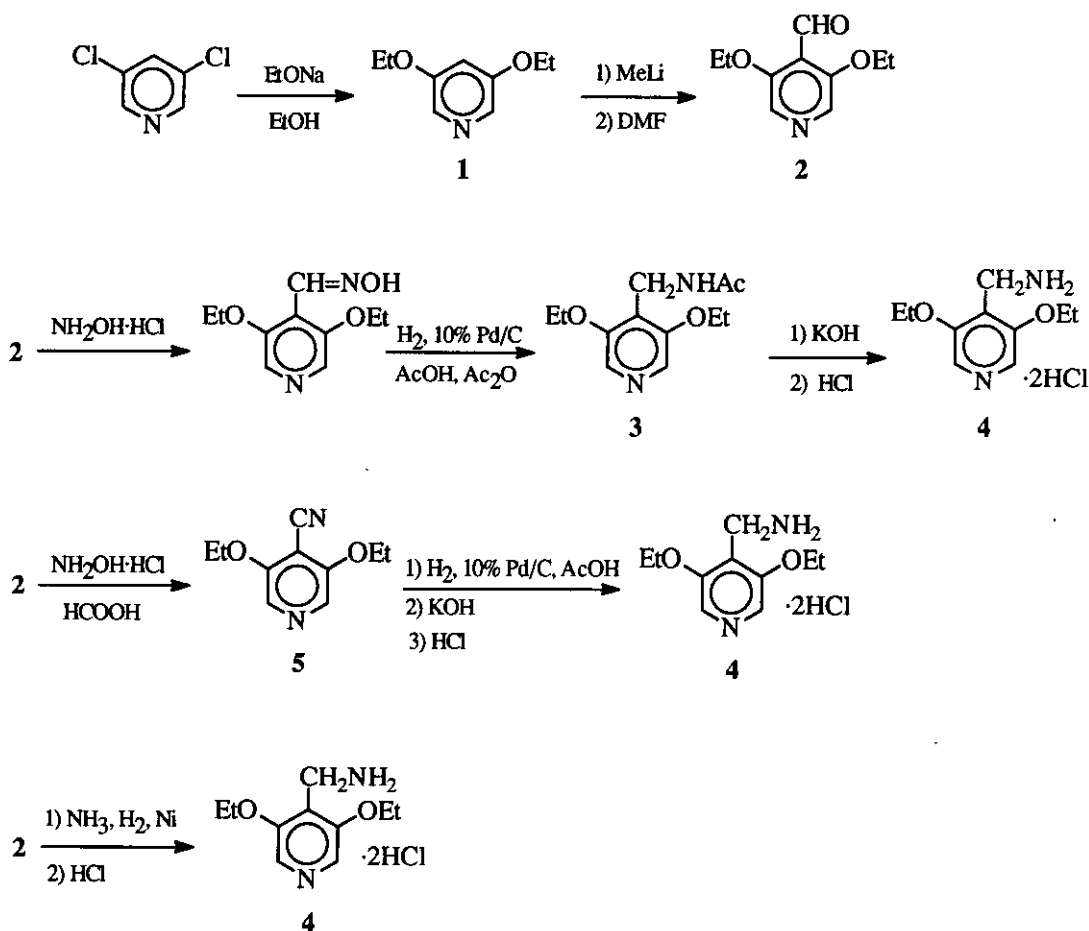
3-Ethoxypyridine undergoes lithiation with methylolithium in THF<sup>6</sup> at the positions 2 and 4 in a 1:1 ratio and with *n*-butyllithium-TMEDA complex in THF<sup>6</sup> regioselectively at the position 2; 2,6-dimethoxypyridine is regioselectively lithiated at the position 3 with either *n*-butyllithium in THF<sup>7</sup> or phenyllithium in THF;<sup>8</sup> 2-chloropyridine<sup>9,10</sup> and 4-chloropyridine<sup>9,11,12</sup> are metallated by LDA in THF at the position 3; 3-chloropyridine is regioselectively lithiated at the position 4 with LDA in THF<sup>9,13</sup> and at the position 2 with *n*-butyllithium-TMEDA complex in ether;<sup>13</sup> 2,4-dichloropyridine undergoes regioselective lithiation with LDA in THF<sup>14</sup> at the position 3, while 2,6-dichloropyridine with the same reagent<sup>14</sup> shares the lithiation between the position 3 and 4. Further, 3,5-dichloropyridine is known to give with LDA and ethyl formate at -78°C 3,5-dichloropyridine-4-carboxaldehyde in 71% yield, although detailed experimental conditions or spectroscopic properties of this interesting compound are not reported.<sup>15</sup>

## RESULTS AND DISCUSSION

The designed and synthesized amine oxidase inhibitors in pyridine series have the structure of 3,5-dialkoxy-4-aminomethylpyridine dihydrochlorides containing alkoxy groups of various length, also bearing hydroxyl functions very effective in lowering the toxicity of the product.

Our research work on 3,4,5-trisubstituted pyridines, aimed to attain productive syntheses of the desired inhibitors, was especially focused on 3,5-diethoxy-4-aminomethylpyridine dihydrochloride (**4**) since this compound, as soon as it was made available, was revealed to be very interesting from a pharmacological point of view. Using commercial 3,5-dichloropyridine as a convenient starting material, two synthetic pathways appeared effective for the preparation of **4** or its precursors: the nucleophilic substitution of the chlorine atoms with sodium ethoxide followed by functionalization at the position 4 through hydrogen-lithium exchange, or the lithiation and functionalization at the position 4 of the starting material followed by substitution of the

chlorine atoms assisted by the introduced functionality. Since the literature reports that 3,5-dichloropyridine is slowly converted into 3,5-dimethoxypyridine with sodium methoxide in DMF at 80 °C in 59% yield,<sup>16</sup> that 3,5-dibromopyridine is transformed into 3,5-diethoxypyridine with sodium ethoxide in ethanol in sealed tube,<sup>17</sup> and that lithium derivatives obtained from hydrogen-lithium exchange in 3-halopyridines<sup>9</sup> are temperature sensitive unstable intermediates shortly living at the temperature of dry ice, the first pathway seemed to be more promising. Thus 3,5-dichloropyridine was transformed into 3,5-diethoxypyridine (**1**), then **1** was lithiated and formylated to afford the aldehyde (**2**) in 67% yield without detectable formation of isomers; the successive transformation of **2** into the desired **4** was carried out by three different methods (Scheme 1).



Scheme 1

The synthetic route through the oxime afforded **4** from **2** in 36% overall yield, and the route through nitrile (**5**) according to a known method<sup>18</sup> and that through reductive amination afforded **4** in 63% and 34% yields, respectively. Nevertheless, the production of **1** from 3,5-dichloropyridine and sodium ethoxide remained

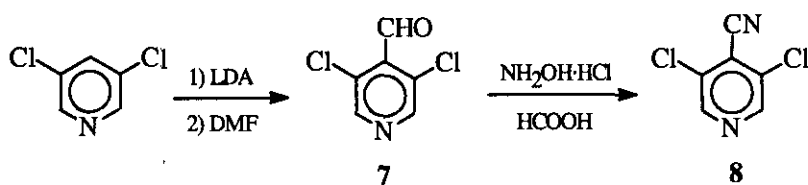
largely unsatisfactory in spite of many efforts. An optimized procedure in autoclave (see experimental) gave **1** in only 31% yield, and the addition of copper(I) bromide, a commonly used catalyst for such reactions,<sup>19</sup> was ineffective causing ring degradation together with a modest yield (24%) of 3-ethoxypyridine<sup>20</sup> (**6**). Attempts to perform the substitution reaction at atmospheric pressure in aprotic solvents such as DMSO or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone were unsuccessful.

The observed inadequate reactivity of 3,5-dichloropyridine toward the nucleophilic substitution of both chlorine atoms drew our attention to the second synthetic pathway (see above) on the assumption that a functionalization at the 4 position of 3,5-dichloropyridine with a proper electron-withdrawing group could improve the chlorine displacement.

It is known that halogen atoms in the 3 or 5 position of the pyridine ring are much less reactive towards nucleophiles than those in the 2 or 4 position, but electron-withdrawing substituents like cyano,<sup>21,22</sup> ester,<sup>22</sup> acetyl<sup>22</sup> groups can effectively increase their mobility so that synthetically useful substitutions can proceed in good yields under mild conditions. Attention must be paid to the possibility that the electron-withdrawing group itself might be involved in the reaction with nucleophiles. For instance the nitro group in 3-chloro-4-nitropyridine is replaced preferentially to chlorine with barium hydroxide,<sup>23</sup> or sodium alkoxides,<sup>23</sup> or ammonia,<sup>23</sup> and the cyano group in 3-chloro-4-pyridinecarbonitrile forms iminoether with sodium alkoxide in alcohol by a reaction suppressible in DMF.<sup>21</sup>

The need for an electron withdrawing function to be introduced at the 4 position of 3,5-dichloropyridine and easily transformed into an aminomethyl group made 3,5-dichloro-4-pyridinecarbonitrile (**8**) the preferred target reagent for explorations on chlorine replacement with alkoxides under conditions avoiding the formation of iminoethers.

The optimized synthesis of **8** was achieved through the known<sup>15</sup> regioselective 4-lithiation and the consecutive formylation with LDA and *N,N*-dimethylformamide rather than ethyl formate to afford 3,5-dichloro-4-pyridinecarboxaldehyde (**7**) in 84% yield, followed by its conversion into **8** with hydroxylamine hydrochloride and formic acid in 79% yield in analogy to the reported preparation of **5** (Scheme 2).

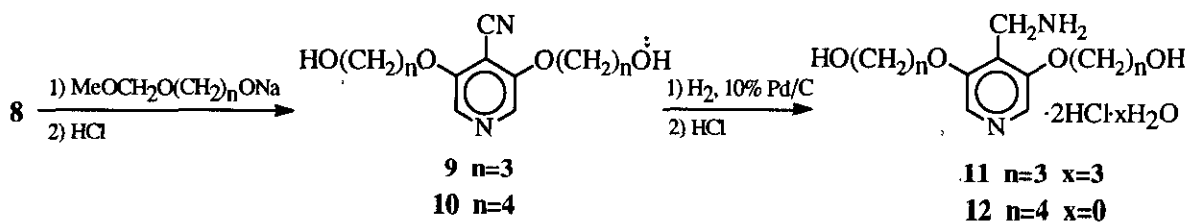


Scheme 2

Curiously, good and reproducible yields of **7** were obtained only after prolonged acidic hydrolysis (24 h) of the reaction mixture.

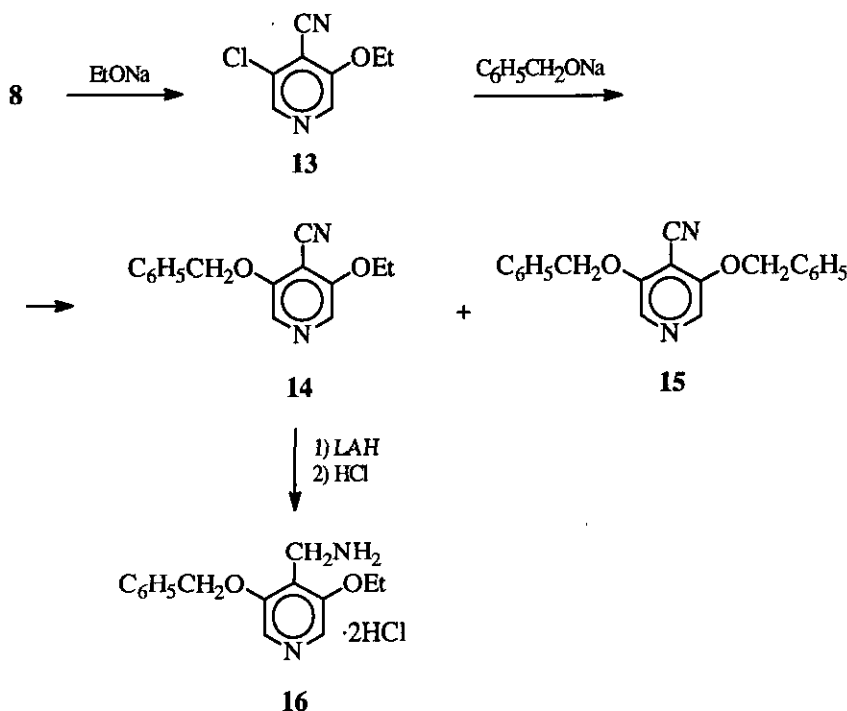
Compound (**8**), whose preparation may be easily scaled up, showed the expected submissiveness for nucleophilic replacement of chlorine atoms affording symmetrical and unsymmetrical derivatives: With slight excess of sodium ethoxide at room temperature compound (**8**) afforded the nitrile (**5**) in 74% yield. Under analogous conditions sodium 3-methoxymethoxy-1-propoxide and sodium 4-methoxymethoxy-1-butoxide, prepared from the corresponding diols through their careful monoprotection with chloromethyl methyl ether<sup>24,25</sup> and reaction with sodium hydride, brought about the nucleophilic substitution of both the chlorine atoms of compound (**8**) affording, after hydrolysis and deprotection of the acetals, the nitriles (**9**) and (**10**) in 86 and 77% yields, respectively (Scheme 3).

The fruitful transformation of the nitrile (**5**) into **4** (79% yield) by catalytic hydrogenation, followed by reaction with hydrochloric acid (see above) was applied to nitriles (**9**) and (**10**) to give **11** and **12** in 66 and 81% yields, respectively, **11** being in form of trihydrated salt (Scheme 3).



Scheme 3

The transformation of **8** into unsymmetrical pyridine derivatives was then explored. Treatment of **8** with stoichiometric sodium ethoxide afforded the monosubstituted product (**13**) in 59% yield; treating **13** with sodium phenylmethoxide afforded a mixture of the expected unsymmetrical compound (**14**) and the symmetrical product (**15**) derived from the displacement of the ethoxy group. Changing the reaction conditions influenced the relative abundance of the products (**14**) and (**15**), but the displacement of the ethoxy group was never completely suppressed (Scheme 4).



Scheme 4

Reaction conditions minimizing the formation of **15** allowed the obtaining of **14** (38%) and **15** (5%) and the recovery of **13** (23%) after chromatographic separation. Similar nucleophilic displacements of alkoxy groups are reported for 2- and 4-methoxypyridine<sup>26</sup> and 4-ethoxy-3-nitropyridine.<sup>27</sup>

The reduction of the nitrile (**14**) to the amine without any hydrogenolysis of the benzyl group was performed with lithium aluminum hydride affording the desired unsymmetrical inhibitor (**16**) separated as dihydrochloride in 34% yield.

In conclusion 3,5-dichloro-4-pyridinecarbonitrile (**8**) is an intermediate easily obtainable from commercial 3,5-dichloropyridine which reacts with one or two equivalent alkoxides under remarkably mild conditions to afford in good yield unsymmetrical 3-alkoxy or symmetrical 3,5-dialkoxy derivatives. It represents a versatile key reagent for the synthesis of many symmetrical or unsymmetrical 3,4,5-trisubstituted pyridines, having great potentialities as amine oxidase inhibitors.

## EXPERIMENTAL

Melting points were determined on a Reichert-Thermovar hot stage apparatus and are uncorrected.  $^1\text{H-Nmr}$  spectra were obtained on Bruker WM-300 or AcP-300 spectrometers. Chemical shifts are reported on the  $\delta$

scale and are referred to TMS. Mass spectra were determined at 70 eV with VG ZAB-2HF or Finnigan TSQ 70 instruments; the spectra of chlorinated compounds are always referred to the chlorine isotope 35; FAB spectra were acquired on the first instrument, using a neutral Xenon atom at 8 kV and *m*-nitrobenzyl alcohol as matrix, mass spectra of **4** and **16** as free bases were recorded on a Hewlett-Packard GC-MSD 5972 instrument. IR spectra were recorded on a 1330 Perkin Elmer spectrophotometer as KBr pellets or films. Chloromethyl methyl ether was prepared according to a recommended procedure<sup>28</sup> to avoid the formation of carcinogenic bis(chloromethyl)ether.

**3,5-Diethoxypyridine (1) and 3-ethoxypyridine (6).** Sodium (7.05 g, 0.307 mol) was dissolved in dry ethanol (80 ml) under reflux, then the hot sodium ethoxide solution was introduced into a stainless steel autoclave containing 3,5-dichloropyridine (11.40 g, 0.078 mol) and heated under stirring for two days. The reaction mixture was filtered, strongly acidified with concentrated HCl and brought to dryness on a steam bath at reduced pressure. The solid residue was dissolved in water (50 ml), treated with charcoal, filtered, made strongly alkaline with solid KOH and extracted with ether (10x20 ml). The combined and dried (K<sub>2</sub>CO<sub>3</sub>) extracts, by evaporation and distillation at reduced pressure, yielded **1** (4.06 g, 31.3%) in the fraction with bp 100-104°C/0.8 torr (lit.,<sup>17</sup> : 107°C/0.7 torr).

The reaction repeated with addition of copper (I) bromide (2.21 g, 0.016 mmol) afforded only **6** (2.27 g, yield 23.8%) in detectable amount; bp 78-82°C/15 torr (lit.,<sup>20</sup> bp 77-78°C/12 torr). picrate mp 125-127°C (benzene, lit.,<sup>20</sup> 126.5-127.5°C).

**3,5-Diethoxy-4-pyridinecarboxaldehyde (2).** A solution of **1** (3.60 g, 21.54 mmol) in dry THF (50 ml) was added with 0.98 M ethereal solution of methyllithium (28.8 mmol) in 10 min at 0°C under nitrogen. The ice bath removed, the reddish solution was stirred for 4 h at room temperature, treated with pure dry DMF (2.5 ml 32.51 mmol), further stirred for 40 min and treated with water (10 ml). The aqueous layer was separated and extracted with ether (3x50 ml), then the extracts were combined with the organic phase and dried (Na<sub>2</sub>SO<sub>4</sub>). After removal of the solvent the residue was sublimed at reduced pressure (100°C/0.2 torr) and crystallized from hexane to afford **2** (2.80 g, 66.6%); mp 72-74°C; ir (KBr,  $\nu$  cm<sup>-1</sup>) 1695, 1555, 1430, 1290, 1230, 1200, 1130; <sup>1</sup>H-nmr (CDCl<sub>3</sub>,  $\delta$  ppm) 1.49 (t, J=7.0 Hz, 6H), 4.24 (q, J=7.0 Hz, 4H), 8.11 (s, 2H), 10.52 (s, 1H); ms (m/z) 195 (75%, M<sup>+</sup>). Anal. Calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>3</sub>: C, 61.57; H, 6.72; N, 7.18. Found: C, 61.60; H, 6.81; N, 7.16.

***N*-Acetyl-3,5-diethoxy-4-aminomethylpyridine (3).** Compound (2) (2.12 g, 10.87 mmol) treated with hydroxylamine hydrochloride (1.51 g, 21.88 mmol) in pyridine (5 ml) afforded the oxime derivative (2.04 g, 89.4%); mp 140-143°C (benzene). All the obtained oxime was dissolved in glacial acetic acid (20 ml), treated with acetic anhydride (3 ml, 31.80 mmol) and 10% palladium activated on carbon (0.30 g), and magnetically stirred under slight hydrogen overpressure (0.5 atm) until no further gas absorption was recorded. The catalyst was filtered off and washed with ethanol, then filtrate and washings were combined and evaporated at reduced pressure on a boiling water bath to give **3** as a solid residue that was crystallized from ethyl acetate (1.12 g, 48.4%); mp 123-124°C; ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3295, 1645, 1560, 1430, 1260, 1135;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.47 (t,  $J=7.0$  Hz, 6H), 1.96 (s, 3H), 4.17 (q,  $J=7.0$  Hz, 4H), 4.55 (d,  $J=5.6$  Hz, 2H), 6.00 (br s, 1H), 7.97 (s, 2H); ms ( $m/z$ ) 238 (80%,  $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_3$ : C, 60.53; H, 7.62; N, 11.76. Found C, 60.24; H, 7.77; N, 11.68.

**3,5-Diethoxy-4-aminomethylpyridine dihydrochloride (4) from *N*-acetyl-3,5-diethoxy-4-aminomethylpyridine (3).** Compound (3) (1.39 g, 5.84 mmol) was dissolved in methanol (5 ml), treated with solid KOH (3.00 g, 53.47 mmol) and refluxed for 6 h. Water (5 ml) was added and the mixture was brought to pH 1 with conc. HCl. After removal of all the volatiles on a boiling water bath at reduced pressure, the solid residue was dissolved in water (20 ml), made strongly alkaline with solid KOH and extracted with ether (3x20 ml). The combined organic extracts were dried (KOH), concentrated up to a volume of about 30 ml and saturated with dry gaseous HCl. The white precipitate was filtered, washed with ether and crystallized from anhydrous ethanol to afford **4** (1.29 g, 82.4%) showing mp 200-220°C (decomp.); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3400-2500 (br), 1535, 1475, 1360, 1265, 1150, 1050;  $^1\text{H-nmr}$  ( $\text{DMSO-d}_6$ ,  $\delta$  ppm) 1.42 (t,  $J=7.0$  Hz, 6H), 4.04 (br q,  $J=5.5$  Hz, 2H), 4.34 (q,  $J=7.0$  Hz, 4H), 8.43 (s, 2H), 8.75 (br s, 3H), 12.55 (br s, 1H); gc/ms, free base,  $m/z$  196 (32%,  $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_2\text{Cl}_2$ : C, 44.81; H, 6.77; N, 10.45. Found: C, 44.50; H, 6.86; N, 10.47.

**3,5-Diethoxy-4-pyridinecarbonitrile (5) from 3,5-diethoxy-4-pyridinecarboxaldehyde (2).** Compound (2) (3.20 g, 16.40 mmol) dissolved in formic acid (10 ml) was treated with hydroxylamine hydrochloride (1.70 g, 24.64 mmol) and two drops of concentrated  $\text{H}_2\text{SO}_4$ , then it was refluxed for 2.5 h. The clear solution was poured into 10% aq. NaOH (100 ml) and the mixture was extracted with ether (2x100 ml). The combined ethereal extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to afford **5** (2.50 g, 79.3%); mp 116-118°C (ethanol); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 2225, 1550, 1430, 1285, 1220, 1115;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.51 (t,



$J=7.0$  Hz, 6H), 4.27 (q,  $J=7.0$  Hz, 4H), 8.06 (s, 2H); ms ( $m/z$ ) 192 (82%,  $M^+$ ). *Anal.* Calcd for  $C_{10}H_{12}N_2O_2$ : C, 62.53; H, 6.30; N, 14.58. Found: C, 62.81; H, 6.36; N, 14.68.

**3,5-Diethoxy-4-aminomethylpyridine dihydrochloride (4) from 3,5-diethoxy-4-pyridinecarbonitrile (5).**

A solution of **5** (5.33 g, 27.75 mmol) in acetic acid (27 ml) treated with 10% palladium on activated coal (0.80 g) was hydrogenated in presence of 0.5 atm of  $H_2$  until no further absorption was observed. The catalyst was filtered off, most of the solvent was removed at reduced pressure on a boiling water bath. The residue was dissolved in water (100 ml), brought to pH 12 with solid KOH and extracted with ether (5x50 ml). The combined ethereal extracts were dried (KOH) and then saturated with dry gaseous HCl. The white precipitate was filtered, washed with ether and crystallized from anhydrous ethanol to give **4** (5.92 g, 79.6%) showing mp, ir and  $^1H$ -nmr spectra coincident with those of the same compound obtained from **3**.

**3,5-Diethoxy-4-aminomethylpyridine dihydrochloride (4) from 3,5-diethoxy-4-pyridinecarboxaldehyde (2).**

Compound **(2)** (1.30 g, 6.66 mmol), Ni Raney (230 mg) and 5 M methanolic ammonia solution (2 ml) were introduced into a 125 ml steel autoclave, pressurized with  $H_2$  (80 atm) and heated for 7 h at  $80^\circ C$ . The solution was filtered, washing the solid catalyst with methanol, and evaporated at reduced pressure. The residue was treated with dry ether (30 ml) and filtered, then the clear filtrate was saturated with dry gaseous HCl. The white precipitate was filtered, washed with ether and crystallized from anhydrous ethanol to afford **4** (0.60 g, 33.6%) showing mp, ir and  $^1H$ -nmr spectra coincident with those of the same compound obtained from **3**.

**3,5-Dichloro-4-pyridinecarboxaldehyde (7).**

A solution of diisopropylamine (21.7 ml, 0.153 mol) in dry THF (130 ml) was cooled to  $-78^\circ C$  and added under nitrogen in 10 min with a 1.70 M solution of *n*-BuLi (0.162 mol) in THF. The obtained solution of lithium diisopropylamide after stirring for 20 min at  $-78^\circ C$  was treated in 15 min with a solution of 3,5-dichloropyridine (21.5 g, 0.146 mol) in dry THF (130 ml) and maintained under efficient stirring for additional 20 min. Dry DMF (15.8 ml, 0.205 mol) was added rapidly, then the mixture, left in the cooling bath to reach overnight the room temperature was poured into a solution of concentrated HCl (60 ml) in water (400 ml) and magnetically stirred for 24 h (this treatment was found to be essential for good and reproducible results). The aqueous layer was separated and extracted with ether (5x100 ml), then the extracts were combined with the organic phase and dried ( $Na_2SO_4$ ). Evaporation of the solvent left a residue which, after sublimation at reduced pressure ( $100^\circ C/0.5$  torr) and crystallization from

hexane yielded **7** (21.5 g, 84.0%); mp 75-78°C; ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 1710, 1525, 1400, 1250, 1190, 1135, 1100;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 8.64 (s, 2H), 10.46 (s, 1H); ms ( $m/z$ ) 175 (100%,  $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_6\text{H}_3\text{NOCl}_2$ : C, 41.19; H, 1.73; N, 8.01. Found: C, 40.92; H, 1.66; N, 8.00.

**3,5-Dichloro-4-pyridinecarbonitrile (8)**. A mixture of compound (**7**) (21.0 g, 0.120 mol), formic acid (100 ml), solid hydroxylamine hydrochloride (10.8 g, 0.155 mol) and two drops of concentrated  $\text{H}_2\text{SO}_4$  was refluxed under magnetic stirring for 3 h. After distillation of the solvent, the residue was dissolved into the minimum amount of ether, washed in turn with water, saturated solution of  $\text{NaHCO}_3$ , water, and finally dried ( $\text{Na}_2\text{SO}_4$ ). The removal of the solvent left a residue that was crystallized two times from hexane to give **8** (16.3 g, 79.0%); mp 114-116°C; ir (KBr  $\nu$   $\text{cm}^{-1}$ ) 2250, 1525, 1500, 1400, 1240, 1190, 1105;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 8.70 (s, 2H); ms  $m/z$  172 (100%,  $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_6\text{H}_2\text{N}_2\text{Cl}_2$ : C, 41.91; H, 1.17; N, 16.29. Found: C, 41.63; H, 1.15; N, 16.22.

**3,5-Diethoxy-4-pyridinecarbonitrile (5) from 3,5-dichloro-4-pyridinecarbonitrile (8)**. A suspension of sodium ethoxide, prepared under nitrogen from sodium hydride (5.62 g, 0.187 mol of 80% commercial dispersion) and dry ethanol (11.0 ml, 0.189 mol), in dry DMF (200 ml) was treated with solid **8** (15.4 g, 89.56 mmol) at 0°C, then the cooling bath was removed and the mixture was stirred for additional 4 h. After removing most of the solvent at reduced pressure on a boiling water bath, the residue was treated with water (500 ml). The precipitated solid was filtered, dried and crystallized twice from ethanol to afford **5** (12.7 g, 73.8%) showing mp, ir and  $^1\text{H-nmr}$  spectra coincident with those of the same compound obtained from **2**.

**3-Methoxymethoxy-1-propanol and 4-methoxymethoxy-1-butanol**. Sodium hydride (9.60 g, 0.320 mol of 80% commercial suspension) was suspended under nitrogen in dry THF (120 ml) and added in 20 min with a solution of diol (0.669 mol) in dry THF (60 ml). The mixture was refluxed under efficient stirring for 2 h, cooled to 0°C and rapidly treated with chloromethyl methyl ether (26.0 g, 0.325 mol). The cooling bath, used to moderate the exothermic reaction up to its subsidence, was removed and then the mixture was left under stirring overnight at room temperature. The precipitated NaCl was filtered off, the clear filtrate was freed from the solvent at atmospheric pressure and the residue was distilled under vacuum. The fraction containing the monoprotected diol was carefully fractionated through a Fenske column (110 cm) to afford a pure product. 3-Methoxymethoxy-1-propanol (26.2 g, 68.1%); bp 78.5-82°C/9 torr; ir (film,  $\nu$   $\text{cm}^{-1}$ )  $\text{cm}^{-1}$  3430 (br), 2950, 2890, 1150, 1110, 1045;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.86 (m, 2H), 2.65 (br s, 1H), 3.38 (s, 3H), 3.70

(t,  $J=6.3$  Hz, 2H), 3.77 (br t, 2H), 4.63 (s, 2H). 4-Methoxymethoxy-1-butanol (26.9 g, 62.1%); bp 99-100°C/12 torr; ir (film,  $\nu$   $\text{cm}^{-1}$ ) 3420 (br), 2950, 2885, 1150, 1105, 1040;  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.68 (m, 4H), 3.38 (s, 3H), 3.58 (t,  $J=6.3$  Hz, 2H), 3.67 (br dt, 2H), 4.63 (s, 2H).

**3,5-Bis(3-hydroxypropoxy)-4-pyridinecarbonitrile (9).** A suspension of sodium hydride (0.264 g, 8.80 mmol of 80% commercial dispersion) in dry DMF (6 ml) was treated under nitrogen with 3-methoxymethoxy-1-propanol (1.03 g, 8.58 mmol) and the mixture was stirred for 2.5 h at room temperature. After cooling to 0°C, solid (8) (0.700 g, 4.07 mmol) was added under nitrogen. The mixture was stirred for additional 4 h at room temperature, diluted with water (35 ml) and extracted with ether (6x15 ml). The ethereal extracts after removal of the solvent were treated with methanol (4 ml), then with concentrated HCl (1.5 ml) and refluxed for 1 h. The mixture, made alkaline with concentrated  $\text{NH}_4\text{OH}$ , was brought to dryness. The white solid residue was extracted with boiling THF and the extracts were cleared by filtration and evaporated to afford **9** (0.880 g, 85.7%); mp 78-82 °C (acetonitrile: ether = 3:1); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3380-3190 (br), 2230, 1560, 1430, 1290, 1230, 1120, 1050;  $^1\text{H}$ -nmr ( $\text{CD}_3\text{OD}$ ,  $\delta$  ppm) 2.05 (m, 4H), 3.78 (t,  $J=6.2$  Hz, 4H), 4.36 (t,  $J=6.2$  Hz, 4H), 8.19 (s, 2H); ms ( $m/z$ ) 252 (9%,  $\text{M}^+$ ), 136 (100%,  $\text{M}^+-2\text{C}_3\text{H}_6\text{O}$ ).

**3,5-Bis(4-hydroxybutoxy)-4-pyridinecarbonitrile (10).** With a similar procedure **10** was obtained from **8** (0.550 g, 3.20 mmol) and 4-methoxymethoxy-1-butanol (0.900 g, 6.71 mmol). **10** was purified through a flash chromatography on a Merck silica gel column (37x1.5 cm, 230-400 mesh), using as eluent a mixture petrol 40-60°C/acetone = 3/7 (0.687 g, 77.1%); mp 58-61°C; ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3400 (br), 2230, 1560, 1430, 1285, 1225, 1115, 1055;  $^1\text{H}$ -nmr ( $\text{CD}_3\text{OD}$ ,  $\delta$  ppm) 1.74 (m, 4H), 1.92 (m, 4H), 3.64 (t,  $J=6.3$  Hz, 4H), 4.28 (t,  $J=6.3$  Hz, 4H), 8.13 (s, 2H); ms ( $m/z$ ) 280 (0.3%,  $\text{M}^+$ ), 136 (100%,  $\text{M}^+-2\text{C}_4\text{H}_8\text{O}$ ). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_4$ : C, 60.03; H, 7.20; N, 10.00. Found: C, 59.63; H, 7.30; N, 9.86.

**3,5-Bis(3-hydroxypropoxy)-4-aminomethylpyridine dihydrochloride trihydrate (11).** A solution of **9** (0.170 g, 0.674 mmol) in glacial acetic acid (5 ml) was treated with 10% palladium on activated carbon (0.03 g) and hydrogenated as reported above for the preparation of **4** from **5**. The catalyst was filtered off, the solvent was removed at 0.2 torr on a warm water bath and the obtained residue was treated with water (1 ml) and concentrated HCl (1 ml). After removing all the volatiles at reduced pressure, the residue was dissolved into ethanol (1 ml) and slowly treated with acetonitrile (5 ml) to precipitate the trihydrated form of **11** (0.170 g, 66.0%); mp 131-168°C (decomp.); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3400-2500 (br), 1555, 1495, 1385, 1280, 1150, 1050;

$^1\text{H-nmr}$  ( $\text{CD}_3\text{OD}$ ,  $\delta$  ppm) 2.12 (m, 4H), 3.81 (t,  $J=5.8$  Hz, 4H), 4.34 (s, 2H), 4.45 (t,  $J=6.0$  Hz, 4H), 8.50 (s, 2H); ms (FAB, free base, 257,  $\text{MH}^+$ ). *Anal.* Calcd for  $\text{C}_{12}\text{H}_{28}\text{N}_2\text{O}_7\text{Cl}_2$ : C, 37.72; H, 7.39; N, 7.33. Found: C, 37.82; H, 7.26; N, 7.32.

**3,5-Bis(4-hydroxybutoxy)-4-aminomethylpyridine dihydrochloride (12).** With a similar procedure **12** (0.330 g, 81.1%) was obtained from **10** (0.32 g, 1.14 mmol); mp 164-172°C (decomp.); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3400-2500 (br), 1545, 1370, 1280, 1160, 1070, 1040;  $^1\text{H-nmr}$  ( $\text{CD}_3\text{OD}$ ,  $\delta$  ppm) 1.76 (m, 4H), 2.02 (m, 4H), 3.67 (t,  $J=6.2$  Hz, 4H), 4.34 (s, 2H), 4.36 (t,  $J=6.4$  Hz, 4H), 8.46 (s, 2H); ms (FAB, free base, 285,  $\text{MH}^+$ ). *Anal.* Calcd for  $\text{C}_{14}\text{H}_{26}\text{N}_2\text{O}_4\text{Cl}_2$ : C, 47.22; H, 7.36; N, 7.87. Found: C, 47.46; H, 7.56; N, 7.82.

**3-Chloro-5-ethoxy-4-pyridinecarbonitrile (13).** A suspension of sodium ethoxide prepared in dry DMF (100 ml) from sodium hydride (2.77 g, 92.34 mmol of the 80% commercial dispersion) and ethanol (5.4 ml, 92.65 mmol) was added in 30 min under nitrogen to a solution of **8** (16.0 g, 93.04 mmol) in dry DMF (40 ml). The mixture stirred at room temperature overnight and evaporated on a boiling water bath at reduced pressure was treated with water (200 ml) and extracted with ether (2x100 ml). The combined ethereal extracts were washed with water, dried ( $\text{MgSO}_4$ ) and evaporated to afford **13** (10.00 g, 59.0%); mp 90.5-93°C (hexane); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 2230, 1550, 1530, 1400, 1290, 1200, 1095, 1025;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.54 (t,  $J=7.0$  Hz, 3H), 4.31 (q,  $J=7.0$  Hz, 2H), 8.34 (s, 1H), 8.37 (s, 1H); ms ( $m/z$ ) 182 (28%,  $\text{M}^+$ ). *Anal.* Calcd for  $\text{C}_8\text{H}_7\text{N}_2\text{OCl}$ : C, 52.79; H, 3.88; N, 15.39. Found: C, 52.39; H, 3.86; N, 15.51.

**3-Ethoxy-5-phenylmethoxy-4-pyridinecarbonitrile (14) and 3,5-bis(phenylmethoxy)-4-pyridinecarbonitrile (15).** Sodium hydride (0.210 g, 7.00 mmol of 80% commercial dispersion) was suspended in dry DMF (8 ml) under nitrogen and treated with benzyl alcohol (0.64 ml, 6.18 mmol). After 3 h stirring at room temperature the mixture was in turn treated under nitrogen with solid **13** (1.12 g, 6.15 mmol), further stirred at room temperature for 45 min, treated with water (10 ml) and extracted with ether (3x10 ml). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated at reduced pressure to yield a residue which by chromatography on Merck silica gel plates (PF<sub>254+366</sub>, 2mm), using a mixture ethyl acetate/hexane = 7/3 as eluent afforded in three different fractions **14** (0.590 g, 37.7%), **15** (0.10 g, 5.1%) and unreacted **13** (0.256 g, 22.9%). Compound **14** [mp 91-93°C (cyclohexane); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 2225, 1550, 1420, 1280, 1215, 1115;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 1.51 (t,  $J=7.0$  Hz, 3H), 4.27 (q,  $J=7.0$  Hz, 2H), 5.30 (s, 2H), 7.35-7.47 (m, 5H), 8.07 (s, 1H), 8.11 (s, 1H); ms ( $m/z$ ) 254 (12%,  $\text{M}^+$ )]. Compound **15** [mp 161-164°C ( $\text{CH}_2\text{Cl}_2$ /hexane); ir (KBr,  $\nu$   $\text{cm}^{-1}$ )

2220, 1550, 1410, 1275, 1215, 1105;  $^1\text{H-nmr}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm) 5.32 (s, 4H), 7.33-7.50 (m, 10 H), 8.12 (s, 2H); ms  $m/z$  316 (19%,  $\text{M}^+$ ).

**3-Ethoxy-5-phenylmethoxy-4-aminomethylpyridine dihydrochloride (16).** A stirred solution of **14** (1.10 g, 4.33 mmol) in dry THF (45 ml) under nitrogen was treated at room temperature with lithium aluminum hydride (0.26 g, 6.84 mmol). After 3 h stirring the mixture was treated with water (0.5 ml), then with 30% NaOH (0.5 ml) and filtered. After evaporation at reduced pressure of the clear filtrate, the residue, by flash chromatography on a Merck silica gel column (17.5x3.5 cm, 230-400 mesh, eluent  $\text{CH}_2\text{Cl}_2/5.6$  M methanolic ammonia = 98/2), afforded crude 3-ethoxy-5-phenylmethoxy-4-aminomethylpyridine that was dissolved in dry ether (30 ml) and saturated with gaseous HCl. The precipitated dihydrochloride (**16**) was filtered off and dried (0.490 g, 34.3%); mp 169-180°C (ethanol/ether, decomp.); ir (KBr,  $\nu$   $\text{cm}^{-1}$ ) 3400-2500 (br), 1530, 1365, 1260, 1155, 1055;  $^1\text{H-nmr}$  ( $\text{DMSO-d}_6$ ,  $\delta$  ppm) 1.41 (t,  $J=6.9$  Hz, 3H), 4.03 (q,  $J=5.5$  Hz, 2H), 4.27 (q,  $J=6.9$  Hz, 2H), 5.36 (s, 2H), 7.37-7.56 (m, 5H), 8.27 (s, 1H), 8.31 (s, 1H), 8.31 (br s, 3H); gc/ms, free base, ( $m/z$ ) 258 (2%,  $\text{M}^+$ ), 91 (100%,  $\text{C}_6\text{H}_5\text{CH}_2^+$ ). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{Cl}_2$ : C, 54.58; H, 6.11; N, 8.49. Found: C, 54.84; H, 6.27; N, 8.43.

#### ACKNOWLEDGEMENT

Work financially supported by Italian MURST, CNR and Progetto Finalizzato Chimica Fine.

#### REFERENCES

1. V. Bertini, A. De Munno, F. Lucchesini, F. Buffoni, and B. Bertocci, Ital. Patent Appl. 47906-A/85 extended to Europe, U.S.A., Canada and Japan (*Chem. Abstr.*, 1987, **106**, 156038m).
2. G. Banchelli, F. Buffoni, J. Elliot, and B. A. Callingham, *Neurochem. Int.*, 1990, **17**, 215.
3. G. Quéguiner, F. Marsais, V. Snieckus, and J. Epsztajn, 'Advances in Heterocyclic Chemistry: Direct metalation in pi-deficient azaaromatics', Vol. 52, ed. by A. R. Katritzky, Academic Press Inc., London, 1991, pp. 187-304.
4. T. D. Bailey, G. L. Goe, and E. F. V. Scriven, "Synthetic and Natural Sources of the Pyridine Ring", Vol. 4, Part 5, (ed. by G. R. Newkome) of "The Chemistry of Heterocyclic Compounds", ed. by A. Weissberger and E. C. Taylor, John Wiley & Sons, Inc., New York, 1984, pp.1-252.
5. F. Marsais and G. Quéguiner, *Tetrahedron*, 1983, **39**, 2009.

6. F. Marsais, G. Le Nard, and G. Quéguiner, *Synthesis*, 1982, 235.
7. S. P. Khanapure and E. R. Blehl, *Heterocycles*, 1990, **31**, 505.
8. M. Mallet, *J. Organometallic Chem.*, 1991, **406**, 49.
9. G. W. Gribble, and M. G. Saulnier, *Tetrahedron Lett.*, 1980, **21**, 4137.
10. F. Trécourt, F. Marsais, T. Güngör, and G. Quéguiner, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2409.
11. F. Marsais, F. Trécourt, P. Bréant, and G. Quéguiner, *J. Heterocycl. Chem.*, 1988, **25**, 81.
12. R. Radinov, M. Haimova, and E. Simova, *Synthesis*, 1986, 886.
13. F. Marsais, P. Bréant, A. Ginguene, and G. Quéguiner, *J. Organometallic Chem.*, 1981, **216**, 139.
14. R. Radinov, C. Chanev, and M. Haimova, *J. Org. Chem.*, 1991, **56**, 4793.
15. Y. Ito, K. Kunimoto, S. Miyachi, and T. Kako, *Tetrahedron Lett.*, 1991, **32**, 4007.
16. L. Testaferri, M. Tiecco, M. Tingoli, D. Bartoli, and A. Massoli, *Tetrahedron*, 1985, **41**, 1373.
17. H. J. Den Hertog and C. Hoogzand, *Rec. Trav. Chim.*, 1957, **76**, 261.
18. G. A. Olah and T. Keumi, *Synthesis*, 1979, 112.
19. M. A. Keegstra, T. H. A. Peters, and L. Brandsma, *Tetrahedron*, 1992, **48**, 3633.
20. Yu I. Chumakov and V. P. Sherstyuk, *Tetrahedron Lett.*, 1967, 771.
21. J. L. LaMattina and R. L. Taylor, *J. Org. Chem.*, 1981, **46**, 4179.
22. A. D. Dunn and R. Norrie, *J. Heterocycl. Chem.*, 1987, **24**, 85.
23. T. Talik, *Roczniki Chem.*, 1963, **37**, 69 (*Chem. Abstr.*, 1963, **59**, 8697f).
24. J. L. Gras and A. Guerin, *C. R. Acad. Sci. Ser.2*, 1985, **301**, 379.
25. D. A. Goff, R. N. Harris, J. C. Bottaro, and C. D. Bedford, *J. Org. Chem.*, 1986, **51**, 4711.
26. H. Yamanaka and S. Ohba, *Heterocycles*, 1990, **31**, 895.
27. D. M. Houston, E. K. Dolence, B. T. Keller, U. Patel-Thombre, and R. T. Borchardt, *J. Med. Chem.*, 1985, **28**, 467.
28. M. Jones, *Synthesis*, 1984, 727.

Received, 11th October, 1994