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Synthesis of functionalised pyrido[4,3-*b*][1,4]oxazine and imidazo[1,2-*a*]pyridine derivatives

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Abstract—Ethyl 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate derivatives were obtained from 3-hydroxy-2-aminopyridine and ethyl 2,3-dibromopropanoate. Reduction of thiolactam **17** obtained from the lactam **9** gave the corresponding ethyl 2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate. The use of ethyl 2-chloro-3-oxopropanoate with 2-amino-3-hydroxypyridine or 3-amino-4-hydroxypyridine led, respectively, to imidazo[1,2-*a*]pyridine derivatives or ethyl pyrido[4,3-*b*][1,4] oxazine-2-carboxylate.

Ethyl 3,4-dihydro-2*H*-1,4-benzoxazine-2-carboxylate derivatives **I**[1,2] are often found embedded in compounds exhibiting a wide range of biological activities[3] but their pyridine derivatives **II** have not been described; only compounds **III** have been scarcely mentioned;[4] moreover, most of them, **III**–**V**, possess a lactam function (Fig. 1).[5–9] Compounds **I** were usually obtained by treatment of 2-aminophenol with ethyl 2,3-dibromopropanoate,[1,2] but this synthetic approach is not valuable for the pyridine series. Thus it is known that 4 or 2-hydroxypyridines, better described as 4 or 2-pyridone derivatives, are less liable to *O*-alkylation[4,10] rendering the synthesis of the 1,4-oxazino ring more problematic with a supplementary difficulty due to the presence of the ester group. A point which also may be considered is the position of the ethoxycarbonyl substituent on the 1,4-oxazino ring: for compounds **I**, Bartsch et al.[1] and us[1] have demonstrated that the regioisomer in 2-position is always largely predominant. In this paper we outline approaches to functionalised pyrido-1,4-oxazines derivatives as potential templates for bioactive compounds.

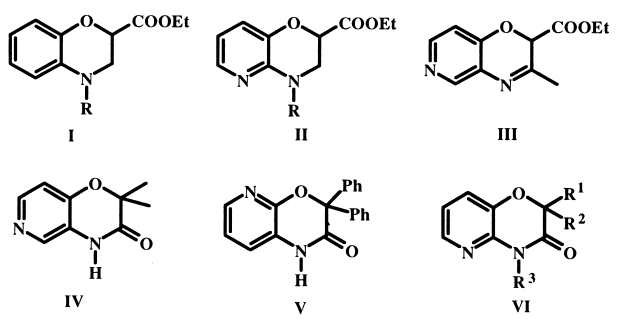
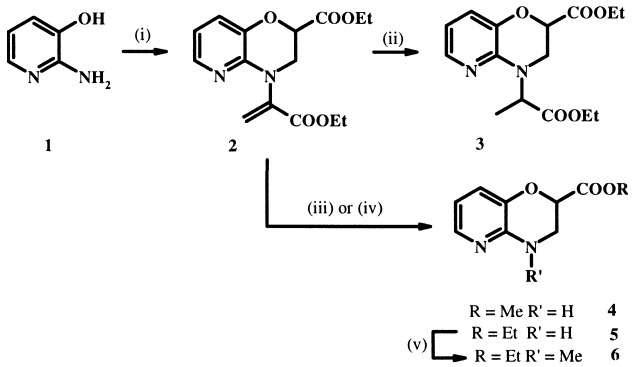


Figure 1.

In our first route to access pyrido[3,2-*b*][1,4]oxazine, when 3-hydroxy-2-aminopyridine **1** was reacted with ethyl 2,3-dibromopropanoate and potassium carbonate in refluxing acetone[1,2] only degradation was observed, due to the low solubility of **1**. Replacement of the solvent by DMF at 60°C afforded compound **2** instead of **5** in a moderate 45% yield (Scheme 1). This compound possesses the required



Scheme 1. *Reagents and conditions*: (i) ethyl 2,3-dibromopropanoate, DMF, K_2CO_3, 60°C; (ii) 10% Pd/C, ethanol, 1 atm, room temperature; (iii) 3N HCl, 60°C, then $SOCl_2$, methanol; (iv) trifluoroacetic acid 1,2-dichloroethane, 60°C; (v) HCHO, $NaBH_3CN$, acetonitrile.

Keywords: pyridine; cyclisation; oxazine; oxazinone.

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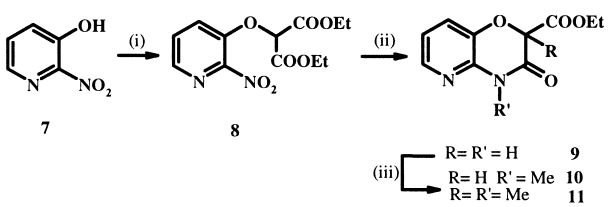
1,4-oxazino ring with an additional undesired enamine functionality which was reduced with hydrogen over palladium yielding **3** (99%); this confirming also the position of attachment of the nitrogen atom on the propenoate chain. Hydrolysis of **2** with hydrochloric acid[11] followed by the esterification with methanol and thionyl chloride gave **4** in only 11% yield. A more rapid transformation into the 1,4-oxazino ester derivative **5** was achieved in one step with trifluoroacetic acid in 40% yield.

In order to increase the stability of this derivative, methylation of the nitrogen atom of **5** was accomplished by reductive amination of methanal on **5** in presence of sodium cyanoborohydride to give compound **6** in 37% yield; the standard conditions used for the introduction of a methyl substituent in the benzo series **I** (iodomethane/potassium carbonate/acetone) proved to be ineffective.

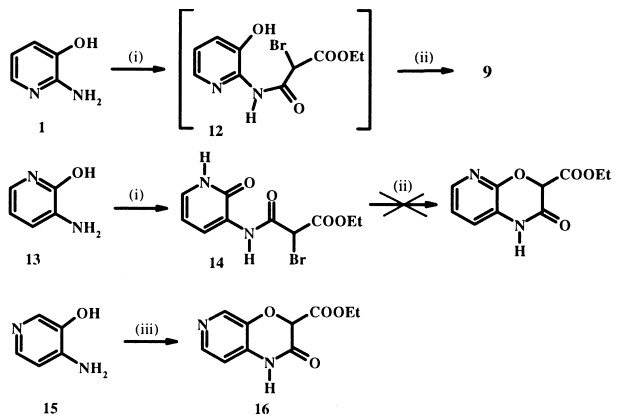
The overall low yield of **5** pushed us to devise a two steps procedure for the generation of the 1,4-oxazino ring. 2-Amino-3-hydroxypyridine **1** did not react with diethyl bromomalonate meanwhile when 3-hydroxy-2-nitropyridine **7** was treated with diethyl bromomalonate and potassium fluoride in DMF, following Kikelj approach,[9] compound **8** was obtained in 99% yield. Hydrogenation of the nitro group over palladium led to the 1,4-oxazino derivative **9** in 51% yield after an intramolecular amidification. Reaction of **9** with iodomethane in presence of sodium hydride gave a mixture of mono N and N,C-dialkylated derivatives **10** and **11** in 63 and 27% yield, respectively (Scheme 2). Attempts to increase the yield of *N*-methyl compound **10** were unsuccessful. It should be noted that **1** can react with diethyl 2-bromo-2-methylmalonate[9] but not with diethyl 2-bromomalonate.

Compound **9** was straightly obtained by reacting **1** with a more reactive malonic reagent such as ethyl bromochlorocarbonyl acetate[12] in THF in presence of triethylamine to give the unstable amide **12** in approximatively 30–35% yield (Scheme 3); the cyclisation of **12** to **9** was achieved (51% yield) with potassium carbonate by an internal nucleophilic displacement of the bromo atom by the alkoxide generated in situ. In order to explore the reactivity of the hydroxy substituent, 3-amino-2-hydroxypyridine **13**[13] was reacted similarly to give compound **14** in 41% yield, isolated as the pyridone tautomeric form which did not cyclise in the presence of potassium carbonate or sodium hydride due to the lack of reactivity of the 2-hydroxy group.

Unlike **1**, 3-Hydroxy-4-aminopyridine **15**[14] was abble to react with diethyl bromomalonate to afford directly



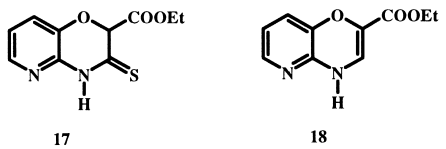
Scheme 2. *Reagents and conditions*: (i) diethyl bromomalonate, KF, DMF, room temperature; (ii) H_2, 10% Pd/C, acetic acid, 1 atm, room temperature; (iii) NaH, DMF, ICH_3, 0°C.



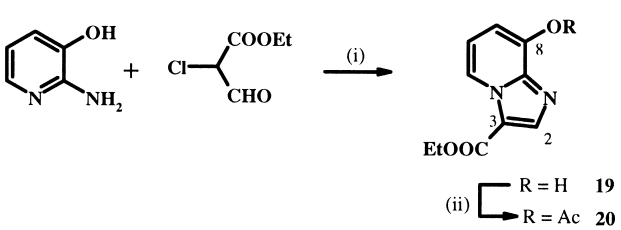
Scheme 3. *Reagents and conditions*: (i) Br-CH(COCl)COOEt, Et_3N, THF, 0°C; (ii) K_2CO_3, acetone, reflux; (iii) diethyl bromomalonate, EtOH, reflux.

compound **16** albeit in a low 19% yield proving that the hydroxy group in **15** is more reactive than in **1**.

Selective reduction with complex metal hydrides of the lactam function of **10** proved to be problematic giving mixture of products where both the ester and lactam functions were reduced. Treatment of **10** with BH_3/Me_2S proved to be the best method of reduction affording the 1,4-oxazino derivative **6** in albeit only 22% yield. (The reduction in the same conditions of compound **11** gave the analoguous 1,4-oxazino derivative in 25% yield). We tried to increase the yield of the lactam reduction by first transforming **9** into thiolactam **17**[6] using Lawesson's reagent[15] in refluxing toluene (49% yield); then subsequent treatment[16] with Raney nickel and sodium borohydride gave the new unsaturated 1,4-oxazine **18** in 33% yield.



Drawbacks in the synthesis of the 1,4-oxazino ring came from the reduction of the lactam, so we have envisaged the generation of an imine which was easier to reduce than a lactam. Thus reaction of ethyl 2-chloro-3-oxopropanoate[17] with **1** in refluxing ethanol led directly to the imidazo derivative **19** in 51% yield (Scheme 4). Imidazo[1,2-*a*]pyridine derivatives were reported to be easily obtained from 2-aminopyridines[18] and halo-ketone according to a Chichibabin reaction. If 2 or 3-functionalized imidazo[1,2-*a*]pyridine were easily obtained[19] by direct condensation,



Scheme 4. *Reagents and conditions*: (i) EtOH, reflux; (ii) AcCl, Et_3N, CH_2Cl_2, room temperature.

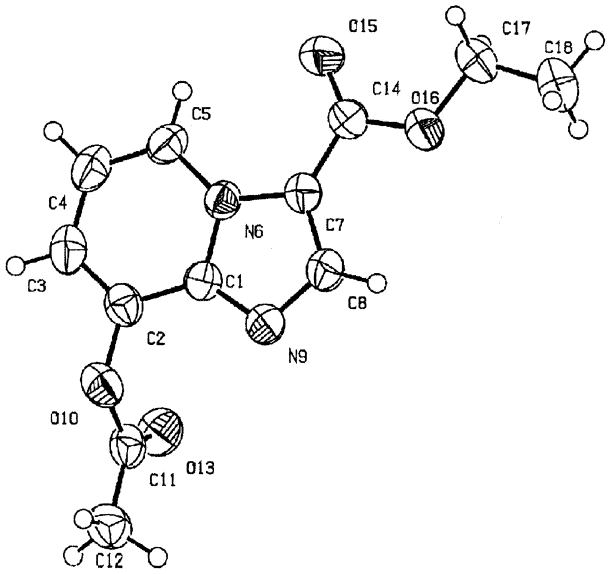


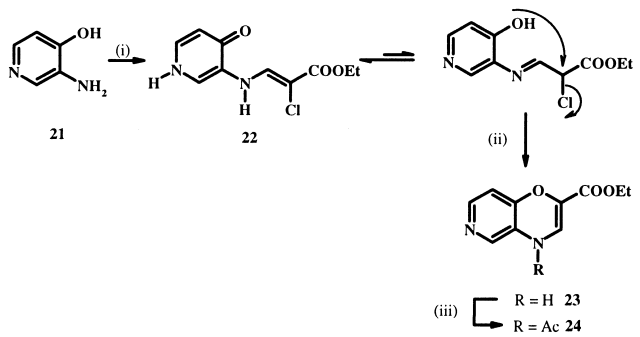
Figure 2. ORTEP diagram of **20**. Thermal ellipsoids are at 50% probability.

electrophilic substitution or lithiation reactions,[20] the corresponding 8-hydroxy derivatives are less accessible.

Acetylation of **19** with acetyl chloride in dichloromethane at room temperature afforded **20** as a crystalline derivative in 89% yield. X-Ray structure analysis was performed on **20** indicating an imidazo[1,2-*a*]pyridine structure (Fig. 2).

The formation of **19** can arise by alkylation of the pyridine nitrogen atom, then cyclisation generating the imidazo ring occurs by imine formation on the 2-amino substituent of the pyridine. An other pathway giving the same final derivative can be envisionned; first an imine formation on the 2-amino group followed by a competitive N-alkylation rather than an *O*-alkylation afforded the imidazopyridine **19**.

We were more successfull starting from 3-amino-4-hydroxypyridine **21**.[21] The enamine **22** (isolated as a tautomeric pyridone form) and not the imine was obtained in 89% yield from the reaction of **21** and ethyl 2-chloro-3-oxopropanoate in refluxing ethanol. (Such spontaneous isomerisation imine/enamine has also been reported during the reaction of ethyl 2-acetyl-2-chloroacetate with 1,2-diaminobenzene).[22] Heating **22** in acetone in basic medium (potassium carbonate) led to the expected oxazino derivative **23** in 96% yield (Scheme 5).



Scheme 5. *Reagents and conditions*: (i) ethyl 2-chloro-3-oxopropanoate, EtOH, reflux; (ii) K_2CO_3, acetone, reflux; (iii) AcCl, Et_3N, CH_2Cl_2, room temperature.

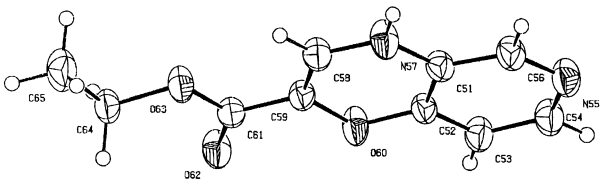
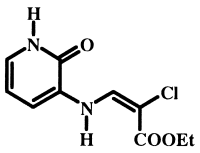


Figure 3. ORTEP diagram of **23**. Thermal ellipsoids are at 50% probability.

By treatment with acetyl chloride in dichloromethane compound **23** gave **24** as a crystalline compound in 89% yield. X-Ray structure analysis were performed on compounds **23** (Fig. 3) and **24** thus confirming the presence of the double bond in the 1,4-oxazino structure.

In order to investigate the influence of the position of the pyridine nitrogen atom, relatively to hydroxy and amino substituents, the 3-amino-2-hydroxypyridine was treated which ethyl 2-chloro-3-oxopropanoate to give the enamine **25** in 81% yield. Ring closure in basic medium was unfruitfull (degradation or no reaction) as in the case of **14**, due to the difficulty of *O*-alkylation of 2-pyridinol which is mainly present as 2-pyridone tautomer.



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1. Conclusions

New pyrido[1,4]oxazine derivatives were easily obtained from 3-hydroxy-4-aminopyridines using reactive malonic reagents. The ester group in position 2 greatly increases the synthetic potential of such derivatives which is under investigation. 3-hydroxy-2-aminopyridine gave access either to 1,4-oxazino derivatives or imidazopyridines depending on the annelating reagent (ethyl 2,3-dibromopropanoate or ethyl 2-chloro-3-oxopropanoate). Only the 3-amino substituent of 2-hydroxy-3-aminopyridine reacted with ethyl 2-chloro-3-oxopropanoate and led to products reluctant to cyclisation.

2. Experimental

2.1. General

^{1}H NMR spectra were recorded at 250 MHz and ^{13}C NMR spectra at 62.5 MHz on Bruker Avance DPX-250 instrument in $CDCl_3$ solution with tetramethylsilane as reference. Coupling constants are expressed in Hz. IR spectra were recorded on Perkin–Elmer Paragon 1000 FT-IR instrument. MS spectra were obtained using a Perkin–Elmer SCIEX API 300 spectrometer using ionspray methodology. Melting points were taken on a Büchi SMP-20 melting point apparatus and are uncorrected. Light petroleum refers to the fraction boiling in the range 40–60°C. Thin-layer chromatography (TLC) was run on precoated silica gel plates (Merck $60F_{254}$) and the spots visualised using an

ultraviolet lamp. Flash chromatography was performed on Merck Silica Gel 60 (230–400 mesh).

2.1.1. Ethyl 4-[1-(ethoxycarbonyl)vinyl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 2. To a solution of 2-amino-3-hydroxypyridine **1** (500 mg, 4.54 mmol) in DMF (5 mL) were added K_2CO_3 (1.37 g, 9.98 mmol) and ethyl 2,3-dibromopropanoate (0.7 mL, 4.99 mmol). After heating at 60°C for 18 h the solvent was evaporated and the resulting oil was partitioned between ethyl acetate (40 mL) and water (100 mL) and then filtered. The aqueous layer was twice extracted with ethyl acetate and the combined extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **2** (626 mg, 45%) as an oil; IR ν (film) (cm^{-1}): 1755 (CO), 1722 (CO); ^1H NMR (δ, ppm): 1.11 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.24 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.90 (d, 2H, J=4.6 Hz, 3-H), 4.15 (m, 4H, OCH_2CH_3), 4.91 (t, 1H, J=4.6 Hz, 2-H), 5.15 (br s, 1H, CH_2=), 5.69 (br s, 1H, CH_2=), 6.67 (dd, 1H, J=7.9, 4.8 Hz, 7-H), 7.15 (dd, 1H, J=7.9, 1.7 Hz, 8-H), 7.71 (dd, 1H, J=4.8, 1.7 Hz, 6-H); ^{13}C NMR (δ, ppm): 14.3 (2 CH_3), 48.4 (NCH_2), 61.5 (OCH_2), 62.4 (OCH_2), 72.5 (CH), 111.0 (CH_2), 116.7 (CH), 123.1 (CH), 139.1 (C), 140.4 (CH), 142.3 (C), 143.7 (C), 165.4 (CO), 168.6 (CO); *m/z* (IS) $(MH)^+$=307. Anal. calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.61; H, 5.78; N, 9.30.

2.1.2. Ethyl 4-[1-(ethoxycarbonyl)ethyl]-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 3. A suspension of compound **2** (199 mg, 0.65 mmol) and 10% Pd/C (20 mg) in ethanol (20 mL) were shaken in a Parr apparatus under 1 atm of hydrogen for 14 h at room temperature; the mixture was filtered over celite and evaporated at reduced pressure to afford **3** (199 mg, 99%) as an oil; IR ν (film) (cm^{-1}): 1722 (CO); ^1H NMR (δ, ppm): 1.20 (m, 6H, OCH_2CH_3), 1.46 (d, 3H, J=7.2 Hz, $CHCH_3$), 3.67 (d, 2H, J=4.7 Hz, 3-H), 4.17 (m, 4H, OCH_2CH_3), 4.75 (d, 1H, J=4.7 Hz, 2-H), 5.27 (m, 1H, $CHCH_3$), 6.56 (dd, 1H, J=7.7, 5.0 Hz, 7-H), 7.07 (d, 1H, J=7.5 Hz, 8-H), 7.70 (d, 1H, J=5.0 Hz, 6-H); ^{13}C NMR (δ, ppm): 14.2 (2 CH_3), 14.4 (CH_3), 43.5 (NCH_2), 52.5 (CH) 60.9 (OCH_2), 61.9 (OCH_2), 72.4 (CHO), 114.5 (CH), 122.1 (CH), 138.8 (C), 139.9 (CH), 145.6 (C), 168.6 (CO), 172.9 (CO); *m/z* (IS) $(MH)^+$=309. Anal. calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.57; H, 6.42; N, 9.23.

2.1.3. Methyl 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 4. Compound **2** (199 mg, 0.65 mmol) in 3N HCl (4 mL) was stirred at 60°C for 20 h; after cooling, 20% NaOH was added till pH 7; water was evaporated at reduced pressure and the residue was dried overnight over P_2O_5; it was then added portionwise to a solution of thionyl chloride (190 μL, 2.6 mmol) in methanol (2 mL) which was stirred at room temperature for 15 h. Evaporation at reduced pressure was followed by addition of water and extraction with ethyl acetate (3×10 mL). The combined extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **4** (14 mg, 11%) as an oil; IR ν (film) (cm^{-1}): 3210 (NH), 1753 (CO); ^1H NMR (δ, ppm): 3.72 (d, 2H, J=4.2 Hz, 3-H), 3.79 (s, 3H, OCH_3), 4.81 (t, 1H, J=4.2 Hz, 2-H), 4.89 (br s, 1H, NH), 6.60 (dd, 1H, J=7.9, 4.9 Hz, 7-H), 7.12 (d, 1H, J=7.9 Hz, 8-H), 7.70 (br s, 1H, 6-H); ^{13}C NMR (δ, ppm): 42.1 (NCH_2), 52.7 (CH_3), 72.2 (CHO), 115.0 (CH), 122.7 (2 CH), 140.4 (CH), 146.2 (C), 169.3 (CO); *m/z* (IS) $(MH)^+$=195. Anal. calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.95; H, 5.36; N, 14.28.

2.1.4. Ethyl 3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 5. A solution of compound **2** (918 mg, 3 mmol) and trifluoroacetic acid (0.69 mL) in dichloromethane (20 mL) was stirred overnigh at reflux; after evaporation at reduced pressure ice was added followed by addition of 30% NaOH till pH 7; the aqueous layer was twice extracted with ethyl acetate and the combined extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **5** (262 mg, 42%) as an oil; IR ν (film) (cm^{-1}): 3389 (NH), 1732 (CO); ^1H NMR (δ, ppm): 1.23 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.69 (d, 2H, J=4.0 Hz, 3-H), 4.21 (q, 2H, J=7.0 Hz, OCH_2CH_3), 4.82 (t, 1H, J=4.0 Hz, 2-H), 5.44 (br s, 1H, NH), 6.57 (dd, 1H, J=8.0, 4.8 Hz, 7-H), 7.08 (d, 1H, J=8.0 Hz, 8-H), 7.63–7.70 (m, 1H, 6-H); ^{13}C NMR (δ, ppm): 14.5 (CH_3), 42.5 (NCH_2), 62.0 (CH_2), 72.5 (CHO), 115.0 (CH), 122.9 (CH), 138.7 (C), 140.6 (CH), 146.9 (C), 169.2 (CO); *m/z* (IS) $(MH)^+$=209. Anal. calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found C, 57.93; H, 5.64; N, 13.31.

2.1.5. Ethyl 4-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 6. *Method A*. To a solution of compound **5** (416 mg, 2 mmol) and 37% aqueous formaldehyde (0.80 mL, 10 mmol) in acetonitrile, sodium cyanoborohydride (200 mg, 3.2 mmol) was added. The mixture was stirred at room temperature for 15 min. Acetic acid was added and the mixture stirred for 45 min. The solvent was evaporated and the resulting oil was partitioned between ethyl acetate (20 mL) and 2N potassium hydroxide (10 mL). The aqueous layer was twice extracted with ethyl acetate and the combined organic extracts were washed with 0.5N potassium hydroxide then with 1N hydrochloric acid (3×15 mL). Addition to the aqueous extracts of 2N potassium hydroxide till pH 7 was followed with extraction with ethyl acetate (3×15 mL). The extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (1:9) yielded **6** as an oil (164 mg, 37%).

Method B. To a solution of compound **10** (200 mg, 0.85 mmol) in THF (2 mL)/ethanol (2 mL) was added 2 M borane–methyl sulfide complex (0.42 mL, 0.85 mmol) in THF. The mixture was heated at reflux for 1 h 30. After cooling a solution of ethanol (0.2 mL) and 4N HCl (0.2 mL) was added and the mixture was heated again at reflux for 1 h 30. Water (150 mL) was added and the mixture was extracted twice with dichloromethane; the combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (1:9) yielded **6** (42 mg, 22%) as an oil; IR ν (film) (cm^{-1}): 1759 (CO); ^1H NMR (δ, ppm): 1.23 (t, 3H, J=7.1 Hz, OCH_2CH_3), 3.07 (s, 3H, NCH_3), 3.59 (d, 2H,

J=4.3 Hz, 3-H), 4.23 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.80 (t, 1H, J=4.3 Hz, 2-H), 6.55 (dd, 1H, J=7.9, 4.8 Hz, 7-H), 7.04 (dd, 1H, J=7.9, 1.9 Hz, 8-H), 7.76 dd, 1H, J=4.8, 1.9 Hz, 6-H); ^{13}C NMR (δ, ppm): 13.7 (CH_3), 35.5 (CH_3), 48.9 (CH_2), 61.4 (CH_2), 71.5 (CH), 113.4 (CH), 121.0 (CH), 138.4 (C), 139.7 (CH), 146.9 (C), 168.3 (CO); m/z (IS) $(MH)^+$=223. Anal. calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.78; H, 6.52; N, 12.47.

2.1.6. Diethyl 2-[(2-nitro-3-pyridyl)oxy]malonate 8. To a suspension of KF (8.7 g, 150 mmol, 3 equiv.) in DMF (50 mL), 2-nitro-3-hydroxypyridine **7** (7.0 g, 50 mmol) was added at 0°C and the mixture stirred for 30 min; diethyl bromomalonate (8.5 mL, 50 mmol) was then added. After stirring for 24 h at room temperature water (150 mL) was added and the mixture was extracted twice with ethyl acetate; the combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **8** as an oil (14.8 g, 99%); IR ν (film) (cm^{-1}): 1766 (CO); ^{1}H NMR (δ, ppm): 1.19 (t, 6H, J=7.0 Hz, OCH_2CH_3), 4.19 (m, 4H, OCH_2CH_3), 5.26 (s, 1H, OCH), 7,50–7.53 (m, 2H, 4-H, 5-H), 8.08–8.11 (m, 1H, 6-H); ^{13}C NMR (δ, ppm): 14.2 ($2CH_3$), 63.6 ($2CH_2$), 78.4 (CH), 127.2 (CH), 129.6 (CH), 142.3 (CH), 144.1 (C), 145.9 (C), 164.6 (2 CO); m/z (IS) $(MH)^+$=299. Anal. calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39. Found: C, 48.10; H, 4.55; N, 9.26.

2.1.7. Ethyl 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 9. *Method A*. Compound **8** (7.45 g, 25 mmol) dissolved in acetic acid (40 mL) and 10% Pd/C (745 mg) were shaken in a Parr apparatus under 1 atm of hydrogen for 24 h at room temperature. The mixture was filtered over celite and evaporated at reduced pressure to afford an oil. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **9** (2.83 g, 51%) as a solid; mp 146–148°C (from CH_2Cl_2/EtOH); IR ν (KBr) (cm^{-1}): 3128, 3060 (NH), 1757 (CO), 1719 (CO); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.15 (t, 3H, J=7.0 Hz, OCH_2CH_3), 4.18 (m, 2H, OCH_2CH_3), 5.52 (s, 1H, 2-H), 7.02 (dd, 1H, J=8.0, 4.9 Hz, 7-H), 7.44 (dd, 1H, J=8.0, 0.9 Hz, 8-H), 7.93 (dd, 1H, J=4.9, 0.9 Hz, 6-H), 11.57 (br s, 1H, NH); ^{13}C NMR (δ, ppm, DMSO-d_6): 14.7 (CH_3), 62,9 (CH_2), 76.4 (CH), 120.3 (CH), 124.4 (CH), 139.0 (C), 141.5 (C), 142.3 (CH), 162.3 (CO), 166.6 (CO); m/z (IS) $(MH)^+$=223. Anal. calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.39; H, 4.72; N, 12.44.

Method B. To a solution of 2-amino-3-hydroxypyridine **1** (330 mg, 3 mmol) and triethylamine (49 μL, 3 mmol) in THF (15 mL) at 0°C, ethyl bromochlorocarbonyl acetate[12] (1.20 g, 3 mmol) was added. After stirring for 2 h at 0°C, ice was added and the mixture extracted with dichloromethane. The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH yielded **12** (300 mg, 33%) as an unstable solid. A suspension of **12** (263 mg, 0.80 mmol) and K_2CO_3 (280 mg, 2 mmol) in acetone (15 mL) was refluxed for 15 h. After filtration over celite, the mixture was evaporated. Water was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with ethyl acetate yielded **9** (91 mg, 51%).

2.1.8. Ethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 10. To a suspension of 60% NaH (40 mg, 1 mmol) in DMF (2 mL), compound **9** (222 mg, 1 mmol) was added at 0°C and the mixture was stirred at 0°C for 30 min; iodomethane (0.18 mL, 3 mmol) was added and the mixture stirred for 1 h at 0°C; water was added and the mixture was twice extracted with ethyl acetate; the combined extracts were washed with water and dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **11** as a solid (68 mg, 27%) then **10** (150 mg, 63%) as a white solid Compound **10**: mp 100–102°C (from CH_2Cl_2); IR ν (KBr) (cm^{-1}): 1747 (CO), 1696 (CO); ^{1}H NMR (δ, ppm): 1.28 (t, 3H, J=7.0 Hz, OCH_2CH_3), 3.49 (s, 3H, NCH_3), 4.24 (m, 2H, OCH_2CH_3), 5.23 (s, 1H, 2-H), 6.97 (dd, 1H, J=8.0, 4.9 Hz, 7-H), 7.33 (dd, 1H, J=8.0, 1.9 Hz, 8-H), 8.04 (dd, 1H, J=4.9, 1.9 Hz, 6-H); ^{13}C NMR (δ, ppm): 14.3 (CH_3), 27.4 (NCH_3), 62.9 (CH_2), 76.6 (CH), 119.8 (CH), 124.0 (CH), 139.9 (C), 141.5 (C), 141.8 (CH), 161.1 (CO), 165.9 (CO); m/z (IS) $(MH)^+$=237. Anal. calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.22; H, 5.30; N, 12.04.

2.1.9. Ethyl 2,4-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 11. Mp 144–146°C (from CH_2Cl_2); IR ν (KBr) (cm^{-1}): 1749 (CO), 1697 (CO); ^{1}H NMR (δ, ppm): 1.06 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.77 (s, 3H, CCH_3), 3.41 (s, 3H, NCH_3), 4.05 (m, 2H, OCH_2CH_3), 6.87 (dd, 1H, J=8.0, 4.9 Hz, 7-H), 7.23 (dd, 1H, J=8.0, 1.2 Hz, 8-H), 7.95 (dd, 1H, J=4.9, 1.2 Hz, 6-H); ^{13}C NMR (δ, ppm): 14.2 (CH_3), 21.3 (CH_3), 27.8 (CH_3), 62.8 (CH_2), 81.5 (C), 119.7 (CH), 124.2 (CH), 140.1 (C), 141.8 (CH), 142.3 (C), 164.3 (CO), 168.4 (CO); m/z (IS) $(MH)^+$=251. Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.57; H, 5.64; N, 11.19. Found: C, 57.93; H, 5.48; N, 11.30.

2.1.10. Ethyl 2-bromo-*N*-(2-hydroxypyridin-3-yl)-malonate 14. To a solution of 2-hydroxy-3-aminopyridine **13** (330 mg, 3 mmol) and triethylamine (49 μL, 3 mmol) in THF (15 mL) at 0°C, ethyl bromochlorocarbonyl acetate[12] (1.20 g, 3 mmol) was added. After stirring for 2 h at 0°C, ice was added and the mixture extracted with dichloromethane. The combined organic layers were washed with water and dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH yielded **14** (372 mg, 41%) as a green solid; mp 206–208°C (from EtOH); IR ν_{max}(KBr) (cm^{-1}): 3134 (NH, OH), 2816, 1745 (CO), 1706 (CO); ^{1}H NMR (δ, ppm, DMSO-d_6): 1.32 (t, 3H, J=7.0 Hz, OCH_2CH_3), 4.32 (q, 2H, J=7.0 Hz, OCH_2CH_3), 5.02 (s, 1H, CHBr), 6.35 (ft, 1H, J=7.0 Hz, 5-H), 7.19 (dd, 1H, J=7.0, 1.5 Hz, 4-H), 8.46 (dd, 1H, J=7.0, 1.5 Hz, 6-H), 9.79 (br s, 1H, NH), 12.72 (br s, 1H, OH); ^{13}C NMR (δ, ppm, DMSO-d_6): 13.9 (CH_3), 42.7 (CH), 63.4 (CH_2), 107.6 (CH), 125.6 (CH), 128.2 (C), 128.6 (CH), 158.7 (C), 162.4 (CO), 166.3 (CO); m/z (IS) $(MH)^+$=303,305. Anal. calcd for $C_{10}H_{11}N_2O_4Br$: C, 39.63; H, 3.66; N, 9.24. Found: C, 39.37; H, 3.52; N, 9.41.

2.1.11. Ethyl 2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*]-1,4-oxazine-3-carboxylate 16. Diethyl bromomalonate (462 mg, 2 mmol), 3-hydroxy-4-aminopyridine **15**[14] (220 mg, 2 mmol) in ethanol (15 mL) were refluxed for 4 h. After evaporation at reduced pressure a residue was obtained. Flash column chromatography on silica gel, eluting with petroleum CH_2Cl_2/EtOH (9:1) yielded **16** (84 mg, 19%) as a gum; IR ν (film) (cm^{-1}): 3123, 3060 (NH), 1744 (CO), 1716 (CO); ^1H NMR (δ, ppm): 1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.28 (s, 1H, 2-H), 6.89 (d, 1H, J=5.1 Hz, 5-H), 8.22 (d, 1H, J=5.1 Hz, 6-H), 8.39 (s, 1H, 8-H), 12.08 (br s, 1H, NH); ^{13}C NMR (δ, ppm): 14.12 (CH_3), 63.12 (CH_2), 76.34 (CH), 110.80 (CH), 132.88 (C), 138.38 (CH), 144.44 (CH), 161.48 (C), 161.52 (CO), 165.27 (CO); *m/z* (IS) $(MH)^+$=223. Anal. calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.86; H, 4.71; N, 12.44.

2.1.12. Ethyl 3-thioxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-2-carboxylate 17.[6] To a solution of **9** (1.11 g, 5 mmol) in toluene (10 mL) Lawesson reagent (2.22 g, 5.5 mmol) was added and the mixtute was refluxed for 2 h. Evaporation at reduced pressure leave a residue. Flash column chromatography on silica gel, eluting with dichloromethane yielded **17** (583 mg, 49%) as a yellow solid; mp 202–204°C (from CH_2Cl_2); IR ν (KBr) (cm^{-1}): 3172, (NH), 1731 (CO), 1536 (CS); ^1H NMR (δ, ppm): 1.28 (t, 3H, J=7.1 Hz, OCH_2CH_3), 4.26 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.58 (s, 1H, OC*H*), 7.09 (dd, 1H, J=8.1, 5.0 Hz, 7-H), 7.41 (dd, 1H, J=8.1, 1.3 Hz, 8-H), 7.93 (dd, 1H, J=5.0, 1.3 Hz, 6-H), 13.58 (br s, 1H, NH); ^{13}C NMR (δ, ppm): 13.9 (CH_3), 62.8 (CH_2), 81.0 (CH), 120.8 (CH), 124.7 (CH), 139.7 (C), 139.9 (C), 141.4 (CH), 166.0 (CO), 187.7 (CS); *m/z* (IS) $(MH)^+$=239. Anal. calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.77; H, 4.06; N, 11.58.

2.1.13. Ethyl 4*H*-pyrido[3,2-*b*]-1,4-oxazine-2-carboxylate 18. To a solution of **17** (238 mg, 1 mmol) in THF (2 mL) and ethanol (2 mL) an aqueous suspension of Raney nickel (0.75 mL, 50% weight) was added at room temperature. After 5 min the same amount of Raney nickel was added followed by addition of $NaBH_4$ (20 mg, 0.5 mmol). After stirring for 15 min at room temperature the mixture was filtered over celite and evaporated at reduced pressure. Ethyl acetate was added and the mixture was extracted with 0.5N HCl (2×3 mL). The aqueous layers were made neutral by addition of 5N NaOH and extracted with CH_2Cl_2; the combined extracts were washed with water and dried over $MgSO_4$; the solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (99:1) yielded **18** (68 mg, 33%) as a brown solid; mp 177–179°C (from EtOH); IR ν (KBr) (cm^{-1}): 3322 (NH), 1748 (CO); ^1H NMR (δ, ppm): 1.26 (t, 3H, J=7.1 Hz, OCH_2CH_3), 4.22 (q, 2H, J=7.1 Hz, OCH_2CH_3), 6.57 (dd, 1H, J=7.9, 5.1 Hz, 7-H), 6.63 (s, 1H, CH=), 6.76 (dd, 1H, J=7.9, 1.5 Hz, 8-H), 7.03 (br s, 1H, NH), 7.45 (dd, 1H, J=5.1, 1.5 Hz, 6-H); ^{13}C NMR (δ, ppm): 14.3 (CH_3), 60.7 (CH_2), 119.6 (CH), 122.0 (CH), 123.6 (CH), 126.6 (C), 141.1 (CH), 142.0 (C), 145.3 (C), 161.2 (CO); *m/z* (IS) $(MH)^+$=207. Anal. calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.53; H, 5.08; N, 13.76.

2.1.14. Ethyl 8-hydroxyimidazo[1,2-*a*]pyridine-3-carboxylate 19. A solution of 3-hydroxy-2-aminopyridine (220 mg, 2 mmol) and ethyl 2-chloro-3-oxopropanoate[17] (300 mg, 2 mmol) in ethanol (15 mL) was refluxed for 18 h. The precipitated solid was filtered, washed with cold ethanol and dried over P_2O_5 to give **19** (210 mg, 51%) as a beige solid; mp 238–240°C (from EtOH); IR ν KBr) (cm^{-1}): 3381 (OH), 1702 (CO); ^1H NMR (δ, ppm, DMSO-d_6): 1.32 (t, 3H, J=7.0 Hz, OCH_2CH_3), 4.37 (q, 2H, J=7.0 Hz, OCH_2CH_3), 7.11 (d, 1H, J=7.8 Hz, 7-H), 7.24 (t, 1H, J=7.3 Hz, 6-H), 8.46 (s, 1H, 2-H), 8.81 (d, 1H, J=7.3 Hz, 5-H); ^{13}C NMR (δ, ppm, DMSO-d_6): 14.9 (CH_3), 62.5 (CH_2), 114.2 (CH), 118.0 (C), 119.4 (CH), 120.5 (CH), 124.4 (CH), 132.9 (C), 145.0 (CH), 159.9 (CO); *m/z* (IS) $(MH)^+$=207. Anal. calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.02; H, 5.07; N, 13.73.

2.1.15. Ethyl 8-acetoxyimidazo[1,2-*a*]pyridine-3-carboxylate 20. A solution of **19** (207 mg, 1 mmol), triethylamine (140 μL, 1 mmol) and acetyl chloride (78 mg, 1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 4 h. Water was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **20** (221 mg, 89%) as a colorless solid; mp 92–94°C (from EtOAc); IR ν (KBr) (cm^{-1}): 1774 (CO), 1700 (CO); ^1H NMR (δ, ppm): 1.41 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.46 (s, 3H, $COCH_3$), 4.40 (q, 2H, J=7.1 Hz, OCH_2CH_3), 7.01 (t, 1H, J=7.2 Hz, 6-H), 7.23 (dd, 1H, J=7.6, 2.0 Hz, 7-H), 8.26 (s, 1H, 2-H), 9.19 (d, 1H, J=7.6 Hz, 5-H); ^{13}C NMR (δ, ppm): 14.5 (CH_3), 21.0 (CH_3), 60.8 (CH_2), 113.7 (CH), 117.2 (C), 119.0 (CH), 125.6 (CH), 139.8 (C), 141.2 (CH), 143.3 (C), 160.6 (CO), 168.5 (CO); *m/z* (IS) $(MH)^+$=249. Anal. calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.30; H, 5.04; N, 11.47.

2.1.16. Ethyl 2-chloro-3-[(4-oxo-1,4-dihydro-3-pyridinyl)-amino]-2-propenoate 22. A solution of 4-hydroxy-3-aminopyridine **21** (220 mg, 2 mmol) and ethyl 2-chloro-3-oxopropanoate (300 mg, 2 mmol) in ethanol (15 mL) was refluxed for 18 h. Evaporation under reduced pressure leave a residue. Flash column chromatography on silica gel, eluting with dichloromethane/ethanol (99:1) yielded **22** (431 mg, 89%) as a beige solid; mp 173–175°C (from EtOH); IR ν (KBr) (cm^{-1}): 3440 (OH), 3363 (NH), 1704 (CO); ^1H NMR (δ, ppm, DMSO-d_6): 1.25 (t, 3H, J=7.2 Hz, OCH_2CH_3), 4.19 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.25 (d, 1H, J=6.7 Hz, 5′-H), 7.62 (d, 1H, J=6.7 Hz, 6′-H), 7.93 (d, 1H, J=13.7 Hz, NH/exchangeable D_2O), 8.06 (s, 1H, 2′-H), 8.43 (d, 1H, J=13.7 Hz, CH=), 11.80 (br s, 1H, NH/exchangeable D_2O); ^{13}C NMR (δ, ppm, DMSO-d_6): 14.7 (CH_3), 61.1 (CH_2), 96.8 (C), 113.4 (CH), 120.9 (CH), 130.0 (C), 135.7 (CH), 136.6 (CH), 163.6 (CO), 170.2 (CO); *m/z* (IS) $(MH)^+$=243, 245. Anal. calcd for $C_{10}H_{11}N_2O_3Cl$: C, 49.50; H, 4.57; N, 11.54. Found: C, 49.26; H, 4.42; N, 11.43.

2.1.17. Ethyl 4*H*-pyrido[4,3-*b*][1,4]oxazine-2-carboxylate 23. A suspension of **22** (243 mg, 1 mmol) K_2CO_3 (280 mg, 2 mmol) in acetone (15 mL) was refluxed for 15 h. After filtration over celite, the mixture was evaporated.

Water was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried over $MgSO_4$. The solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with ethyl acetate yielded **23** (196 mg, 95%) as a yellow solid; mp 200–202°C dec. (from EtOAc); IR ν (KBr) (cm^{-1}): 3230 (NH), 1669 (CO); ^1H NMR (δ, ppm): 1.29 (t, 3H, J=7.2 Hz, OCH_2CH_3), 4.20 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.47 (d, 1H, J=5.3 Hz, 8-H), 6.53 (br s, 1H, NH/exchangeable D_2O), 6.63 (d, 1H, J=5.3 Hz, 3-H, s after D_2O exchange), 7.47 (s, 1H, 5-H), 7.83 (d, 1H, J=5.3 Hz, 7-H); ^{13}C NMR (δ, ppm): 14.5 (CH_3), 60.8 (CH_2), 111.4 (CH), 125.5 (CH), 125.5 (C), 128.2 (C), 134.6 (CH), 147.1 (CH), 153.0 (C), 161.4 (CO); m/z (IS) $(MH)^+$=207. Anal. calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 57.95; H, 5.06; N, 13.79.

2.1.18. Ethyl 4-acetyl-4*H*-pyrido[4,3-*b*][1,4]oxazine-2-carboxylate 24. A solution of **23** (206 mg, 1 mmol), triethylamine (140 μL, 1 mmol) and acetyl chloride (78 mg, 1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 4 h. Water was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried over $MgSO_4$ and the solvent was removed at reduced pressure. Flash column chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:7) yielded **24** (211 mg, 85%) as a colorless solid; mp 143–145°C (from EtOAc); IR ν (KBr) (cm^{-1}): 1731 (CO), 1685 (CO); ^1H NMR (δ, ppm): 1.35 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.38 (s, 3H, $COCH_3$), 4.34 (q, 2H, J=7.1 Hz, OCH_2CH_3), 6.87 (d, 1H, J=5.6 Hz, 8-H), 7.20 (s, 1H, 3-H), 8.28 (d, 1H, J=5.6 Hz, 7-H), 9.26 (s, 1H, 5-H); ^{13}C NMR (δ, ppm): 14.3 (CH_3), 23.1 (CH_3), 62.1 (CH_2), 112.8 (CH), 119.6 (CH), 124.0 (C), 131.3 (C), 143.6 (CH), 149.1 (CH), 153.5 (C), 160.2 (CO), 166.8 (CO); m/z (IS) $(MH)^+$=249. Anal. calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.38; H, 5.01; N, 11.12.

2.1.19. Ethyl 2-chloro-3-[(2-oxo-1,2-dihydro-3-pyridinyl)-amino]-2-propenoate 25. Same procedure as for **22** starting from 2-hydroxy-3-aminopyridine (220 mg, 2 mmol) and ethyl 2-chloro-3-oxopropanoate (300 mg, 2 mmol); gum (422 mg, 87%); IR ν (film) (cm^{-1}): 3346 (NH), 1700 (CO); ^1H NMR (δ, ppm): 1.25 (t, 3H, J=7.1 Hz, OCH_2CH_3), 4.19 (q, 2H, J=7.1 Hz, OCH_2CH_3), 6.24 (t, 1H, J=6.8 Hz, 5-H), 7.09 (dd, 1H, J=6.5, 1.3 Hz, 4-H), 7.43 (dd, 1H, J=7.3, 1.3 Hz, 6-H), 7.95 (d, 1H, J=13.6 Hz, NH/exchange D_2O), 8.41 (d, 1H, J=13.6 Hz, CH=), 12.08 (br s, 1H, OH); ^{13}C NMR (δ, ppm): 14.7 (CH_3), 61.4 (CH_2), 98.1 (C), 106.6 (CH), 118.4 (CH), 127.4 (CH), 130.1 (C), 135.9 (CH), 157.4 (C), 163.6 (CO); m/z (IS) $(MH)^+$=243, 245. Anal. calcd for $C_{10}H_{11}N_2O_3Cl$: C, 49.50; H, 4.57; N, 11.54. Found: C, 49.83; H, 4.46; N, 11.63.

X-Ray structure. Selected data: compound **20**: N(6)–C(7) 1.394(2); C(8)–N(9) 1.347(3); C(1)–N(9) 1.339(2); C(1)N(6)C(7) 106.02(15); C(7)C(8)N(9) 112.95(17). Compound **23**: C(58)–C(59) 1.350(5); C(58)–N(57) 1.349(5); C(52)–O(60) 1.376(4); C(51)N(57)C(58) 118.7(3); C(52)O(60)C(59) 116.0(3) (Table 1).

Acknowledgments

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Table 1. Crystal data and parameters pertaining to structural analyses of **20**, **23**

Parameters	Compound **20**	Compound **23**
Chemical formula	$C_{12}H_{12}N_2O_4$	$C_{10}H_{10}N_2O_3$
Formula weight (g mol^{-1})	248.23	206.20
Crystallization solvent	CH_2Cl_2	Acetone/ethanol
Temperature (K)	296(2)	296(2)
Crystal size (mm)	0.50×0.50×0.45	0.25×0.25×0.10
Wavelength (Å)	1.54178	1.54178
Crystal system, space group	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$
Goodness-of-fit on F^2	1.089	1.106
Unit-cell dimensions	a=8.370(3) Å	a=5.577(1) Å
	b=11.766(4) Å	b=7.822(2) Å
	c=13.202(6) Å	c=22.724(4) Å
	α=103.86(3)°	α=95.54(2)°
	β=105.25(4)°	β=95.37(4)°
	γ=91.38(3)°	γ=103.37(2)°
Volume ($Å^3$)	1212.6(8)	953.0(3)
Z, calculated density	4, 1.360 Mg m^{-3}	4, 1438 Mg m^{-3}
Absorption coefficient	0.874 mm^{-1}	0.454 mm^{-1}
F(000)	520	432
θ Range for data collection	3.59–64.93°	3.94–64.88°
Index ranges	$-9\leq h\leq 9$	$-6\leq h\leq 6$
	$-13\leq k\leq 13$	$-9\leq k\leq 9$
	$-0\leq l\leq 15$	$0\leq l\leq 26$
Reflections collected	4019	3211
Maximum and minimum transmission	0.6945 and 0.6691	0.9560 and 0.8949
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data, restraints, parameters	4019, 0, 326	3211, 0, 272
Final R indices ($I>2\sigma(I)$)	R_1=0.0466, wR_2=0.1397	R_1=0.0659, wR_2=0.1805
R indices (all data)	R_1=0.0496, wR_2=0.1426	R_1=0.0798, wR_2=0.1887
Extinction coefficient	0.020(2)	0.040(4)
Largest diff. peak and hole	0.293 and −0.287 e. $Å^{-3}$	0.274 and −0.276 e. $Å^{-3}$

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