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Synthesis of Annelated NADH Models in Benzothieno[2,3-b]pyridine and Pyrido[2,3-b]indole Series

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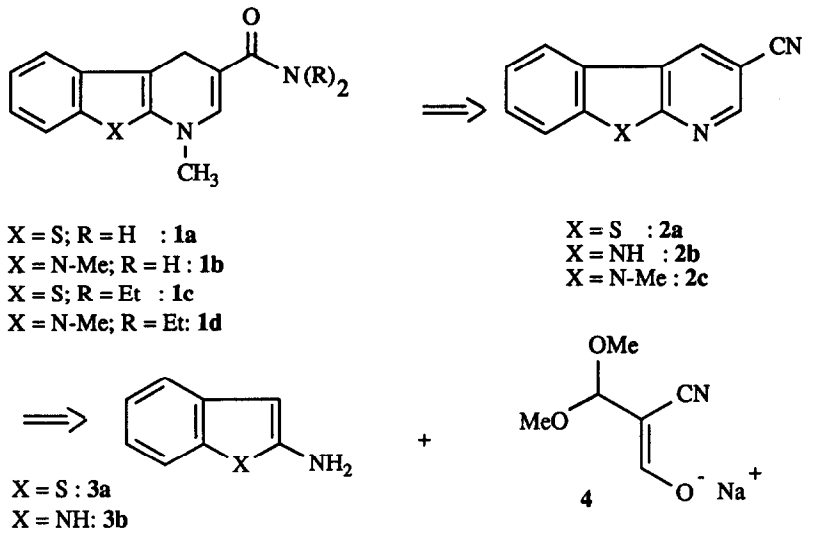
Abstract: *NADH models in the benzothieno[2,3-b]pyridine and pyrido[2,3-b]indole series have been synthesized. The key step of the synthesis is the ring closure reaction between the appropriate indole or benzothiophene amines and a masked 1,3-dicarbonyl compound. This method afforded four new annelated NADH models . One of these models allowed the first preparative reduction of acetophenone with a NADH model.*

In previous papers (1) we described the synthesis and reactivity of some annelated NADH models in the thieno and pyrrolo pyridine series. These reagents are promising NADH models with very good reactivity under mild laboratory conditions. Mg^{2+} catalysis allowed us to reduce efficiently a large number of carbonyl substrates. Though it is frequently claimed that only activated unsaturated bonds with electron-withdrawing substituents can be efficiently reduced with NADH models, we have already shown that the use of very reactive NADH models like pyrrolodihydropyridine derivatives can broaden notably the scope of such reduction reagents (2). Moreover, good enantiomeric excesses were obtained in the reduction of prochiral substrates (3). It was shown that acid catalysis promotes reduction of a few nonactivated substrates by annelated models in the quinoline series in which the fragile 5,6 carbon-carbon double bond is protected (4) (the reactivity of quinoline NADH models is rather weak and the reduction yields are low). We tried to use acid catalysis with our thieno and pyrrolo[2,3-b]pyridine NADH models ; however, in all cases the reduction yields of nonactivated substrates such as benzaldehyde in acidic media were low and we observed as side reaction, a Friedel-Crafts type acylation of the pi-excess ring (e.g. pyrrole or thiophene). In order to avoid this kind of side reactions we planned to protect the pi-excess ring with a benzene nucleus. So, we focused our interest on the synthesis of NADH models in the benzothieno[2,3-b]pyridine and pyrido[2,3-b]indole series (scheme 1, compounds **1a-d**).



Scheme 1

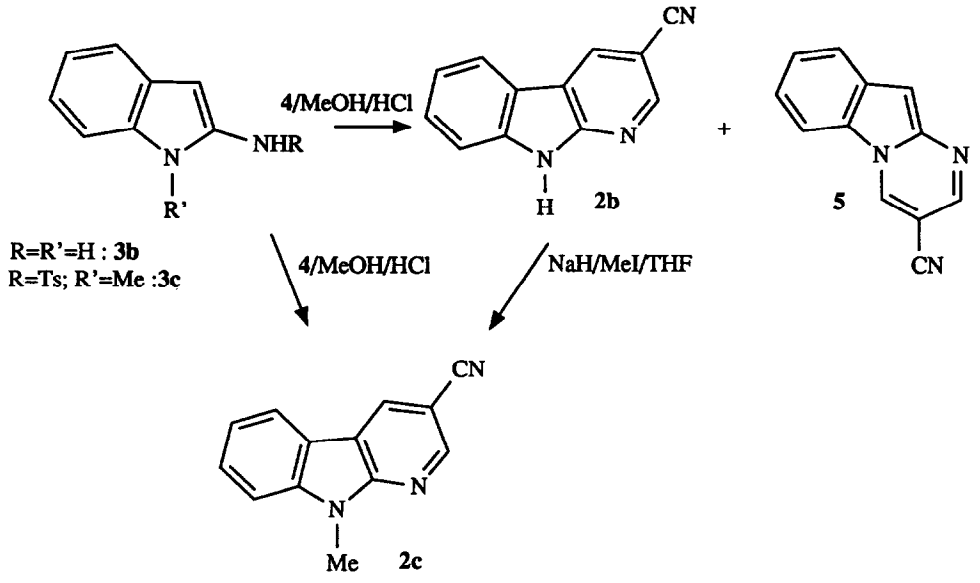
Our choice can be explained on the basis of two main reasons : 1) benzene is less reactive than thiophene or pyrrole in $SEAr_2$ reactions, so it could be anticipated that the above mentioned side reactions would not occur with Lewis or Brönsted acid catalysis; 2) it could also be anticipated that the stabilizing effect exerted by the presence of two aromatic rings fused to the dihydropyridine structure would increase the stability of the tricyclic models in acidic media.

The key precursors of the target products **1** are the gamma substituted annelated pyridines **2**. To our knowledge, these precursors have not been described in the literature and, moreover, few methods are available for the synthesis of their skeleton. We selected the construction of the tricyclic system by annelation of a suitable pyridine ring to a benzo[b]thiophene or an indole derivative. Other methods involving insertion of a thiophene or a pyrrole ring in a phenyl pyridine compound would be more difficult, could not be used with a nitrile or carboxamide group and are known to give poor yields. Recently, we have reported a facile synthesis of annelated NADH models precursors (5) involving the reaction of 3,3-dimethoxy-2-formyl-propionitrile sodium salt **4** with amines, derived from various electron-donating heterocycles, in an easy one pot process. We now report the synthesis of the target compounds **1a-d** using this methodology following the retro-synthetic approach summarized in scheme 1.

Benzothieno[2,3-b]pyridines

Large amounts of 2-amino-benzo[b]thiophene **3a** were required for the proposed approach. We first used the amine hexachlorostannate obtained from tin/hydrochloric acid reduction of 2-nitro-benzo[b]thiophene (5). However, this reduction was rather irreproducible and we preferred the synthesis of the free amine described by Stacy et al (6). Starting from thiosalicylic acid, the required amino compound was obtained in five steps with an overall yield of 45 %. This very unstable amine had to be immediately reacted with synthon **4** to afford quantitatively benzo[b]thieno[2,3-b]pyridine-3 carbonitrile **2a**.

Pyrido[2,3-b]indoles

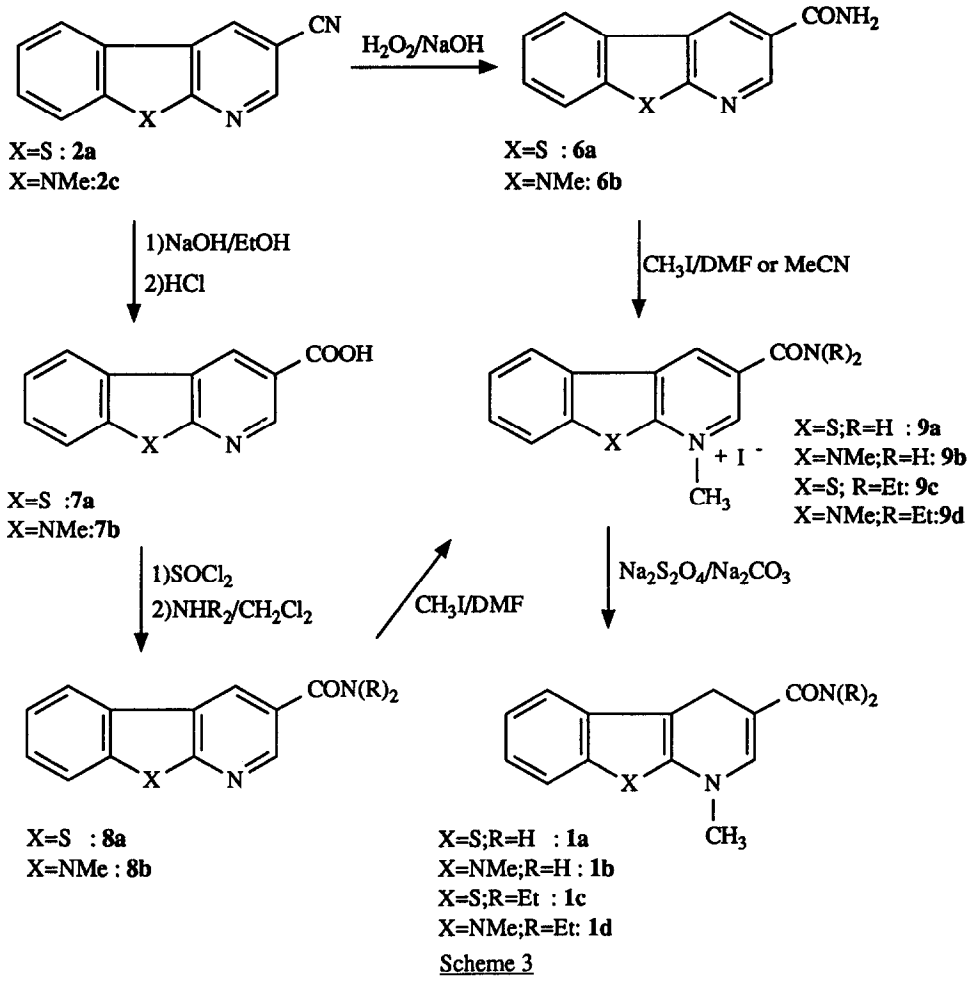


Scheme 2

Starting from 2-nitrophenylacetic acid, 2-amino-indole **3b** could be readily obtained in four steps by the Pschorr and Hoppe method (7). However, the reaction of this amine with compound **4** was more difficult than in the preceeding case. Under the usual conditions (reflux in acidic methanol) a lot of tarry materials were obtained with a small amount of the target compound **2b**. It was impossible to separate **2b**, so the crude reaction mixture was submitted to methylation with the sodium hydride/methyl iodide system in THF yielding **2c** with a 17 % overall yield. When performed at lower temperature, the same reaction afforded less tarry materials but a mixture of two compounds : the expected pyridoindole and the pyrimido[1,2-a]indole **5**, resulting from N-ring closure with the in situ liberated 1,3-dicarbonyl compound. In order to avoid this N-ring closure we reacted the synthon **4** with a N-methylated derivative of the amine **3b**. Preparation of 2-amino-1-methylindole is rather tedious on large scale (8) and this compound, like **3b**, is not very stable. For these reasons, we reacted synthon **4** with the N-methyl tosylated amine **3c**, readily obtained from 1-methylindole and tosyl azide (9). Using classical conditions, i.e. reflux in acidic methanol, alpha carboline **2c** was obtained in a good yield (70 %) and the product could be easily purified by column chromatography.

Synthesis of the annelated NADH models:

Having in hand the tricyclic precursors with a good substituent in the desired position, we transformed the nitrile groups into carboxamides moieties. This transformation was achieved by classical hydrolysis in alkaline medium containing hydrogen peroxide, whereupon carboxamides **6a** and **6b** were obtained in good yields (scheme 3):

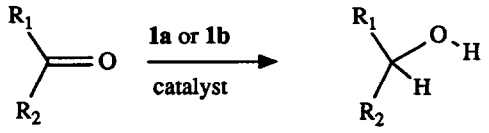


Scheme 3

The NADH models were obtained via quaternization of annelated pyridines **6a** and **6b** with methyl iodide followed by regioselective reduction of the pyridinium salts **9a** and **9b** with sodium dithionite in aqueous sodium carbonate. The so obtained annelated NADH models **1a,b** had a poor solubility in organic solvents such as acetonitrile. In order to get more soluble reagents, we decided to replace the carboxamide group by a diethylcarboxamide moiety. Another feature of this replacement could be the improvement of reactivity of the corresponding NADH models. Such an increase has already been observed in the literature (10) in the case of simple NADH models where the two ethyl groups lower the electron withdrawing character of the amide and thus facilitate the departure of a hydride equivalent in the reduction process. After total hydrolysis of the nitriles **2a** and **2c**, the corresponding carboxylic acids were obtained in almost quantitative yields. Reaction of these acids with an excess of thionyl chloride and subsequent treatment with diethylamine afforded the diethylcarboxamides **8a,b**. As in the preceeding case, the NADH models were synthesized in two steps (scheme 3) : 1)-quaternization with methyl iodide to give the pyridinium salts **9c,d**.

2)-subsequent regioselective reduction with sodium dithionite yielding the dihydropyridines **1c,d**. This methodology allowed us to obtain four new annelated NADH models in good overall yields, with different solubilities and various potential reactivities.

First results in reduction of carbonyl compounds using acid catalysis:



R_1= $pNO_2C_6H_4$-,R_2 = H : **11**

R_1= Ph, R_2 = COOMe : **12**

R_1= Ph, R_2 = CH_3 : **13**

Scheme 4

As already mentioned, NADH models of type **1** are chemoselective reagents and could be used under influence of acid catalysts. Up to now, some acid stable models have been used, under drastic conditions, for performing the reduction of nonactivated substrates (11) but within a rather narrow scope, e.g. 2-haloacetophenones under Lewis acid catalysis or benzaldehydes and alpha haloketones with perchloric acid. It should be emphasized that reduction of acetophenones or alkyl ketones with a NADH model remains a challenge. We first tried to use reagent **1a** with various Brönsted acids (hydrochloric acid, trichloro or trifluroacetic acids, perchloric acid) in the reduction of p. nitrobenzaldehyde, a substrate commonly used in our laboratory to evaluate the reactivity of NADH model compounds. In all cases, no reduction was observed. So, we decided to use Lewis acids like aluminium halides. The results are reported in the following table:

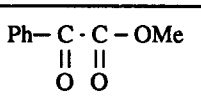
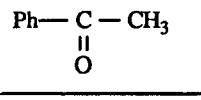
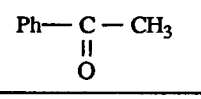
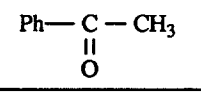
Compound	Solv.	Reag.	Cata.	θ (°C)	Yield (%)
	CH_3CN	**1a**	$AlCl_3$	25	87
	PhH	**1a**	$AlBr_3$	55	85
	CH_3CN	**1a**	$AlCl_3$	25	96
	CH_3CN	**1a**	$AlCl_3$	25	0
	PhH	**1a**	$AlBr_3$	55	80
	CH_3CN	**1b**	$AlCl_3$	55	35

Table 1: reduction of various substrates with reagents **1a** and **1b**.
The reaction time was 24 h, with 3 eq. of Lewis acid.

As it can be seen, both p. nitrobenzaldehyde and methyl benzoylformate could be reduced with model **1a** and aluminium chloride (3 eq mol.) in acetonitrile as a solvent. However, acetophenone was not reducible in these conditions or at higher temperatures. Aluminium bromide is known to be a better Lewis acid than aluminium chloride but not compatible with acetonitrile (12). For these reasons, benzene was used as a solvent and in despite of the fact that the reaction mixture was not homogeneous, aluminium bromide (3 eq.) allowed, with model **1a**, the reduction of acetophenone to sec-phenethyl alcohol **13** (scheme 4). The yield was good (80 %) and, to our knowledge, it is the first successfull reduction of acetophenone with a NADH model. With reagent **1b** side-reactions were observed with the aluminium bromide/benzene system, but acetophenone could be reduced in 35 % yield with aluminium chloride/acetonitrile. These first results are interesting and we are now investigating more versatile reaction mediums, with other Lewis acids and the work concerning the reactivity of the other reagents is in progress. Tricyclic chiral models have also been synthesized in this series and their reactivity will be published soon.

EXPERIMENTAL SECTION

The infrared spectra were recorded on a BECKMAN IR 4250 spectrometer. The ^1H NMR spectra were recorded on a 60 MHz VARIAN EM 360 L spectrometer or on a 400 MHz BRUCKER AM 400 spectrometer. Chemical shifts are recorded in parts per million (ppm). Unless otherwise stated, the solvent was deuteriochloroform. Microanalyses were obtained from a CARLO ERBA 1106 apparatus. Melting points were determined with a KOFLER bank. TLC was performed on silica gel (precoated silica gel plate 60 F_{254}, Merck).

Benzo[b]thieno[2,3-b]pyridine-3-carbonitrile : **2a**.

To a stirred mixture of 2-amino-benzo[b]thiophene **3a** (3.6 g, 24.1 mmoles) (6) and 3,3-dimethoxy-2-formyl propionitrile sodium salt **4** (9 g, 54.6 mmoles) in methanol (50 ml) were added dropwise 2 ml of concentrated aqueous hydrochloric acid.

The reaction mixture was then gently heated and refluxed for 24 h. After cooling, the solution was concentrated on a rotary evaporator to half of its initial volume, the yellow solid was filtered and washed with cold ethanol (ca 50 ml). After drying, the yield was 4.86 g (96 %). m.p. = 210°C. ^1H NMR (60 MHz, DMSO-d6) : 7.4-8.2 (m, 4H, H_5, H_6, H_7 and H_8); 8.53 (d, J = 2 Hz, 1H, H_4); 8.80 (d, J = 2 Hz, 1H, H_2). IR : 2235 (C≡N); 1590 (C=C). Anal. calcd for $C_{12}H_6N_2S$: C, 68.55; H, 2.88; N, 13.32. Found : C, 68.0; H, 2.85; N, 13.2.

9-methyl-[9H]-pyrido[2,3-b]indole-3-carbonitrile: **2c**.

A mixture of tosylated amine **3c** (4 g, 13.3 mmoles) (9), 3,3-dimethoxy-2-formyl propionitrile sodium salt **4** (4.7 g, 28.5 mmoles) and concentrated hydrochloric acid (3 ml) in methanol (50 ml) was heated at 70°C for 18 h. The solvent was then removed under reduced pressure and a small amount of water was added. The product was filtered, dried and purified by flash chromatography (silica, dichloromethane). m.p. = 158 °C. ^1H NMR (60 MHz, $CDCl_3$): 3.9 (s, 3H, N-CH_3); 7.55 (m, 3H, H_6, H_7, and H_8); 8.10 (m, 1H, H_5); 8.3 (d, 1H, J= 2 Hz, H_2); 8.65 (d, 1H, J= 2 Hz, H_4). IR: 2220 (C≡N). Anal. calcd for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.0; H, 4.3; N, 20.2.

Benzo[b]thieno[2,3-b]pyridine-3-carboxamide : **6a**.

A mixture of nitrile **2a** (3 g, 14.3 mmoles), 30 % hydrogen peroxide (6 ml, 58.7 mmoles) and aqueous 6N sodium hydroxide (1.2 ml, 7.2 mmoles) in methanol (50 ml) was stirred at 40 °C for 24 h under an argon atmosphere. After cooling, the solid was collected and washed with hot water. The yield was quantitative (3.26 g). m.p.>250°C. ^1H NMR (60 MHz, DMSO-d6) : 7.6 (m, 2H, H_6 and H_7); 7.9-8.5 (m, 2H, H_5 and H_8); 9.1 (s, 2H, H_2 and H_4). IR : 3360 and 3120 (NH); 1685 (C=O). Anal. Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.27. Found : C, 62.9; H, 3.4; N, 12.2.

9-methyl-[9H]-pyrido[2,3-b]indole-3-carboxamide: **6b**.

A mixture of nitrile **2c** (1.85 g, 9 mmoles), 30 % hydrogen peroxide (4.6 ml, 45 mmoles), aqueous 3N sodium hydroxide (1.2 ml, 3.6 mmoles) in ethanol (90 ml) was stirred at 30 °C for 18 h. The reaction was monitored by TLC (silica, dichloromethane). The resulting mixture was acidified with 1N sulphuric acid, the precipitated material was filtered and dried to afford 1.61 g (80 %) of crude amide **6b**. This compound can be purified by recrystallization from ethanol/water (1/1). m.p.= 230°C. ^{1}H NMR (60 MHz, DMSO d-6); 3.95 (s, 3H, N-CH_3); 7.4 (m, 3H, H_6, H_7 and H_8); 8.2 (m, 1H, H_5); 8.9 (d, J= 2 Hz, 1H, H_4); 9.0 (d, J= 2 Hz, 1H, H_2). IR: 1680 (C=O); Anal. calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.4; H; 4.7; N, 18.5.

3-aminocarbonyl-1-methyl-benzo[b]thieno[2,3-b]pyridinium iodide: **9a**

A suspension of amide **6a** (5 g, 21.9 mmoles) in acetonitrile (150 ml) and methyl iodide (20 ml, 320.8 mmoles) was gently refluxed for 24 h. After cooling, ether (100 ml) was added and the pyridinium salt filtered and washed with a small amount of ether. After drying the yield was 8.1 g (quantitative) of pure **9a**. m.p.>250°C. ^{1}H NMR (200 MHz, DMSO-d6): 4.58 (s, 3H, N-CH_3); 7.83 (m, 2H, H_6 and H_7); 8.21 (broad s, 1H, NH); 8.43 (m, 1H, H_8); 8.56 (s, 1H, NH); 8.62 (m, 1H, H_4); 9.66 (d, J = 2 Hz, 1H, H_4); 9.84 (d, J = 2 Hz, 1H, H_2). IR: 1690. (C=O). Anal. calcd for $C_{13}H_{11}IN_2OS$: C, 42.18; H, 2.96; N, 7.57. Found: C, 42.0; H, 2.65; N, 7.62.

3-aminocarbonyl-1,9-dimethyl[9H]pyrido[2,3-b]indolium iodide: **9b**.

A solution of amide **6b** (1.68 g, 7.5 mmoles) in freshly distilled DMF (7ml) and methyl iodide (5 ml, 80.2 mmoles) was stirred at 70°C for 5 days. The product was filtered washed with ether and dried. The yield was 2.7g (98 %) m.p.>250°C . ^{1}H NMR (60 MHz, DMSO-d6): 4.35 (s, 3H, N-CH_3 indole); 4.8 (s, 3H, N-CH_3); 7.7(m, 3H, H_6, H_7 and H_8); 8.4 (m, 1H, H_5); 9.1 (d, J= 2 Hz, 1H, H_2); 9.6 (d, J= 2 Hz, 1H, H_4). IR: 1675 (C=O). Anal. calcd for $C_{14}H_{14}IN_3O$: C, 45.79; H, 3.84; N, 11.44. Found: C, 45.4; H, 3.8; N, 11.3

3-aminocarbonyl-1,4-dihydro-9-methyl-benzo[b]thieno[2,3-b]pyridine: **1a**.

The pyridinium salt **9a** (0.37 g, 1mmole) was dissolved in desoxygenated water (100 ml). A freshly prepared solution of sodium dithionite (1 g, 5.75 mmoles) and anhydrous sodium carbonate (0.5 g, 4.7 mmoles) in desoxygenated water (40 ml) was then added to the stirred mixture under an argon atmosphere, in the dark. The precipitated material was filtered, washed with a lot of water and recrystallized from ethanol/water (70/30) to yield fine yellow needles. m.p. not defined. ^{1}H NMR (60 MHz, DMSO-d6): 3.2 (s, 3H, N-CH_3); 3.25 (s, 2H, CH); 6.8 (broad s, 2H, NH); 7.0-7.4 (m, 4H, H_2, H_5, H_6 and H_7); 7.8 (m, 1H, H_5). ^{13}C NMR (DMSO-d6): 22.9 (CH_2); 39.8 (N-CH_3); 103.2 (C_3); 108.5 (C_{4a}); 119.4 (C_8); 122.3 (C_5 and C_7); 125.09 (C_6); 132.7 (C_{8a}); 138.1 (C_2); 138.9 (C_{4b}); 141.1 (C_{8b}); 169.1 (C=O). Anal. calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47. Found: C, 63.2; H, 4.8; N, 11.2.

1,9-dimethyl-1,4-dihydro[9H]pyrido[2,3-b]indole-3-carboxamide: **1b.**

A solution of the above pyridinium salt **9b** (0.367 g, 1 mmole) in water (10 ml) was added in one portion to a freshly prepared solution of sodium dithionite (1.54 g, 8.6 mmoles) and sodium carbonate decahydrate (1.34 g, 4.7 mmoles) in water (10 ml). The mixture was stirred in the dark under an argon atmosphere for 1 h. The dihydropyridine was extracted with dichloromethane, the organic layers were dried with magnesium sulphate and evaporated to dryness to give a red oil. It was impossible to obtain an analytical sample of this compound but it was pure enough to be engaged in reduction reactions. ^{1}H NMR (60 MHz, $CDCl_3$): 3.5 (s, 3H, N-CH_3); 3.8 (s, 5H, N-CH_3 and CH_2); 7.25 (m, 5H, H_2, H_5, H_6, H_7, H_8). ^{13}C NMR (DMSO d-6): 27.16; 44.20; 37.57; 97.66; 110.71; 114.46; 121.61; 125.07; 125.24; 131.92; 141.37; 143.4; 146.38; 174.79. IR: 1650 (C=O).

Benzo[b]thieno[2,3-b]pyridine-3-carboxylic acid: **7a**.

A suspension of nitrile **2a** (3 g, 14.3 mmoles), 20 % aqueous sodium hydroxide (60 ml) in ethanol (100 ml) was refluxed, with stirring for 48 h. After cooling, water (100 ml) was added and the solution was extracted twice with dichloromethane (2 x 50 ml) in order to remove the impurities. The solution was slowly acidified with 10 % sulphuric acid, with cooling and stirring, the precipitated material was collected by filtration and thoroughly washed with hot water. After drying the yield was 3.1 g (96 %) of pure **7a**. m.p. not defined because of decomposition. ^{1}H NMR (60 MHz, DMSO-d6): 7.1-7.7 (m, 2H, H_6 and H_7); 8.0 (m, 1H, H_8); 8.45 (m, 1H, H_5); 9.05 (s, 2H, H_2 and H_4). IR: 1720 (C=O). Anal. calcd for $C_{12}H_7NO_2S$: C, 62.87; H,

3.08; N, 6.11. Found: C, 62.2; H, 2.8; N, 5.9.

9-methyl[9H]pyrido[2,3-b]indole-3-carboxylic acid: **7b**

A mixture of nitrile **2c** (2g, 9.65 mmoles), 25 % aqueous sodium hydroxide (47ml) in ethanol (20 ml) was refluxed with stirring for 24 h. After cooling, the reaction mixture was acidified with diluted hydrochloric acid at pH = 6. The white precipitate was filtered and dried. The yield was quantitative. m.p.> 250 °C. ^{1}H NMR (60 MHz, DMSO-d6) : 3.85 (s, 3H, N-CH_3); 7.4 (m, 3H, H_5, H_6 and H_7); 8.25 (m, 1H, H_8); 9.0 (s, 2H, H_2 and H_4). IR: 1690 (C=O). Anal. calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.9; H, 4.1; N, 12.1.

3-(N,N)-diethylaminocarbonyl-benzo[b]thieno[2,3-b]pyridine: **8a**

A mixture of acid **7a** (3 g, 13.09 mmoles) and freshly distilled thionyl chloride (20 ml) was refluxed for 24 h. After removal of the excess of thionyl chloride by distillation and classical work-up with benzene, the residue was dissolved in anhydrous dichloromethane (20 ml) and the resulting solution added at 0°C, via a syringe, to a stirred mixture of triethylamine (1.6 g, 15.8 mmoles) and diethylamine (1 g, 13.7 mmoles) in dichloromethane (20 ml). After addition, the mixture was allowed to warm to room temperature and stirred for 24 h. The organic layer was washed with water, dried with magnesium sulphate. After removal of solvent, an oil was obtained. ^{1}H NMR (60 MHz, $CDCl_3$): 1.25 (t, J = 7 Hz, 6H ,CH_3); 3.45 (q, J = 7 Hz, 4H, CH_2); 7.4-7.75 (m, 2H, H_6 and H_7); 7.8-8.25 (m, 2H, H_5 and H_8); 8.5 (d, J = 2 Hz, 1H, H_4); 8.7 (d, J = 2 Hz, 1H, H_2). It was impossible to obtain an analytical sample of this compound. It was employed, without further purification in the following quaternization with methyl iodide.

3-(N,N)-diethylaminocarbonyl-9-methyl-benzo[b]thieno[2,3-b]pyridinium iodide: **9c**.

The above amide **8a** was dissolved in acetonitrile (20 ml) containing methyl iodide (10 ml) and the mixture refluxed for 24 h. The reaction mixture was then concentrated to half of its initial volume and ether (20 ml) was added. The precipitated material was filtered, washed with ether and dried to yield 3.8 g (68 % on **7a**) of pure pyridinium salt **9c**. m.p. = 220 °C. ^{1}H NMR (200 MHz, DMSO d-6): 1.15 (m, 6H, CH_3); 3.35 (m, 4H, CH_2); 4.55 (s, 3H, CH_3); 7.6-8.0 (m, 2H, H_6 and H_7); 8.4 (m, 1H, H_8); 8.75 (m, 1H, H_5); 9.4 (d, J = 2 Hz, 1H, H_4); 9.55 (d, J = 2 Hz, 1H, H_2). IR : 1630 (C=O). Anal. calcd for $C_{17}H_{19}IN_2OS$: C, 47.90; H, 4.49; N, 6.57. Found: C, 48.0; H, 4.3; N, 6.6.

3-(N,N)-diethylaminocarbonyl-1,4-dihydro-9-methyl-benzo[b]thieno[2,3-b]pyridine: **1c**.

We used the procedure described for compound **1a**. Starting from **9c** (0.43 g, 1 mmole), no precipitated material was obtained after reaction with sodium dithionite. The mixture was extracted twice with dichloromethane, the organic layer concentrated in vacuo after drying on magnesium sulphate, leaving **1c** as an oil (0.216 g, 72 %). It was impossible to obtain an analytical sample of this compound. ^{1}H NMR (60 MHz, $CDCl_3$): 1.2 (t, J = 7 Hz, 6H, CH_3); 3.15 (s, 3H, N-CH_3); 3.4 (q, J = 7 Hz, 4H, CH_2); 3.7 (s, 2H, CH_2); 6.2 (s, 1H, H_2); 7.0-7.5 (m, 3H, H_6, H_7 and H_8); 7.7 (m, 1H, H_5).

3-(N,N)-diethylaminocarbonyl-9-methyl[9H]pyrido[2,3-b]indole: **8b**.

A solution of acid **7c** (2.45 g, 10.8 mmoles) in thionyl chloride (50 ml) was refluxed for 12 h. The excess of thionyl chloride was distilled under reduced pressure, benzene was then added to the residue and removed by distillation.

The crude acid chloride was dissolved in dichloromethane (20 ml) and added, via a syringe to a well cooled mixture of freshly distilled diethylamine (1.58 g, 2.25 ml, 21.6 mmoles) in dichloromethane (20 ml). During the addition, the temperature was maintained at 0 °C and then the resulting mixture was kept at 0 °C under stirring. Water (10 ml) was added, the organic layer separated and the aqueous layer extracted with dichloromethane. The organic layers were dried and evaporated to give 2.44 g (80 %) of amide **8b**. The product was purified by flash chromatography (silica/ethyl acetate). Oil. ^{1}H NMR (60 MHz, $CDCl_3$): 1.25 (t, J= 7Hz, 6H, CH_3); 3.5 (q, J = 7 Hz, 4H, CH_2); 3.95 (s, 3H, N-CH_3); 7.45 (m, 3H, H_6, H_7, H_8); 8.05 (m, 1H, H_5); 8.4 (d, J = 2 Hz, 1H, H_4); 8.55 (d, J = 2 Hz, 1H, H_2). IR: 1630 (C=O); 2930 and 2970 (CH). Anal. calcd for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.81; N, 14.93. Found: C, 72.4; H, 6.7; N, 15.0.

3-(N,N)-diethylaminocarbonyl-1,9-dimethyl[9H]pyrido[2,3-b]indolium iodide : **9d**.

A solution of the above amide **8b** (2.55 g, 9.1 mmoles purified by flash chromatography) in dry acetonitrile (10 ml) and methyl iodide (10 ml) was refluxed for 4 days. The pyridinium salt was filtered and

dried. The yield was 3.0 g (78 %). m.p. > 250 °C. ^{1}H NMR (60 MHz, DMSO-d6): 1.15 (t, J = 7 Hz, 6H, CH_3); 3.4 (q, J = 7 Hz, 4H, N-CH_2); 4.35 (s, 3H, N-CH_3); 4.75 (s, 3H, N-CH_3); 7.65 (m, 3H, H_6, H_7, H_8); 8.45 (m, 1H, H_5); 8.8 (d, J = 2 Hz, H_4); 9.25 (d, J = 2 Hz, H_2). Anal. calcd for $C_{18}H_{22}IN_3O$: C, 51.07; H, 5.24; N, 9.93. Found: C, 50.8; H, 4.8; N, 9.5.

3-(N,N)-diethylaminocarbonyl-1,4-dihydro-1,9-dimethyl-[9H]pyrido[2 ,3-b]indole : **1d.**

A solution of the above pyridinium salt **9d** (0,52 g, 1.23 mmoles) in methanol (20 ml) was added in one portion to a stirred mixture of sodium dithionite (1.71 g, 9.8 mmoles) and anhydrous sodium carbonate (0.62 g, 5.8 mmoles) in desoxygenated water (20 ml). The resulting solution turned red and then became yellow. Extraction with dichloromethane, drying and removal of the solvent afforded 0.33g (89 %) of a red oil. No analytical sample could be obtained. ^{1}H NMR (60 MHz, $CDCl_3$): 1.2 (t, J = 7 Hz, 6H, CH_3); 3.25 (s, 3H, N-CH_3); 3.45 (q, J = 7 Hz, 4H, N-CH_2); 3.7 (s, 3H, N-CH_3 indole); 3.75 (s, 2H, CH_2); 6.15 (s, 1H, H_2); 7.15 (m, 4H, H_5, H_6, H_7, H_8).

Reduction of acetophenone with the dihydropyridines **1a**, **1b**:

A suspension of the dihydropyridine **1a** (0.27 g, 1.1 mmole) and acetophenone (0.12 g, 1mmole) in anhydrous benzene (5 ml) was stirred for 5 mn, at 0 °C, under an argon atmosphere, in the dark. Anhydrous aluminium bromide (0.8 g, 3.0 mmoles) was then added and the mixture allowed to warm to room temperature under vigorous stirring. A gummy solid appeared and the reaction mixture was stirred at 55 °C for 24 h. After cooling to room temperature, ice (10 g) was added and the aqueous layer extracted twice with dichloromethane (100 ml). The combined organic layers were washed with 0.1 N NaOH (10 ml) and then twice with brine (10 ml). After drying with magnesium sulphate, the solvent was removed and the residue chromatographied on silica (hexane and then progressive addition of diethyl ether in the elution solvent, the final composition of the eluent system was 40 % ether and 60 % hexane). The yield of pure 1-phenylethanol **13** was 0.097 g (80 %).^{1}H NMR (60 MHz, $CDCl_3$): 1.45 (d, J = 7 Hz, 3H, CH_3); 2.15 (s, 1H, OH); 4.75 (q, J = 7 Hz, 1H, CH); 7.25 (s, 5H, phenyl ring).

A similar reduction was performed with dihydropyridine **1b**, affording alcohol **13** in 35 % yield after the same work up.

Reduction of p.nitrobenzaldehyde with the dihydropyridine **1a**:

p.nitrobenzaldehyde (1 mmole) was reduced with reagent **1a** in acetonitrile (5 ml) and aluminium chloride (3 mmoles) or in benzene (5 ml) and aluminium bromide (3 mmoles) as described above but the reaction mixture was homogeneous. The reduction product, p.nitrobenzyl alcohol **11** was purified by flash chromatography on silicagel (hexane/diethyl ether 30/70). ^{1}H NMR (60 MHz, $CDCl_3$): 2.25 (s, 1H, OH); 4.85 (s, 2H, CH_2); 7.5 (d, J = 9 Hz, 2H); 8.2 (d, J = 9 Hz, 2H).

Reduction of methyl benzoylformate with the dihydropyridine **1a**:

Methyl benzoylformate (1 mmole) was reduced with **1a** in acetonitrile (5 ml) and aluminium chloride (3 mmoles) as described above but the reaction mixture was homogeneous. The reduction product, methyl mandelate **12**, was purified by flash chromatography on silicagel (hexane/diethyl ether 70/30). ^{1}H NMR (60 MHz, $CDCl_3$): 3.65 (s, 3H, CH_3); 5.1 (s, 1H, CH); 7.35 (s, 5H, phenyl ring).

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