Tetrahedron Vol. 44, No. 4, pp. 1079 to 1090, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

SYNTHESIS, COMPLEXATION STUDY AND REACTIVITY OF ANNELATED THIOPHENIC NADH MODELS.

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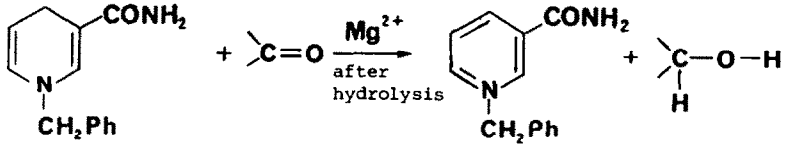
(*Received in Belgium* 30 *November* 1987)

Abstract - The synthesis of two carbamoyl 4,7- dihydrothieno [2,3] pyridines 1a and 1b is described. These derivatives are potential new NADH models. A NMR study of the complexation of magnesium ions by these compounds has been performed. The behaviour of the thieno [2,3-b] derivative is different of that of the thieno [3,2-b] derivative: in the former the sulfur atom plays an important role in the complexation. The biomimetic reduction of p.nitrobenzaldehyde with 1a or 1b has been studied. The reactivity of the thiophenic annelated NADH models is very superior to that of quinoline analogous. It can be compared to the reactivity of common models such as N-Benzyl 1,4-dihydronicotinamide (BNAH). Moreover 1a and 1b can be used in conditions were BNAH is much more less effective.

Reductions with 1,4-dihydropyridine derivatives have been extensively studied as models of reduced pyridine nucleotide (NADH) mediated enzymatic reactions.[1] Among these models,one of the most widely used are N-benzyl 1,4-dihydronicotinamide (BNAH) derivatives. There are a great many references in the literature which give informations about :

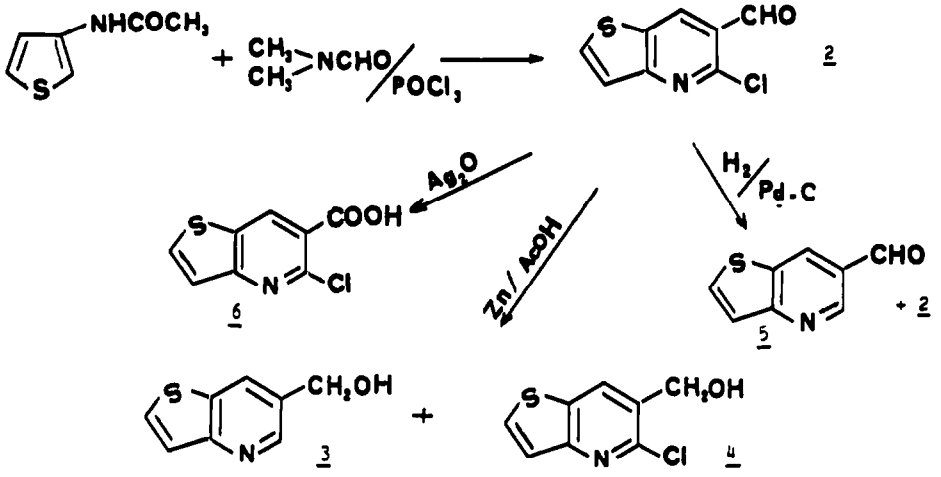
* the scope and limitations of BNAH, its functional group selectivity and the use of chiral derivatives in asymmetric synthesis.[2]

* the mechanism of the hydrogen transfer in such reductions and the role of the divalent metal ion often implicated.[3] The reduction of a carbonyl compound for example can be summarized as follow :



BNAH derivatives undergo side-reactions which cause a dramatic decrease in the efficiency of the reagent. These reactions affect the 5,6-double bond and are favored by the presence of water.[4] We have shown that in drastic conditions the yields in the reduction of some substrates could be greatly improved by the use of hyper dry conditions.[5] In some cases, substrates known to be unreactive towards BNAH, could be reduced. However the experimental conditions involved in these reactions limit the use of BNAH.

Scheme 1 : Attempts to dechlorinate 6-formyl 5-chloro thieno [3,2-b] pyridine



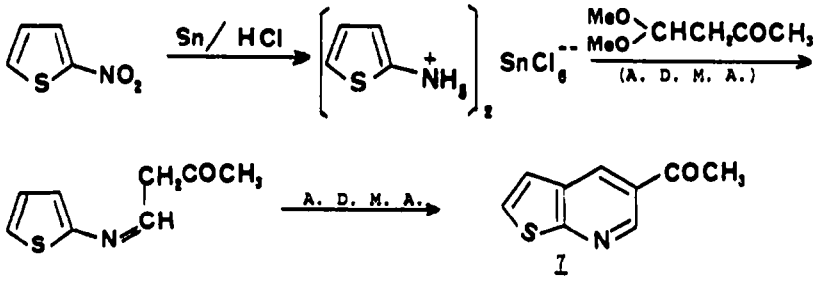
Dechlorination of 2 seemed problematical, so we tried the same methods on the carboxylic acid 6. The product was unreactive towards catalytic hydrogenation, and to the action of zinc and acetic acid.

In the second method, 4-hydroxy 5-cyanothieno [2,3-b] pyridine [9] is obtained from 2-aminothiophene through a difficult cyclisation reaction which is performed at high temperature. Moreover the access to 5-cyanothieno [2,3-b] pyridine implies the chlorination of the oxo derivative, followed by the removal of the chlorine which could also be a problematical reaction.

The third method which we did not try requires the synthesis of the thiophenic precursor (an amino ester derivative) followed by several steps to obtain a chloro thienopyridine derivative.[10]

Finally we used KLEMM,s method which allows access to a carbonyl substituted thieno [2,3-b] pyridine in a one-pot reaction with a 32% yield.[11] By some improvements of the procedure (high dilution, careful control of the temperature) we could obtain 7 in 45% yield from bis-(-2 thienyl ammonium) hexachlorostannate (scheme 2).

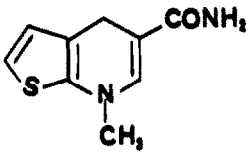
Scheme 2 : Synthesis of 5-acetyl thieno [2,3-b] pyridine 7



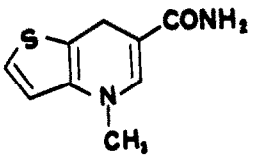
So, a few years ago, molecules have been developed which limit or suppress the side-reactions on the 5,6-double bond. One of the easiest way to do this is to block this bond by annelation with an aromatic ring. This method has been developed by Japanese workers who synthesised NADH models in the quinoline serie.[6]

With these types of models, some good results have been obtained, especially in proton catalysed reduction of aldehydes. However in the classical conditions used with BNAH [solvent CH_3CN, catalyst $Mg(ClO_4)_2$] these models are notably less reactive. We can suppose that the withdrawing effect of the annelated benzene ring, hinders the departure of the hydrogen involved in the reaction.

For this reason we have synthesised models 1a and 1b with an annelated thiophene ring in order to protect the 5,6-double bond of the dihydropyridine as well as to favor the departure of hydrogen through the electrondonating effect of the thiophenic ring.



5-carbamoyl 4,7-dihydro thieno [2,3-b] pyridine 1a



6-carbamoyl 4,7-dihydro thieno [3,2-b] pyridine 1b

The first results obtained with this type of model has been described in a preliminary communication:[7] the models are reactive. The reduction of activated carbonyl compounds occurs at satisfactory rates and the reactivity of models remains high in conditions were BNAH is very much deactivated by water.

We wish to report now the synthesis of these models, a spectral study of their complexation with magnesium ions, and some new results in the reduction of various substrates.

I. SYNTHESIS

There are only a few reported methods, to our knowledge, which can be used to obtain thieno [2,3] pyridines bearing a carbamoyl (or a precursor) in the γ-position of the pyridinic ring.

The first method starts from 3-acetamido thiophene as the non substituted thiophenic amine derivative.[8] We obtained in the best case 6-formyl 5-chloro thieno [3,2-b] pyridine 2 in 50% yield (scheme 1).

The replacement of chlorine by hydrogen has been tried by several methods giving the following results :

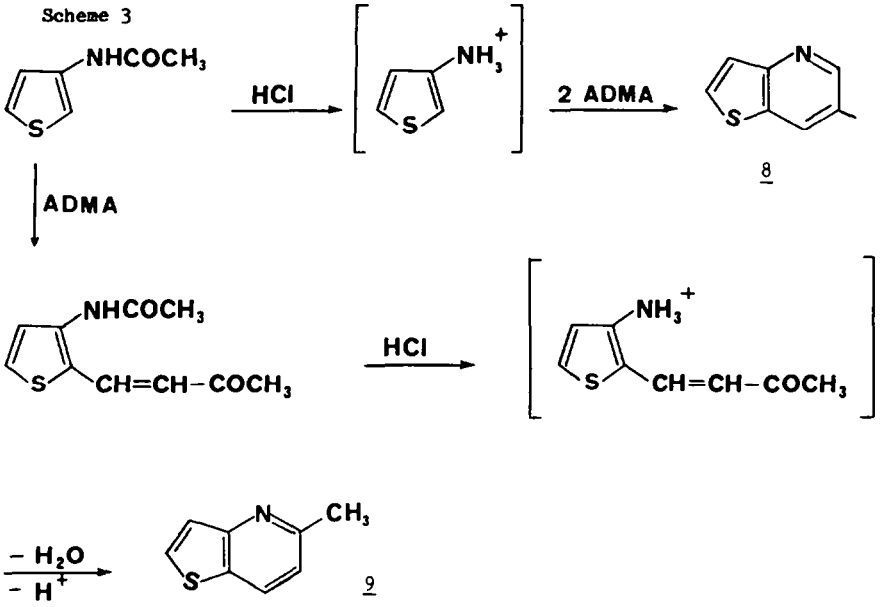
* zinc and acetic acid[11] give a mixture of 6-hydroxymethyl thieno [3,2-b] pyridine 3 and 6-hydroxymethyl 5-chloro thieno [3,2-b] pyridine 4.

* catalytic hydrogenolysis (hydrogen with Pd catalyst) gives a mixture of 6-formyl thieno [3,2-b] pyridine 5 and 30 % of unreacted 2 from which pure 5 could be isolated in poor yield.

To obtain 6-acetyl thieno [3,2-b] pyridine 8 a similar procedure was used. The starting material is 3-acetylaminothiophene and the first step is the in-situ deacetylation of the acetamido group with hydrochloric acid. In these conditions ADMA is involved in two competiting reactions (scheme 3) :

* condensation on the free amine leading to the desired 6-acetyl thieno [3,2-b] pyridine 8.
* condensation on the highly reactive 2-position of the 3-acetylamino thiophene leading to 5-methyl thieno [3,2-b] pyridine 9.[12]

Scheme 3



It is possible to suppress the second reaction by liberating the amino group before introduction of ADMA. With HCl in refluxing ethanol this reaction requires too long (8 hours). By using butanol as solvent, the reaction may be carried out at a higher temperature and the free amine is obtained in 2 hours.

Preparation of NADH models (scheme 4).

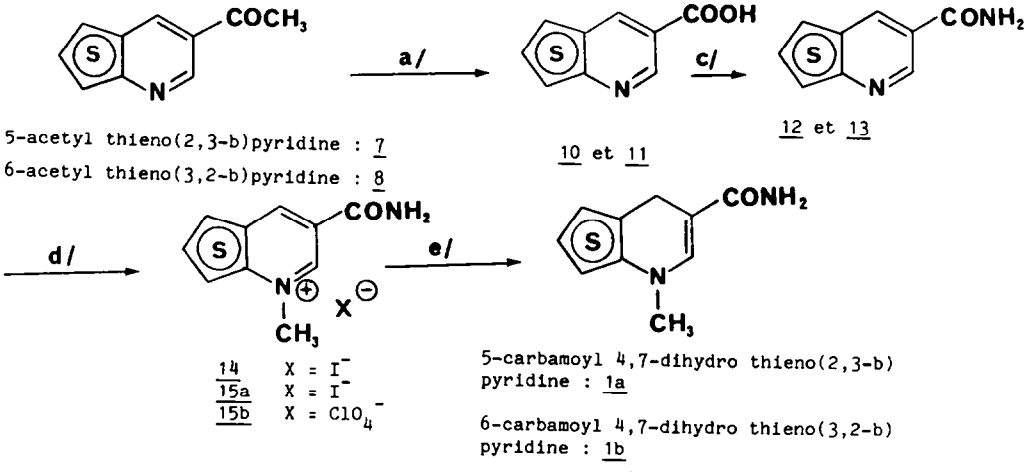
Acetyl derivatives 7 and 8 are oxydized to the corresponding carboxylic acids 10 and 11 by the haloform reaction. The carbamoyl derivatives 12 and 13 are obtained after treatment of the acid chloride with ammonia in CH_2Cl_2 as solvent.

The conversion to the dihydropyridine derivatives is performed by the following sequence : quaternization of compounds 12 and 13 with methyl iodide leading to 14 and 15 and regioselective reduction of the pyridinium salts. In the case of quinolinium isosters, this reduction was accomplished through a transhydrogenation, with BNAH itself.[6c] In our case this reagent is ineffective. (that means that our dihydrothieno [2,3] derivatives are probably stronger reducing agents than quinoline analogs). So we needed to use the classical reducing agent (sodium dithionite) to obtain dihydropyridines 1a and 1b.

However some problems remained : in the case of 14 it is difficult to obtain 1a in a crystalline form and with an analytical purity. It is necessary to carry out the quaternization in DMF (instead of CH_3CN in other cases) and to wash the dihydro thieno pyridine 1a carefully in order to eliminate mineral impurities thoroughly.

With 15 we had still greater difficulties : by using the above procedure described for 14, the yield was never better than 20%. Finally after some unsuccessful attempts it was found necessary to change the counter-ion of 15 by substitution of iodide with perchlorate.[13] Following this modification the reduction yield reaches 60%.

Scheme 4 : Synthesis of carbamoyl 5,7-dihydro thieno [2,3] pyridines 1a and 1b



Reagents : a) Br_2/NaOH b) $SOCl_2$ c) NH_3 in CH_2Cl_2 d)ICH_3 than $Mg(ClO_4)_2$ in the case of 14 ---> 15b e) $Na_2S_2O_4$.

The regioselectivity of the reduction is confirmed by the examination of the NMR spectra of compounds 1a or 1b : the presence of signals in the 3,8 ppm region corresponds to a 1,4-dihydropyridine derivative and the absence of signals in the 4,2 ppm region corresponds to a 1,2-dihydropyridine derivative 14.

II. SPECTRAL STUDY OF THE COMPLEXATION OF MAGNESIUM IONS.

Most of the reductions performed with NADH models require the use of a divalent metal ion as cofactor. This ion probably plays a triple role.[13c and 15]

-it enhances the reactivity of the substrate (a carbonyl compound for example) by complexation, lowering the energy of the lowest unoccupied molecular orbital (LUMO).

-through complexation with the model it lowers its reactivity : the energy of the highest occupied molecular orbital (HOMO) is increased and the departure of the hydrogen involved in the reduction is more difficult.

-it seems, however, that this departure is possible only if a ternary complex between the substrate, the metal ion and the model can be built.[16] The process of hydrogen transfer mediated by a metal ion in an intermediate ternary sandwich-type charge transfer complex is particularly important in asymmetric reductions with chiral models.[17]

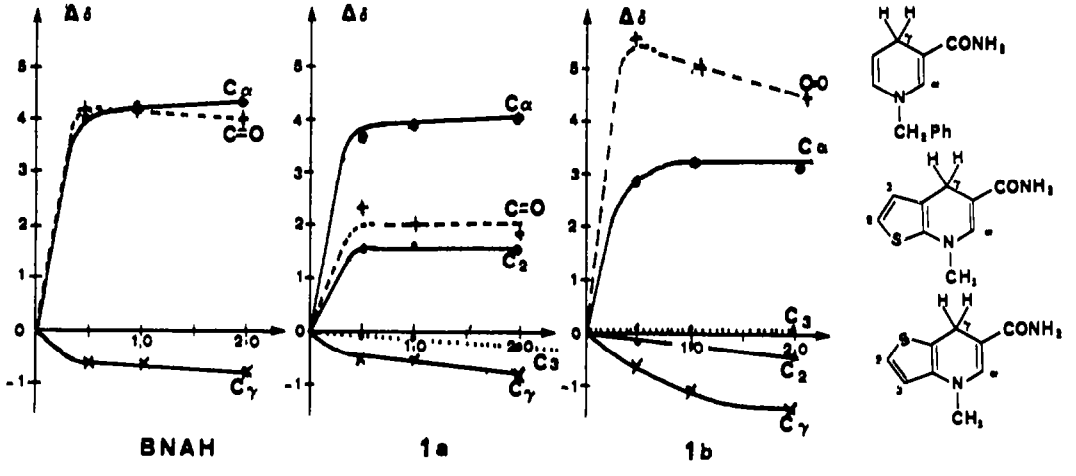
So it appears, that the mode of complexation of Mg^{2+} with our models is important in view to appreciate the reactivity of models 1a and 1b.

A spectroscopic study of the complexation of BNAH with Zn^{2+} has been developed by HUGHES and PRINCE.[18]

In our case, we recorded ^{13}C NMR spectras of 1a and 1b, first without and then with increasing amounts of $Mg(ClO_4)_2$ in CD_3CN as solvent. The chemical shifts of carbon atoms are compared with those of homolog atoms in BNAH in the same conditions.

The variation of chemical shifts ($\Delta\delta$) as a function of amount of magnesium is represented on the following curves (fig. 1).

Fig.1 $\Delta\delta$ of carbon atoms in BNAH, 1a and 1b as a function of magnesium



From these results it can be observed :

1) the $\Delta\delta$ for homolog carbons in BNAH and in 1b are similar.

2) for compound 1a the situation is different :

- the $\Delta\delta$ of the carbon atom of the carbamoyl group is notably lower than that of homolog carbons in BNAH or in 1b.

- on the other hand the 2-thiophenic carbon has a $\Delta\delta$ higher that the $\Delta\delta$ of the same carbon atom in 1b. In fact the thiophenic ring seems more affected by magnesium complexation in the thieno [2,3-b] derivative than in the thieno [3,2-b] derivative.

We think that in the former the vicinity of the sulfur and nitrogen atoms leads to a possibility of complexation of Mg^{2+} by the cleft formed by these atoms. As a consequence the carbamoyl group is less involved than in 1a or in BNAH to insure the complexation : so its effect on the chemical shift of the carbon atom is lowered.

III. REDUCTION OF SUBSTRATES.

1) Reduction of p. nitrobensaldehyde.

In a previous publication, we have shown that models 1a or 1b remain reactive in the presence of water, in conditions, where BNAH becomes less effective (5).

The major reinvestigated results concerning the reduction of p.nitrobenzaldehyde (p.NBA) are summarized in table 1.

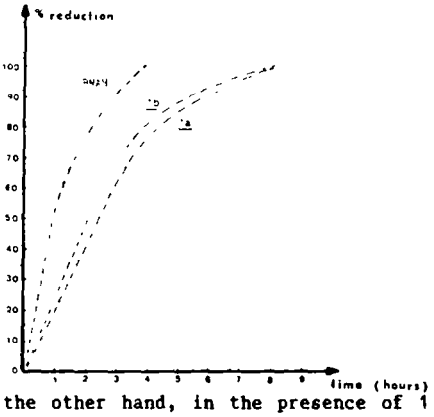
Table 1. Reduction of p. nitrobenzaldehyde with NADH models.

	reaction time at 65°C	water added	yield in reduction
BNAH	4 hours	-	100 %
1a	8 h.	-	100 %
1b	8 h.	-	100 %
BNAH	until no	1 equiv.	76 %
1a	further	1 equiv.	100 %
1b	reation	1 equiv.	100 %

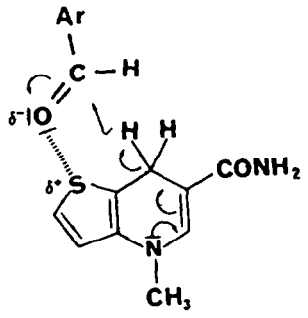
Note : reductions are performed with 1 equivalent of each reagent (substrate, $Mg(ClO_4)_2$ and model) in acetonitrile as solvent.

These results confirm the validity of our strategy : thiophenic annelated NADH models are perhaps a little less reactive than BNAH (see the results reported on fig.2) but they are still effective in the presence of water. Moreover they are much more reactive than quinoline analogs : with 3-carbamoyl 1,4-dihydroquinoline, (even in drastic conditions), the maximum yield of reduction of p.NBA is low.

Fig.2 Reactivity of BNAH, 1a, 1b towards p.NBA.



Scheme 5: activation of a substrate by 1b



On the other hand, in the presence of 1 equivalent of water(i.e. if we use technical grade acetonitrile instead of hyper-dry acetonitrile which is difficult to prepare) thiophenic models become superior to BNAH : quantitative yields can always be obtained, whereas with BNAH the yield decreases quickly as a function of the amount of water.

Moreover in a CH_3CN/H_2O mixture (4/1) we observed that p.NBA could still be reduced with model 1b (yield in isolated alcohol 15%). In the same conditions, BNAH is destroyed and 1a is unreactive.

This important difference between models 1a and 1b can be explained :

- with a large amount of water (in this case it represents 30 times the water concentration used in the experiments reported in table 2) the magnesium ions are completely complexed by water : activation of the reduction through the ternary complex cannot occur.

- in the case of 1b the situation is different : activation of the substrate can be carried out by the slight polarization of the sulfur atom (scheme 5). Activation of the substrate is slightly insured by the model and moreover this phenomenon sets the former in the neighbourhood of the transferred hydrogen. This activation can be enhanced by the solvents used in the experiment.

2) Other substrates.

By using standard conditions defined in table 1, we have reduced other aromatic aldehydes such as 3-formyl pyridine. The yield for reduction of this compound was previously reported to be very poor with BNAH.[19] With 1a this substrate is reduced quantatively, after 20 hours, in technical grade acetonitrile. This confirms the efficiency of our models in mild conditions.

So as to extend the scope of the 5,7-dihydro thieno [2,3] pyridines, we performed the reduction of the carbon carbon double-bond with 1a.

Activated ethylenic bonds are reduced with dihydro-pyridine derivatives in various conditions. For example 2-cyclohexenone is reduced in poor yield with N.propyl 1,4-dihydronicotinamide (PNAH) after activation with chloro tris (triphenylphosphine) rhodium.[20] Nitrostyrenes are reduced with HANTZSCH ester or BNAH in different ways of activation.[21]

We studied the reduction of 2-cyclohexenone and 2-pheny21 1-nitroethene in technical grade acetonitrile in presence of $Mg(ClO_4)_2$.

The results are as follows :

- 2-cyclohexenone gave cyclohexanone in 76% yield after 4 days ; the reaction was stopped because the model was eventually consumed. The remaining 2-cyclohexenone was recovered. This behaviour of the model in slow reductions will be discussed in another publication.

- 2-phenyl 1-nitroethene gave 2-phenyl 1-nitroethane in 77% yield and dimeric or polymeric compounds [which are often formed in such reductions[22]] after 17 hours. No starting material was recovered.

From these results it is of interest to observe that :

- reduction of the conjugated double-bond is regioselective : it occurs on the soft site of the molecule that means that it is placed under orbital control.

- 2-phenyl 1-nitroethene appears to be more reactive than 2-cyclohexenone in these conditions ; this feature is confirmed by the values of the energy of the molecular orbital which are implicated in the reaction. By the CNDO method the calculated values of the energy of the lowest unoccupied molecular orbitals are as follow :

LUMO of 2-phenyl 1-nitroethene : 0.593 eV.

LUMO of 2-cyclohexenone : 2.494 eV.

As can be seen there is a large difference between the respective energies which may explains the difference in reactivities.

EXPERIMENTAL

The infra red spectra were recorded on a BECKMAN IR 4250 spectrometer.

The ^1H NMR spectra were recorded on a VARIAN EM360L spectrometer and the ^{13}C spectra on a BRUCKER WH 90 spectrometer.

Microanalyse were recorded on a CARLO ERBA 1106 apparatus.

Hyper-dry acetonitrile was obtained by refluxing and distillation on calcium hydride and storage under molecular sieves.

Anhydrous $Mg(ClO4)_2$ was purchased from Merck.

1) Synthesis of thieno [3,2-b] pyridine derivatives after condensation of DMF + $POCl_3$ on 3-acetamido thiophene.

This condensation was performed by the method described in the literature.[8]

Yield in 5-chloro 6-formyl thieno [3,2-b] pyridine 2:51%.

a) Reduction of 2 with Zn + CH_3COOH.

A suspension of 0.5 g. of 2 (0.0025 mole) and 1.0 g. of zinc powder in 15 ml. of acetic acid and 1.0 ml. of water was warmed at 75°C during 4 hours. After cooling then filtration the resulting solution was neutralized with HCO_3Na and extracted with CH_2Cl_2. The solvent was evaporated and the residue was analyzed by ^1H NMR : it contains 6-hydroxymethyl thieno [3,2-b] pyridine and 6-hydroxymethyl 5-chloro thieno [3,2-b] pyridine.

After chromatography on silica gel (ether as eluent) 120 mg. of the chloro alcohol 4 and 120 mg. of impure alcohol 3 were obtained.

Yield in 4:24%; F=133-134°C; Analysis: C_8H_6ClNOS; Cal % C= 48.12; H= 3.01; N= 7.02. Found % C= 47.7; H= 3.0; N= 7.3; NMR:(DMSO d6): 8.49(s,1H:H7); 8.06(d,1H:H2); 7.42(d,1H:H3); 4.42(d,2H:CH2).

b) Reduction of 2 with hydrogen

A suspension of 3.0 g. of 2 (0.015 mole), 0.6 g. of MgO, 4.0 g. of 10% Pd/C in 100ml of ethanol was stirred under an hydrogen atmosphere for 18 hours. After filtration followed by evaporation of the solvent the solid was analysed by ^1H NMR : it contains 6-formyl thieno [3,2-b] pyridine 5 and unreacted 2. After chromatography on a silica column (elution with ether/hexane 1/1), 0.4 g. of 6-formyl thieno [3,2-b] pyridine 5 was obtained.

Yield 16%; F=126-127°C ; Analysis:C_8H_5NOS; Cal % C= 58.89; H= 5.07; N= 8.59. Found % C= 58.5; H= 3.4; N= 8.7; IR ν(C=O): 1680cm^{-1} ; NMR ($CDCl_3$) : 10.15(s,1H:CHO); 9.10(d,1H:H_5) ; 8.60(d,1H:H_7); 8.0(d,1H:H_2); 7.65(d,1H:H_3).

c) 5-chloro thieno [3,2-b] pyridine 6-carboxylic acid : 6

To a suspension obtained from 1.8 g. of $AgNO_3$ (0.01 mole) and 0.8 g. of NaOH (0.02 mole) in 15 ml. of water is slowly added, at 0°C,1.0 g.(0.005 mole) of 2. After two hours at 0°C, the filtrate is acidified with HNO_3 and the precipitate is isolated, and dried.

Yield 90%; P>250°C ; Analysis: $C_8H_4ClNO_2S$; Cal % C= 44.96; H= 1.87; N= 6.55. Found % C= 44.9; H= 1.8; N= 6.6; IR:ν(C=O): 1740cm^{-1} ; NMR (DMSO d6): 8.9(s,1H:H_7); 8.35(d,1H:H_2); 7.60(d,1H:H_3).

2) Synthesis of acetyl thieno [2,3] pyridine derivatives.

a) 5-acetyl thieno [2,3-b] pyridine : 7

To a suspension of 30 g.of bis (2-thienyl ammonium) hexachlorostannate (0.056mole) in 350 ml of ethanol and 50 ml of concentrated HCl, was added 40 g. of 4,4-dimethoxy 2-butanone (ADMA)

(0.303 mole). The mixture was warmed to 75°C for 8 hours, then cooled and made basic with 590 ml of 2N NaOH. After extraction with CH_2Cl_2, the organic layer was evaporated. The residue was extracted several times with hot hexane.

Yield: 41%; F= 117°C (litt.[11] F=116-17°C).

b) 6-acetyl thieno [3,2-b] pyridine : 8

10 g. of 3-acetylamino thiophene (0.071 mole) in 120ml. of n.butanol and 40ml. of concentrated HCl were refluxed under an argon atmosphere for 2.5 hours. After cooling, 55 g. of ADMA (0.417 mole) were added and the temperature was gradually raised 80°C in 4 hours and maintained for 8 hours. The cold solution was made basic with NaOH 2N and extracted with CH_2Cl_2. After evaporation, the residue was extracted with hot hexane.

Yield: 55%; F= 134°C (litt.[11] F=134°C).

3) Synthesis of 5,7-dihydro thieno [2,3] pyridines 1a and 1b

a) Thieno [2,3] pyridine carboxylic acids 10 and 11.

To a solution of 20.5 g. of NaOH in 360 ml of water, maintained at 5°C, was slowly added 6.1 ml of bromine (0.11 mole). The acetyl derivative (8 or 9), 6.0 g (0.034 mole) was poured into the mixture which was stirred for 12 hours at room temperature. After acidification to pH 2-3 , the precipitate was filtered, then recrystallised in ethanol.

Thieno[2,3-b]pyridine 5-carboxylic acid 10

Yield: 71%; F>250°C; Analysis:$C_8H_5NO_2S$; Cal % C= 53.63; H= 2.79; N= 7.82. Found % C= 53.6; H= 2.55; N= 7.7; IR: ν(C=O): 1715 cm^{-1}; NMR (DMSO d6): 9.0(d,1H:H_6); 8.75(d,1H:H_4); 7.95(d,1H:H_2); 7.55(d,1H:H_3)

Thieno [3,2-b] pyridine 6-carboxylic acid 11.

Yield: 80%; F>250°C; Analysis:$C_8H_5NO_2S$; Cal % C= 53.63; H= 2.79; N= 7.82. Found % C= 53.35; H= 2.65; N= 7.65; IR:ν(C=O):1705 cm^{-1}; NMR (DMSO d6): 9.15(d,1H:H_5); 9,0(d,1H:H_7); 8.35(d,1H:H3); 7.65(d,1H:H_2).

b) Carbamoyl thieno [2,3] pyridines 12 and 13.

2 g.(0.011 mole) of the acid (10 or 11) were refluxed with 30 ml of thionyle chloride for 12 hours. After elimination of volatile products, the residue was dissolved in CH_2Cl_2, then treated with ammonia at 0°C for 2 hours. The solvent is evaporated and the solid is recrytallised in ethanol or in ethanol-water.

5-carbamoyl thieno [2,3-b] pyridine 12.

Yield: 90%; F>250°C; Analysis: $C_8H_6N_2OS$; Cal % C= 53.93; H= 3.37; N= 15.73. Found % C= 53.5; H= 3.3; N= 15.5. IR: ν(C=O): 1680 cm^{-1}; NMR (DMSO d6) 9.05(d,1H:H_6); 8.75(d,1H:H_4); 8.30(m,1H:N-H); 7.90(d,1H:H_2); 7.60(m,1H:N-H); 7.50(d,1H:H_3).

6-carbamoyl thieno [3,2-b] pyridine 13.

Yield: 90%; F=225°C; Analysis: $C_8H_6N_2OS$; Cal % C = 53.93; H= 3.37; N= 15.73. Found % C= 53.75; H= 3.3; N= 16.0. IR: ν(C=O): 1680 cm^{-1}; NMR (DMSO d6): 9.15(d,1H:H_7); 8.95(d,1H:H_5); 8.30(d,1H:H_3); 7.65(d,1H:H_2).

c) Quaternization of 12 and 13.

They were performed by warming 7.0 g. of the above products (0.039 mole) with 25 ml. of methyl iodide in 70 ml. of DMF during 8 hours. After filtration the pyridinium derivatives 14 and 15 are obtained in nearly quantitative yields.

N-methyl 5-carbamoyl thieno [2,3-b]pyridinium iodide 14.

F>250°C; Analysis: $C_9H_9N_2OSI$; Cal % C= 33.75; H= 2.81; N= 8.75. Found % C= 33.8; H= 2.6; N= 8.7. IR:v(C=O):1690 cm^{-1}; NMR (DMSO d_6): 9.60(s,1H:H_6); 9.40(s,1H:H_4); 8.33(d,1H:H_2); 7.90(d,1H:H_3); 4.60(s,3H:CH_3)

N-methyl 6-carbamoyl thieno [3,2-b] pyridinium iodide 15a.

F: 240°C(dec.); Analysis: $C_9H_9N_2OSI$; Cal % C= 33.75; H= 2.81; N= 8.75. Found % C= 33.7; H= 2.75; N= 8.5; IR: VC=O:1680 cm^{-1}; NMR (not soluble in common solvents).

d) Exchange iodide/perchlorate in 15a.

0.32 g. of 15a (0.001 mole) and 0.5 g. (0.002 mole) of $Mg(ClO_4)_2$ in 50 ml. of acetonitrile were refluxed during 2 hours; the pyridinium perchlorate salt is soluble, but the iodide is not soluble in the middle. So the progress of the exchange could be monitored by the disappearance of the yellow precipitate. After evaporation, the salt was recritallised in water.

Yield 95%; F>250°C Analysis: $C_9H_9ClN_2O_5S$; Cal % C= 36.92; H= 3.08; N= 9.57. Pound % C= 36.55; H= 3.3; N= 9.7; IR:1680 cm^{-1}; NMR (DMSO d6): 9.20(s,1H:H_5);9.10(s,1H:H_7); 8.5(d,1H:H_3); 7.7(d,1H:H_2); 7.5(m,2H:NH_2); 4.1(s,3H:CH_3).

e) Reduction of pyridinium salts : obtention of dihydro-thieno pyridines 1a and 1b

The pyridinium salt 14 (2.0 g : 0.01 mole) or 15b was dissolved in 40 ml. of hot water. The solution was poured , with stirring, in a solution of 4.0 g. of sodium dithionite (0.023 mole) and 5.0 g. of sodium carbonate decahydrate (0.017 mole) in 40 ml. of water. After 15 minutes, the solution was extacted with CH_2Cl_2, dried and concentrated at room temperature. The residue was purified by the following procedure :

1a : was carefully washed with water then recristallised in ethanol/water (1/1)

5-carbamoyl -4,7 dihydro thieno [2,3-b] pyridine: 1a

Yield: 91%; F= 94°C; Analysis: $C_9H_{10}N_2OS$; Cal % C= 55.67; H= 5.15; N= 14.43. Found % C= 55.3; H= 5.0; N= 14.35; IR:v(C=O): 1660 cm^{-1}; NMR ($CDCl_3$): 7.15(s,1H:H_6); 6.65(s,2H:H_2 and H_3); 3.70(s,2H:H_4 and H'_4); 3.20(s,3H:CH_3).

1b: in a flask 0.132 g. of crude product was dissolved in 30 ml. of deoxygenated ethanol at 30°C under an atmosphere of argon. A small amount of water (1 to 1 ml.) was then introduced until a light turbidity appears. The flask was storred in a refrigerator during sevral days. The precipitate was filterd and dried at 40°C under 0.5 torr. (Drying is necessary because 1b cristallizes with one molecule of water)

6-carbamoyl -4,7 dihydro thieno [3,2-b] pyridine: 1b

Yield: 58%; F: 84°C; Analysis: $C_9H_{10}N_2OS$; Cal % C= 55.67; H= 5.15; N= 14.43. Foun d % C= 55.7; H= 5.1; N= 14.3; IR: v(C=O): 1655cm^{-1}; NMR ($CDCl_3$): 7.25(d,1H:H_5); 7.15(d,1H:H_2); 6.70(d,1H:H_3); 5.50(m,2H: NH_2); 3.87(s,2H:H_4 and H'_4); 3.25(s,3H:CH_3).

4) Typical procedure for the reduction of a substrate.

In a flask stopped with a septum were introduced 0.194 g.(0.001 mole) of model 1a or 1b, 0.223 g. of Mg $(ClO_4)_2$ (0.001 mole) and 0.001 mole of the substrate dissolved in 5 ml. of acetonitrile (technical or super-dry). The course of the reduction was monitored by NMR spectroscopy or by HPLC until no dihydro-pyridine derivative can be detected.

The reactionnal mixture was treated with 1 ml. of water. The solvent was evaporated the residue was suspended in 10 ml. of water and extracted with 3x50 ml. of CH_2Cl_2. After elimination of the solvent, the crude product is purified by conventionnal procedures.

REFERENCES

1) a) Zehani, S., Gelbard, G. *Nouv. Journ. de Chimie*, 1986, *10*, 511 and references cited.
b) Kuthan J., Kurfürst, A. *Ind. Eng. Prod. Res. Dev.*, 1982, *21* and references cited.

2) a) Inouye, Y., Oda, J., Baba, N. *Reductions with chiral dihydropyridines reagents. Asymetric synthesis.* Vol. II, part A, p. 91 (1983), Ed. Academic Press, New-York.
b) Ohno, A., Ushida, S. *Mechanistic Models of Asymetric Reduction. Lecture Notes in Bio-Organic Chemistry.* Ed. Springer Verlag Berlin, (1986).

3) a) Powell, M.F., Bruice, T.C. *J. Amer. Chem. Soc.*, 1982, *104*, 5834.
b) Powell, M.F.Bruice, T.C. *J. Amer. Chem. Soc.*, 1983, *105*, 7139.
c) Inagaki, S., Hirabayashi, Y.*Bull. Chem. Soc. Japan*, 1977, *50*, 3360.

4) a) Johnston, C.C., Gardner, J.L., Suelter, C.H., Metzler, D.E. *Biochemistry*, 1963, 689.
b) Kim, C.S.Y., Chaykin, S. *Biochemistry*, 1968, 2339.
c) Van Ekeren, P., Grier, D.L., Eliason, J. *J. Amer. Chem. Soc.*, 1977, *101*, 7406.

5) Tintillier, P., Dupas, G., Bourguignon, J., Quéguiner, G. *Tetrahedron Lett.*, 1986, *27*, 2537.

6) a) Shinkaĭ, S., Hamada, H., Ide, T., Manabe, O. *Chem. Lett.*, 1978, 685.
b) Shinkaĭ, S., Hamada, H., Manabe, O. *Tetrahedron Lett.*, 1979, 1397.
c) Shinkaĭ, S., Hamada, H., Kusano, Y., Manabe, O. *Bull. Chem. , Soc. Japan*, 1979, *52*, 2600.
d) Shinkaĭ, S., Hamada, H., Kusano, Y., Manabe, O. *J. Chem. Soc. Perkin II*, 1979, 699.
e) Ohno, A., Ishihara, Y., Ushida, S., Oka, S. *Tetrahedron Lett.*, 1982, *23*, 3185.

7) Cazin, J., Dupas, G., Bourguignon, J., Quéguiner, G. *Tetrahedron Lett.*, 1986, *27*, 2375.

8) Meth-Cohn, O., Narine, B., Tarnowski, B. *J. Chem. Soc. Perkin I*, 1981, 1531.

9) Ain-Khan, M., Guarçoni, A., *J. Het. Chem.*, 1977, *14*, 807.

10) Barker, J.M., Huddleston, P., Holmes, D. *J. Chem. Research (S)*, 1985, 214; *(M)* 1985, 2501.

11) Klemm, L.H., Klopfenstein, C.E., Zell, R., Mc Coy, D.R., Klemm, R.A. *J. Org. Chem.* 1969, *34*, 347.

12) Barker, J.M., Huddelston, P., Keenan, G.J. *J. Chem. Research (S)*, 1982, 158; *(M)* 1982, 1726.

13) Kellogg, R.M. and al. *J. Amer. Chem. Soc.* 1985, *107*, 3981.

14) Roberts, R.M.G., Ostovic, D., Kreevoy, M.M. *J. Org. Chem.* 1983, *48*, 2053.

15) a) Creighton, D.H., Sigman, D.S. *J. Amer. Chem. Soc.*, 1971, *93*, 6314.
b) Creighton, D.J., Hadjn, J., Sigman, D.S. *J. Amer. Chem. Soc.*, 1976, *98*, 4619.

16) Newkome, G.R., Marston, C.R. *J. Org. Chem.*, 1985, *50*, 4238.

17) Kimura, T., Oka, S. *J. Amer. Chem. Soc.*, 1979, *101*, 7036.

18) a) Hughes, M., Prince, R.H., Wyeth, P. *J. Inorg. Nucl. Chem.*, 1980, *40*, 713.
b) Hughes, M., Prince, R.H., Wyeth, P. *J. Inorg. Nucl. Chem.*, 1980, *40*, 719.

19) Shirai, M., Chishina, T., Tanaka, M. Bull. *Chem. Soc. Japan*, 1975, *48*, 1079.

20) Nakamura, K., Fujii, M., Ohno, A., Oka, S. *Chem. Letters*, 1984, 925.

21) a) Shinkaĭ, S., Kusano, Y., Ide, T., Sone, T., Manabe, O. *Bull. Chem. Soc. Japan*, 1978, *51*, 3544.
b) Nakamura, K., Fujii, M., Ohno, A., Oka, S. *Tetrahedron Letters*, 1984, 3985.
c) Nakamura, K., Fujii, M., Oka, S., Ohno, A. *Chem. Letters*, 1985, 523.

22) a) Kruse, L.I., Hilbert, E.L., *Heterocycles*, 1983, *20*, 1373.
b) Meyers, A.I., Sricar, J.C., *J. Org. Chem.*, 1967, *32*, 4134.