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BROADENING IN THE SCOPE OF NADH MODELS BY USING CHIRAL AND NON CHIRAL PYRROLO [2,3-b] PYRIDINE DERIVATIVES.

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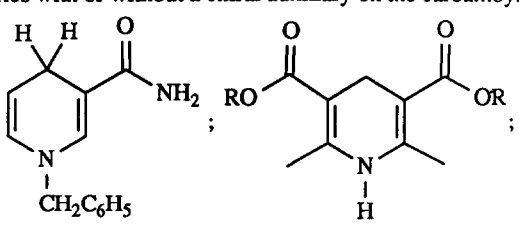
Abstract: Non chiral and chiral NADH models in the pyrrolo [2,3-b] pyridine series have been synthesized. These reagents 1) allow reductions of substrates previously found to be non reducible with similar reagents, 2) can give either one enantiomer or the other during the reduction of a prochiral ketone depending on the experimental conditions, 3) can be used in the synthesis of chiral precursors of target molecules obtained with good enantiomeric excesses.

The goal of chemoselective and enantioselective reductions is a challenge for chemists in organic chemistry. Many reagents have been described to attain this objective (1). Among them, enzymes or coenzymes are promising compounds. Some enzymes such as Baker's yeast can be easily handled for performing asymmetric reductions of prochiral ketones However, these enzymes have generally a high enantiotopic face specificity for a substrate: starting from a given prochiral ketone the configuration of the chiral product is fixed. For example, reduction of ethylacetoacetate gives (S)-ethyl-3-hydroxybutanoate. This behaviour is often a limiting factor in the use of enzymic systems (2). On the other hand, NADH is a coenzyme which occurs in many biochemical reductions and it can also be used in organic synthesis. However, it is a very expensive reagent and its recycling is a difficult problem. So models of the coenzyme derived from 1-benzyl-1,4-dihydronicotinamide (BNAH) **1** or Hantzsch ester **2** have been largely used in numerous biomimetic reductions (3).

We will now describe the synthesis and the use of new NADH models **3** in the pyrrolo [2,3-b] pyridine series with or without a chiral auxiliary on the carbamoyl moieties



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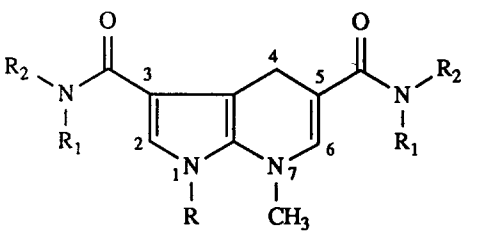


3

I Non chiral dihydro-4,7 pyrrolo [2,3-b] pyridine derivatives

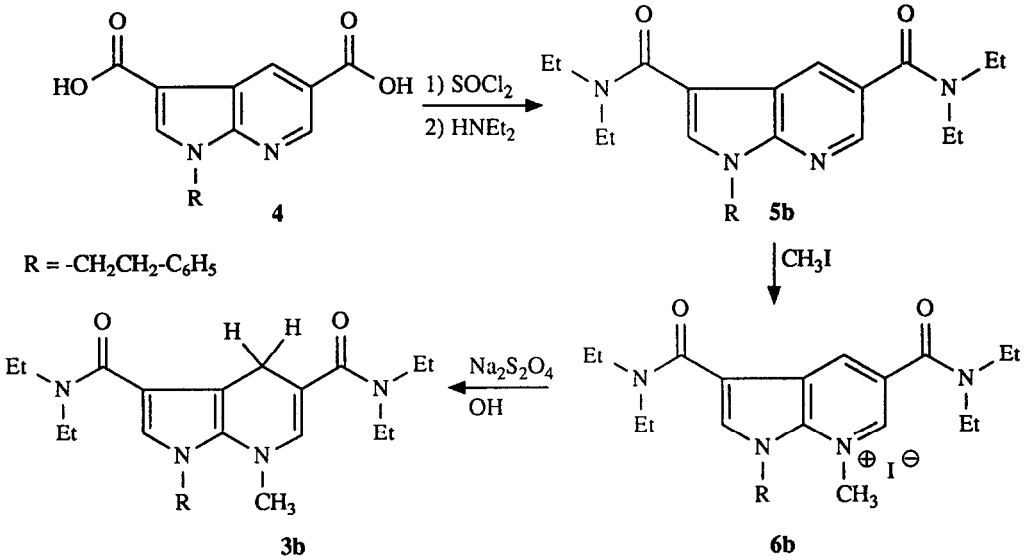
1) Synthesis

Dihydronicotinamide derivatives fused to a π excessive ring are promising reducing agents. They are very much less sensitive than simple NADH models such as **1** towards secondary reactions which affect the efficiency of these models (4). For example, the annelated thiophenic NADH models have a good reactivity and can be handled in mild laboratory conditions where BNAH is much more less effective (5). In a previous paper we described the synthesis and some good results obtained with reagent **3a** (R=-$CH_2CH_2C_6H_5$, R_1, R_2=H) in the reduction of p.nitrobenzaldehyde (p.NBA)(6)

Commonly, reductions with NADH models occur in acetonitrile as solvent in the presence of magnesium perchlorate which plays an important role in the transfer of hydrogen: a ternary complex is formed between the model, magnesium ions and the substrate. Previous studies have shown that the carbamoyl substituent of a dihydronicotinamide derivative is involved in the complexation of Mg^{2+} ions (7).

Reagent **3a** itself is practically insoluble in acetonitrile. It was necessary to use 2 equivalents of magnesium perchlorate for insuring solubilisation of 3a probably through complexation with the two carbamoyl groups. So it was difficult to study the reactivity of this reagent. In order to enhance the solubility of dihydropyrrolo [2,3-b] pyridine derivatives in acetonitrile, we decided to modify the structure of the carboxamido moieties. We therefore synthesized reagent **3b** (R_1, R_2=Et) assuming that the lipophilic ethyl groups could improve the solubility of the reagent in organic solvents (scheme 1).

Scheme 1: Synthesis of 3,5-diethylaminocarbonyl 4,7-dihydro pyrrolo [2,3-b] pyridine **3b**.



4 **5b** **3b** **6b**

The synthesis of the different compounds represented on scheme 1 was realized without difficulties. The overall yield of dihydro derivative **3b** from **4** was 77 %

As hoped, reagent **3b** had a good solubility in acetonitrile, even in the absence of magnesium perchlorate, which allowed us to study the reactivity of dihydro pyrrolo [2,3-b] pyridine derivative in classical conditions.

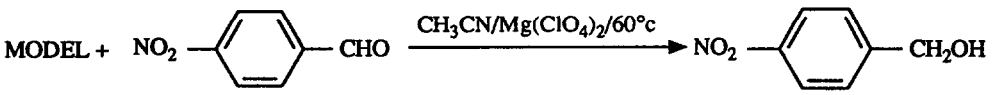
2) Reactivity

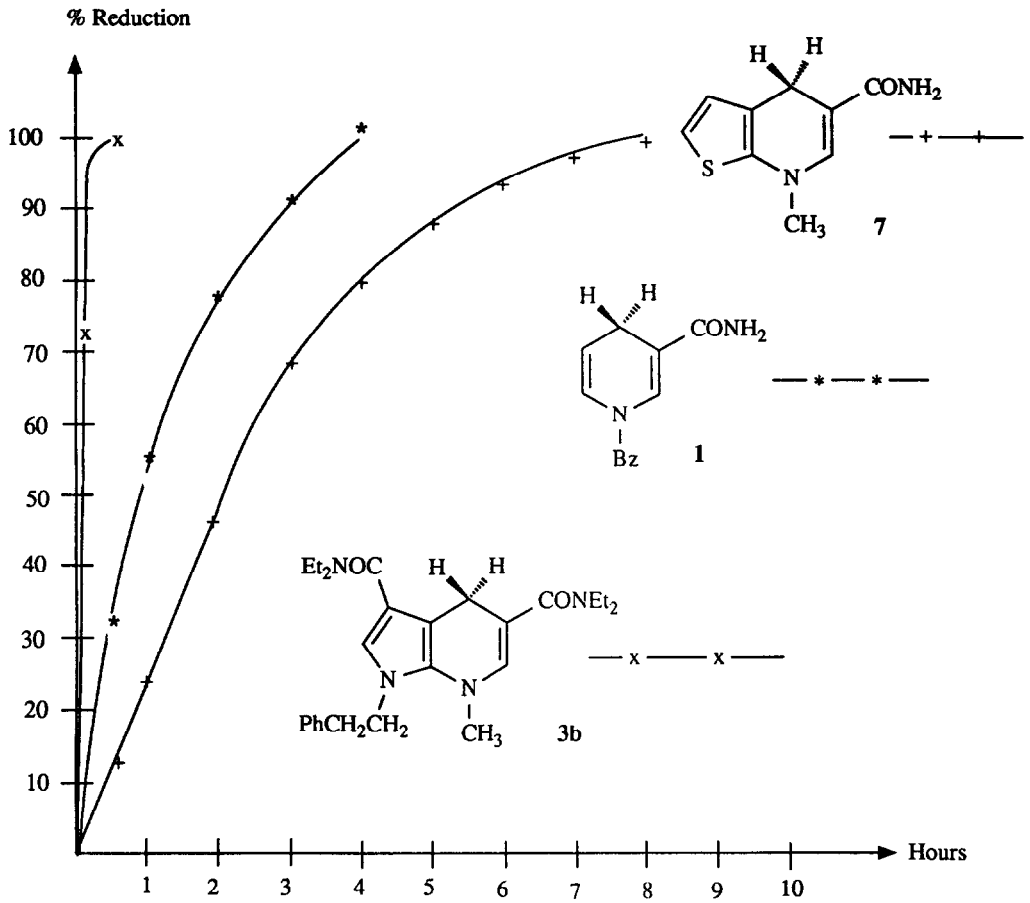
a) Reduction of p.NBA

Reagent **3b** was tested in the reduction of p.NBA at 60°C in the following conditions **3b**/Mg^{2+}/p.NBA = 1/1/1.

The results compared with those obtained with 1 and with 5-carbamoyl-4,7 dihydro thieno [2,3-b] pyridine **7** (5b) in similar conditions are summarized in figure 1

Figure 1: reduction of p.NBA with **3b**, **1** and **7**.





With **3b** and **7** technical grade acetonitrile could be used as solvent. With **1** it was necessary to use hyper dry solvent (5). Error limits are ±3 % on the % Reduction.

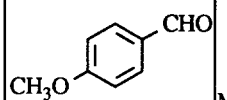
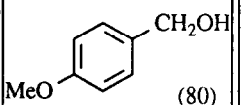
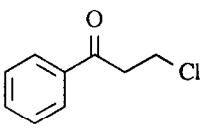
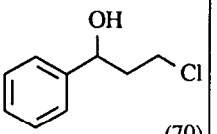
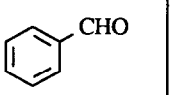
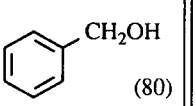
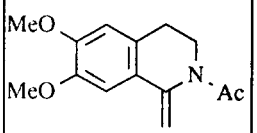
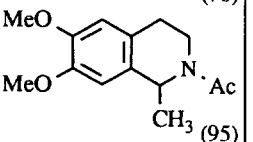
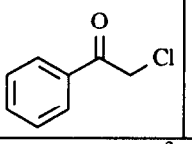
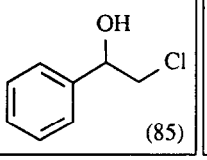
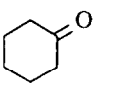
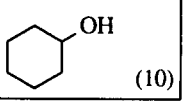
As can be seen, reagent **3b** allows reduction of p.NBA at higher rates than reagent **1**. This behaviour can be the consequence of two factors: 1) Despite the presence of the electron withdrawing carbamoyl group the high electron donor effect exerted by the pyrrole ring (8) facilitates the departure of the hydrogen atom involved in the reduction. 2) In the condensed pyrrolo series the dihydro pyridine structure is slightly stabilized by the pyrrole ring owing to the low aromatic character of the five membered ring. So the passage of **3b** to the aromatic pyridinium structure during the reduction of p NBA is easy.

b) Reduction of other substrates

As already mentioned, NADH models such as **1** or **2** are chemoselective reagents. For example, only activated benzaldehydes are successfully reduced with **1** by using standard conditions i.e. Mg^{2+} as a catalyst. On the other hand, under forcing conditions some acid stable models could be used for performing reduction of non-activated substrates (9). However the field of such reductions is rather narrow.

We used reagent **3b** in the reduction of substrates which were previously not reduced with reagent **1** or **2** in standard conditions. Some of these substrates (entries 3, 4, 5) are precursors of target molecules (table 1).

Table 1: Reduction of various substrates with **3b**

entry	substrate	product (yield %)	entry	substrate	product (yield %)
1		 (80)	4		 (70)
2		 (80)	5		 (95)
3		 (85)	6		 (10)

Conditions **3b**/Mg^{2+}/Substrate: 1/1/1, 60°C; solvent CH_3CN

The most important features are that:

1) Methoxy benzaldehyde and benzaldehyde, (entries 1 and 2) are reduced in high yields. It is the first report to our knowledge of such a result in the reduction of non-activated aromatic aldehydes with NADH model in the presence of magnesium ions Benzaldehyde was reduced in good yields in the presence of $AlCl_3$ or with hard acids (H_2SO_4, $HClO_4$) by using very stable NADH models (10) which have limited scope.
2) Ketones used in entries 3 and 4 are also reduced in high yields. These ketones are activated to some extent by the chlorine atom. The alcohols obtained can be precursors of target molecules (11). Cyclohexanone (entry 6) which is not activated is reduced in poor yield. With common models only very activated ketones such as αα trifluoro acetophenone or methyl benzoylformate were reduced in good yields. Cyclohexanone is the first simple ketone reduced by a NADH model.
3) Reduction of the carbon carbon double bond of the substrates used in entry 5 leads to racemic N acetylsalsolidine. This result is very interesting because reductions of ethylenic compounds with NADH models have only rarely been reported in the literature. In our laboratory we have succeeded in the reduction of enones or various β nitrostyrenes (12) but it is the first time, to our

knowledge that a N acetylenamine is reduced with a dihydropyridine derivative. It can be mentioned that reagent **3b** is more efficient than $NaBH_4$ in the reduction of the enamine. Despite our efforts, reduction of the ethylenic double bond of the precursor of N acetylsalsolidin with $NaBH_4$ in classical conditions failed (solvent EtOH at room temperature or at reflux, large excess reagent for 12 hours).

It can be assumed that in the case of reduction with **3b** the acetyl group "activates" the carbon carbon double bond perhaps through the complexation of the amide moiety with magnesium ions.

II Chiral models

1) Synthesis

Numerous results have been reported concerning reductions of prochiral substrates with NADH models bearing a chiral auxiliary (13). The best results were obtained with models involved in self immolative reactions or with models which were obtained with difficulty.

On the other hand, the presence of a double functionality either on the pyrrole and on the pyridine rings of compounds of type **3** could be used for the introduction of a double chirality in the NADH model. A similar approach have been described by Kellog (14) and Gelbard (15) who obtained good results with models of type **2**. In theses cases the NADH derivatives had a C2 symmetry. The origin of the enantioselectivity of the hydrogen transfer is a result of the existence of the ternary complex (model/magnesium ions/substrate) which occurs in the transition state of the reduction. In our case the molecule has no symmetry and moreover one of the chiral auxiliaries is not directly linked to the dihydropyridine structure.

As already mentioned the ternary complex plays an important role in the hydrogen transfer. As a probe some reductions of very reactive substrates can be performed without Mg^{2+} but in this circumstance there is no or very poor enantioselectivity in the reduction (16) compared with the results obtained in the presence of Mg^{2+}. In our laboratory we used aminoalcohols as chiral auxiliaries and we showed that the alcoholic oxygen enhances the chelation of the magnesium ions (17) As a consequence the "rigidity" of the chiral auxiliary is reinforced and the hydrogen transfer occurs from the less hindered face of the dihydro pyridine structure.

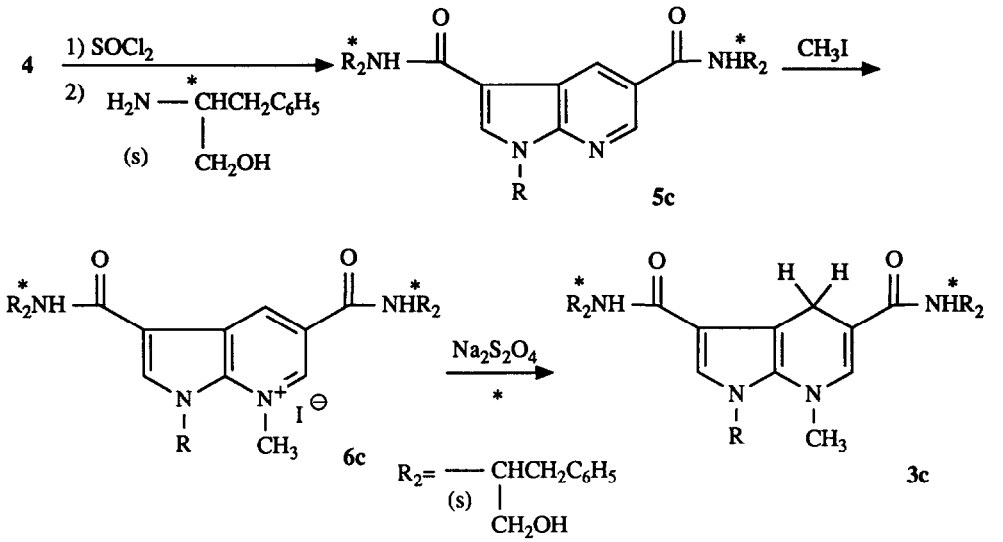
Following a similar methodology we synthesized reagent **3c**(R_1=H, R_2= $-\underset{\displaystyle CH_2OH}{\overset{\displaystyle |}{CH}}-CH_2C_6H_5$)(scheme 2).

The synthesis of **5c** was easy (yield: 70 %). It is necessary to perform the reaction between the acid chloride and phenylalaninol at -10°C in order to avoid ester formation (as can be seen in the IR spectra). The quaternization of **5c** with methyl iodide was not complete even with a large excess of reagent for a long reaction time. The crude product always contained **5c** which was unreacted as could be seen by HPLC determination and confirmed by examination of the ^1H 400 MHz NMR spectra (see experimental). **6c** was therefore purified by chromatography on silica with ethyl acetate/methanol (9/1) as eluant. In these conditions residual **5c** was first eluted and pure **6c** was then eluted by using methanol alone.

The pyridinium salt **6c** was slightly soluble in water, so it was necessary to perform the reduction with sodium dithionite by using a mixture of methanol/water, which ensured the solubilisation of $Na_2S_2O_4$, as well. The dihydropyridine derivative **3c** was obtained pure and identified by examination of its ^1H 400 MHz

NMR spectra (see experimental).

Scheme 2: Synthesis of chiral reagent 3c.



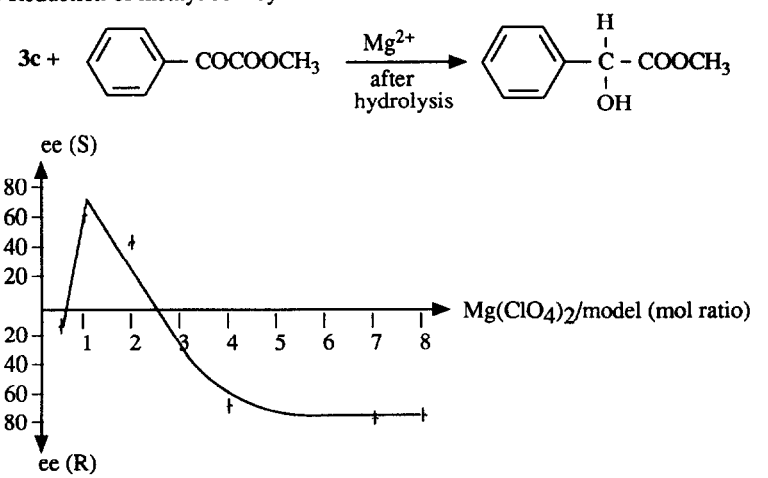
2 Asymmetric reductions

Two substrates were studied.

a) Methyl benzoylformate reduction

This substrate is commonly used in asymmetric reductions with NADH models. We performed the reaction in the presence of various amounts of magnesium ions in order to obtain information on the participation of one or of the two carbamoyl moieties in the complexation of Mg^{2+}. The results are summarized on the following curve (Figure 2).

Figure 2: Reduction of methyl benzoyl formate with 3c.



First of all in the absence of Mg^{2+} ions the chemical yield is very low (5 %) and the e.e. is null. This result affords a probe of the fundamental role played by Mg^{2+} in the hydrogen transfer.

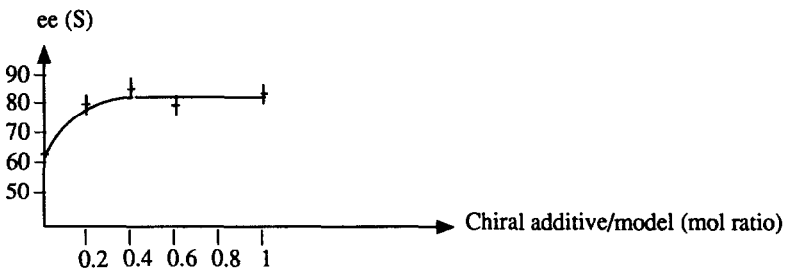
More important, as can be seen, the behaviour of **3c** is unique since the major enantiomer of methyl mandelate can be either the S or the R depending on the magnesium ions concentration. The dependance of enantiomeric excess on the concentration of magnesium ions was already reported with derivative possessing a C2 symmetry (18) but:

1) the e.e. were lower. With **3c** the highest e.e. were obtained with 1 equivalent of Mg^{2+} ions (S isomer, e.e.: 64 %) or with 6 or more equivalents of Mg^{2+} ions (R isomer, e.e.: 78 %).
2) the change in the configuration of the predominant product was studied in a smaller intervall of Mg^{2+} ions concentration.

As a consequence a reagent like **3c** examplifies a possibility not open to a single enzyme, namely the obtention of either enantiomer of the product by variation of experimental conditions.

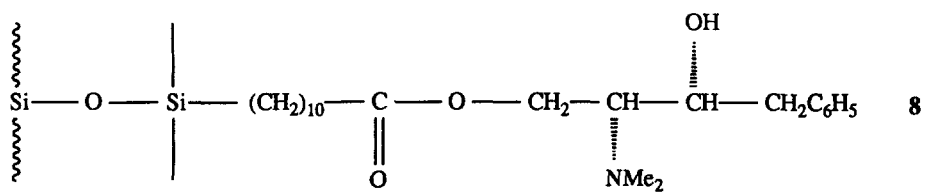
In an experiment performed with impure **3c** containing again 30 % of **5c** the e.e. was 87 %. This result prompted us to make a study of the variation of e.e. with pure **3c** as a function of the concentration of 5c (figure 3).

Figure 3: Variation of e.e. in the presence of **5c**.



The increase of e.e., by addition of **5c** may be due to the complexation between the reductant and the additive by the assistance of Mg^{2+} through the polar groups. This behaviour probably reinforces the stereodifferentiation of the two faces of the dihydropyridine structure in the ternary complex.

During work up of the reaction mixture the additive **5c** was lost. We therefore used a chiral additive **8** grafted on an insoluble support which was available in our laboratory. The e.e. was again improved since it was 73 % for the following conditions: **3c/8**/substrate. The chiral additive could be reused.



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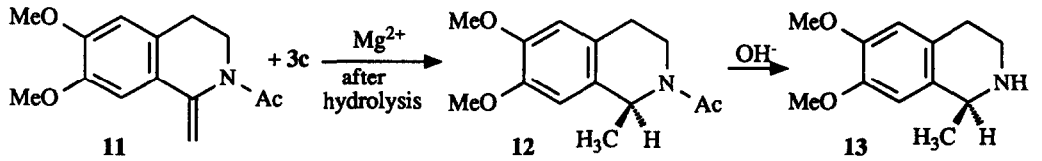
The structure of the reaction intermediates in these experiments and hence the variation of e.e. with Mg^{2+} ion concentration, and the role of additives, is best studied by NMR spectroscopy. The results will be published later.

b) Salsolidine precursor reduction.

Salsolidine is an important alkaloid. Only the (S) form is active. We performed the reduction of the N acetyl insaturated precursor of salsolidine **11** with **3c** in presence of different amounts of magnesium ions.

Scheme 3: Reduction of the salsolidine precursor with **3c**.



First the reaction was performed with a stoichiometry of 1/1/1 in substrate Mg^{2+} ions and 3c. The e.e. in **12** was 55 % (determined by HPLC analysis, see experimental). The absolute configuration of the major enantiomer of **12** was unknown, so **12** was hydrolysed (which required vigorous conditions : several hours reflux with N NaOH). In these conditions we obtained preferentially (S) salsolidine **13**.

EXPERIMENTAL

The infra red 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. Microanalyses were obtained from a Carlo Erba 1106 apparatus. Optical rotations were determined on a Perkin Elmer 241 micropolarimeter, or by h.p.l.c. by using a Waters apparatus and a L.K.B. Enantiopac as chiral column or after derivatisation of the chiral alcohols by Mosher's method (19) and analysis by g.p.c.

1-(Phenyl-2-ethyl)-3,5-N,N-diethylaminocarbonyl pyrrolo [2,3-b] pyridine: **5b**

A solution of 0.7 g (2.26 mmoles) of the diacid **4** (6) in 20 ml of thionyl chloride was refluxed for 12 hours. After evaporation of the excess thionyl chloride, the residue was taken with 20 ml of benzene, then evaporated to dryness. The residue, dissolved in 20 ml of dichloromethane was then added dropwise to a solution of 0.66 g (9.04 mmoles) of diethylamine in 10 ml of dichloromethane maintained at -10°C. After addition the mixture was stirred at room temperature for 3 hours.

The organic phase was washed with water (10 ml), the dichloromethane was dried on magnesium sulfate and the solvent was evaporated. The brown oil obtained was purified by column chromatography on a silica column (eluent: ethyl acetate/methanol: 90/10), yield 85 %. (light yellow oil).

Analysis: $C_{25}H_{32}N_4O_2$; Cal % C=71.43; H=7.62; N=13.33. Found % C=71.3; H=7.70; N=13.2. I.R.: ν(C=O): 1680 cm^{-1}; N.M.R. ($CDCl_3$): 8.5 (d, 1H); 8.35 (d,1H); 7.1 (m,6H), 4.55 (t, 2H); 3.35 (m, 10 H); 1.15 (m, 12H)

1-(Phenyl-2-ethyl)-7-methyl-3,5-N,N-diethylaminocarbonyl pyrrolo [2,3,b] pyridininium iodide: **6b**

A mixture of 1 g (2.4 mmoles) of compound **5b** and 5 ml of methyl iodide in 15 ml of acetonitrile was refluxed for 4 days. After addition of diethyl ether (50 ml) the precipitate of pyridinium salt **6b** was filtered and dried. Yield 95 % m.p. 200°C.

Analysis: $C_{26}H_{35}IN_4O_2$; Cal % C=55.52; H=6.23; N=9.96. Found % C=55.4; H=6.10; N=9.9. I.R.: ν(C=O): 1630 cm^{-1}; N.M.R. ($DMSOd_6$): 8.95 (d, 1H); 8.75 (d,1H); 7.75 (s, 1H), 7.23 (s, 5H); 4.90 (m, 2H); 4.65 (s, 3H); 3.33 (m, 10 H); 1.1 (m, 12H)

1-(Phenyl-2-ethyl)-7-methyl-3,5-N,N-diethylaminocarbonyl-4,7 dihydro pyrrolo [2,3-b] pyridine: **3b**

A solution of 0.562 g (1 mmole) of **6b** in 15 ml of methanol was added to a solution of 1.39 g (8 mmoles) of sodium dithionite and 1.43 g (5 mmoles) of sodium carbonate decahydrate in 15 ml of water. The mixture was stirred at room temperature, in the dark and under argon for 2 hours. Methanol was evaporated under vacuum (temperature below 35°C) and the dihydropyridine **3b** was extracted with dichloromethane (3 x 20 ml). The organic phase was dried with magnesium sulfate, then evaporated to dryness. The crude product was not further purified. Yield: 95 %. (oil).

I.R.: ν(C=O): 1640 cm^{-1}; N.M.R. ($DMSOd_6$): 7.15 (m, 5H); 6.35 (s,1H); 6.05 (s, 1H), 4.10 (m, 2H); 3.15 (m, 15H); 1.00 (m, 12H)

Reductions with **3b**

a) Reduction of p.NBA

In a flask stoppered with a septum were introduced 0.436 g of **3b** (1 mmole), 0.245 g of $Mg(ClO_4)_2$ (1.1 mmole) and 0.136 g of p.NBA (0.9 mmole) dissolved in 5 ml of acetonitrile. The course of the reduction was monitored by g.p.c. (column A, see table 2, with a temperature profile of 150°C to 200°C in 3°C/minute.

p.NBA was reduced in the same conditions with 5-carbamoyl-4,7 dihydro thieno[2,3-b]pyridine (5b) and in hyperdry acetonitrile with BNAH.

b) Reduction of various substrates

A solution of 0.436 g of **3b** (1 mmole), 0.9 mmole of the substrate and 0.245 g of $Mg(ClO_4)_2$ (1.1 mmole) in 3 ml of acetonitrile was refluxed in the dark under argon at 60°C. The reduction was monitored by G.P.C. When no evolution was observed the reaction medium was directly purified by thin layer chromatography or by column chromatography (see below). The results are summarized in table 2.

-1-(Phenyl-2-ethyl)-3,5-N-(S)(-1-benzylhydroxyethyl)aminocarbonyl pyrrolo [2,3-b] pyridine: **5c**

The acid chloride of **4** was prepared as indicated in the synthesis of **5b** starting from 2.65 g (8.55 mmoles) of the diacid. The residue was dissolved in 30 ml of dichloromethane and added dropwise at -10°C added to a solution of 2.58 g (17 mmoles) of (S) phenylalaninol and 1.72 g (17 mmoles) of triethylamine in 40 ml of dichloromethane. The mixture was stirred 12 hours at room temperature. The solvent was evaporated, then 40 ml of water were added. The aqueous phase was extracted with 3 x 50 ml of ethyl acetate. The organic phase was washed with water, dried with magnesium sulfate then evaporated to dryness. The residue was purified by column chromatography (eluent: AcOEt/MeOH: 9/1), Yield: 77 %. m.p.: 92°C.

Analysis: $C_{35}H_{36}N_4O_4$; Cal % C=72.92; H=6.25; N=9.72. Found % C=72.7; H=6.3; N=9.6. I.R.: ν(C=O): 1635 cm^{-1} ν(NH): 3290 cm^{-1}; N.M.R. (CD_3CN)(recorded on a 400 MHz spectrometer): 8.56 (d, 1H); 8.49 (d, 1H); 7.6 (s, 1H), 7.35-7.05 (m, 15H); 6.77 (d, 1H); 4.47 (m, 1H); 4.36 (m, 1H); 4.31 (m, 2H); 3.6 (m, 6H); 3.05 (t, 2H); 2.95 (m, 2H); 2.85 (m, 2H).

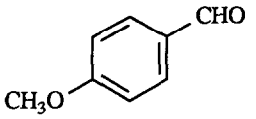
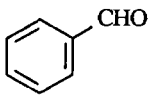
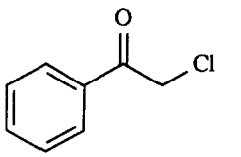
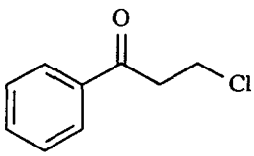
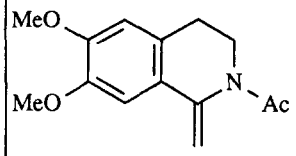
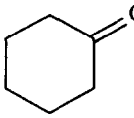
-1-(Phenyl-2-ethyl)-7-methyl-3,5-N-(S)(-1-benzylhydroxyethyl)amino carbonyl pyrrolo [2,3-b] pyridinium iodide: **6c**

The above diamide **5c** 1 g (1.74 mmole) in 10 ml of acetonitrile and 1 ml (18.4 mmoles) of methyl iodide was refluxed 24 hours. Every day, for 8 days, 1 ml of methyl iodide was added to the reaction mixture. After cooling, the solvents were eliminated. By h.p.l.c. analysis (C_{18} column; eluent: acetonitrile) it could be

showed that 30 % of diamide **5c** was not quaternized. The crude product was column chromatographied on silica: the diamide was first eluted with a mixture of AcOEt/MeOH: 95/5 methanol and the pyridinium salt **6c** was then eluted with methanol. Yield 56 %.

Analysis: $C_{36}H_{39}IN_4O_4$; Cal % C=60.17; H=5.43; N=7.80. Found % C=59.8; H=5.5; N=7.7. I.R.: ν(C=O): 1635 cm^{-1}; N.M.R. ($DMSOd_6$)(recorded on a 400 MHz spectrometer): 9.47 (d, 1H); 9.08 (d, 1H); 8.93 (d, 1H); 8.49 (s, 1H); 8.26 (d, 1H); 7.33-7.14 (m, 15H); 4.95 (t, 2H); 4.88 (m, 2H); 4.64 (s, 3H); 4.28 (m, 2H); 3.53 (m, 4H); 3.3 (t, 2H); 3.02 (m, 2H); 2.83 (m, 2H).

Table 2: Reduction of various substrates with **3b**

Substrate	Chromatographic conditions for monitoring	Conversion rate/time	Purification	Yield in isolated product
	Column A temperature profile 100 to 200°C in 5°/min	85 % 3 hours	Alumina column eluent: AcOEt	80 %
	Column B temperature 110°C	85 % 3 hours	Silica column eluent: CH_2Cl_2	80 %
	Column B temperature 150°C	85 % 10 hours	as above	85 %
	as above	83 % 48 hours	as above	70 %
	no monitoring	100 % 48 hours	t.l.c. on silica eluent: CH_2Cl_2	95 %
	Column C temperature 40°C	20 % 24 hours	Silica column eluent: CH_2Cl_2	10 %

Column A: DB 17 (purchased from Interchim). Length 15 m, film thickness 15 µm, detector temperature: 250°C; injector temperature: 250°C; vector gas: He, pressure 0.6 bar. Column B: XE-60-S valine (purchased from Chrompack). Length 25 m, film thickness: 0.11 µm, detector temperature: 250°C; injector temperature: 250°C, vector gas: H_2 pressure 0.8 bar. Column C: RSL-150 (purchased from Interchim) Length 25 m, film thickness: 0.25 µm, detector and injector temperature: 250°C; vector gas: H_2 pressure 0.8 bar.

-1-(Phenyl-2-ethyl)-7-methyl-3,5-N-(S)(-1-benzylhydroxyethyl)amino carbonyl-4,7 dihydro pyrrolo [2,3-b] pyridine: 3c

The above pyridinium salt (0.718 g, 1 mmole) in a mixture of 10 ml of water/methanol (1/1) was added to a solution of 0.286 g of sodium carbonate decahydrate (1 mmole) and 0.174 g of sodium dithionite (1 mmole) in 20 ml of water/methanol (1/1)(all solvents were previously degassed with argon). The mixture was stirred for 1 hour at room temperature under argon, in the dark.

Every hour, for 4 hours, 1 mmole of each sodium dithionite and sodium carbonate in 2 ml of water were added to the reaction mixture. During the following 3 hours only 1 mmole of sodium dithionite was added every hour. The reaction mixture was stirred under argon, in the dark for 12 hours, then extracted with 3 x 30 ml of dichloromethane. The organic phase was dried with magnesium sulfate and evaporated to dryness at a temperature below 35°C. The crude product was not further purified. Yield: 93 %

I.R.: v(C=O): 1640 cm^{-1}; N.M.R. (CD_3CN)(recorded on a 400 MHz spectrometer): 7.22-7.06 (m, 15H); 6.73 (s,1H); 6.64 (s, 1H); 6.27 (d, 1H); 6.05 (d, 1H); 4.16-4.12 (m, 4H); 3.74 (s, 2H); 3.50 (m, 2H); 3.49-3.39 (m, 2H); 2.91 (t, 2H); 2.87 (m, 2H); 2.71 (m, 2H) (alcoholic hydrogen were not detected).

Reduction of methylbenzoylformate

In a flask were introduced 1 mmole of **3c**, 0.9 mmole of substrate and magnesium perchlorate (for amounts, see fig. 1) in 5 ml of acetonitrile degassed with argon. The reaction mixture was stirred for 12 hours at room temperature (In experiments where additive **8** was used, it was recovered after a simple filtration; it could reused). Methyl mandelate was isolated by thin layer chromatography (silica plates, eluent: Et_2O/hexane: 1/1). The enantiomeric excess was determined by Mosher's method (19): in a dry tube stopped with a septum were introduced 300 µl of anhydrous pyridine and 25 µl of (+)-α-(methoxy)-α-(trifluoromethyl)-phenylacetic chloride (obtained from the acid). To this solution was added 0.1 mmole of methyl mandelate in 300 µl of carbon tetrachloride. The reaction mixture was treated, after 30 minutes, with 100 µl of methanol and the diastereoisomers were analysed by g.p.c. (column RSL-150 purchased from Interchim. length 25 m, film thickness: 0.25 µm; detector and injector temperatures: 250°C; column temperature: 170°C; vector gas: H_2, pressure 0.8 bar).

Reduction of the precursor of salsolidine: **11**

The reduction was performed in the conditions mentionned above by using 0.156 g (0.45 mmole) of **11**, 0.100 g (0.45 mmole) of $Mg(ClO_4)_2$ and 0.296 g (0.50 mmole) of 3c in 3 ml of acetonitrile for 3 days at 60°C. The e.e. was determined by the following method: sample was dissolved in 8 mM $Na_2HPO_4/Na_2H_2PO_4$ buffer (pH=7) containing 0.1 M NaCl and 2-propanol (14 ml/1 ml). Injection volume: 20 µl. Eluent: 8 mM Na_2HPO_4/NaH_2PO_4 buffer containing 0.1 M NaCl (pH=7) and 2-propanol (99/1; v/o). Flow rate 0.2 ml/min. Temperature: 16°C. Column LKB Enantiopac Cartridge column, 4 x 100 mm. Detector: polychrom 9060 Varian, 210 mm. Integrator spectra-physics SP 4290.

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