Synthesis and Study of Chiral NADH Models in the Thieno[2,3-*b*]pyridine Series

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Thieno[2,3-*b*]pyridine derivatives, functionalized on the thiophene ring have been synthesized in two different ways: electrophilic substitution of thieno[2,3-*b*]pyridine derivatives or construction of a pyridine ring starting from disubstituted thiophene compounds. The products obtained were used in the synthesis of chiral NADH models.

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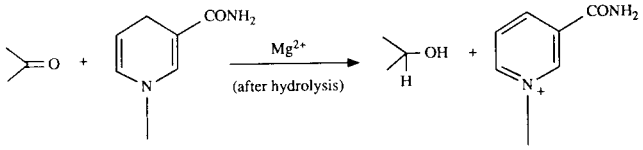
NADH models are widely studied in the literature as chemio and enantioselective reagents in organic synthesis. The active part of the reagent is the 1,4 dihydronicotinamide moiety which can transfer one hydrogen to a substrate. For example, the reduction of a carbonyl derivative mediated in the presence of magnesium ions (generally necessary to insure the reduction towards the existence of a ternary complex built between the substrate, the ion and the model) can be represented by Scheme 1 [1].

Scheme 1



With common models, derived from *N*-benzyl-1,4-dihydronicotinamide (BNAH) bearing a chiral center some excellent results were obtained in the reduction of prochiral substrates. However, these models are unstable under the usual laboratory conditions. Side reactions can occur on the -5,6 double bond of the dihydropyridine structure which perturb extensively the efficiency of the reagent [2a-c]. "Hyper dry" conditions are necessarily used with these models [3]. It is possible to minimize these side reactions by using annelated models where the fragile 5,6-double bond is protected with a fused benzene ring, but the reactivity of the model is low. In our laboratory we synthesized annelated NADH models in which the dihydropyridine ring is fused with an electron donating heterocycle such as thiophene or pyrrole. The corresponding reagents seem to be promising NADH models: they can be used in mild laboratory conditions allowing the reduction in high yields of numerous substrates [4a,b].

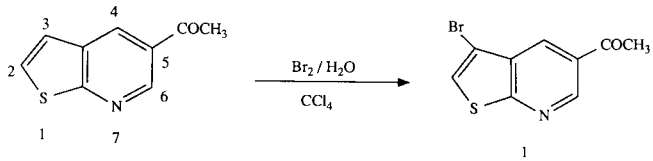
These models offer another possibility. The presence of an annelated ring can be used for the introduction of an external chiral auxiliary not directly linked to the dihydropyridine structure. Moreover a substituent can be introduced at the β position of the thiophenic ring, that is in the vicinity of the active site of the dihydropyridine ring. It can be assumed that the rigidity of the fused rings system could ensure a stereospecific clamping of one of the two faces of the dihydropyridine structure. We wish to report our first results in the synthesis of such chiral derivatives in the thieno[2,3-*b*]pyridine series.

I. Attempts to Functionalize the Thiophene Ring of Thieno[2,3-*b*]pyridine Derivatives Through Electrophilic Substitutions.

Thieno[2,3-*b*]pyridine derivatives can undergo electrophilic attacks on the β position of the electron rich ring [5]. However, very little is known about derivatives bearing an electron withdrawing group on the 5 position of the pyridine ring.

We first tried to perform bromination of 5-carbamoyl (or 5-acetyl thieno[2,3-*b*]pyridine) [6] under various conditions (the bromo derivative should be metalated after halogen/lithium exchange [6] and the lithio derivative could be further converted in numerous compounds): the bromination with bromine, water, carbon tetrachloride [7] afforded a poor yield in the bromo derivative **1**. The bromination with bromine, sulphuric acid, silver sulphate [8] gave only a small amount of the starting compound as identificable compound and bromination with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in sulphuric acid at 20° (instead of dibromoisocyanuric acid [9]) gave probably a dibromo derivative.

Scheme 2



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Even by varying the stocchiometry of the bromating agent the mono bromo derivative was not obtained. The presence of two bromine atoms would complicate the halogen/metal exchange, so we did not persue in this direction.

Other substitutions (acetylation, nitration) did not give satisfactory results.

II. Synthesis of 3-Substituted Thieno[2,3-*b*]pyridine Derivatives Starting from 2,4-Disubstituted Thiophenes.

In our laboratory we have developed an efficient synthesis of annelated NADH models precursors starting from amino derivatives of electron donating rings [10]. With a view to obtaining the desired products and following this methodology it appeared that 2-aminothiophene derivatives substituted at the 4-position were needed.

1) Synthesis Starting from 4-acetyl-2-nitrothiophene **3** [11].

The carbonyl function is very reactive and could be transformed into suitable compounds later. The reduction of the nitro group was tried in various conditions: with tin/hydrochloric acid we obtained non identificable compounds. The ^1H and ^{13}C nmr spectra showed only aliphatic protons and carbons suggesting that the aromatic ring was destroyed. Under milder conditions (hydrogen in the presence of a catalyst) no reduction was observed.

By supposing that the presence of two electron withdrawing groups (acetyl and nitro) induces the destruction of the thiophenic ring during the reduction, we decided to transform the acetyl group prior to trying the reduction.

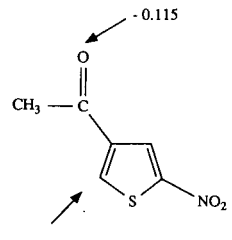
Reductive amination of the acetyl group was tested by using benzylamine and sodium borohydride (later a chiral benzylamine derivative should be used). Destruction of the thiophene ring was again observed as could be seen after examination of the nmr spectra of the reaction mixture. On the other hand, reduction of the acetyl group leading to the alcoholic derivative **4** was easily performed after treatment with sodium borohydride in methanol. (Scheme 3).

The reduction of the nitro group with tin/hydrochloric acid gave a mixture of two amino salts **5** and **6**. The separation of these compounds was difficult, so the mixture was subjected to the action of methyl 3,3-dimethoxy-2-(dimethoxymethyl)propanoate [12] leading to the two thieno[2,3-*b*]pyridines **7** and **8**, in a 7/3 ratio (overall yield 50%).

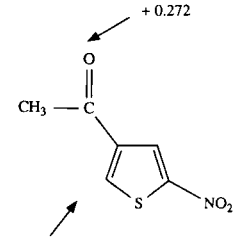
Note: At this point one question can be raised concerning the behaviour of 4-acetyl-2-nitrothiophene in the presence of nucleophiles (benzylamine during reductive amination leads to a destruction of the ring; sodium borohydride provides a facile reduction of the acetyl group into carbinol or ethyl group). Calculations made with the MNDO method [13], using Pople parameters [14] gave the following results after full optimization of the geometry of the molecule:

energy of frontier orbitals: H.O.M.O: -10.85305 eV
L.U.M.O: -1.79235 eV

Orbital coefficients in the LUMO



Net atomic charges

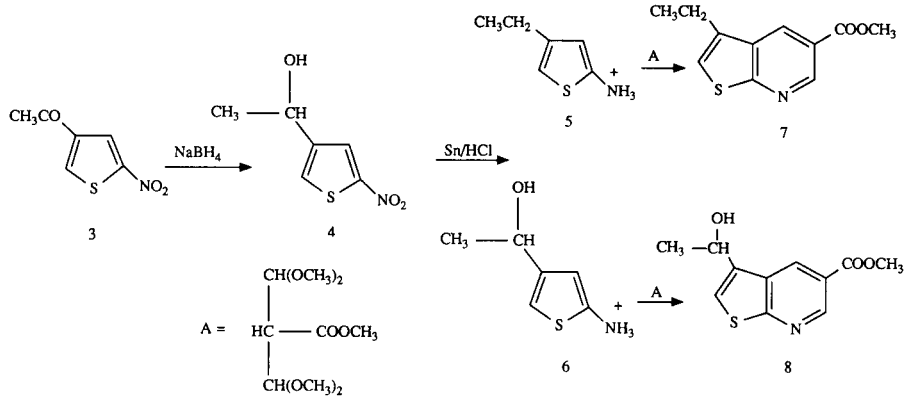


The energy of the LUMO is low: the molecule is normally sensitive to nucleophilic attacks. Moreover orbital coefficients show that with a soft reagent (such as benzylamine) involved in a reaction under orbital control, the most reactive site is the 5 position which could lead further to ring opening. With a harder reagent (sodium borohydride) the most reactive site, under charge control, is the carbonyl group as observed in our experiments.

2) Synthesis Starting from 2-nitro-4-thiophenecarboxylic Acid.

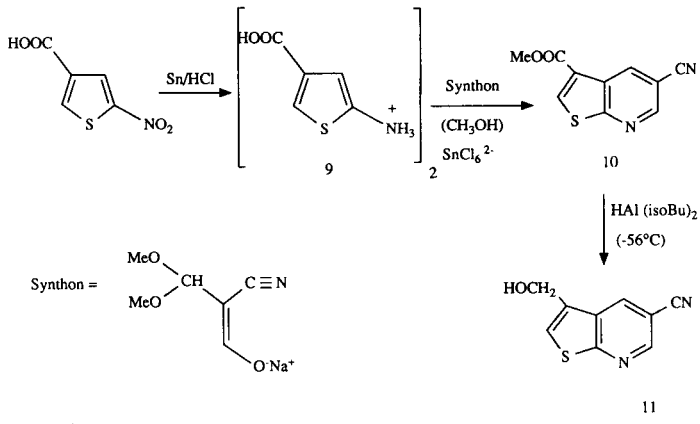
This compound was easily obtained in high yield (74% instead of 60%) after improvement of the conditions of the nitration [11]. The reduction of the nitro group with tin/hydrochloric acid gave the amino derivative **9** which was

Scheme 3



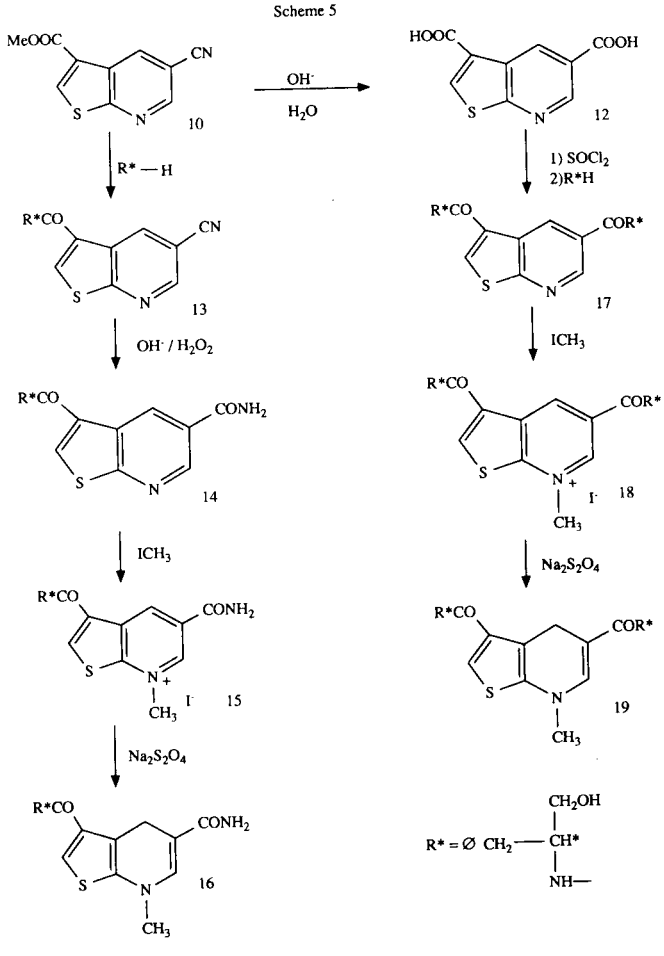
converted into the thieno[2,3-*b*]pyridine derivative **10** (during the reaction the acid was esterified) (overall yield 75%) (Scheme 4).

Scheme 4



With a view to extending the number of derivatives which could be used in the synthesis of chiral precursors we tried to reduce the ester function of **10** into hydroxymethyl group. A careful study of the experimental conditions showed that the reduction with diisobulylaluminium hydride led to **11** at -56° with a 77% yield. At higher temperature, the nitrile function was partly reduced (Scheme 4). Unfortunately we were not able to transform **11** into a suitable dihydropyridine derivative in a later attempt.

Scheme 5



III. Chiral Derivatives.

1) Synthesis.

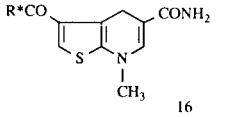
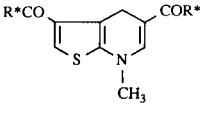
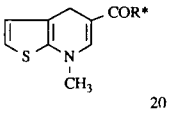
The chiral auxiliary used was (*S*)-phenylalaninol [15]. Previously reported results showed that the presence of an alcoholic function plays an important role in the rigidity of the ternary complex involved between the substrate, magnesium ions and the model during the course of a reduction [16a,b]. So the enantioselectivity of the hydrogen transfer is enhanced.

Starting from **10** and **12** NADH models **16** and **19** were obtained following the reactions outlined on Scheme 5:

The reaction between **10** and phenylalaninol was difficult: pure **13** was obtained in a 15% yield only. The other steps were carried out without major problems. However, the regioselective reduction of the pyridinium salt **18** was very slow probably because steric hindrance caused by the substituents at the 3,5 positions. In the first experiments the yield in **19** was only 30% certainly because sodium dithionite is not very stable in alkaline conditions. So, it was necessary to add small amounts of the reducing agent at regular periods, during several hours. By this way the yield reached 74%.

2) Reduction of Methyl Benzoylformate.

Table 1

Model	Chemical Yield	e.e. and configuration of major enantiomer
 16	31	18% (S)
 19	75	41% (S)
 20	100	53% (R) [16b]

Conditions: 1 equivalent of model, magnesium perchlorate and substrate. Solvent acetonitrile temperature 60°C. Determination of e.e. by hplc analysis by using a chiral column.

Under standard conditions the reduction of methyl benzoylformate with **16** and **19** gave the following results. (See Table 1).

With **16** the chemical yield is low. It can be assumed that this behaviour is due, for a part, to the insolubility of the pyridinium salt formed leading consequently, to a difficult extraction of methyl mandelate from the reaction mixture.

However, the 18% *e.e.* in (*S*)-methyl mandelate is to our knowledge the first example of an enantioselective transfer of hydrogen with a NADH model bearing a chiral auxiliary not directly linked to the dihydro pyridine ring.

With **19**, where the two rings bear a (*S*)-phenylalaninol group, the result is doubly interesting because the *e.e.* is higher than with **16** and the major enantiomer is the same as with **16**.

It must be remembered that with model **20** bearing the same chiral auxiliary, but only on the dihydropyridine ring, the major enantiomer was the opposite. That means that the ternary complex (model/magnesium ions/substrate) involved in these reductions has a different structure in these different cases. Work is under way to refine the steric course of the hydrogen transfer with these models.

EXPERIMENTAL

The ir spectra were recorded on a Beckman Acculab 3 spectrophotometer. The nmr spectra were recorded on a Varian EM 360L apparatus in deuterated solvents; resonance positions are given on the δ scale (parts per million) relative to internal hexamethyldisiloxane when the spectra were recorded in DMSO-d_6 or relative to tetramethylsilane when the spectra were recorded in deuteriochloroform. The nmr peaks were designed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The usual constants were observed: for example 2 Hz between the α and γ protons of the pyridine ring. Melting points were determined on a Kofler bank and are uncorrected. Microanalyses were recorded on a Carlo Erba 1106 apparatus. Optical rotations were determined by hplc by using a Waters apparatus and a L. K. B. enantiopac as chiral column.

3-Bromo-5-acetylthieno[2,3-*b*]pyridine (**1**).

A solution of 0.8 g (4.5 mmoles) of 5-acetylthieno[2,3-*b*]pyridine [6] and 2.2 g (13.8 mmoles) of bromine in 7 ml of carbon tetrachloride and 30 ml of water was maintained at room temperature under stirring for 12 hours. After elimination of the solvents, the residue was stirred with an excess of sodium sulfite in concentrated ammonia. After extraction with methylene chloride and evaporation, the residue was filtered on a silica column, yield 25%, mp 154°; ir: 1675 cm^{-1}; ^1H nmr (deuteriochloroform): 9.10 (d, 1H), 8.50 (d, 1H), 7.60 (s, 1H), 2.70 (s, 3H).

Anal. Calcd. for C_9H_6BrNOS: C, 42.19; H, 2.34; N, 5.47. Found: C, 42.0; H, 2.2; N, 5.5.

2-Nitro-4-acetylthiophene (**3**).

In a solution of 20 ml of concentrated nitric acid (d = 1.49) and 11 ml of concentrated sulphuric acid maintained at -10°, was introduced 5 g (40 mmoles) of 3-acetylthiophene [6] by portions, at a temperature comprised between -5 and -10°. The reaction mixture was poured on ice. The orange precipitate was filtered, the aqueous phase extracted with dichloromethane. The solvent was evaporated and the solids were collected and purified by chromatography on silica (eluent ether/hexane = 1/1), yield 70%, mp 62°, Lit [17] 62-63°; ir: 1680, 1530, 1335 cm^{-1}; ^1H nmr (deuteriochloroform): 8.25 (d, 1H), 8.15 (d, 1H), 2.55 (s, 3H).

Anal. Calcd. for $C_6H_5NO_3S$: C, 42.10; H, 2.94; N, 8.18. Found: C, 42.3; H, 2.9; N, 7.7.

2-Nitro-4-(1-hydroxyethyl)thiophene (**4**).

Sodium borohydride (4 g, 79 mmoles) in 30 ml of methanol was added dropwise to a solution of 3 g (17.5 mmoles) of 2-nitro-4-acetylthiophene **3** in 30 ml of methanol, the temperature being maintained at 10-20°. The reaction mixture was then treated with 100 ml of water and the aqueous phase extracted with 3 x 200 ml of dichloromethane. The solvent was dried, evaporated. An oil was obtained, yield 66%; ir: 1505 cm^{-1}; ^1H nmr (deuteriochloroform): 7.80 (d, 1H), 7.40 (d, 1H), 4.80 (q, 1H), 3.10 (m, 1H), 1.40 (d, 3H).

Anal. Calcd. for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09. Found C, 41.3; H, 4.0; N, 8.0.

3-Ethyl-5-carbomethoxythieno[2,3-*b*]pyridine (**7**) and 3-(1-Hydroxyethyl)-5-carbomethoxythieno[2,3-*b*]pyridine (**8**).

In a solution of 0.5 g of the above compound **4** in 8 ml of concentrated hydrochloric acid was added 1 g of powdered tin by small portions at a temperature maintained at 40-45°. After cooling, the precipitate was filtered and dried. By this mean, 0.62 g of hexachlorostannate salts **5** and **6** were obtained. The solid was dissolved in a mixture of 15 ml of methanol and 1 ml of concentrated hydrochloric acid. This solution was added to a solution of 0.5 g (2.25 mmoles) of methyl-3,3-dimethoxy-2-(dimethoxymethyl)-propanoate [12]. The mixture was then refluxed for 20 hours. After elimination of the solvent, the residue was taken up in dichloromethane, washed with water, dried and concentrated leading to a mixture of **7** and **8** (ratio 7/3) which have the following nmr characteristics (Solvent deuteriochloroform): 3-ethyl-5-carbomethoxythieno[2,3-*b*]pyridine: **7** 9.15 (d, 1H), 8.60 (d, 1H), 7.30 (s, 1H), 4.0 (s, 3H), 2.90 (q, 2H), 1.40 (t, 3H); 3-(1-hydroxyethyl)-5-carbomethoxythieno[2,3-*b*]pyridine: **8**, 9.15 (d, 1H), 8.85 (d, 1H), 7.50 (s, 1H), 4.75 (q, 1H), 4.00 (s, 3H), 1.60 (d, 3H).

3-Carbomethoxy-5-cyanothieno[2,3-*b*]pyridine (**10**).

Nitration of 2-Thiophenecarboxylic Acid.

To a solution of 80 ml of nitric acid (d = 1.49) and 46 ml of concentrated sulphuric acid was added, at -10° to -5°, 20 g (156 mmoles) of 2-thiophenecarboxylic acid. After the end of the introduction, the mixture was kept at -5° for 3 minutes, then cooled to -25° and poured on ice. After filtration 4-nitro-2-thiophenecarboxylic acid was obtained, yield 74%, mp 146° (litt [11] mp 145-146°).

To 10 g (58 mmoles) of 2-nitro-4-thiophenecarboxylic acid in 200 ml of concentrated hydrochloric acid, was added protion wise, 21.7 g of powdered tin at a temperature maintained between 40 and 45°. After cooling, the precipitate was filtered, the mother liquor concentrated to 2/3 and a further crop of hexachlorostannate double salt of 2-amino-4-thiophenecarboxylic acid **9** was obtained, overall yield 64%, mp 170-180° dec; ir: 1680

cm^{-1}; ^1H nmr (deuteriochloroform): 10.5 (m, 4H), 7.90 (d, 1H), 7.15 (d, 1H). This product was not obtained analytically pure and was used without further purification.

A solution of 13.9 g (45 mmoles) of **9** in 300 ml of methanol and 51 ml of concentrated hydrochloric acid, was added, under argon, to a suspension of 9 g (55 mmoles) of 3,3-dimethoxy-2-formylpropionitrile sodium salt [10] in 100 ml of methanol and 5 ml of concentrated hydrochloric acid. After the end of the addition the mixture was refluxed for 24 hours and maintained at room temperature for 24 hours. A part of methanol (200 ml) was evaporated, replaced by water and the remaining methanol was then removed. The precipitate was filtered and purified by crystallisation in a mixture of water/methanol (30/70), yield 75%, mp 123°; ir: 2240, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): 9.15 (d, 1H), 8.85 (d, 1H), 8.60 (s, 1H), 4.00 (s, 3H).

Anal. Calcd. for $C_{10}H_6N_2O_2S$: C, 55.04; H, 2.51; N, 12.84. Found: C, 54.6; H, 2.5; N, 12.5.

3-Hydroxymethyl-5-cyanothieno[2,3-*b*]pyridine (**11**).

A solution of 0.89 g (4 mmoles) of **10** in 25 ml of anhydrous tetrahydrofuran was cooled at -56° (the flask was immersed in a cryostat). A cooled toluene solution (1.5 *M*) of aluminium diisobutyl hydride (6 ml) was introduced dropwise under argon, the temperature being maintained at -56°, 1 hour after the end of the addition.

A solution of 30 ml of water and 5 ml of concentrated hydrochloric acid was added. The solvents were removed under reduced pressure and the obtained precipitate was filtered. The aqueous phase was extracted with dichloromethane, the solvent evaporated. The residue and the above precipitate were purified by chromatography on silica (eluent dichloromethane/THF: 90/10), yield 77%, oil; ir: 2230 cm^{-1}; ^1H nmr (DMSO-d_6): 8.85 (d, 1H), 8.75 (d, 1H), 7.80 (s, 1H), 4.70 (s, 2H), 3.35 (m, 1H).

Anal. Calcd. for $C_9H_5N_2OS$: C, 56.83; H, 3.18; N, 14.73. Found: C, 56.5; H, 2.8; N, 14.4.

3,5-thieno[2,3-*b*]pyridinedicarboxylic Acid (**12**).

A solution of 5 g (29 mmoles) of **10** in 100 ml of 20% sodium hydroxyde and 85 ml of ethanol was refluxed for 36 hours. After cooling, ethanol was eliminated and the solution acidified at *p*H = 1 with 6*N* hydrochloric acid. The precipitate was filtered and purified after recrystallisation in methanol, yield 74%, mp >250°; ir: 1695 cm^{-1}; ^1H nmr (DMSO-d_6): 9.20 (d, 1H), 9.05 (d, 1H), 8.80 (s, 1H), 7.90 (m, 1H).

Anal. Calcd. for $C_9H_5NO_4S$: C, 48.43; H, 2.26; N, 6.28. Found: C, 48.7; H, 2.7; N, 6.3.

N-3-(-(*S*)-1-Hydroxymethyl-2-phenylethyl)carboxamide-5-cyanothieno[2,3-*b*]pyridine (**13**).

A solution of 1 g of **10** (4.6 mmoles) in 20 ml of toluene and 2 g (14 mmoles) of (*S*)-phenylalaninol was refluxed in a flask fitted with a Dean Stark apparatus for 48 hours. After cooling the mixture was dissolved in dichloromethane, then washed with 6*N* hydrochloric acid. After decantation, the organic phase was concentrated and the residue was chromatographied on silica (eluent dichloromethane/THF: 80/20), yield 15%, mp 209°; ir: 2230, 1655 cm^{-1}; ^1H nmr (DMSO-d_6): 8.90 (s, 2H), 8.60 (s, 1H), 8.35 (m, 1H), 7.15 (s, 5H), 4.80 (m, 1H), 4.15 (m, 1H), 3.45 (m, 2H), 2.80 (m, 2H).

Anal. Calcd. for $C_8H_{15}N_3O_2S$: C, 64.08; H, 4.48; N, 12.45. Found: C, 64.3; H, 4.5; N, 12.0.

N-3-(-(*S*)-1-Hydroxymethyl-2-phenylethyl)carboxamide-5-carbamoylthieno[2,3-*b*]pyridine (**14**).

The above product **13** was dissolved in 50 ml of methanol and 40 ml of ethanol. A solution of 0.4 ml of 30% hydrogen peroxyde and 0.05 ml of 5*M* sodium hydroxide was added and the mixture warmed at 40-50° for 80 hours. After elimination of organic solvents the product was filtered, yield 84%, mp 230°; $[\alpha]D^{21}$ = -23.7° (c = 0.333/methanol); ir: 1670 cm^{-1}; ^1H nmr (DMSO-d_6): 9.05 (d, 1H), 8.95 (d, 1H), 8.45 (s, 1H), 7.20 (s, 5H), 4.10 (m, 2H), 3.50 (m, 2H), 2.85 (m, 2H).

*Anal.*Calcd. for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.5; H, 4.7; N, 11.5.

N,*N*'-3,5-((*S*)-1-Hydroxymethyl-2-phenylethyl)dicarboxamidethieno[2,3-*b*]pridine (**17**).

The diacid **12**, (3.65 g, 16 mmoles) was refluxed with 30 ml of thionyl chloride for 12 hours. After cooling, the excess of reagent was removed and the residue, dissolved in 30 ml of dichloromethane, was introduced at -10° in a solution of 5.44 g (36 mmoles) of (*S*)-phenylalaninol and 3.64 g (36 mmoles) of triethylamine in 30 ml of dichloromethane. After introduction the solution was stirred at room temperature for 12 hours. The solvent was removed, the precipitate recrystallized in ethanol-water (70/30), yield 69%. This compound was not obtained analytically pure, $[\alpha]^{20}D$ = -105.2° (c = 0.533/acetonitrile); ir: 1645 cm^{-1}; ^1H nmr (DMSO-d_6): 9.0 (d, 1H), 8.85 (d, 1H), 8.50 (s, 1H), 8.40 (m, 2H), 7.20 (s, 10H), 4.80 (m, 2H), 4.10 (m, 2H), 3.45 (m, 4H), 2.80 (m, 4H).

Quaternization of Compounds **14** and **17**.

The amide **14** or **17** was dissolved in hot acetonitrile (50-60°) and a large excess (10 equivalents) of methyl iodide was added. The mixture was refluxed for 24 hours. A fraction of the solvent (about 3/4) was removed and ether was added until no further precipitate was formed. After filtration and drying the pyridinium salts were used without purification for the next step.

N-3-((*S*)-1-Hydroxymethyl-2-phenylethyl)-carboxamide-5-carbamoyl-7-methylthieno[2,3-*b*]pyridinium Iodide (**15**).

The yield was 84%; ir: 1690 cm^{-1}; ^1H nmr (DMSO-d_6): 9.60 (s, 2H), 8.80 (s, 1H), 7.3 (m, 5H), 4.6 (s, 3H), 3.9 (m, 2H), 3.55 (m, 2H).

This compound was not analytically pure.

N,*N*'-3,5-((*S*)-1-Hydroxymethyl-2-phenylethyl)dicarboxamide-7-methylthieno[2,3-*b*]pyridinium Iodide (**18**).

The yield was 73%; ir: 1655 cm^{-1}; ^1H nmr (DMSO-d_6): 9.55 (s, 2H), 8.90 (m, 2H), 8.85 (s, 1H), 7.20 (m, 10H), 4.90 (m, 2H), 4.55 (s, 3H), 4.20 (m, 2H), 3.40 (m, 4H), 2.85 (m, 4H).

Anal. Calcd. for $C_{28}H_{30}IN_3O_4S$: C, 53.25; H, 4.79; N, 6.65. Found: C, 52.8; H, 4.8; N, 6.3.

Reduction of pyridinium salts **15** and **18**.

Pyridinium salt **15** or **18** (3.3 mmoles) was dissolved in a minimum of methanol at room temperature. A solution of 4.72 g (16.5 mmoles) of sodium carbonate decahydrate and 0.58 g (3.3 mmoles) of sodium dithionite in 90 ml of water was prepared. To this solution was added the above solution of pyridinium salt. The mixture was stirred under argon, in the dark. After 30-45 minutes, another amount of sodium dithionite (0.58 g) was added, this procedure being repeated seven fold. After the end of the reaction, the solution was extracted with 3 x 80 ml of dichloromethane. The organic phase was dried, and the solvent was

removed. Dihydropyridines **16** and **19** were not further purified. Their structures were proved after examination of their nmr spectra.

N-3-((*S*)-1-Hydroxymethyl-2-phenylethyl)carboxamide-5-carbamoyl-7-methyl-4,7-dihydrothieno[2,3-*b*]pyridine (**16**).

The yield was 32%; ir: 1660 cm^{-1}; ^1H nmr (DMSO-d_6): 7.25 (m, 7H), 4.05 (m, 1H), 3.6-3.4 (m, 4H), 3.2 (s, 3H), 2.8 (m, 2H).

N,*N'*-3,5-((*S*)-1-hydroxymethyl-2-phenylethyl)dicarboxamide-7-methyl-4,7-dihydrothieno[2,3-*b*]pyridine (**19**).

Yield 74%; ir: 1655 cm^{-1}; ^1H nmr (DMSO-d_6): 7.25 (m, 12H), 6.55 (m, 2H), 4.70-2.35 (m, 17H).

General Procedure for the reduction of Methyl Benzoylformate with a Dihydropyridine Derivative.

The NADH model (1 mmole), **16** or **19** was dissolved in 5 ml of dry acetonitrile, with 0.223 g (1 mmole) of magnesium perchlorate and 0.149 g (0.9 mmole) of methyl benzoylformate. The mixture was stirred at 60° for 2 days, in the dark under argon. After cooling 90 ml of ether and 10 ml of water were added and methyl mandelate was extracted in the organic phase. After evaporation of the solvent, the pure mandelate was obtained after thin layer chromatography on silica (eluent ether/hexane: 1/2). The enantiomeric excess was determined by high performance liquid chromatography using a L. K. B. Enantiopac column.

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