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Synthesis of New Thieno[2,3-*b*:5,4-*c*′]dipyridines

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Summary. We describe the formation of thieno[2,3-*b*:5,4-*c*′]dipyridines from 5,6-dihydropyridine-2(1*H*)-thiones. The two-step reaction mechanism was revealed by isolation of an intermediate. The oxo and thioxo groups of the obtained tricyclic compounds were hydrogenated selectively. The structures of all new compounds were elucidated by NMR experiments.

Keywords. Cyclizations; Heterocycles; Hydrogenations; Thienodipyridines.

Introduction

The so far synthesized partially hydrogenated thieno[2,3-*b*:5,4-*c*′]dipyridine derivatives have been reported to exhibit anxiolytic [1], anticonvulsive [1], or antiinflammatory properties [2–4]. They have been prepared in several steps from 4-piperidones [1–4] *via* thieno[2,3-*c*]pyridines. This paper deals with the dimerization of 5,6-dihydropyridine-2(1*H*)-thiones to thieno[2,3-*b*:5,4-*c*′]dipyridin-4-ones and with the selective hydrogenation of the products obtained.

Results and Discussion

6-Substituted 5,6-dihydro-4-(dimethylamino)pyridine-2(1*H*)-thiones **1** are available from α,β-unsaturated ketones and dialkylammonium thiocyanates in one-pot reactions [5, 6]. Upon treatment with dilute caustic soda the dimethylamino group of the 6,6-dimethyl substituted compound has been replaced by a hydroxy substituent giving a tautomeric mixture of the 5,6-dihydro-4-hydroxypyridine-2(1*H*)-thione **2** and the 2,3,5,6-tetrahydro-6-thioxopyridin-4(1*H*)-one **3** [7]. Those have been treated with alkyl- and aryl-amines affording the 4-amino derivatives **4** in moderate to good yields [7, 8]. However, upon heating with a non-reactive aniline, compounds **2** and **3** were dimerized (Scheme 1). The NMR spectra of

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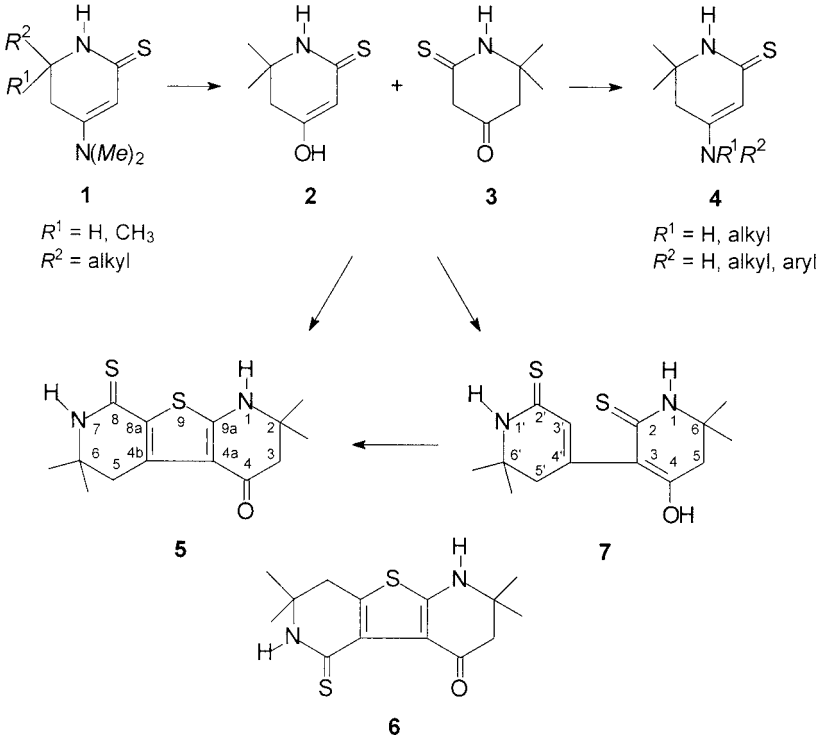


Scheme 1

the product revealed one methylene group neighbouring a carbonyl group and a second connected with a quaternary olefinic carbon. From this, the isomeric structures **5** and **6** were conceivable for the product. The chemical shifts in the ^{13}C NMR spectra and the cross-peaks in the 2D-NMR spectra (*HSQC*, *HMBC*) matched well with structure **5**, however, they did not rule out structure **6** beyond all doubt.

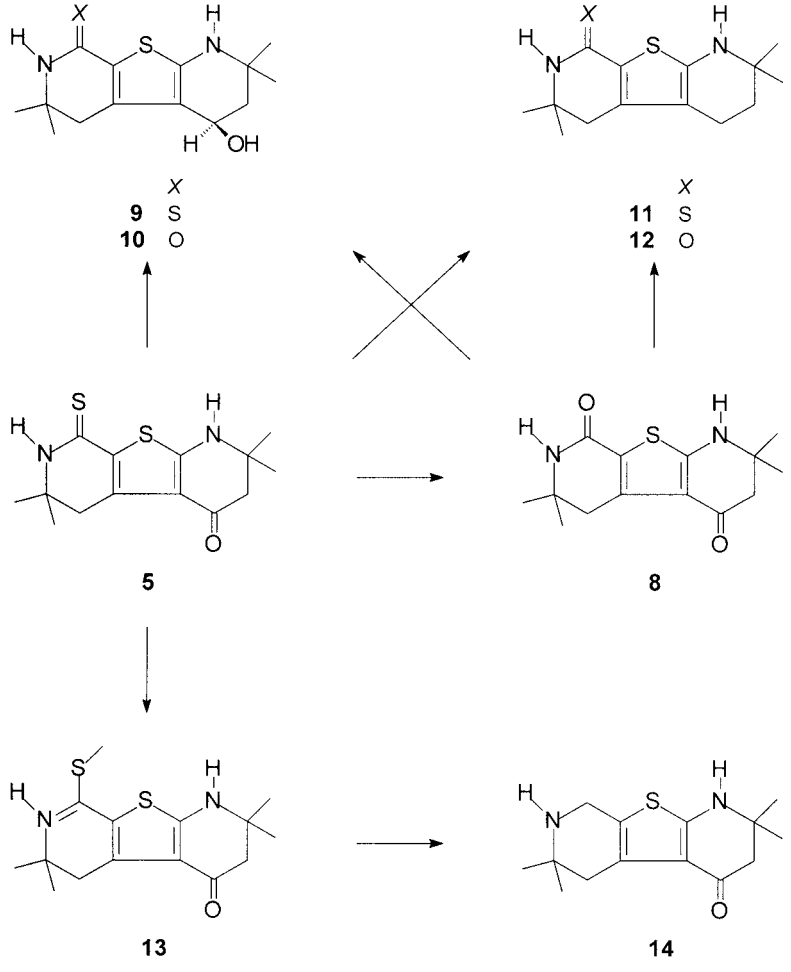
The thieno[2,3-*b*:5,4-*c*′]dipyridine structure **5** was established in the course of the investigation of the reaction pathway. Since the elemental analysis of the product indicated elimination of water and a dehydrogenating process, the fusion of **2** and **3** was carried out in an inert-gas atmosphere to prevent the oxidation step. The asymmetric bipyridinyldithione **7** was formed selectively thereby. Its structure was unambigously determined by *HMBC* and *NOE* experiments ruling out structure **6** which is not accessible from **7**. To be on the safe side, **7** was fused under base catalysis in the presence of air giving a product, which was identical with **5**.

The influence of the base was investigated fusing **2** and **3** without base catalysis in the presence of air. The dithione **7** was the main product accompanied by smaller amounts of **5** indicating that the dehydrogenation occurs also in the absence of the base. However, compound **5** was not accessible in acceptable yields by this method. Its 8-oxo analogue **8** was obtained by treatment of **5** with concentrated hydrogen peroxide in alkaline medium. Due to the exchange of the thioxo by an oxo group the signal for the C-8 in the ^{13}C NMR spectrum was typically shifted 20 ppm to lower frequencies. In addition, the signal for C-8a was shifted 9 ppm upfield, whereas the resonance of C-4b was shifted 5 ppm downfield.

Subsequently, we examined reactions of compounds **5** and **8** with hydrogenating agents in order to reduce the oxo group in ring position 4 to a hydroxy substituent, as well as to remove the 8-thioxo function. Their reaction with $NaBH_4$ gave mainly the 4-hydroxy compounds **9** and **10** (Scheme 2). In the ^{13}C NMR spectra of **9** and **10** the presence of a hydroxy group was indicated by a signal at 61 ppm. In their ^{1}H NMR spectra their 4-hydroxy structure was established by ^{3}J couplings from the carbinol protons to the 3-Hs. Due to the changes in the mesomeric system the signals of the C-9a were shifted more than 10 ppm to lower frequencies.

Prolonged treatment of **5** and **8** with $NaBH_4$ afforded mixtures of compounds **9** and **11**, and **10** and **12**. However, **11** and **12** were obtained in good yields by treatment of **5** and **8** with $LiAlH_4$. The reduction of the 4-oxo function to a methylene group caused remarkable shifts in the ^{13}C NMR spectra. In addition to the expected highfield shift for the signal of C-4, the signals for C-3 and C-9a were shifted more than 10 ppm to lower frequencies.

Although $NaBH_4$ and $LiAlH_4$ have been reported to reduce substituted thiobenzamides to the corresponding benzylamines [9–11], the 8-thioxo group of



Scheme 2

compound **5** remained unchanged during the above-mentioned reactions. The hydrogenation of **5** with *Raney* nickel W-2 [12] yielded multicomponent mixtures, whereas no reaction was observed using further deactivated *Raney* nickel. Retaining the oxo group in ring position 4, we removed the 8-thioxo group of **5** by a two-step procedure. The 8-thioxo compound **5** was converted to its methylthio derivative **13**. The latter was hydrogenated with *Raney* nickel, which has been inactivated by treatment with acetic acid. Purification of the reaction mixture afforded the octahydrothieno[2,3-*b*:5,4-*c*′]dipyridine **14**. In the ^{1}H NMR spectrum of **14** we observed 3 singlets of methylene protons. Those were assigned by their chemical shifts and their cross-peaks in the *HMBC* spectrum.

All resonances were assigned with the aid of 1D *NOE* and 2D NMR spectra (*HSQC*, *HMBC*). The discrimination of the resonances of the 4 quaternary carbons of the thiophene ring was accomplished by means of *HMBC* experiments, which were optimized for 10 Hz couplings. In their spectra we observed long-range couplings from the 2-methyl protons to the C-9a and from the 6-methyl protons to C-4b. The signal for C-4a was identified from a cross-peak to the 3-Hs.

The present method provides a quick access to 2,6-disubstituted thieno[2,3-*b*:5,4-*c*′]dipyridines from easily available starting materials. The oxo and thioxo groups of the obtained compounds were selectively hydrogenated by the use of different catalysts. For the synthesis of compounds with pharmacological activities ring positions 3 and 4 of compounds **5**, **9**, **10**, and **14** will be further functionalized.

Experimental

Melting points were obtained on a digital melting point apparatus Electrothermal IA 9200 and are uncorrected. IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). NMR spectra: Varian Inova 400 (298 K) 5 mm tubes, *TMS* as internal standard. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. Microanalyses: Microanalytical Laboratory at the Institute of Physical Chemistry, Vienna; their values were found to be in satisfactory agreement with the calculated ones. Column chromatography (CC), flash chromatography [13]: column diameter 30 mm, layer thickness 300 mm, Merck silicagel 60, 0.040–0.063 mm (230–400 mesh), rate of flow 10 cm^3/min. thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F_{254} 0.2 mm, 200 × 200 mm).

2,3,5,6,7,8-Hexahydro-2,2,6,6-tetramethyl-8-thioxothieno[2,3-b:5,4-c′]dipyridin-4(1H)-one (**5**, $C_{14}H_{18}N_2OS_2$)

Method A: 3.15 g (20 mmol) of **2** and **3** and 2.94 g of 2,6-dichloroaniline (20 mmol) were triturated with a pestle in a mortar. The mixture was transfered into an *Erlenmeyer* flask and melted with agitation at 140°C on an oil-bath for 8 h. The solidified mixture was allowed to cool down. Then 30 cm^3 of $CHCl_3$ were added and the mixture was stirred for 1 h. The suspension was filtered with suction. The residue was recrystallized from ethanol/$CHCl_3$ yielding 2.13 g (72%) of **5**.

Method B: Compound **7** (2.96 g, 10 mmol) and 2.94 g of 2,6-dichloroaniline (20 mmol) were treated according to method A yielding 2.51 g (85%) of **5**.

Mp 345°C; IR (KBr): $\bar{\nu} = 3253$ (m), 3167 (m), 2963 (m), 2925 (w), 1616 (s), 1543 (s), 1478 (s), 1445 (s), 1402 (s), 1250 (s) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.26$ (s, $(CH_3)_2$-C-6), 1.27 (s, $(CH_3)_2$-C-2), 2.42 (s, 2 3-H), 2.94 (s, 2 5-H), 8.78 (s, 1-H), 9.30 (s, 7-H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 26.73$ ((CH_3)$_2$-C-2), 27.61 ((CH_3)$_2$-C-6), 36.74 (C-5), 49.50 (C-3), 54.48 (C-6), 56.15 (C-2), 112.98 (C-4a), 120.42 (C-8a), 136.56 (C-4b), 169.22 (C-9a), 182.58 (C-8), 188.38 (C-4) ppm.

5,6,5′,6′-Tetrahydro-4-hydroxy-6,6,6′,6′-tetramethyl-[3,4′-bipyridinyl]-2,2′(1H,1′H)-dithione (**7**, $C_{14}H_{20}N_2OS_2$)

Compounds **2** and **3** (3.15 g, 20 mmol) were placed in an *Erlenmeyer* flask while a stream of Ar was passed through the apparatus. The apparatus was sealed with a balloon and the mixture was fused with agitation at 160°C on an oil-bath for 1 h. The mixture was allowed to cool down and the residue was recrystallized from ethanol/$CHCl_3$ yielding 2.65 g (89%) of **7**, mp 254°C; IR (KBr): $\bar{\nu} = 3180$ (m), 2969 (m), 1649 (s), 1622 (s), 1532 (s), 1508 (s), 1455 (m), 1387 (s), 1371 (s), 1328 (s), 1264 (s), 1099 (s), 958 (s) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.24$ (s, (C*H*$_3$)$_2$-C-6), 1.28 (s, (C*H*$_3$)$_2$-C-6′), 2.38 (s, 2 5′-H), 2.49 (s, 2 5-H), 5.94 (s, 3′-H), 9.14 (s, 1-H), 9.60 (s, 1′-H), 10.69 (s, OH) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 27.03$ ((*C*H$_3$)$_2$-C-6), 28.06 ((*C*H$_3$)$_2$-C-6′), 40.57 (C-5), 40.89 (C-5′), 52.43 (C-6), 53.55 (C-6′), 112.24 (C-3), 129.46 (C-3′), 141.12 (C-4′), 159.55 (C-4), 189.70 (C-2′), 190.93 (C-2) ppm.

2,3,6,7-Tetrahydro-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridine-4,8(1H,5H)-dione (**8**, $C_{14}H_{18}N_2O_2S$)

Compound **5** (0.59 g, 2 mmol) was dissolved in 30 cm^3 of *DMF* by heating. Then the solution was allowed to cool. Meanwhile 13 cm^3 of ethanol were added to a solution of 0.4 g of KOH in 13 cm^3 of H_2O. This solution was added at 0°C to the *DMF* solution followed by dropwise addition of 3 cm^3 of 30% aqueous H_2O_2. The mixture was stirred at room temperature over night. Excess H_2O_2 was removed with $Na_2S_2O_5$ and the solvents were removed *in vacuo*. The residue was suspended in boiling $CHCl_3$, cooled, and filtered off. The residue was dissolved in ethanol and reprecipitated with $CHCl_3$ giving 0.51 g (91%) of **8**, mp 280°C; IR (KBr): $\bar{\nu} = 3252$ (m), 2963 (w), 1621 (s), 1553 (m), 1533 (m), 1432 (m), 1405 (m) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.22$ (s, (C*H*$_3$)$_2$-C-6), 1.26 (s, (C*H*$_3$)$_2$-C-2), 2.40 (s, 2 3-H), 2.90 (s, 2 5-H), 7.30 (s, 7-H), 8.57 (s, 1-H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 26.65$ ((*C*H$_3$)$_2$-C-2), 28.84 ((*C*H$_3$)$_2$-C-6), 37.56 (C-5), 49.48 (C-3), 53.02 (C-6), 56.14 (C-2), 111.90 (C-8a), 112.72 (C-4a), 141.90 (C-4b), 161.72 (C-8), 167.52 (C-9a), 187.66 (C-4) ppm.

(RS)-(±)-1,2,3,4,6,7-Hexahydro-4-hydroxy-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridine-8(5H)-thione (**9**, $C_{14}H_{20}N_2OS_2$)

DMF (3 cm^3) was added to a suspension of 1.03 g of **5** (3.5 mmol) in 100 cm^3 of *THF*. Then 1.32 g of $NaBH_4$ (35 mmol) were added under Ar to the ice-cooled solution in portions. The mixture was refluxed for 5 h on an oil-bath. Then H_2O was slowly added at 0°C and the mixture was concentrated *in vacuo*. The moist residue was partitioned between diethyl ether and H_2O. Compound **9** was insoluble in both layers and was filtered off. The residue was washed with diethyl ether, dried, and recrystallized from ethanol/H_2O yielding 0.70 g (68%) of **9**, mp 253°C; IR (KBr): $\bar{\nu} = 3254$ (m), 3184 (m), 2965 (m), 1545 (m), 1527 (m), 1458 (m), 1435 (s), 1411 (s), 1366 (m), 1181 (m), 1125 (m), 1063 (m) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.15$ (s, C*H*$_3$-C-2), 1.22 (s, C*H*$_3$-C-6), 1.26 (s, C*H*$_3$-C-2), 1.27 (s, C*H*$_3$-C-6), 1.69 (dd, $J = 13.6$, 5.6 Hz, 3-H), 1.78 (dd, $J = 13.6$, 5.6 Hz, 3-H), 2.63, 2.81 (2d, $J = 17.2$ Hz, 2 5-H), 4.54–4.60 (m, 4-H), 4.75 (br s, OH), 7.41 (s, 1-H), 8.61 (s, 7-H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 27.40$, 27.90 ((*C*H$_3$)$_2$-C-6), 28.42, 28.56 ((*C*H$_3$)$_2$-C-2), 36.60 (C-5), 43.89 (C-3), 52.24 (C-2), 54.15 (C-6), 61.03 (C-4), 114.78 (C-4a), 118.52 (C-8a), 140.26 (C-4b), 158.21 (C-9a), 181.48 (C-8) ppm.

(RS)-(±)-1,2,3,4,6,7-Hexahydro-4-hydroxy-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridin-8(5H)-one (**10**, $C_{14}H_{20}N_2O_2S$)

In analogy to **9** the reaction of 0.97 g of **8** (3.5 mmol) with 1.32 g of $NaBH_4$ (35 mmol) yielded 0.56 g (57%) of **10**, mp 223°C; IR (KBr): $\bar{\nu} = 3257$ (s), 2963 (m), 1618 (s), 1596 (m), 1516 (m), 1476 (s), 1460 (s), 1424 (s), 1384 (m), 1366 (m), 1179 (m), 1126 (m), 1058 (m) cm^{-1}; ^{1}H NMR (400 MHz,

DMSO-d_6): $\delta = 1.13$ (s, CH_3-C-2), 1.19 (s, CH_3-C-6), 1.24 (s, 2CH_3), 1.68 (dd, $J = 13.3$, 5.8 Hz, 3-H), 1.76 (dd, $J = 13.3$, 5.8 Hz, 3-H), 2.59, 2.78 (2d, $J = 16.5$ Hz, 2 5-H), 4.56 (ddd, $J = 5.8$, 5.8, 5.8 Hz, 4-H), 4.71 (d, $J = 5.8$ Hz, OH), 6.88 (s, 7-H), 6.92 (s, 1-H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 28.34$, 28.47 ((CH$_3$)$_2$-C-2), 28.77, 29.15 ((CH$_3$)$_2$-C-6), 37.25 (C-5), 44.19 (C-3), 52.04 (C-2), 52.89 (C-6), 61.21 (C-4), 109.73 (C-8a), 114.07 (C-4a), 144.64 (C-4b), 154.25 (C-9a), 162.44 (C-8) ppm.

1,2,3,4,6,7-Hexahydro-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridine-8(5H)-thione
(**11**, $C_{14}H_{20}N_2S_2$)

Compound **5** (0.32 g, 1 mmol) were suspended in 30 cm^3 of dry *THF* under Ar. Then, 1.9 g of $LiAlH_4$ (50 mmol) were added to the ice-cooled solution in portions. The mixture was stirred for 16 h at room temperature, excess hydride was decomposed with ethyl acetate at 0°C, the suspension was filtered, and the filtrate was evaporated to dryness. The residue was purified by CC eluting with toluene:ethyl acetate = 1:7. Recrystallization from ethanol/H_2O yielded 0.22 g (72%) of **11**, mp 294°C; $R_f = 0.52$ ($CHCl_3$:benzene:ethanol = 2:2:1); IR (KBr): $\bar{\nu} = 3331$ (m), 3186 (m), 2961 (m), 2924 (s), 2854 (m), 1441 (s), 1415 (s), 1154 (m) cm^{-1}; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 1.15$ (s, (CH_3)$_2$-C-2), 1.23 (s, (CH_3)$_2$-C-6), 1.57 (t, $J = 6.3$ Hz, 2 3-H), 2.39 (t, $J = 6.3$ Hz, 2 4-H), 2.54 (s, 2 5-H), 7.35 (s, 1-H), 8.55 (s, 7-H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 18.53$ (C-4), 27.61 ((CH$_3$)$_2$-C-6), 27.97 ((CH$_3$)$_2$-C-2), 33.45 (C-3), 35.84 (C-5), 51.25 (C-2), 54.20 (C-6), 110.40 (C-4a), 117.97 (C-8a), 139.42 (C-4b), 157.84 (C-9a), 181.18 (C-8) ppm.

1,2,3,4,6,7-Hexahydro-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridin-8(5H)-one
(**12**, $C_{14}H_{20}N_2OS$)

Using the same procedure as described for the synthesis of **11**, the reaction of 0.3 g of **8** (1 mmol) with 1.9 g of $LiAlH_4$ (50 mmol) yielded 0.24 g (84%) of **12**, mp 273°C; $R_f = 0.54$ ($CHCl_3$:benzene:ethanol = 2:2:1); IR (KBr): $\bar{\nu} = 3357$ (m), 3190 (m), 2966 (m), 1643 (s), 1469 (m), 1433 (m), 1395 (m), 1160 (m), 1132 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$ (s, (CH_3)$_2$-C-2), 1.34 (s, (CH_3)$_2$-C-6), 1.69 (t, $J = 6.5$ Hz, 2 3-H), 2.47 (t, $J = 6.5$ Hz, 2 4-H), 2.60 (s, 2 5-H), 4.22 (br s, 1-H), 5.02 (br s, 7-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.19$ (C-4), 28.23 ((CH$_3$)$_2$-C-2), 29.35 ((CH$_3$)$_2$-C-6), 33.80 (C-3), 36.80 (C-5), 51.71 (C-2), 53.63 (C-6), 110.69 (C-8a), 111.67 (C-4a), 143.94 (C-4b), 153.40 (C-9a), 163.19 (C-8) ppm.

2,3,5,6-Tetrahydro-2,2,6,6-tetramethyl-8-(methylthio)thieno[2,3-b:5,4-c′]dipyridin-4(1H)-one
(**13**, $C_{15}H_{20}N_2OS_2$)

Compound **5** (2.94 g, 10 mmol) was dissolved in 40 cm^3 of acetone:$CHCl_3$ = 1:1. Then 5.68 g of CH_3I (40 mmol) were diluted with 20 cm^3 of $CHCl_3$ and added dropwise at room temperature to the stirred solution. The mixture was stirred over night and the solvent was evaporated. The residue was triturated with acetone:$CHCl_3$ = 4:1 and filtered with suction. The crystalline residue was dried and subsequently stirred in 50 cm^3 of a 1 *M* solution of caustic soda (50 mmol) in H_2O for 2 h. The suspension was extracted three times with 50 cm^3 of CH_2Cl_2, the combined extracts were washed twice with H_2O, and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from ethanol/H_2O yielding 2.71 g (88%) of **13**, mp 212°C; IR (KBr): $\bar{\nu} = 3443$ (m), 3208 (m), 1615 (s), 1542 (s), 1426 (m), 1232 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$ (s, (CH_3)$_2$-C-6), 1.38 (s, (CH_3)$_2$-C-2), 2.44 (s, SCH_3), 2.51 (s, 2 3-H), 2.96 (s, 2 5-H), 4.98 (s, 1-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.95$ (SCH_3), 27.35 ((CH$_3$)$_2$-C-2), 28.88 ((CH$_3$)$_2$-C-6), 35.98 (C-5), 50.26 (C-3), 56.50 (C-6), 57.04 (C-2), 113.62 (C-8a), 114.66 (C-4a), 138.99 (C-4b), 152.99 (C-8), 165.70 (C-9a), 188.22 (C-4) ppm.

2,3,5,6,7,8-Hexahydro-2,2,6,6-tetramethylthieno[2,3-b:5,4-c′]dipyridin-4(1H)-one
(**14**, $C_{14}H_{20}N_2OS$)

Freshly prepared *Raney* nickel W-2 [12] (5 g) was washed for 1 min with 60 cm^3 of 0.02 *M* aqueous acetic acid. The aqueous layer was decanted from the catalyst and this procedure was repeated twice. Then the Ni was washed twice with 50 cm^3 of H_2O and ethanol. The catalyst was added to a solution of 0.63 g of **13** (2 mmol) in 50 cm^3 of ethanol. The apparatus was sealed with a balloon and the mixture was stirred at room temperature until **13** was no more detectable by TLC. The mixture was filtered and the solvent was removed *in vacuo*. The residue was purified by CC eluting with CH_2Cl_2:methanol = 4:1. Recrystallization from ethanol/H_2O yielded 0.24 g (44%) of **14**, mp 245°C; $R_f = 0.11$ (CH_2Cl_2:methanol = 4:1); IR (KBr): $\bar{\nu} = 3205$ (m), 2969 (m), 1638 (s), 1523 (s), 1421 (s), 1224 (m) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): $\delta = 1.36$ (s, $(CH_3)_2$-C-2), 1.38 (s, $(CH_3)_2$-C-6), 2.44 (s, 2 3-H), 2.91 (s, 2 5-H), 4.00 (s, 2 8-H) ppm; ^{13}C NMR (100 MHz, CD_3OD): $\delta = 26.09$ ($(CH_3)_2$-C-6), 27.16 ($(CH_3)_2$-C-2), 38.59 (C-5), 40.28 (C-8), 50.89 (C-3), 52.91 (C-6), 57.75 (C-2), 112.20 (C-8a), 114.18 (C-4a), 130.61 (C-4b), 168.63 (C-9a), 189.84 (C-4) ppm.

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