

SYNTHESIS AND PROPERTIES OF 4,5-trans-4-ARYL-3-CYANO-6-HYDROXY-6-METHYL-5-PYRIDINIO -1,4,5,6-TETRAHYDROPYRIDINE-2-THIOLATES

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Abstract: 4,5-trans-4-Aryl-3-cyano-6-hydroxy-6-methyl-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates **4** were obtained by cyclocondensation of 1-acetylpyridinium chloride **1**, aromatic aldehyde **2** and cyanothioacetamide **3**. 6-Hydroxy-6-methyl-4-phenyl-5-pyridiniohexahydropyridine-2-thione chlorides **5**, occurring as a mixture of thione and enethiol tautomers, were prepared by treatment of thiolate **4a** with hydrochloric acid. Dehydration and dehydrogenation of thiolates **4** have been carried out as well. Steric structures of hydrogenated 6-hydroxypyridines **4**, **5** are discussed in the light of NMR spectra.

Introduction

3-Cyano-1,4-dihydropyridine-2(3H)-thiones are of interest both for synthetic organic chemistry (particularly as intermediates in the synthesis of new heterocyclic systems) and for the search of biologically active compounds [1-4]. 5-Acetyl-2-alkylthio-6-hydroxy-4-pyridyl-1,4,5,6-tetrahydropyridines have revealed pronounced cardiovascular activity [5], but unfortunately they were unstable compounds capable of splitting off water (usually completely at pH 2-3 and 40°C). Electron-withdrawing substituents in position 5 and bulky aryl groups in position 6 were found to be suitable for obtaining such compounds [4-10].

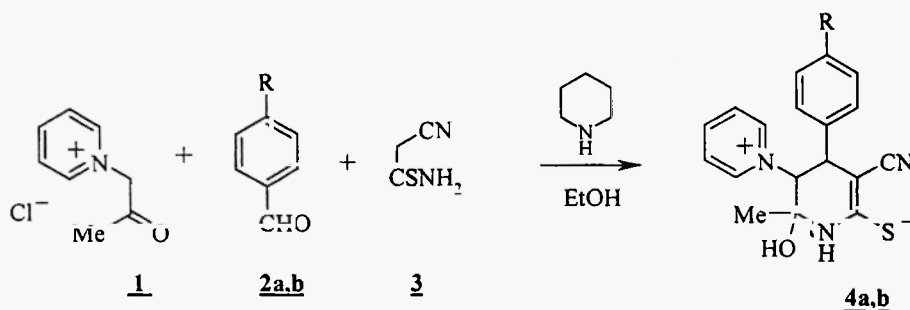
On the other hand, 3-cyano-1,4-dihydropyridine-2(3H)-thiones bearing a pyridyl group in positions 4 or 5 were found to exist in the form of betaines [4,9-14]. So far, betaines of 6-hydroxy-4-(2-, 3- or 4-pyridyl) or 5-(2-,3- or 4-pyridyl)-1,4,5,6-tetrahydropyridine-2-thiones have not been described in literature, obviously, since they are unstable due to dehydration.

In continuation of our work on the synthesis of 2-alkylthio-6-hydroxy-1,4,5,6-tetrahydropyridines [10] and on the use of pyridinium ylides [15,16] as building blocks for new heterocyclic systems, we

have synthesized 4,5-trans-4-aryl-3-cyano-6-hydroxy-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates which appeared to be stable compounds and studied their reactivity in basic and acidic conditions.

Results and discussion

4,5-trans-4-Aryl-3-cyano-6-hydroxy-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates **4** were obtained in 88-96 % yields by the condensation of 1-acetonilpyridinium chloride **1**, aromatic aldehyde **2** and cyanothioacetamide **3** on brief heating in ethanol, using piperidine acting as base to generate the pyridinium ylide and as a condensing agent (Scheme 1).



2a, 4a R = H ; 2b, 4b R = OH

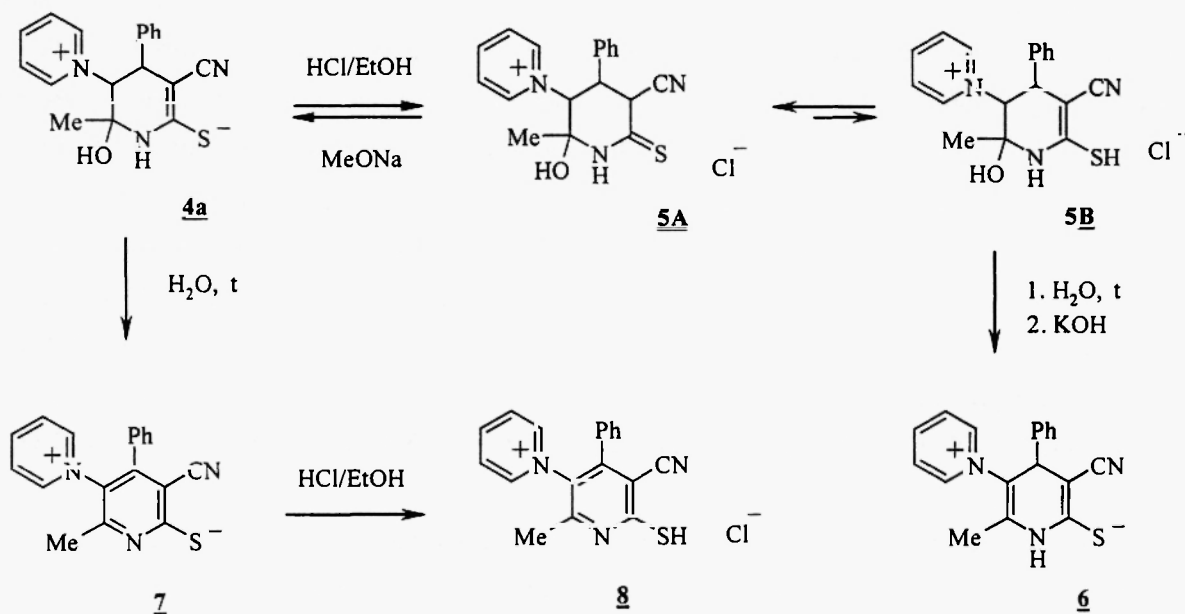
Scheme 1

The structures of betaines **4** were proved by spectroscopy. In the IR spectra the stretching vibrations of the cyano group observed at 2160 - 2172 cm^{-1} are the most important thus demonstrating cross conjugation of cyano group with the thiolate anion. Stretching vibrations of NH and OH groups give characteristic absorption bands at 3196 - 3540 cm^{-1} . In the ^1H NMR spectra characteristic doublets of 4-H and 5-H protons at 4.22 - 4.32 and 4.93 - 5.08 ppm, respectively with $^3J_{4,5}=12.0$ Hz are observed, which, according to [6,17], indicate the trans pseudodiaxial arrangement of 4-H and 5-H protons and, correspondingly, the trans pseudodiequatorial arrangement of bulky aryl and pyridinio substituents in positions 4 and 5. The delocalization of the positive charge of the pyridinium ring in position 5 leads to a downfield shift of the signals for the pyridinio protons compared with the signals of the uncharged pyridyl substituent [10]. Rapid deuterium exchange in the OH and NH groups provides further evidence for the structure of compounds **4**. The structure of betaine **4a** is confirmed by ^{13}C NMR spectrum.

As mentioned above, 6-hydroxytetrahydropyridine-2-thiones bearing in position 5 an electron withdrawing group different from the pyridinio group are unstable in acid medium: they easily undergo dehydration at room temperature to yield the corresponding 1,4-dihydropyridine-2-thiones [4-

10, 18]. Dehydration of betaines **4** to betaines **6** by short treatment with a small excess of 0.5 M hydrochloric acid in warm ethanol occurs much more slowly. 6-Hydroxytetrahydropyridine-2-thione chlorides **5** were isolated as main products (Scheme 2). With equimolar amount of sodium methoxide they are reconverted into the starting betaine **4**. As follows from IR and ^1H NMR spectra of chloride **7**, it exists both in crystalline aggregation and in solutions, as a mixture of thione **5A** and enethiol **5B** tautomers. The thione tautomer **5A** reveals the characteristic stretching vibrations of cyano group at 2256 cm^{-1} , but the enethiol tautomer **5B** at 2192 cm^{-1} . In ^1H NMR spectra of **5** the value $^3J_{4,5}=12.0\text{ Hz}$ of the enethiol tautomer **5B** indicates the trans pseudodiequatorial orientation of 4-phenyl and 5-pyridinio groups, but in case of the thione tautomer **5A** the characteristic downfield shift of NH group at 12.45 ppm is observed. Evaluation of the spectral data shows that the ratio **5A** / **5B** ratio is approximately 4:1. Unfortunately, the signals of three adjacent proton system of the thione tautomer **5A** are broadened, which does not allow to characterize its steric arrangement.

A 30 min refluxing of an aqueous solution of chlorides **5** with subsequent neutralization and fractional crystallization from ethanol gave 1,4-dihydropyridine-2-thiolate **6** as a main product. In the IR spectrum of thiolate **6** the ν_{CN} is observed at 2166 cm^{-1} , which is similar to that in **4**, but in the ^1H NMR spectrum the characteristic singlet of 4-H proton is shown at 4.68 ppm.



Scheme 2

On prolonged heating of betaine **4a** at $> 100^{\circ}\text{C}$, dehydration and dehydrogenation occur to form betaine **7**. Thermal treatment in high-boiling solvents (DMF, dioxane, their mixture with water or alcohol) gives rise to a mixture of betaine **7** and decomposition products of **4a**. The best yield (60 %) of **7** was reached by 1 h reflux of **4a** in water. The salt **8** was obtained in quantitative yield by the treatment of **7** with excess of 1 M hydrochloric acid in ethanol.

In conclusion, acid-stable 4,5-trans-6-hydroxy-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates **4** have been synthesized. The presence of 5-pyridinio cation in 6-hydroxytetrahydropyridine-2-thiolates **4** leads to a pronounced enhancement of their stability to dehydration.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra of suspensions of compounds in mineral oil (ν , cm^{-1}) were recorded with a Perkin Elmer 580B spectrometer. ^1H NMR spectra of solutions in CDCl_3 or DMSO-d_6 (δ , ppm; J, Hz) were obtained with a Bruker WH 90/DC (90 MHz) and an AM-360 (360 MHz) spectrometers using TMS as internal standard. Reaction courses and substance uniformity were monitored by TLC on Silufol UV-54 plates with ethanol-water-aq. ammonia (6:2:1) as eluent.

4,5-trans-3-Cyano-6-hydroxy-6-methyl-4-phenyl-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolate (4a)

A. A mixture of cyanothioacetamide **3** (1.0 g, 10 mmol) and benzaldehyde **2** (1.06 ml, 10 mmol) in 15 ml of ethanol was heated to $40\text{--}50^{\circ}\text{C}$, stirred 10 min at ambient temperature and a mixture of 1-acetonylpyridinium chloride **1** (1.71 g, 10 mmol) and piperidine (1.0 ml, 10 mmol) in 5 ml of ethanol was added. After 1 h stirring at room temperature, the reaction mixture was cooled to 0°C , the precipitate was removed by filtration and washed with 10 ml of cold ethanol and 10 ml of water to give 3.12 g (96 %) of **4a** as yellow powder; mp $168\text{--}170^{\circ}\text{C}$ (from water) ($163\text{--}165^{\circ}\text{C}$ [19]). IR: 2160 (CN); 3200, 3410, 3500 (NH,OH). ^1H NMR (DMSO-d_6), δ : 9.4 - 7.1 (complex, 10H (4- C_6H_5 and 5- $\text{C}_5\text{H}_5\text{N}^+$); 6.65 (s, 1H, NH); 6.45 (s, 1H, OH); 5.08 (d, 1H, J = 12.0 Hz, 5-H); 4.32 (d, 1H, J = 12.0 Hz, 4-H); 1.12 (s, 3H, 6-Me). ^{13}C NMR (DMSO-d_6), δ : 171.35 (s); 146.29 (d); 140.01 (s); 128.17 (d); 127.78 (d); 127.45 (d); 127.03 (d); 125.74 (s); 78.31 (s); 78.04 (d); 73.24 (s); 45.24 (d); 25.16 (q). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{OS} \cdot 0.25 \text{H}_2\text{O}$: C 65.93, H 5.38, N 12.81, S 9.78; Found: C 66.04, H 5.56, N 12.88, S 9.67.

B. A mixture of thione **5** (0.68 g, 2 mmol) and 2.5 ml of 1 M sodium methoxide in 20 ml of ethanol was briefly heated and stirred for 1 h at room temperature. The precipitated crystals were filtered off and washed with 5 ml of ethanol and 10 ml of water to give 0.64 g (99 %) of **4a**.

In a similar manner using 4-hydroxybenzaldehyde **2b** instead of benzaldehyde **2a** 4,5-trans-3-Cyano-6-hydroxy-6-methyl-4-(4-chlorophenyl-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolate (4b) (yield 88 %)

was obtained as yellow powder; mp 196-198°C. IR: 2172 (CN); 3216, 3424 (NH, OH). ¹H NMR (DMSO-d₆), δ: 9.5 - 7.8 (complex, 5H, 5-C₅H₅N⁺); 6.92 and 6.46 (4H, d and d, 4-C₆H₄); 6.42 and 6.37 (s and s, 2H, NH and OH); 4.93 (d, 1H, J = 12.0 Hz, 5-H); 4.22 (d, 1H, J = 12.0 Hz, 4-H); 1.12 (s, 3H, 6-Me). Anal. Calcd for C₁₈H₁₇N₃O₂S: C 63.69, H 5.05, N 12.38, S 9.45; Found: C 63.50, H 5.22, N 12.27, S 9.29.

4,5-trans-3-Cvano-6-hydroxy-6-methyl-4-phenyl-5-pyridiniohexahydropyridine-2-thione chloride (5)

Thiolate **4a** (3.23 g, 10 mmol) was briefly heated for 2-3 min at 50-60°C in 30 ml of 0.5 M hydrochloric acid in ethanol. After 30 min stirring at ambient temperature, the reaction mixture was cooled to 0°C, the precipitate was removed by filtration and washed with 20 ml of cold ethanol to give 2.84 (83 %) of **5** as slightly yellow powder; mp > 210°C (decomp). IR: 2192, 2256 (CN); 3140, 3376, 3440 (NH, OH). ¹H NMR (DMSO-d₆): 12.45 (s, 0.8H, NH); 11.45 (s, 0.8H, OH); 9.4 - 7.1 (complex, 10H, 4-C₆H₅ and 5-C₅H₅N⁺); 6.42 (s, 0.2H, NH); 6.28 (s, 0.2H, OH); 5.00 (d, 0.2H, J = 12.0 Hz, 5-H); 4.60 (d, 0.2H, J = 12.0 Hz, 4-H); 5.66 - 4.68 (complex, 2.4H, 5-H, 4-H and 3-H), 1.78 (s, 2.4H, 6-Me); 1.40 (s, 0.6H, 6-Me). Anal. Calcd for C₁₈H₁₈ClN₃OS: C 60.08, H 5.04, N 11.68, S 8.91; Found: C 59.89, H 5.11, N 11.57, S 8.92.

3-Cvano-6-methyl-4-phenyl-5-pyridinio-1,4-dihydropyridine-2-thiolate (6)

A sample of salt **5** (1.08 g, 3 mmol) was refluxed in 10 ml of water for 30 min, cooled and neutralized with 1N KOH solution. The obtained crude product was recrystallized from ethanol to give 0.36 g (39 %) of **6** as slightly yellow powder; mp > 230°C (decomp.). IR: 2166 (CN); 3110, 3150 sh (NH). ¹H NMR (DMSO-d₆): 8.8 - 7.0 (complex, 10H, 4-C₆H₅ and 5-C₅H₅N⁺); 8.22 (s, 1H, NH); 4.68 (s, 1H, 4-H); 1.58 (s, 3H, 6-Me). Anal. Calcd for C₁₈H₁₅N₃S • 0.25 H₂O: C 69.76, H 5.04, N 13.57, S 10.31; Found: C 70.00, H 5.00, N 13.40, S 9.81.

3-Cvano-6-methyl-4-phenyl-5-pyridiniopyridine-2-thiolate (7)

A suspension of betaine **6a** (3.23 g, 10 mmol) in 100 ml of water was refluxed for 1 h. The precipitate was filtered off and washed with 20 ml of ethanol to give 1.82 g (60 %) of **7** as yellow powder; mp > 270°C (decomp). IR: 2216 cm⁻¹ (CN). ¹H NMR (DMSO-d₆): 9.2 - 7.2 (complex, 10H, 4-C₆H₅ and 5-C₅H₅N⁺); 2.06 (s, 3H, 6-Me). Anal. Calcd for C₁₈H₁₃N₃S: C 71.26, H 4.32, N 13.85, S 10.57; Found: C 71.14, H 4.43, N 13.82, S 10.37.

3-Cvano-2-mercapto-6-methyl-4-phenyl-5-pyridiniopyridine chloride (8)

Betaine **7** (0.21 g, 0.7 mmol) was refluxed for 2-3 min in 5 ml of 1 M hydrochloric acid in ethanol. After 1h stirring at room temperature, the precipitate was removed by filtration and washed with 5 ml of ethanol to give 0.24 g (100 %) of **8** as yellow powder; mp > 270°C (decomp). IR: 2232 (CN). ¹H NMR (DMSO-d₆): 9.2 - 7.2

(complex, 9H, 4-C₆H₅ and 5-C₅H₅N⁺); 2.30 (s, 3H, 6-Me). Anal. Calcd for C₁₈H₁₄ClN₃S : C 63.62, H 4.15, N 12.36, S 9.43; Found: C 63.43, H 4.17, N 12.32, S 9.59.

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