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LETTERS TO THE EDITOR

Conformational States and Crystal Structure of *N*-Formylcytisine

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Abstract—*N*-Formylcytisine has been synthesized and characterized using ^{1}H NMR spectroscopy. Two conformers of *N*-formylcytisine have been found to exist in the DMSO-d_6 solution. The structure of the most stable conformer has been studied by means of X-ray diffraction analysis.

Keywords: alkaloid, cytisine, *N*-formylcytisine, NMR spectroscopy, X-ray crystallography

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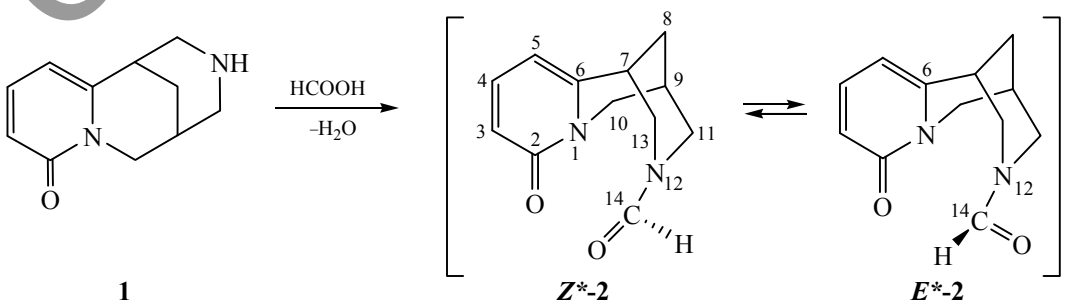
It is known that the introduction of pharmacophoric fragments (including physiologically active heterocyclic moieties) in the structure of plant alkaloids is among basic approaches in chemical design of new biologically active substances. So far, many cytisine derivatives exhibiting biological activity (for instance, lipid-lowering, anti-inflammatory, cholinotropic, hemostatic, and antiarrhythmic) have been synthesized [1, 2].

We have earlier reported the synthesis and spatial structure of 1,4-dihydropyridine derivative substituted in positions 2 and 6 with cytisine units [3]. In order to obtain the other interesting compounds, 1,4-dihydropyridine derivatives substituted in position 4 with cytisine fragment, we performed the following transformations. First, *N*-formylcytisine **2** was obtained via the formylation of cytisine **1** with formic acid as described elsewhere [4] (Scheme 1).

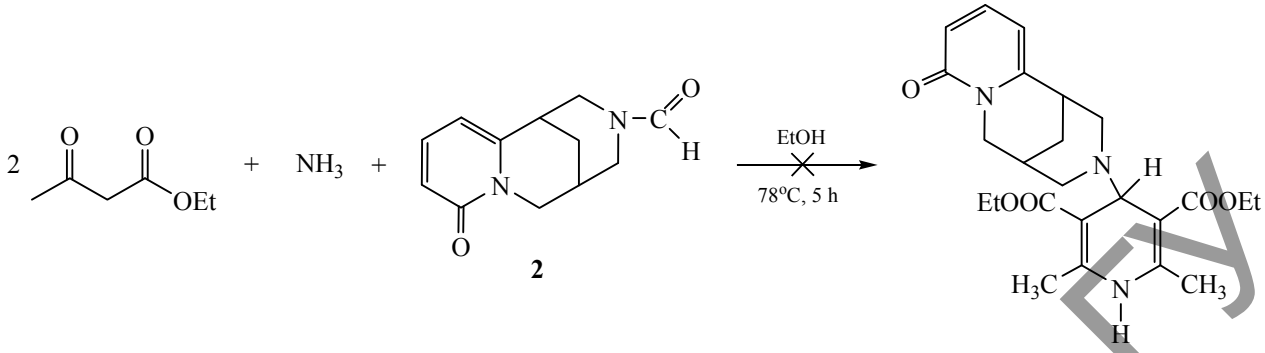
Then, *N*-formylcytisine **2** was used as an aldehyde in the conventional Hantzsch synthesis of 1,4-dihydropyridines. The reactants were heated for 5–8 h in an alcoholic solution (Scheme 2). White crystal substance was separated from the reaction mixture, soluble in most of organic solvents and (in contrast to the starting *N*-formylcytisine **2**) could be readily recrystallized from benzene, ethyl acetate, or propanol-2. However, the ^{1}H NMR analysis revealed that the isolated substance was initial *N*-formylcytisine **2.**

Scheme 1.



1 ***Z**-2** ***E**-2**

Scheme 2.



Melting point of the twice recrystallized compound **2** isolated from the reaction mixture was 141–142°C, significantly differing from the melting point of the non-recrystallized *N*-formylcytisine prepared in the first stage (160–165°C) after purification by column chromatography on silica gel ($CHCl_3$: CH_3OH = 1 : 1) as well as from the reference data (169–171°C [4]). Such deviation of physicochemical parameters including solubility inspired us to perform detailed spectroscopic, X-ray diffraction, and quantum-chemical simulation studies of the considered substance.

^{1}H NMR spectrum of the isolated *N*-formylcytisine **2** contained the signals corresponding to two conformers formed due to the amide conjugation with hindering the rotation about the N^{12}–C^{14} bond. It should be noted that similar structures have been tentatively described as the *Z** and *E** isomers with the $C^{11}N^{12}C^{14}H$ torsion angle of 0 and 180°, respectively [4]. The duplicating pairs of the signals of different intensity at 0.12–0.16 ppm have been earlier observed in the ^{1}H NMR spectrum, on top of the signals of H^7, H^8, and H^9 protons ($CDCl_3$, 300 MHz) [4]. Despite the use of polar DMSO-d_6 as the solvent, the formyl proton signals of the ***Z**-2a*** and ***E**-2b*** isomers appeared in the same spectral range (7.88 and 7.58 ppm, respectively, comparable to 7.88 and 7.65 ppm reported in [4]), with marginal difference in the intensities of the major and minor resonances of the formyl proton, 7 : 6 (3 : 2 [4]). Using two-dimensional COSY-45 and COSYLR-45 spectroscopy techniques it has been unambiguously confirmed that the aldehyde proton resonating at weaker field (7.88 ppm) is due to the *Z** isomer [4]. This fact has been related to deshielding effect of magnetically anisotropic carbonyl group C^2, which distorts the symmetry of the molecule.

The quantum-chemical simulations at the AM1 [5] and PM3 [6] levels of theory with complete geometry optimization performed in this work revealed approximately equal probabilities for the two conformers of molecule **2**: –168.39 and –168.06 kJ/mol (AM1), –229.50 and–229.19 kJ/mol (PM3) for structures ***E**-2b*** and ***Z**-2a***, respectively

In view of the above discussion, we performed X-ray diffraction study on the crystals grown during recrystallization of *N*-formylcytisine **2** and attempted evaluation of the occupancy of molecular conformational states in the crystal. It was found that the ***E**-2b*** conformer exclusively existed in the crystalline state. The general view of *N*-formylcytisine structure is presented in the figure. Configuration of chiral centers C^7 and C^9 was elucidated in view of the known (–)-cytisine configuration.

It was found that bond lengths and bond angles in cytisine scaffold of structure **2** were common of organic molecules, except for the elongated C^{14}=O^2 bond [1.219(3) Å] and shortened N^{13}–C^{14} bond [1.331(3) Å] [8]. Those changes were due to the mesomeric effect between a lone electron pair of the nitrogen atom and the C^{14}=O^2 double bond. This effect changed the nitrogen atom coordination. For instance, *N*-formylcytisine [7] and *N*-acetonylcytisine [9] molecules contain the N^{12} atom in the pyramidal coordination (the sum of the bond angles is 335.7° and 334.3°, respectively), while the nitrogen atom coordination was found planar for *N*-formylcytisine **2** (the sum of the bond angles equaled 360°). Dihydropyridine cycle was planar within 0.01 Å, the carbonyl oxygen O^1 was located in the plane formed by the other atoms with deviation of 0.06 Å. Tetrahydropyridine cycle $N^1C^6C^7C^8C^9C^{10}$ took the conformation of distorted 8α-*sofa* (ΔC_S^8 = 9.4°), the bridging C^8 atom was off the average plane of other atoms (±0.04 Å) by 0.72 Å. The piperidine cycle took the conformation of distorted *chair* ΔC_S^{12} = 3.8°). The carbonyl group was located in

the plane of the C^{11}, N^{12}, and C^{13} atoms (the $C^{13}N^{12}C^{14}O^2$ torsion angle equaled 1.0°).

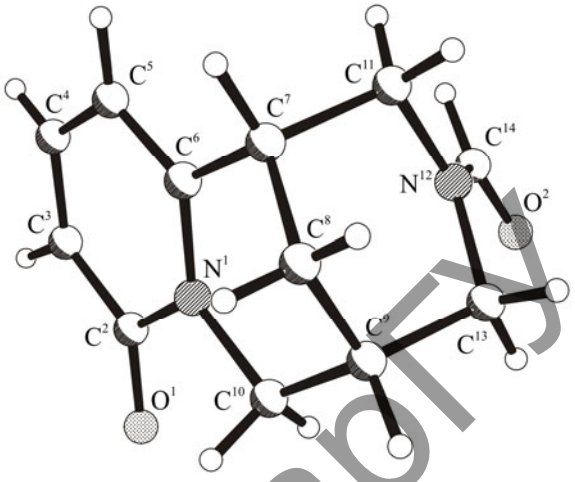
In summary, as a result of the failed Hantzsch reaction with *N*-formylcytisine in an ammonia media we isolated and characterized in the crystal state of the most stable conformer (the *E**-isomer). This structure existed in the DMSO-d_6 solution in two conformations with approximately equal populations, due to amide conjugation.

***N*-formylcytisine (2)** was synthesized as described elsewhere [4] in 95% yield; mp 160–165°C (mp 169–171°C [4]). After performing the Hantzsch reaction the product was recrystallized twice from ethyl acetate. Transparent crystals were obtained, mp 141–142°C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.94–2.04 m (2H, H^8), 2.45 br.s (1H, H^9), 2.88 d (1H, $H^{11}{}_a$, *E*-isomer, *J* = 13.1), 2.94 d.d (1H, $H^{13}{}_a$, *Z*-isomer, ^2J = 12.7, $^3J_{13a,7}$ = 2.6), 3.13 br.s (1H, H^7, *Z*-isomer), 3.16 br.s (1H, H^7, *E*-isomer), 3.43 d.d (1H, $H^{13}{}_a$, *E*-isomer, ^2J = 12.9, ^3J = 2.3), 3.53 d (1H, $H^{11}{}_a$, *Z*-isomer, ^2J = 12.9), 3.61–3.76 m (2H, $H^{10}{}_a$), 3.30–3.34 m (2H, $H^{11}{}_e$, *Z*-isomer + $H^{13}{}_e$, *E*-isomer), 3.79 d (1H, $H^{10}{}_e$, *E*-isomer, ^2J = 15.6), 3.91 d (1H, $H^{10}{}_e$, *Z*-isomer, ^2J = 15.7), 4.13 d (1H, $H^{13}{}_e$, *Z*-isomer, ^2J = 12.7), 4.29 d (1H, $H^{11}{}_e$, *E*-isomer, ^2J = 13.1), 6.15 d.d (1H, H^5, $^3J_{5,4}$ = 6.7, $^4J_{5,3}$ = 1.4), 6.21 d.d (1H, H^3, $J_{3,4}$ = 9.3, $J_{3,5}$ = 1.4), 7.31 d.d (1H, H^4, *Z*-isomer, $^3J_{4,5}$ = 6.8, $^3J_{3,4}$ = 9.0), 7.36 d.d (1H, H^4, *E*-isomer, $^3J_{4,5}$ = 6.8, $^3J_{3,4}$ = 9.0), 7.58 s (1H, COH, *E*-isomer), 7.88 s (1H, COH, *Z*-isomer).

^{1}H NMR spectrum was recorded using a Bruker DRX500 spectrometer operating at 500 MHz, in DMSO-d_6 solution, TMS used as the internal reference. Melting points were measured using a Boetius apparatus. The reaction course and the product were examined using thin-layer chromatography with Sorbfil plates and an isopropanol–benzene–ammonia system as eluent. The plates were developed with iodine vapor. The ratio between *Z*- and *E*- isomers was established from the signals intensity (7 : 6).

X-rays diffraction experiment was carried out using an Xcalibur diffractometer [MoK_α, graphite monochromator, φ,θ-scan, 293(2) K]. The extinction correction was not performed. Single crystals for the X-ray diffraction analysis were obtained from compound **2** by twice recrystallization from ethyl acetate.

Crystals of compound **2** were orthorhombic, $C_{12}H_{14}N_2O_2$, *M* 218.3 g/mol, space group $P2_12_12_1$, *a* 7.909(2), *b* 11.057(3), *c* 12.149(3) Å, *V* 1062.4(5) Å^3, *Z* 4, d_{calc} 1.364 g/cm^3, μ 0.094 mm^{-1}. Scan range was $2.49° \le \theta \le 24.0°$, 2650 reflections were registered (R_{int} 0.0163).



General view of *N*-formylcytisine **2b** in the crystal.

Structure of compound **2** was solved via the direct method. The positions of non-hydrogen atoms were refined under anisotropic approximation using full-matrix least-squares method. Hydrogen atoms were put in the geometric positions and refined using *rider* model under isotropic approximation. The structure was analyzed and solved using SHELXS-97 and SHELXL-97 [10, 11] software packages. 1408 independent reflections were used in the refinement with $I \ge 2\sigma(I)$, 146 parameters were refined. Final *R*-factors: R_1 0.0375, wR_2 0.0991 [over reflections with $I \ge 2\sigma(I)$], R_1 0.0393, wR_2 0.1011 (over all reflections), GooF 1.057. Peaks of residual density: Δρ = 0.123 and –0.153 *e*/Å^3. Crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1515622).

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