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TAUTOMERISM OF THE THIOAMIDE GROUP IN 4-METHYL-7-NITRO-2,3,4,5-TETRAHYDRO-1,5-BENZODIAZEPINE-2-THIONE

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When 4-methyl-7-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one were reacted with phosphorus pentasulfide, the corresponding benzodiazepine-2-thione and its thiol tautomer were formed, which via the 2-methylmercapto derivative were converted to 4-(2-acetylhydrazino)-2-methyl-8-nitro-2,3-dihydro-1H-1,5-benzodiazepine.

Keywords: 4-methyl-7-nitro-2,3,4,5-tetrahydro-1,5-benzodiazepine-2-thione, thione–thiol tautomers.

The traditional route to obtaining heterocyclic thiolactams by thionylation of dihydro- and tetrahydro-1,5-benzodiazepin-2-ones has been described in [1, 2]. Reaction of 8-R-4-phenyl-2,3-dihydro-1H-1,5-benzodiazepin-2-ones (R = H, Cl, CH_3O, CH_3) or their N-methyl derivatives with phosphorus pentasulfide results in formation of the corresponding diazepine thiones [1]. Based on spectroscopic data, the authors have confirmed that in solutions of different polarity, dihydrobenzodiazepine thiones exist predominantly in the thione form.

We have established that the reaction of 4-methyl-7-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (**1**) [3] with phosphorus pentasulfide in boiling dry pyridine occurs, as suggested by chromatographic monitoring, with formation of a mixture of compounds **2** and **3** with total yield up to 75%. Crystallization of the mixture from ethylacetate allowed us to obtain chromatographically pure diazepine thione **2** and the imine thiol tautomer **3**. The ratio of tautomers **2** and **3** is 1:2. Compounds **2** and **3** melt at different temperatures and have unique UV and IR spectra and ^{1}H NMR spectra. The electronic absorption spectrum in the UV region for compound **3** has long-wavelength maxima at 438 nm and 397 nm, which suggests formation of a conjugated structural moiety.

By alkylation of compounds **2** and **3** with methyl iodide under phase transfer catalysis conditions in toluene and a 40% aqueous KOH solution, we obtained the S-methyl derivative **4**, which is easily reacted with acetylhydrazine, forming the crystalline acetylhydrazino derivative **5**. The mixture of crude and recrystallized samples of compound **5** obtained from **2** and **3** did not depress the melting point. The ^{1}H NMR spectra are identical.

In contrast to tetrahydro-1,5-benzodiazepine-2-thiones containing only alkyl substituents on the heterocycle [2], in the case of 7-nitro derivative **2** for the first time we observe formation of the stable thiol form **3**.

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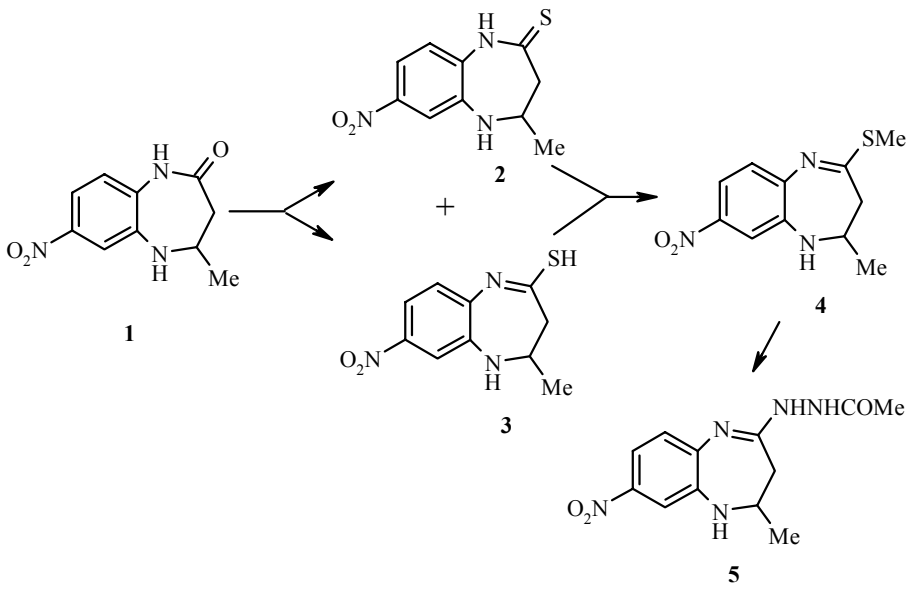

The data obtained suggest that the nitro group in the 7 position of the benzene ring has an effect on the prototropic mobility of the hydrogen atom of the thioamide group. An effect of the electron-acceptor substituent on the reactivity of the amide group was noted previously when studying N-alkylation of 7-nitro-substituted benzodiazepinone **1** [4].

EXPERIMENTAL

The UV spectra were obtained on a Specord UV-vis spectrometer (in ethanol), the IR spectra were obtained on a Perkin-Elmer FT Spectrum BX II (in KBr disks). The ^{1}H NMR spectra were recorded on a Tesla BS-587 A spectrometer (80 MHz), internal standard TMS. The course of the reaction and the purity of the compounds were monitored using TLC on Silufol UV-254 plates; the eluent was benzene–methyl alcohol, 6:1 (A) and butyl alcohol–acetic acid–water, 4:1:2 (B).

Thionylation of 4-Methyl-7-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-2-one (1). A suspension of P_2S_5 (1.1 g, 5 mmol) in absolute pyridine (150 ml) was stirred with boiling for 1 h, then benzodiazepinone **1** (1.1 g, 5 mmol) was added and the mixture was boiled for 1.5 h more. After cooling, the solution was decanted from the tarry substance and evaporated to dryness under vacuum. The residue was dissolved with boiling in dichloroethane (200 ml), filtered off, washed with a saturated aqueous solution of Na_2CO_3 and then water, dried with Na_2SO_4, and evaporated down. When the solid substance obtained was crystallized from EtOAc, 0.6 g (50%) of compound **3** and 0.3 g (25%) of compound **2** successively precipitated.

4-Methyl-7-nitro-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-2-thione (2). Mp 234-236°C (orange crystals); R_f 0.46 (A). According to data in [5], the (+)-enantiomer, mp 246°C. UV spectrum, λ_{max}, nm (log ε): 413 (4.27), 363 (4.15), 308 (4.22), 246 (3.90). IR spectrum, ν, cm^{-1}: 1139 (C=S), 1340, 1517 (NO_2), 3176-3394 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, J (Hz): 1.27 (3H, d, CH_3); 2.67-3.17 (2H, m, CH_2); 3.88 (1H, m, CH); 6.33 (1H, br. s, NHCH); 7.22 (1H, d, J_{89} = 8.8, 9-H); 7.56 (1H, dd, J_{68} = 2.4, J_{89} = 8.8, 8-H); 7.81 (1H, d, J_{68} = 2.4, 6-H); 12.05 (1H, br. s, NHCS). Found, %: C 50.47; H 4.45; N 17.56. $C_{10}H_{11}N_3O_2S$. Calculated, %: C 50.62; H 4.67; N 17.71.

4-Mercapto-2-methyl-8-nitro-2,3-dihydro-1H-1,5-benzodiazepine (3). Mp 179-181°C (red crystals); R_f 0.33 (A). UV spectrum, λ_{max}, nm (log ε): 438 (4.62), 397 (4.41), 297 (4.14), 241 (4.60). IR spectrum, ν, cm^{-1}: 1336, 1522 (NO_2), 1570, 1620 (C=N), 2550-2620 (two absorption bands of very weak intensity may be assigned

to stretching vibrations of the S–H group), 3151-3270 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 (3H, d, CH_3); 2.40-3.00 (2H, m, CH_2); 3.74 (1H, m, CH); 6.34 (1H, br. s, NH); 7.54 (2H, m, 6-H and 7-H); 7.83 (1H, m, 9-H). Found, %: C 50.39; H 4.37; N 17.87. $C_{10}H_{11}N_3O_2S$. Calculated, %: C 50.62; H 4.67; N 17.71.

2-Methyl-4-methylmercapto-8-nitro-2,3-dihydro-1H-1,5-benzodiazepine (4). A 40% aqueous KOH solution (4 ml) was added with stirring to a mixture of compound **3** (0.6 g, 2.5 mmol), methyl iodide (0.62 ml, 10 mmol), benzyltriethylammonium chloride (0.74 g, 3.25 mmol) in toluene (45 ml) and held for 1 h at 60°C. The reaction solution was washed with water until neutral pH was achieved and then it was dried with Na_2SO_4. After the toluene was driven off, the methylmercapto derivative was obtained as a thick oil with solid starting material as impurities. The mixture was dissolved in diethyl ether (75 ml) and filtered. After the solvent was driven off, 0.43 g (67%) of product **4** was obtained as an oil. The material obtained was used without further purification. Light yellow oil, R_f 0.67 (A). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 (3H, d, CH_3); 2.48 (3H, s, SCH_3); 2.39-2.79 (2H, m, CH_2); 3.52 (1H, br. s, NH); 4.07 (1H, m, CH); 7.20 (1H, d, J_{67} = 8.8, 6-H); 7.61 (1H, d, J_{79} = 2.4, 9-H); 7.74 (1H, dd, J_{67} = 8.8, J_{79} = 2.4, 7-H).

Methylmercapto derivative **4** (0.22 g, 72%) was obtained similarly from compound **2** (0.3 g, 1.26 mmol). The material obtained was chromatographically homogeneous in solvent system A with the sample obtained from tautomer **3**.

4-(2'-Acetylhydrazino)-2-methyl-8-nitro-2,3-dihydro-1H-1,5-benzodiazepine (5). A mixture of compound **4** (obtained from compound **3**) (0.43 g, 1.7 mmol) and acetylhydrazine (0.23 g, 3.1 mmol) in absolute alcohol (25 ml) was stirred for 24 h at room temperature. The precipitate was filtered off and recrystallized from a mixture of isopropyl and methyl alcohols, 3:1. Obtained 0.36 g (76%) of compound **5**; mp 217-219°C (yellow crystals), R_f 0.69 (B). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz); 1.21 (3H, d, CH_3); 1.93 and 2.08 (3H, s and s, CH_3CO); 2.08-2.80 (2H, m, CH_2); 3.79 (1H, m, CH); 5.70 (1H, br. s, NHCH); 7.05 and 7.10 (1H, d and d, J_{67} = 8.8, 6-H); 7.59-7.80 (2H, m, 7-H and 9-H); 8.79, 9.76, 9.90 (2H, br. s, NHNH). Found, %: C 52.25; H 5.65; N 25.58. $C_{12}H_{15}N_5O_3$. Calculated, %: C 51.98; H 5.45; N 25.26.

Compound **5** (0.16 g, 66%) was isolated similarly from compound **4** (obtained from compound **2**) (0.22 g, 0.9 mmol); mp 216-218°C.

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