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Hydroxymethylation of Rhodanine

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Abstract—Rhodanine in alcohol solution reacts with formaldehyde aqueous solution to form 3-hydroxymethylrhodanine. In the presence of triethylamine occurred also bis-hydroxymethylation at 5 position of the thiazolidine ring, but we failed to isolate the 3,5,5-trishydroxymethyl derivative in an individual form. The treatment of crude rhodanine 3,5,5-trishydroxymethyl derivative with benzaldehyde in boron trifluoride etherate leads to thioxo-8-phenyl-7,9-dioxa-1-thia-3-azaspiro[4.5]decan-4-one. The dissolution of the latter in aqueous alkali followed by neutralization with acid gives 5-sulfanyl-2-phenyl-1,3-dioxane-5-carboxylic acid.

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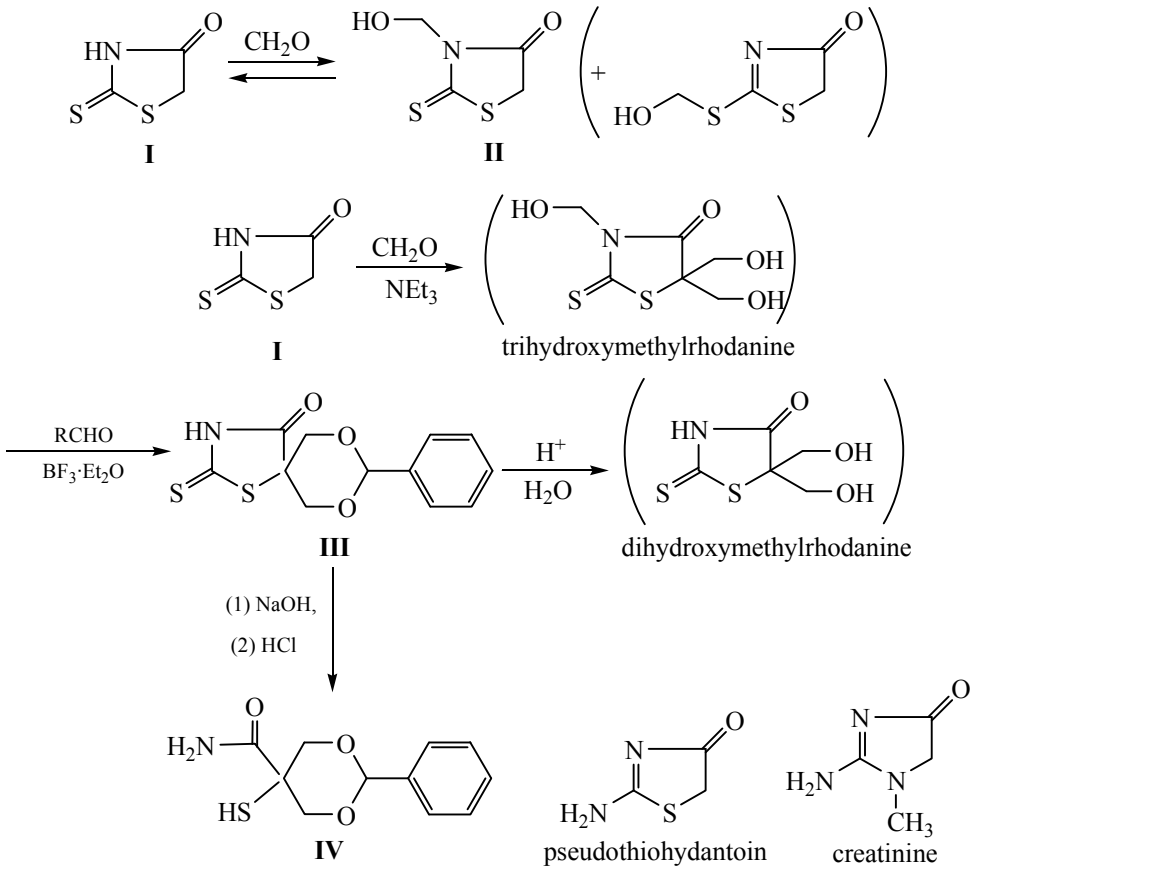
In [1] has been argued that hydroxymethylation of rhodanine (**I**) and its 5-R-methylidene derivatives by the traditional way with formaldehyde in an organic solvent in the presence of an organic base leads to 3-hydroxymethylrhodanine (**II**) or 3-hydroxymethyl-5-R-methylidenrhodanines, respectively. This method of synthesis of these compounds was protected by the USSR Inventor Certificates [2, 3]. Later on, the hydroxymethylation of 5-R-5-methylidenerhodanines was carried out also by the interaction in solid phase of their triethylammonium salts with gaseous formaldehyde [4]. However, in [1], and in the invention descriptions [2, 3] we did not find any information on the preparation and properties of 3-hydroxymethylrhodanine (**II**), besides the mentioned statement. The search for this compound in the databases Beilstein (MDL CrossFire Commander) and CAS (SciFinder) led to the same source materials [1–3]. Apparently, actually it has not been obtained.

Previously we showed that pseudothiohydantoin, which is similar in the structure to rhodanine (**I**) and creatinine, forms 5,5-bishydroxymethyl derivative under the action of formaldehyde in weakly basic medium [5, 6], while in the absence of a base in an alcohol–water medium it adds one molecule of formaldehyde to the exocyclic nitrogen atom with the formation of 2'-monohydroxymethyl derivative [7]. The above results prompted us to study the reaction of hydroxymethylation of rhodanine **I** with formaldehyde in the presence and in the absence of the basic reagent.

It was found that in water–alcohol medium at room temperature in the presence of ~3-fold excess of formaldehyde, rhodanine **I** forms with formaldehyde a monoadduct which, judging from the presence in the IR spectrum of absorption bands of the thioamide fragment [1], is 3-hydroxymethylrhodanine **II**. This adduct is unstable and at the attempted recrystallization from water or ethanol partially (85 and 70%, respectively) splits formaldehyde off, converting into the initial rhodanine **I**. Moreover, the dissociation of the dissolved adduct **II** takes place at room temperature: on the walls of the tube containing its solution in alcohol crystallizes rhodanine **I**.

In the ^{1}H NMR spectrum of the product of hydroxymethylation isolated from the reaction mixture along with the signal of methylene protons of *N*-hydroxymethyl group of the adduct **II** at 5.19 ppm another signal at 5.28 ppm is often detected with an intensity up to ~2–8% of the intensity of the first signal. The latter signal probably is related to the resonance of methylene protons of *S*-hydroxymethyl group of the isomeric adduct, which we have failed to isolate in the individual form.

At conducting hydroxymethylation with 4–5-fold excess of formaldehyde in the presence of a catalytic amount of triethylamine, despite the distinct indication of the interaction, i.e., rapid dissolution of rhodanine **I**, we failed to isolate an individual product of hydroxymethylation: the oil remaining after removal of the solvent consisted, according to ^{1}H NMR spec-



troscopy data, of rhodanine 3,5,5-trishydroxymethyl derivative and unidentified impurities (in the ^{1}H NMR spectrum of this oil in DMSO-d_6 there are the signals of the protons of three methylene groups), but our manipulations did not lead to its crystallization.

We treated this crude oil with benzaldehyde in boron trifluoride etherate and obtained, by analogy with [8], the corresponding spiro compound **III**. This compound by its chemical nature is a cyclic acetal and can be hydrolyzed in acidic medium with the formation of the rhodanine 5,5-dihydroxymethyl derivative. Apparently, it is the hydrolytic splitting of the crude (with acidic impurities) spirane **III** owing to the presence of residual moisture in the solvent that can explain the appearance in the ^{1}H NMR spectrum of the substance "recrystallized" from commercial toluene of an additional quadruplet (doublet of doublets) at 3.76 and 3.65 ppm (J = 11.2 Hz) characteristic of the spin system CH_AH_B, that lies close to the corresponding quadruplets in the spectra of similar 5,5-dihydroxymethyl derivatives of pseudothiohydantoin (3.65 and 3.59 ppm, J = 10.8 Hz) and creatinine (3.44 and 3.39 ppm, J = 10.8 Hz) [5, 6]. In different samples of the "recrystallized" spirane **III** the content of the presumed dihydroxymethyl derivative ranged from 34 to 66%, but complete conversion of spirane **III** into the dihydroxymethyl derivative through a "recrystallization" could not be reached. The dihydroxymethyl derivative impurities could be easily washed out from spirane **III**, but we failed to isolate it in individual form from washing water or in special experiments of splitting spirane **III** in toluene in the presence of boron trifluoride etherate and its hydrolysis in acidic aqueous–alcohol media: After removal of the solvent a viscous oil was obtained, which, according to NMR and TLC data, consisted of a mixture of spirane **III**, the rhodanine 5,5-bis-dihydroxymethyl derivative, and unidentified impurities.

When compound **III** was dissolved in aqueous alkali and the resulting solution was neutralized, derivative of thioglycolic acid **IV** precipitated. Its structure was determined from the spectral characteristics. The presence of characteristic vibration bands of the carboxy and thiol groups in the IR spectrum, signals of the protons in the ^{1}H NMR spectrum, and

the molecular ion $[MH]^-$ in the ESI mass spectrum, *m*/*z* 239.0386, is consistent with the structure **IV**. The easy cleavage of thiazolidine ring in an alkaline medium apparently owes to steric strain in the dioxane-*spiro*-thiazolidine structure **III**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-400 (400 MHz), solvent DMSO-d_6. The IR spectra were taken on a spectrophotometer Shimadzu FTIR-8400S from KBr tablets. Elemental analysis was performed on the analyzer LECO CHNS(O) 942. TLC was performed on Silufol UV-254 plates, eluent acetone–hexane, 1:1 (compound **II**) and 2:3 (compounds **III**, **IV**). The mass spectrum of compound **IV** was registered on a Bruker micrOTOF 10223 by ESI (ElectroSpray Ionization) method in solution in acetonitrile.

3-(Hydroxymethyl)-2-thioxothiazolidin-4-one (II). To a solution of 6.65 g (0.050 mol) of rhodanine **I** in 50 ml of alcohol at 40°C was added 13.8 ml (0.172 mol) of 37% formaldehyde. The reaction mixture was stirred with a magnetic stirrer for 20 min (complete dissolution does not occur), then the reaction mixture was poured into a Petri dish and left overnight (or the solvent was partially evaporated by a flow of warm air over 2–3 h). Then to the reaction mixture (yellow oil or oily solution) was added 50 ml of water (oil and water do not mix) and allowed to stand in a Petri dish overnight (or the solvent was partially evaporated by a flow of warm air over 2–3 h). The oil gradually solidified in water. The solid was crushed, the resulting precipitate was filtered off and dried in air for 10 h. Yield 6.59 g (81%), mp 45–47°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 4.23 s (2H, C^5H_2), 5.20 s (2H, NCH_2OH). IR spectrum, ν, cm^{-1}: 3434 [ν(O–H)], 1719 [ν(C=O)], 1229 (thioamide **II**), 1049 (thioamide **I**). Found, %: C 28.79; H 2.99; N 8.96; S 38.96. $C_4H_5NO_2S_2$. Calculated, %: C 29.44; H 3.09; N 8.58; S 39.29.

2-Thioxo-8-phenyl-7,9-dioxa-1-thia-3-azaspiro-[4.5]decan-4-one (III). To a flat-bottom flask with a magnetic stirrer was loaded 5.18 g (0.0389 mol) of rhodanine **I** and 14.2 ml (0.177 mol) of 37% formaldehyde, and at stirring was added 0.2 ml of triethylamine. The solution was warmed to 40–50°C, and rhodanine dissolved completely. The stirring was continued for 1 h at room temperature, then the solution was neutralized with 0.7 ml of 10% HCl. The reaction mixture of dark claret color was transferred to a round-bottom flask, 50 ml of water was added and then water was distilled off at a reduced pressure on a rotary evaporator (temperature of the heating water bath was 100°C) until an oily residue in the flask did not yet solidify, but the distilled off water slowly dropped into the receiver (approximately after 40–50 min). Then to the remaining oil was added 25–30 ml of alcohol, the resulting solution was boiled for 10 min, and alcohol was distilled off on a rotary evaporator at a reduced pressure when the temperature of heating bath was maintained at 80–100°C till oil remained liquid, but the alcohol already slowly distilled into the receiver (approximately after 1–2 h).

The residue was dark claret oil immiscible with water (crude trihydroxymethylrhodanine). ^{1}H NMR spectrum, 400 MHz (DMSO-d_6), δ, ppm, *J*, Hz: 5.17 s (2H, NCH_2OH); 3.80 d [2H, J^{gem}(AB) = 10.8, C^4H_A, C^6H_A], 3.64 d [2H, J^{gem}(AB) = 10.8, C^4H_B, C^6H_B], 3.75 d [2H, J^{gem}(AB) = 10.8, C^4H_A, C^6H_A], 3.71 d [2H, J^{gem}(AB) = 10.8, C^4H, C^6H_B] (two quadruplet, overlapping).

To 7.54 g (0.0338 mol) of crude trihydroxymethylrhodanine with stirring by a magnetic stirrer was added 5.3 ml (5.539 g, 0.5219 mol) of benzaldehyde. The oil was not dissolved and the liquid phase became red. To the resulting mixture was added 10 ml of boron trifluoride etherate, therewith the oil thickened and yellow emulsion formed over it. The thickened and split into lumps oil was rubbed with a metallic spatula for 30 min, therewith it gradually "diverged," transforming into thick emulsion, while occurred a slight warming and darkening of the reaction mixture. After 3.5 h of stirring, the mixture was left overnight. On the next day, the emulsion was stirred by a magnetic stirrer for an hour, then 20 ml of ether was added, and the stirring was continued for another 1.5 h. There was a slight self-heating, the reaction mass became less colored and gradualy transformed from the emulsion to a suspension of a yellow precipitate. The latter was filtered off on a vacuum filter and dried in a vacuum desiccator for 4 h. Yield of crude product 5.40 g (49% of rhodanine **I**, 57% of trihydroxymethylrhodanine). ^{1}H NMR spectrum, 400 MHz (DMSO-d_6), δ, ppm, *J,* Hz: 7.37 m (5H, C_6H_5), 5.71 s (1H, C^2H), 4.48 d [2H, J^{gem}(AB) = 11.8, C^4H_A, C^6H_A], 4.44 d [2H, J^{gem}(AB) = 11.8, C^4H_B, C^6H_B]. The spectrum also contains signals of dihydroxymethylrhodanine (about 6%) 3.75 d [2H, J^{gem}(AB) = 10.8, CH_A], 3.64 d [2H, J^{gem}(AB) = 10.8, CH_A].

To 5.00 g (0.0178 mol) of crude product was added 40 ml of water, the precipitate was carefully ground, filtered off on a vacuum filter, washed with water, 3×15 ml (to pH 4–5 of washings) and dried for 4 h in a vacuum desiccator. Yield 3.00 g (27% on rhodanine **I**, 60% at the stage of washing). The product was recrystallized from toluene (4–5 ml of toluene per 0.1 g of the substance) and dried in a vacuum desiccator for 5 h. Yield at the stage of recrystallization 40–50%, mp 198–200°C. ^{1}H NMR spectrum, 400 MHz (DMSO-d_6), δ, ppm, *J*, Hz: 7.38 m (5H, C_6H_5), 5.74 s (1H, C^2H), 4.50 d [2H, J^{gem}(AB) = 10.8, C^4H_A, C^6H_A], 4.45 d [2H, J^{gem}(AB) = 10.8, C^4H_B, C^6H_B]. IR spectrum, ν, cm^{-1}: 3165 [ν(N–H)], 3075 [ν(N–H)], 1709 [ν(C=O)], 1220 (thioamide **II**), 1081 (thioamide **I**). Found, %: C 51.17; H 3.98; N 4.83. $C_{12}H_{11}NO_3S_2$. Calculated, %: C 51.23; H 3.94; N 4.98.

Attempt to prepare 5,5-di(hydroxymethyl)-2-thioxothiazolidin-4-one. Combined filtrates obtained after washing with water of crude spirane **III** (previous experiment) was evaporated on a rotary evaporator in a vacuum at a temperature of water bath 60–70°C for 1.5 h. The residue (about 2 ml of yellow syrup) was poured from the flask to a beaker, and the precipitate remained on the walls of the flask was washed out with about 5 ml of water to a Petri dish. After 5 days, the Petri dish with the remaining yellow oily liquid and a small amount of yellow solid residue (about 1 ml) was put to a flow of warm air for 3 h, therewith a visible change was not observed. ^{1}H NMR spectrum of the oily residue, 400 MHz (DMSO-d_6), δ, ppm, *J,* Hz: 3.74 d [2H, J^{gem}(AB) = 10.8, CH_A], 3.62 d [2H, J^{gem}(AB) = 10.8, CH_A]. Judging from the spectrum of the sample, besides the main substance, the product contains a small amount of impurities.

5-Sulfanyl-2-phenyl-1,3-dioxane-5-carboxylic acid (IV). 0.200 g (0.711 mmol) of compound **III** was dissolved at stirring with a magnetic stirrer in 3.5 ml (0.350 g, 8.75 mmol) of 10% aqueous NaOH. To the resulting solution was added 12–15 drops of concentrated HCl to pH = 4. After 2 h a white precipitate formed was filtered off, washed with 2×5 ml of water, and dried first in air and then for 4 h in a vacuum desiccator. Yield 0.120 g (70 %), mp 128–130°C (from 6 ml of ethanol, the yield at the stage of recrystallization 50%). ^{1}H NMR spectrum, 400 MHz (DMSO-d_6), δ, ppm, *J,* Hz: 13.38 br (1H, COOH), 7.41 m (5H, C_6H_5), 5.49 s (1H, C^2H), 4.52 d [2H, J^{gem}(AB) = 10.8, C^4H_A, C^6H_A], 4.26 d [2H, J^{gem}(AB) = 10.8, C^4H, C^6H_A], 3.17 br (SH). IR spectrum, ν, cm^{-1}: 3450 [ν(O–H)], 2577 [ν(S–H)], 1699 [ν(C=O)], 1380 [δ(O–H)], 1299, 1281 [ν(C–O)]. Found, %: C 53.47; H 5.28; S 13.14. $[MH]^-$, *m/z* 239.0386. $C_{11}H_{12}O_4S$. Calculated, %: C 54.99; H 5.03; S 13.35. $[MH]^-$ 239.0384.

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