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Synthesis and Crystal Structure of (4*S*,5*R*)-2-[2-(Hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine

O. A. Nurkenov[a], A. M. Gazaliev[a], M. K. Ibraev[a], D. M. Turdybekov[b], A. S. Sultanov[a], K. M. Turdybekov[b], and S. M. Adekenov[b]

[a] *Institute of Organic Chemistry and Coal Chemistry of Kazakhstan, ul. Alihanova 1, Karaganda, 100000 Kazakhstan*
e-mail: mkibr@yandex.ru

[b] *Institute of Phytochemistry, Ministry of Science and Education of Kazakhstan, Karaganda, Kazakhstan*

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Abstract — Acid hydrolysis of *l*-*N*-[*N*′-(2-vinyloxy)ethylcarbamothioyl]ephedrine was studied. The synthesized (4*S*,5*R*)-2-[2-(hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine was studied by means of X-ray diffraction.

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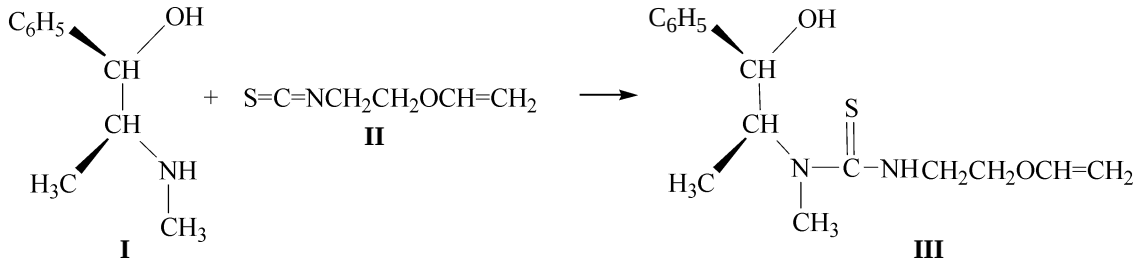
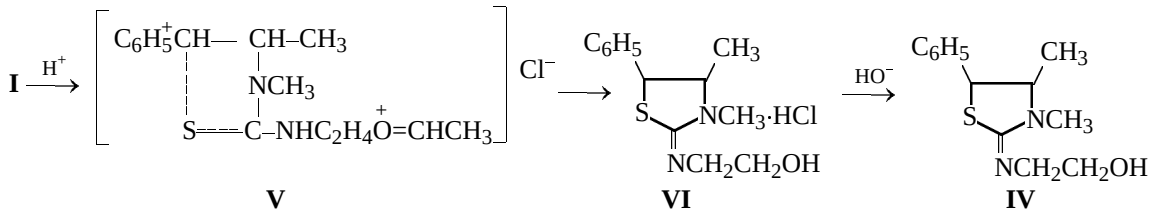
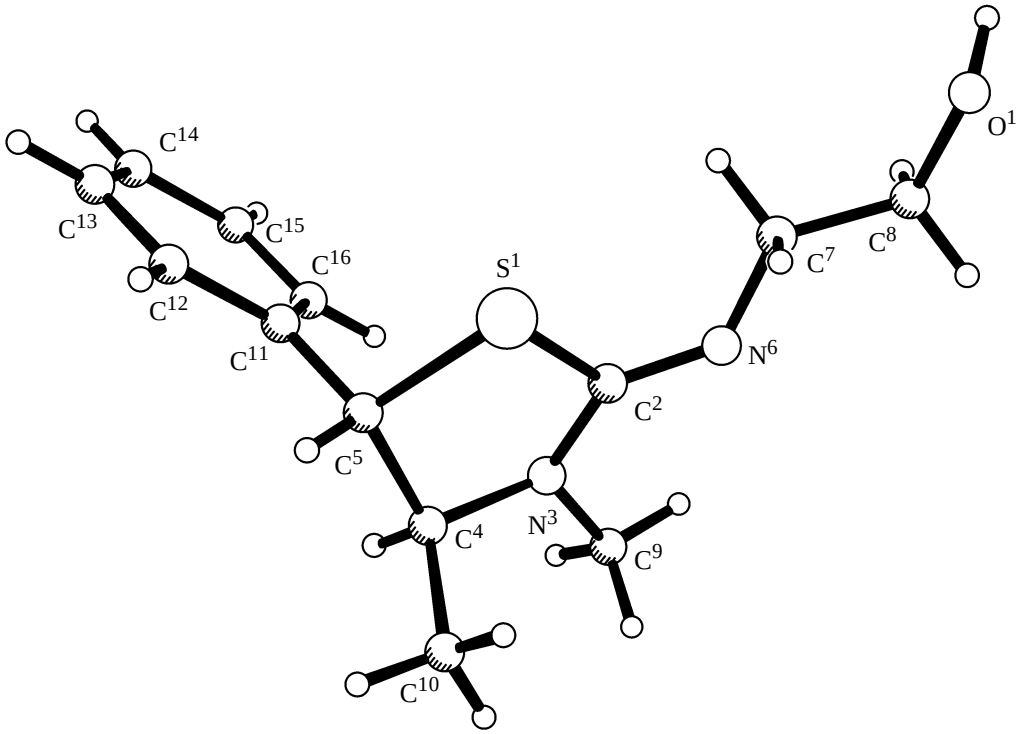
Thiourea derivatives exhibit antimicrobial, anti-inflammatory, antiulcer, and nematocide properties; growth-regulating and high insecticide and acaricide activity of such compounds has also been reported [1, 2]. The interest in thiourea derivatives is explained not only by their biological activity, but also by the fact that they are convenient synthons in organic synthesis, especially in heterocyclic synthesis [3, 4].



The information on hydrolysis of thiourea derivatives of ephedrine alkaloids is scarce. It is known that thioamides are difficult to hydrolyze, especially in alkaline medium; complete hydrolysis to form carboxylic acids, hydrogen sulfide, and ammonia or amines is possible, but not infrequently hydrolysis gives rise to nitroles, heterocyclic compounds, or oxidative cleavage products [6].

Proceeding with the research toward the synthesis and biological activity of thioamides [5], we synthesized *l*-*N*-[*N*′-(2-vinyloxy)ethylcarbamothioyl]ephedrine (**III**) by the reaction of *l*-ephedrine (**I**) with 2-vinyloxyethyl isothiocyanate (**II**) in alcoholic medium.





Structure of (4*S*,5*R*)-2-[2-(hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine

To study the reactivity of a thioamide derived from *l*-ephedrine containing a substituted 2-hydroxyethyl group, we accomplished acid hydrolysis of compound **III** in the presence of concentrated hydrochloric acid at room temperature. It was found that the acid hydrolysis provides a five-membered sulfur-containing heterocyclic compound, viz. 2-imino-1,3-thiazolidine **IV**.

The cyclization appears to involve intramolecular nucleophilic attack of the sulfur atom on a positively charged carbon atom in intermediate **V**. Free base **IV** was isolated by treatment of hydrochloride **VI** with alkali.

Thus, the acid hydrolysis of the thiourea ephedrine derivative at room temperature gives 2-imino-1,3-thiazolidine **IV**. The steric structure of (4*S*,5*R*)-2-[2-(hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine was studied by X-ray diffraction (see figure).

The bond lengths and bond angles in molecule *V* are close to normal values [7]. The conformation of the thiazolidine ring in molecule *IV* is a slightly distorted 4β-envelope (ΔC_s^4 9.57°). The C^4 atom deviates from the ring plane by ±0.49 A, and the S^1, C^2, N^3, and C^5 atoms are coplanar within ±0.05 Å. In the 4β-envelope conformation, the methyl group on C^4 and the phenyl group on C^5 are axial (the $C^{10}C^4N^3C^2$ and $C^{11}C^5C^2N^3$ torsion angles are ±91.72° and ±88.54°, respectively). The methyl and hydroxyethylamino groups on N^3 and C^2 are equatorial ($C^5C^4N^3C^9$ –169.49°, $C^4N^3C^2N^6$ 167.0°). The 4β-envelope conformation is also characteristic of (2-*p*-bromophenyl)-3,4-dimethyl-5-phenyl-1,3-oxazolidine [8].

Because of the presence in the oxazolidine derivatives of *l*-ephedrine and *d*-pseudoephedrine of substituents on C^4, C^5, and N^3, another favorable ring conformation is 3α-envelope. In this case, the methyl group on N^3 is equatorial, and the other two substituents on the above atoms are preudoequatorial. It is this conformation that is characteristic of most oxazolidine derivatives of pseudoephedrine, for example, (2*S*,4*S*,5*S*)-3,4-dimethyl-5-phenyl-2-phenylethynyl-1,3-oxazolidine [9].

EXPERIMENTAL

The IR spectra were measured on a UR-20 instruent in KBr. The ^{1}H NMR spectra were obtained on a Varian Mercury-300 instrument (300 MHz) in CD_3Cl against internal HMDS. The melting points were measured on a Boetius hot stage.

X-ray diffraction analysis of (4*S*,5*R*)-2-[2-(hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine (4*S*,5*R*-IV). The unit cell parameters and the intensities of 1383 unique reflections of compound **IV** were measured at 20°C on a Bruker-P4 automated

four-circle diffractometer (graphite monochromator, MoK_α radiation, $\theta/2\theta$ scanning, $2\theta < 50°$). Rhombic crystals, *a* 7.0181(6), *b* 10.891(1), *c* 17.511(2) Å; *V* 1338.4(2) Å^3, d_{calc} 1.242 g cm^{-3}, *Z* 4 ($C_{13}H_{18}N_2OS$). Space group $P2_12_12_1$.

Calculations involved 1341 reflections with $I > 2\sigma$. The structure was solved by the direct method and refined by full-matrix least squares anisotropically for non-hydrogen atoms. Hydrogen atoms were located geometrically and fixed by the rider model. Absorption correction by the ψ curves was applied. Weight parameter 0.71073. Final divergence factors *R* 0.0391 and R_W 0.1069. The structure solution and refinement were performed using the SHELXS-97 program.

***l*-*N*-[*N*'-(2-vinyloxy)ethylcarbamothioyl]ephedrine (III).** 2-Vinyloxyethyl isothiocyanate (**II**), 1.5 g, was added to a solution of 2 g of *l*-ephedrine (**I**) in 5 ml of ethanol. The mixture was stirred at 20°C for 20–30 min, reduced by 1/3, and left to stand for 12 h at 20°C. The precipitate that formed was filtered off and washed with ether to obtain 2.9 g (86%) of compound **III**, mp 96–97°C. IR spectrum, ν, cm^{-1}: 1530–1500 [(NHC(S)], 3400–3200 (OH). ^{1}H NMR spectrum, δ, ppm: 0.86 d (CH_3CH, J_{HH} 8.4 Hz), 2.01 s (CH_3N), 2.34–2.52 m ($CHCH_3$), 4.43 d (CHO, J_{HH} 10.6 Hz), 7.10–7.24 m (C_6H_5), 3.06–3.40 d.d (CH_2), 6.44 d (CH=C), 3.50 d (C=C^2). Found, %: C 61.27; H 7.36. $C_{15}H_{22}N_2O_2S$. Calculated, %: C 61.22; H 7.48.

(4*S*,5*R*)-2-[2-(Hydroxyethyl)imino]-3,4-dimethyl-5-phenyl-1,3-thiazolidine (4*S*,5*R*-IV). Concentrated HCl, 10 ml, was added dropwise to 1.5 g of compound **III** at room temperature. The mixture was stirred for 3 h, diluted with six volumes of water, and the water was distilled in a vacuum. The residue was treated with 40% aqueous NaOH to ®H 10–11. The reaction product was extracted with benzene, the organic layer was dried with Na_2SO_4, and the solvent was removed to obtain 0.76 g (60%) of a crystalline substance, mp 108?109°C. IR spectrum, ν, cm^{-1}: 1680–1650 (C=N), 3500–3000 (OH). ^{1}H NMR spectrum, δ, ppm: 0.92 d (CH_3CH, J_{HH} 8.6 Hz), 2.10 s (CH_3N), 2.30–2.50 m ($CHCH_3$), 4.93 d (CHS, J_{HH} 10.6 Hz), 7.00–7.15 m (C_6H_5), 3.20 d (NCH_2), 3.40 d (CH_2CH_2). Found, %: C 62.35; H 7.12. $C_{13}H_{18}N_2OS$. Calculated, %: C 62.40; H 7.20.

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