ISSN 1070-3632, Russian Journal of General Chemistry, 2006, Vol. 76, No. 7, pp. 1134–1137. © Pleiades Publishing, Inc., 2006.
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Acylation of Dithiocarbamates Derived from *l*-Ephedrine and *d*-Pseudoephedrine

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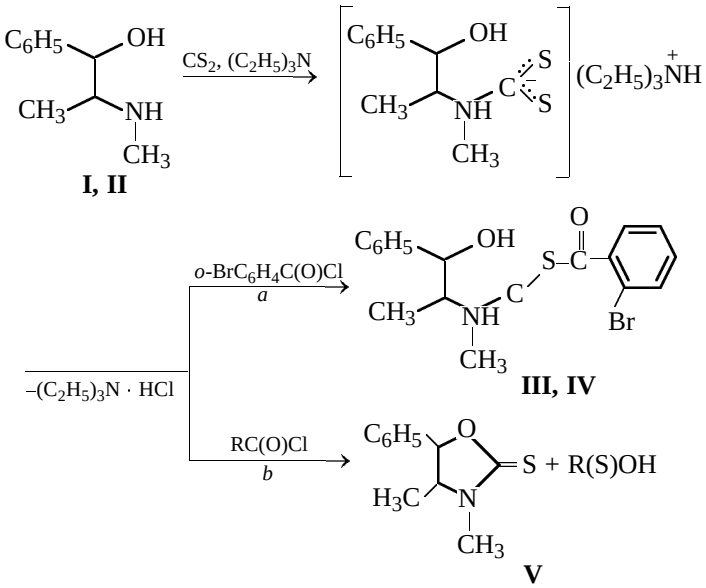
Received June 15, 2005

Abstract — The acylation of dithiocarbamates derived from *l*-ephedrine and *d*-pseudoephedrine gives, depending on the structure of the acylating agent, acyl derivatives of the dithiocarbamates or their cyclic decomposition products, viz. oxazolidinethiones.
DOI: 10.1134/S107036320607022X

The reactions of *l*-ephedrine (**I**) and *d*-pseudoephedrine (**II**) with α-haloketones yield morpholine derivatives [1, 2, 6].

To study the steric and electronic effects on the heterocyclization of ephedrine alkaloids, we performed acylation of their derived dithiocarbamates. It was shown that the reactions of dithiocarbamates derived from *l*-ephedrine (**I**) and *d*-pseudoephedrine (**II**) with α-bromobenzoyl chloride give rise to expected acyl derivatives **III** and **IV** (route *a*). The acylation with benzoyl chloride or pyromucic acid chloride provide, instead of the corresponding acyl derivatives, a heterocyclization (route *b*) product 3,4-dimethyl-5-phenyl-1,3-oxazolidine-2-thione (**V**) as a mixture of two stereoisomers: *l*-ephedrine derivative 4*S*,5*R*-**V** and *d*-pseudoephedrine derivative 4*S*,5*S*-**V**.

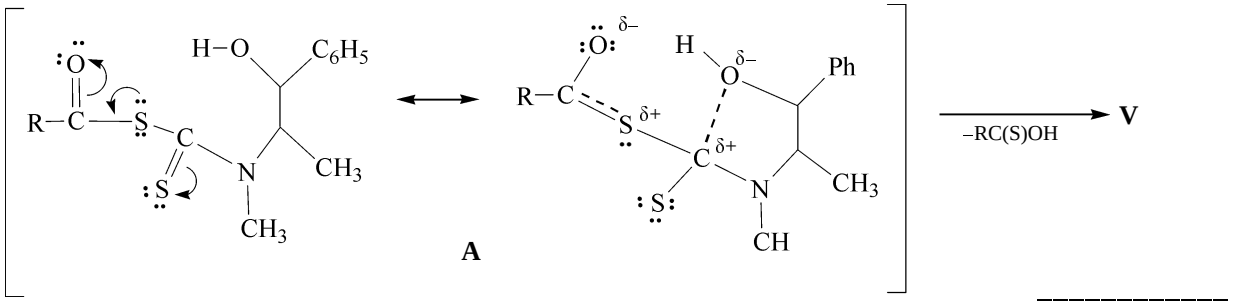


l (**I, III**), *d* (**II, IV**); R = C_6H_5, 2-furyl.

Oxazolidinethione **V** is probably formed via acyl derivative **A**, i.e. the first step of the reaction is dithiocarbamate acylation. The reactive electron-deficient thiocarbonyl group makes possible cyclization of the alkaloid via intramolecular nucleophilic attack of the hydroxy group on the carbonyl carbon atom to form the final reaction product (route *b*).

The intramolecular cyclization involving the carbon atom at the double bond occurs more effectively if the molecular structure, apart from electronic, better meets the steric demand of the transition state [7]. These demand is better met when R = C_6H_5 and 2-furyl.

The high electronic deficit on the thiocarbonyl carbon is associated (along with the electron-acceptor effect of the thionic sulfur) with a strong electron-acceptor effect of the acyl carbonyl group. As a result, the negatively charged hydroxyl oxygen and the positively charged thiocarbonyl carbon attract each other. Simultaneously, mutual repulsion of the neighboring positively charged carbon and sulfur arises. As a result, the C–S bond in compounds **A** (R = C_6H_5, 2-furyl) gets longer and weaker, thus creating one more prerequisite for this bond cleavage and formation of a cyclic product.



Mechanistically, this reaction has much in common with the formation of isothiocyanates from dithiocarbamates derived from primary amines, which, too, involves intermediate formation of an acyl derivative with subsequent C–S bond and thiobenzoic acid cleavage [8].

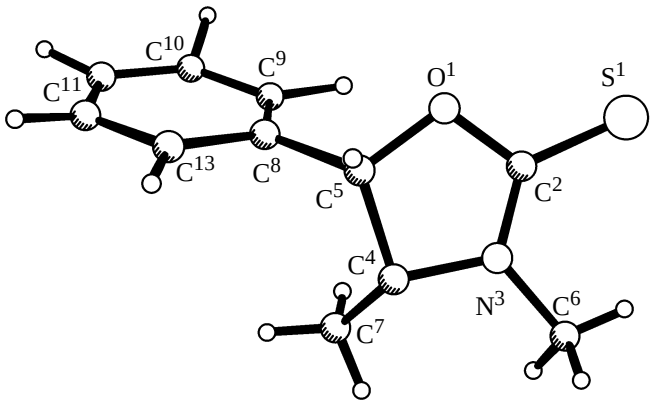
In *o*-bromobenzoyl derivatives **III** and **IV**, the electron-acceptor effect of the carbonyl carbon is most likely attenuated by its conjugation with the bromophenyl group. The effect of the carbonyl group on the thio ester sulfur is much weaker, and, as a result, compounds **III** and **IV** remain stable and undergo no cyclization in the reaction conditions.

The structure and composition of the synthesized compounds were proved by elemental analysis and ^{1}H NMR and IR spectroscopy.

The ^{1}H NMR spectrum of compound **V** contains a multiplet of aromatic protons at 7.29–7.43 ppm. The doublet at 5.88 ppm relates to the CHO proton. The CH_3N methyl protons appear as a strong singlet at 3.14 ppm. The quartet at 4.08–4.44 ppm belongs to the CHN group. The alkaloid CH_3C protons appear as a doublet at 0.80 ppm (*J* 7.2 Hz).

The IR spectrum of compound **V** lacks characteristic OH absorption bands. The spectra of compounds **III** and **IV** shows a broad band at 3261–3083 cm^{-1} (OH), as well as a strong band at 1609–1587 cm^{-1} (C=O).

The steric structure of compound **V** was established by X-ray diffraction analysis (see figure). The bond lengths and bond angles are close to normal values [9] (see table). Unlike molecules in which the oxazolidine ring assumes the chair and envelope conformations, the oxazolidine ring in molecule **V** is planar within 0.017 Å, on account of the π-conjugation with the lone electron pairs of the oxygen and nitrogen atoms and the C^2=S^1 bond. The C^4 atom deviates from the ring plane by ±0.015 Å. The methyl group on C^4 and the phenyl group on C^5 are axial (the $C^7C^4N^3C^2$ and $C^{13}C^8C^5C^4$ angles are 121.1° and 88.25°, respectively). The methyl group on N^3



Molecular structure of (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine-2-thione.

Bond lengths (*d*) and bond angles (ω) in 4*S*,5*R*-**V**

Bond	*d*, Å	Angle	ω, deg
S^1–C^2	1.663(4)	$C^2O^1C^5$	109.9(3)
O^1–C^2	1.339(5)	$N^3C^2O^1$	110.8(4)
O^1–C^5	1.452(6)	$N^3C^2S^1$	128.4(4)
C^2–N^3	1.299(5)	$O^1C^2S^1$	120.7(3)
N^3–C^6	1.450(6)	$C^2N^3C^6$	124.2(4)
N^3–C^4	1.480(6)	$C^2N^3C^4$	114.7(4)
C^4–C^7	1.505(7)	$C^6N^3C^4$	120.9(4)
C^4–C^5	1.551(7)	$N^3C^4C^7$	111.2(4)
C^5–C^8	1.505(6)	$N^3C^4C^5$	98.7(4)
C^8–C^9	1.386(6)	$C^7C^4C^5$	115.9(4)
C^8–C^{13}	1.390(6)	$O^1C^5C^8$	109.6(4)
C^9–C^{10}	1.389(7)	$O^1C^5C^4$	105.7(3)
C^{10}–C^{11}	1.371(7)	$C^8C^5C^4$	118.8(4)
C^{11}–C^{12}	1.367(7)	$C^9C^8C^{13}$	119.0(4)
C^{12}–C^{13}	1.378(7)	$C^9C^8C^5$	122.2(4)
		$C^{13}C^8C^5$	118.8(5)
		$C^8C^9C^{10}$	120.3(5)
		$C^{11}C^{10}C^9$	119.9(5)
		$C^{12}C^{11}C^{10}$	120.0(5)
		$C^{11}C^{12}C^{13}$	120.9(5)
		$C^{12}C^{13}C^8$	119.9(5)

and the S^2 atom are equatorial (the $C^5C^4N^3C^6$ and $C^4N^3C^2S^1$ angles are 173.54° and 178.8°, respectively). A flattened oxazolidine ring is also characteristic of 4,4-dimethyloxazolidine-2-thione [10].

EXPERIMENTAL

The IR spectra were measured on a UR-20 instrument in KBr. The ^{1}H NMR spectra were taken on a Varian MERCURY–300 instrument (300 MHz) in CD_3Cl, internal reference HMDS. The melting points were measured on a Boetius hot stage.

Single-crystal X-ray diffraction analysis of compound V. The unit cell parameters and the intensities of 1162 unique reflections of compound **V** were measured at 20°C on a Bruker-P4 automatic four-circle diffractometer (graphite monochromator, λ(MoK_α) radiation (θ/2θ scanning, 2θ ≤ 50°). Rhombic crystals, *a* 6.9635(7), *b* 7.5791(8), *c* 20.899(2) Å; *V* 1103.01(2) Å^3, d_{calc} 1.248 mg m^{-3}, *Z* 4 ($C_{11}H_{13}NOS$). Space group $P2_12_12_1$. The calculations involved 1162 reflections with $I \geq 2\sigma(I)$. The structure was solved by the direct method and refined by full-matrix least squares anisotropically for non-hydrogen atoms. Hydrogen atoms were located by difference synthesis in the anisotropic approximation, except from hydrogens at C^6 and C^7, that were located geometrically. Absorption correction by the ψ curves was applied. Weight parameter 0.0655. Final divergence factors *R* 0.0477 and R_W 0.1132. The structure solution and refinement were performed using the SHELXS-97 program.

***S*-[*N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N*-methylamino]carbonothioyl *o*-bromobenzenecarbothioate (III).** To a solution of 1.5 g of *l*-ephedrine and 0.91 g of triethylamine in 10 ml of chloroform, 0.55 g of hydrogen sulfide was added dropwise with stirring and cooling (–5 to 0°C). Triethylamine, 0.91 g, and 1.05 g of *o*-bromobenzoyl bromide were then added. The reaction mixture was stirred for 0.5 h at room temperature and then washed with two portions of water and dried with potash. The solvent was removed, and the residue was passed through a column of silica gel, eluent benzene. Yield of compound **III** 82%, mp 167–168°C. Found, %: C 51.00; H 4.31; N 3.33. $C_{18}H_{18}BrNO_2S_2$. Calculated, %: C 50.94; H 4.28; N 3.30.

***S*-[*N*-[(1*S*,2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-*N*-methylamino]carbonothioyl *o*-bromobenzenecarbothioate (III)** was prepared similarly to compound **III**, yield 85%, mp 49–50°C. Found, %: C 51.09; H 4.33; N 3.35. $C_{18}H_{18}BrNO_2S_2$. Calculated, %: C 50.94; H 4.28; N 3.30.

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine-2-thione (4*S*,5*R*-V) was prepared in a similar way, yield 84%, mp 60–61°C. Found, %: C 63.70; H 6.29; N 6.78. $C_{11}H_{13}NOS$. Calculated, %: C 63.73; H 6.32; N 6.76.

(4*S*,5*S*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine-2-thione (4*S*,5*S*-V) was prepared in a similar way, yield 81%, mp 125–126°C. Found, %: C 63.69; H 6.38; N 6.71. $C_{11}H_{13}NOS$. Calculated, %: C 63.73; H 6.32; N 6.76.

REFERENCES

1. Bukeeva, A.B., *Cand. Sci. (Chem.) Dissertation*, Karaganda, 2002.

2. Baramysova, G.T., *Cand. Sci. (Chem.) Dissertation*, Almaty, 1999.

3. Chang, Ch.-J.-M., Hisan, G., and Yu Wang, *J. Chem. Soc., Perkin Trans. 1*, 1994, no. 2, p. 3587.

4. Isabaeva, M.B., Baikenova, G.G., Nurkenov, O.A., Gazaliev, A.M., Bukeeva, A.B., Tursynova, A.K., and Vorontsova, O.Yu., *Trudy mezhdunarodnoi nauchno-prakticheskoi konferentsii "Teoreticheskaya i eksperimental'naya khimiya"* (Proc. Int. Scientifc and Practical Conf. "Theoretical and Experiemental Chemistry"), Karaganda, 2002, p. 137.

5. Gazaliev, A.M., Bitenov, S.E., Fazylov, S.D., Isabaeva, M.B., Karimova, A.B., and Muldakhmetov, Z.M., *Vestn. Pavlodar. Gos. Univ.,* 2002, no. 4, p. 32.

6. Nurkenov, O.A, Bukeeva, A.B., Tursynova, A.K., and Gazaliev, A.M., *Trudy mezhdunarodnoi konferentsii "Khimiya: nauka, obrazovanie, promyshlennost'. Vozmozhnost' i perspekti-vy razvitiya* (Proc. Int. Conf. "Chemistry: Science, Education, Industry. Possibilities and Perspectives of Development"), Pavlodar, 2001, p. 31.

7. *Khimiya organicheskih soedinenii sery* (Chemistry of Organic Sulfur Compounds), Belen'kii, L.I., Ed., Moscow: Khimiya, 1988.