ACID-CATALYZED CYCLIZATION OF N-3-HYDROXYALKYL-DITHIOCARBAMATES

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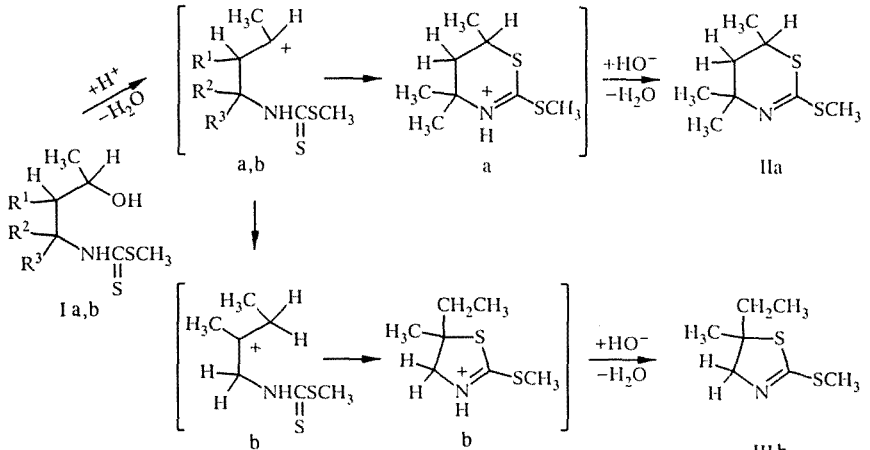
A study was carried out on the reaction of N-3-hydroxyalkyldithiocarbamates with concentrated sulfuric acid, which may lead to the formation of alkyl derivatives of 2-methylthio-5,6-dihydro-4H-1,3-thiazines or 2-methylthio-2-thiazolines, depending on the structure of the hydroxyalkyl fragment.

N-3-Hydroxyalkyl amides and 2-alkenylamides cyclize upon the action of acids to give 5,6-dihydro-4H-1,3-oxazines, oxazolines, or their mixture [1, 2]. The cyclization of 2-alkenylthioamides, 2-alkenyldithiocarbamates, and 2-alkenylthiocarbamates under analogous conditions leads to 1,3-thiazines or thiazolines or mixtures of these products [3-5]. The regioselectivity of these reactions depends primarily on the structure of the N-hydroxyalkyl or N-alkenyl fragment of the starting compound.

The cyclization of N-3-hydroxyalkyldithiocarbamates by the action of acids has not yet been studied. Methyl esters of N-(2-methyl-4-hydroxy-2-pentyl)dithiocarbamic acid (Ia) and N-(2-methyl-3-hydroxy-1-butyl)dithiocarbamic acid (Ib) were obtained according to our previous work [6] in order to study the reaction of these compounds with sulfuric acid.

Analysis of the products of the reaction of dithiocarbamate Ia with concentrated sulfuric acid showed that this reaction proceeds regioselectively and leads to the formation of 4,4,6-trimethyl-2-methylthio-5,6-dihydro-4H-1,3-thiazine (IIa) in 57.4% yield. The PMR spectrum of IIa has signals for the protons of 6-CH_3 as a doublet centered at 1.10 ppm, for the magnetically equivalent 4-CH_3 groups at 1.20 ppm, and for the methylthio group at 2.22 ppm. The signals of the equatorial and axial methylene protons are seen each as doublets at 1.83 and 1.38 ppm with common coupling constant ^2J = 14 Hz. The coupling constants of the proton at $C_{(6)}$ (^3J = 7.0, ^3J = 4.0, ^3J = 12.0 Hz), whose multiplet is found at 3.29 ppm, indicate equatorial orientation of this proton.



I a R^1 = H, R^2 = R^3 = CH$_3$; b R^1 = CH$_3$, R^2 = R^3 = H

The heterocyclization of dithiocarbamate Ib also proceeds regioselectively but with the formation not of 5,6-dimethyl-2-methylthio-5,6-dihydro-4H-1,3-thiazine as might have been expected but rather isomeric 5-methyl-2-methylthio-5-ethylthiazoline IIIb in 57.1% yield.

The PMR spectrum of IIIb has a signal for the protons of 5-CH_3 at 1.48 ppm, SCH_3 at 2.49 ppm, and the ethyl group at 1.48 ppm (quartet) and 0.98 ppm (triplet, ^3J = 7.0 Hz). The protons at $C_{(5)}$ give rise to an AB system (3.91 and 3.85 ppm, ^2J = 14 Hz).

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The IR spectra of IIa and IIIb have bands at 1590 and 1570 cm^{-1} characteristics for the C=N bond.

The formation of different products in the cyclization of Ia and Ib is attributed to the low stability of the secondary carbocations generated from these compounds upon the action of acid. Stabilization of these carbocations is possible either by heterocyclization to the 5,6-dihydro-4H-1,3-thiazinium cation or intramolecular rearrangement to a tertiary carbocation. When R^2 = Me, tertiary carbocation formation is favored. Heterocyclization of the more stable tertiary carbocation generated leads to the formation of thiazolinium salts. The heterocyclic cations formed after alkaline treatment are converted into II and III.

EXPERIMENTAL

The PMR spectra were taken on a Bruker M-250 spectrometer at 250 MHz in $CDCl_3$. The IR spectra were taken neat on a Specord IR-71 spectrometer.

The elemental analysis data for C, H, and S corresponded to the calculated values for IIIb.

Reaction of methyl N-3-hydroxyalkyldithiocarbamates Ia and Ib with sulfuric acid. A sample of 10.3 mmoles dithiocarbamate Ia or Ib was added dropwise with stirring to 8 ml 98% sulfuric acid at room temperature. The reaction mixture was stirred for 2 h in the case of Ia and 5 h in the case of Ib and then poured into 50 g ground ice. The solution obtained was extracted with two 20-ml ether portions. The organic layer was separated and the aqueous layer was neutralized by adding sodium sulfate. The solvent was distilled off and the residue was distilled in vacuum.

4,4,6-Trimethyl-2-methylthio-5,6-dihydro-4H-1,3-thiazine (IIa). Bp 75-76°C (1 mm Hg), n_D^{20} 1.5471 (bp 240°C (761.5 mm Hg) [7]).

2-Methyl-2-methylthio-5-ethyl-2-thiazoline (IIIb). Bp 134-135°C, n_D^{20} 1.5310.

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