SYNTHESIS OF 2-METHYLTHIO-4H-1,3-THIAZINES

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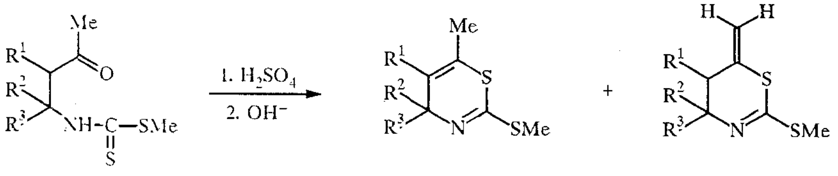
2-Methylthio-4H-1,3-thiazines or their mixtures with 5-alkylidene-4H-5,6-dihydro-1,3-thiazines were obtained by cyclization of methyl N-3-oxoalkyldithiocarbamates in sulfuric acid. The regiospecificity of the reaction is determined by the structures of the starting compounds. The structures of the synthesized thiazines were confirmed by spectral methods of analysis (IR and ^1H and ^{13}C spectroscopy).

Despite the fact that substituted 1,3-thiazines have been known for more than 100 yr and constitute the structural basis of several biologically active substances of both natural and synthetic origin, methods for the synthesis of these heterocyclic systems have not been sufficiently well developed.

The recently proposed method for obtaining methyl N-3-oxoalkyldithiocarbamates without using carbon disulfide [1] makes these compounds promising precursors of 2-methylthio-4H-1,3-thiazines, just like N-acetoacetyldithiocarbamates, which are used for the synthesis of 2-alkylthio-4-oxo-1,3-thiazines [2].

We have established that N-3-oxoalkyldithiocarbamates I-III are converted to substituted 1,3-thiazines in 65-80% yields at 20-25°C under the influence of concentrated H_2SO_4. The cyclization of I and III leads exclusively to 2-methylthio-4H-1,3-thiazines IV and VI, while the cyclization of dithiocarbamate III leads to a mixture of isosteric 4,4,6-trimethyl-2-methylthio-4H-1,3-thiazine (V) and 4,4-dimethyl-6-methylene-5,6-dihydro-4H-1,3-thiazine (VII) in a ratio of 6:1.



I-III IV-VI VII

I, IV R^1=Me, R^2=R^3=H; II, V, VII R^1=H, R^2=R^3=Me; III, VI R^1=R^2=R^3=Me

The regiospecificity of the cyclization of dithiocarbamates I-III is associated with their structures and evidently depends on the presence in the thiazine formed of an alkyl substituent in the 5 position , which stabilizes the endocyclic orientation of the double bond. We have previously observed similar principles in the dehydration of 6-hydroxytetrahydro-1,3-thiazine-2-thiones [3] and the production of 3,4-dihydro-2H-1,3-thiazin-2-ones [4], in which, depending on the structure, either thiazines with only an endocyclic orientation of the double bond or both types of thiazines were also detected.

The structures of the synthesized compounds were confirmed by the data obtained by spectral methods (^1H and ^{13}C NMR and IR spectroscopy) and the results of elementary analysis.

Absorption bands of vibrations of C=N bonds at 1590 and 1580 cm^{-1} and C=C bonds at 1650 and 1640 cm^{-1} are present in the IR spectra of thin layers of IV and VI.

The ^1H spectra of IV-VII are simple to interpret and correspond completely to their structures (Table 2).

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TABLE 1. Substituted 1,3-Thiazines IV-VII

Compound	bp, °C/mm	IR spectra, ν, cm^{-1}		Yield, %
		C=N	C=C	
IV	71/0,6	1590	1650	65.0
VI	128/12	1580	1640	79,3
V+VII	122/20	1585	1650	87,9

TABLE 2. Parameters of the PMR Spectra of Thiazines IV-VII

Compound	S—CH_3	4-$R^{2,3}$	5-R^1	6-CH_3	6=CH_2
IV	2,35	3,88	1,78	1,85	—
V	2,37	1,20	5,34	1,83	—
VI	2,39	1,29	1,79	1,89	—
VII	2,33	1,12	2,16	—	5,0; 4,96

TABLE 3. Chemical Shifts of the ^{13}C Nuclei of Thiazines IV, V, and VII

Compound	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	S—CH_3	4-$R^{2,3}$	5-R^1	6-CH_3	6=CH_2
IV	158,7	58,1	121,2	123,5	14,5	—	18,0	17,8	—
V	152,5	58,8	123,6	125,1	13,8	28,3	—	21,2	—
VII	152,3	57,8	41,3	123,6	12,9	28,0	—	—	109,5

Two sets of signals that differ in intensity are present in the ^1H NMR spectrum of the mixture of isomeric thiazines V and VII. The multiplet signal at $\delta = 5.32$ ppm belongs to the $C_{(5)}$—H proton of V, which couples with the 6-CH_3 group and shows up in the form of a doublet (2.39 ppm) with $^4J = 1.4$ Hz. The signals with $\delta = 5.0$ ppm and 4.96 ppm correspond to the resonance of the vinyl protons of thiazine VII.

In the ^{13}C NMR spectra of the mixture obtained in the cyclization of dithiocarbamate II the chemical shifts of the ^{13}C nuclei of the ring atoms and of the substituents of thiazines V and VII have close values, with the exception of the $C_{(5)}$ atom and the substituent attached to the $C_{(6)}$ atom, which exist in different hybridization states in these compounds. The chemical shifts of the ^{13}C nuclei of the atoms of 2-methylthio-4H-1,3-thiazines IV and V are in good agreement with the known values for alkyl-substituted thiazines [3] (Table 3).

EXPERIMENTAL

The IR spectra of thin layers of the compounds were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla-80 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectra of solutions in $CHCl_3$ were recorded with a Bruker WP-80 DS spectrometer.

General Method for Obtaining Thiazines IV-VII. A 20-mmole sample of dithiocarbamate I-III was added to 20 ml of concentrated sulfuric acid at 20-25°C, after which the reaction mixture was stirred for 1 h and then poured slowly into a beaker containing 600 ml of a cooled 10% solution of sodium carbamate and 70 ml of ether. The organic layer was separated, and the aqueous layer was extracted with ether (2 × 70 ml). The combined ether extract was dried with sodium sulfate, the solvent was removed by distillation, and the residue was fractionally distilled in vacuo.

The results of elementary analysis for C, H, and S were in agreement with the calculated values.

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