

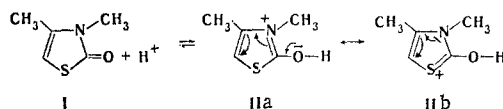
ACID - BASE PROPERTIES OF 3,4-DIMETHYL-2-THIAZOLONE,  
4-METHYL-2-THIAZOLONE, AND 5-ACETYL-4-METHYL-2-  
THIAZOLONE

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In contrast to 2-methoxy-4-methylthiazole and 2,4-dimethylthiazole, the protonation of 3,4-dimethyl-2-thiazolone does not proceed in media with acidities up to  $H_0 = -3.99$ . The acidity of N-H increases by 2.4 orders of magnitude on passing from 4-methyl-2-thiazolone to its 5-acetyl derivative. The data obtained from a study of the acid-base properties in conjunction with the results of calculations of the 3,4-dimethyl-2-thiazolone and thiazole molecules by the MO method make it possible to conclude that there is a  $\delta$  charge in the 5 position of 2-thiazolones and that this is the reason for the facile acylation of these compounds.

In a previous communication we described the acylation of 2-thiazolones with acetic anhydride in the presence of catalytic amounts of sulfuric acid, and it was proved that the thiazolone form of the compound enters into the reaction [1].



It seemed logical to attempt to explain the ability of this form to undergo acylation in the same way as Éfros and El'tsov [2] did to explain the nitration of benzimidazolones, namely, by the formation of a conjugated acid with generation of a donor hydroxyl group (IIa). In addition to this, one should take into account an investigation of the charge distribution in the thiazolium cation [3], which provided us with the possibility of assuming the presence of a donor effect of the amino group in structure IIb as the reason for the facile acetylation in the 5 position. Moreover, one cannot exclude the possibility of the coexistence of both effects in a structure intermediate between IIa and IIb.

With this end in mind, we undertook a study of the basic properties of 3,4-dimethyl-2-thiazolone (I), 2-methoxy-4-methylthiazole (III), and 2,4-dimethylthiazole (IV). Acylation is carried out in acetic anhydride, but the basic properties were studied in water and aqueous solutions of acids, since the lower boundary of transmission of acetic anhydride in the UV region is 285 nm, while I has an absorption maximum at 245 nm.

The identical character of the UV spectra of solutions in water, 0.02 N hydrochloric acid, and 0.02 N sulfuric acid (Fig. 1) attests to the absence of spectrally determinable amounts of II under the acylation conditions. In order to ascertain whether acylation proceeds through spectrally indeterminate amounts of II ( $\leq 1\%$ ), we recorded the spectrum of a solution in 11 N hydrochloric acid ( $H_0 = -3.99$ ) [4] and, for comparison, the spectra of III and IV in water and 11 N hydrochloric acid (Figs. 2 and 3). Although acylation is carried out with sulfuric acid catalysis, the basic properties of I were studied in hydrochloric acid in view of the resinifying action of concentrated sulfuric acid. The data on the basicity of thiazole ( $pK_a^{20} = 2.53$ ) [5]

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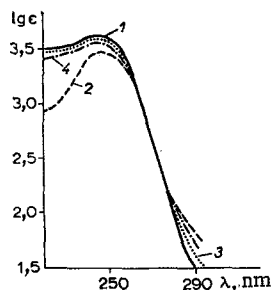


Fig. 1

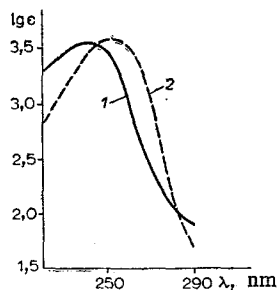


Fig. 2

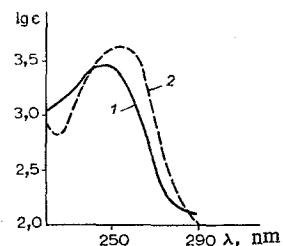


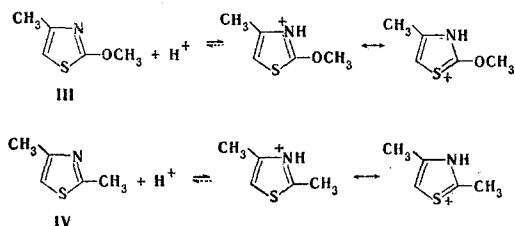
Fig. 3

Fig. 1. Absorption spectra of 3,4-dimethyl-2-thiazolone: 1) in water; 2) in 35% hydrochloric acid; 3) in 0.02 N sulfuric acid; 4) in 0.02 N hydrochloric acid.

Fig. 2. Absorption spectra of 2-methoxy-4-methylthiazole: 1) in water; 2) in 35% hydrochloric acid.

Fig. 3. Absorption spectra of 2,4-dimethylthiazole: 1) in water; 2) in 35% hydrochloric acid.

make it possible to suppose that its alkoxy and alkyl derivatives exist as conjugate acids in 11 N hydrochloric acid:



A comparison of the character of the changes in the spectra of I, III, and IV in water and 11 N hydrochloric acid makes it possible to conclude that I, in contrast to III and IV, does not give spectrally determinable amounts of the conjugate acid under high acidity conditions. The difference in the spectra on passing from water and dilute acids to concentrated acid is explained by the change in the dielectric constant of the medium.

We then calculated the possible amount of II under the acylation conditions; this value is not revealed by the spectrophotometric method even in media with high acidities. If it is assumed that there is  $\leq 1\%$  conjugate acid (the error in the method) in this sort of medium ( $H_0 = -3.99$ ), the hypothetical  $pK_a$  value is  $\leq -5.99$ . The sulfuric acid concentration during acylation is 0.02 N, and the appropriate calculations gave  $\leq 0.005\%$  II under the acylation conditions.

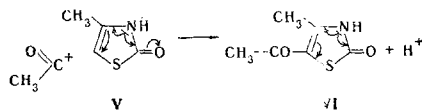
The realization of the reaction through this small percentage of active form (II), which, in addition, has the same charge as the attacking agent, should have resulted in an extremely slow reaction rate, whereas acylation proceeds rapidly (in 1-2 min) and quantitatively.

The assumption of the +M effect of the sulfur and nitrogen atoms then arises as the reason for the capacity of these compounds for acylation. The role of sulfur is apparent from the inability of 1-methyl-2-pyridone and 1,3-dimethyl-2-imidazolone to undergo acylation [1]. It is extremely likely that the unshared electrons of the sulfur atom, which is weakly electronegative [6], saturate the  $\text{C}=\text{O}$  acceptor group to a considerable degree. As a result, the unshared electrons of nitrogen are delocalized to a much lesser extent on the carbonyl group than in ordinary cyclic lactams and, as a result, there is a certain possibility for dynamic conjugation with the electrophilic acylating agent at the instant that it attacks the 5 position of the 2-thiazolone. To obtain experimental reinforcement of these assumptions, we undertook a comparative study of the acid properties of 4-methyl-2-thiazolone (V) and its 5-acetyl derivative (VI).

The ionization constant of V was determined by potentiometric titration in aqueous media [7]. At  $20 \pm 1^\circ$ , the  $pK_a$  value is  $10.65 \pm 0.03$ . In view of the insolubility of VI in water, a similar method was used to determine the ionization constants of V and VI in nonaqueous media [8,9]. It was not expedient to make the measurements in the acylating medium - acetic anhydride - in view of the interaction between it and

the titrant - alkali. The optimum solvent with the strongest differentiating action proved to be a mixture of 50% methanol and 50% acetonitrile. The investigated compounds did not undergo irreversible structural changes during the titration; this was proved by comparison of the UV spectra of the solutions prior to titration and after acidification of the alkaline solutions. The spectra were identical:  $\lambda_{\max}$  295 nm ( $\log \epsilon$  3.64) before titration,  $\lambda_{\max}$  295 nm ( $\log \epsilon$  3.63) after acidification. At  $20 \pm 1^\circ$ , the  $pK_a$  is  $11.72 \pm 0.03$  for V and  $9.32 \pm 0.03$  for VI.

The increase in the acidity of N-H by 2.4 orders of magnitude when an acetyl substituent is introduced into the 5 position is evidence for conjugation between it and the unshared electron pair of the nitrogen atom. It is evident that similar dynamic conjugation can also be realized at the instant of collision of the 2-thiazolone molecule with the acetylating agent.

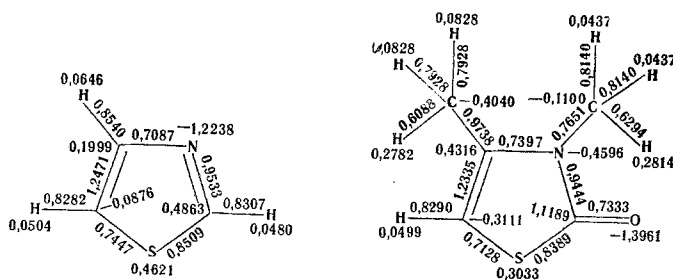


Delocalization of the unshared electron pair of the nitrogen atom in two directions (V, VI) is not specific for 2-thiazolones. However, it can be used to explain, for example, the relatively high acidity of N-H of hexanitrodiphenylamine [7] ( $pK_a^{20^\circ}$  5.42), the instability of p-nitrophenyl-N-methylnitrosamine to form a conjugate acid [10], etc. It is completely possible that the  $\delta$  charge in the 5 position of 4-methyl-2-thiazolone (V) develops not only at the instant of impact of the molecule with the acylating cation but also in the substance as such prior to the reaction. This assumption finds confirmation in the results of calculations of the effective charges in the thiazole and 3,4-dimethyl-2-thiazolone molecules by the MO method.

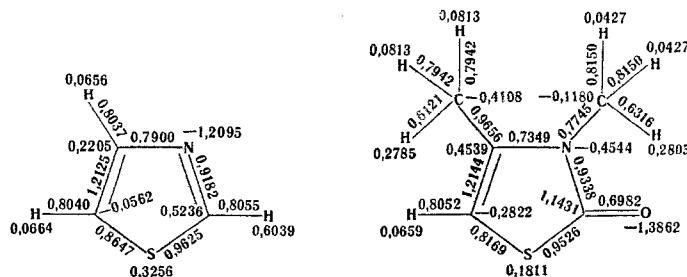
The calculations were performed via the Hoffmann method [11] (an extended Hückel method) with allowance for all of the valence electrons. The results of two calculations with allowance for and disregarding the d AOS orbitals are presented below for each molecule.\*

There is a considerable (as compared with thiazole)  $\delta$  charge ( $-0.3111$  or  $-0.2822$ ) on  $C_{(5)}$  in the 3,4-dimethyl-2-thiazolone molecule. This charge is substantially smaller ( $-0.0876$  or  $-0.0562$ ) in the thiazole molecule; this is in agreement with the facile acylation of the first compound and the inability of the second compound to undergo this reaction.

With allowance for the d-AOS



Disregarding the d-AOS



\*The calculations were performed at Rostov State University by R. P. Minyaev under the direction of Professor V. I. Minkin, to whom the authors express their thanks.

## EXPERIMENTAL

Compounds I and III-VI were synthesized via the method in [1].

The UV spectra of  $3 \cdot 10^{-4}$  M solutions were recorded with an SF-4a spectrophotometer using 1-cm thick layers.

Potentiometric titration was performed with an LPM-60M potentiometer in a thermostatted cell with glass and silver chloride electrodes. The potentiometric data were treated as in [7-9].

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