

Acid-base equilibria of some 2-substituted derivatives of 7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole

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Dedicated to Professor S. Stankoviánsky on his 70th birthday

On the basis of spectrophotometric study of acid-base equilibria of 2-amino, 2-*N,N*-diethylamino, 2-hydroxy, and 2-chloro derivatives of 7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole in aqueous alcoholic medium within the acidity range from 1 M- H_2SO_4 to 1 M-NaOH, the following information was obtained: The chloro derivative exists in a single fundamental acid-base form in the whole pH range, but it quite rapidly and irreversibly changes in alkaline medium to give the corresponding 2-hydroxy derivative. In contrast to the 2-chloro and 2-hydroxy derivatives, the 2-amino and 2-*N,N*-diethylamino derivatives are protonated in the medium of 1 M- H_2SO_4 while the 2-amino derivative is more basic ($\Delta pK = 3.00 - 2.35 = 0.65$). The 2-*N,N*-diethylamino derivative is not subject to any transformation in an alkaline medium. As for the 2-amino derivative, we can observe that the keto-enol tautomeric equilibrium shifts in favour of the nondissociated enol form with increasing content of ethanol at a constant concentration of NaOH. The 2-hydroxy derivative dissociates readily ($pK 7.04 \pm 0.05$).

На основании спектрофотометрического изучения кислотно-основных равновесий 2-амино-, 2-*N,N*-диэтиламино-, 2-гидрокси- и 2-хлорпроизводных 7-оксо-5,5-диметил-4,5,6,7-тетрагидробензтиазола в водно-спиртовой среде с 1 м- H_2SO_4 по 1 м- $NaOH$ было найдено следующее: Хлорпроизводное существует в целом диапазоне рН в одной, исходной кислотно-основной форме, но в щелочной среде относительно быстро подвергается необратимому превращению в соответствующее 2-гидроксипроиз-

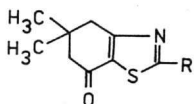
водное. 2-Амино- и 2-*N,N*-диэтиламинопроизводные, в отличие от 2-хлор- и 2-гидроксипроизводных, протонизированы в среде 1 м- H_2SO_4 , причем 2-аминопроизводное является более основным ($\Delta pK = 3,00 - 2,35 = 0,65$). В щелочной среде 2-*N,N*-диэтиламинопроизводное не подвергается никаким изменениям. В случае 2-аминопроизводного наблюдается, что с увеличением щелочности среды или же с повышением концентрации этанола при постоянной концентрации NaOH, смещается кето-энольное равновесие в сторону недиссоциированной энольной формы. 2-Гидроксипроизводное диссоциирует относительно легко ($pK 7,04 \pm \pm 0,05$).

The u.v. and i.r. spectrometric investigation of amino-imino tautomerism of the 2-amino derivatives of thiazole is dealt with in [1]. The authors of that paper observed that the absorption bands in u.v. spectrum of the imino forms were shifted to shorter wavelengths with respect to their positions found for the corresponding amino forms and interpreted this phenomenon by suggesting an impairment of conjugation of the double bonds in thiazolines. The exocyclic nitrogen of the imino form of the aminothiazole derivatives studied is more basic than the hetero nitrogen of the corresponding amino form and this is, however, more basic than the nitrogen of the amino group.

On the basis of infrared spectra of some derivatives of 7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole, the oxothiazoline structure [2] is attributed to the 2-hydroxy derivative but it is assumed that the 2-amino derivative has the aminothiazole structure [3].

Vanag [4] studied the properties of β -diketones of which the keto-enol tautomerism is typical. The keto-enol tautomeric equilibrium depends on polarity of the solvent and proton-acceptor properties of the medium. A decrease in polarity of the solvent enhances the formation of the hydrogen bond which stabilizes the enol form, which results in a shift in the tautomeric equilibrium in favour of the enol form.

The heterocycle studied is a base of a series of azo compounds the acid-base and chelating equilibria of which are topics of several papers [5, 6] and the hydrazo compounds of which are considerably resistant against disproportionation [7]. In this paper, we characterize the acid-base equilibria of some 2-substituted derivatives of 7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole



- R:
- I — NH_2
 - II — $N(C_2H_5)_2$
 - III — OH
 - IV — Cl

We confront the results of this study with the conclusions of papers [2] and [3] which refer to the tautomeric forms of compounds *I* and *III* as well as with the results of polarographic study of the redox properties of compounds *I*, *III*, and *IV* which are treated in [8].

Experimental

2-Amino-7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole *I* (m.p. 207—208°C) was prepared from thiourea and bromodimedone [3]. 2-*N,N*-Diethylamino-7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole *II* (m.p. 79°C) was obtained by the procedure described in [9]. 2-Chloro-7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole *IV* (m.p. 43°C) was synthesized by the Sandmayer method according to [2]. 2-Hydroxy-7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole *III* (m.p. 166°C) was prepared according to [2].

On the basis of the properties of compound *IV* described in Results and discussion, we elaborated the following procedure for preparing compound *III*: We dissolve 1.8 g of compound *IV* in 40 ml of C₂H₅OH, add 50 ml of 2 M-NaOH and 10 ml of water and allow to stand for 3 h at laboratory temperature. We acidify the reaction mixture to pH 1 — pH 5 and distill off alcohol. We extract the precipitate with chloroform, evaporate and allow the rest to crystallize from a water—alcohol mixture. The yield is 1.5 g of compound *III* and represents 90% of the theoretical yield. The u.v. spectrum of this product was identical with the spectrum of compound *III* as prepared according to [2] and the mixed melting point of both preparations of compound *III* did not exhibit any depression.

Other chemicals used were anal. grade preparations.

The spectrophotometric measurements were performed on a recording spectrophotometer Specord UV VIS (Zeiss, Jena). The polarographic measurements were carried out with a Kalousek vessel equipped with separated SCE and a polarograph OH-102 (Radelkis, Hungary). A pH-meter PHM 26 (Radiometer, Denmark) with glass electrode G 202 B and reference calomel electrode K 401 was used for pH measurements.

Results and discussion

The spectrophotometric study of the pH dependence of acid-base equilibria of compound *I* has shown that the absorption curves intersect in two distinct isosbestic points, which indicates the existence of two equilibria, *i.e.* three acid-base forms *Ia*—*Ic*. They are clearly separated from each other (Figs. 1 and 2). Both equilibria are reversible. Form *Ia* is the only form existing in the medium with $c_{\text{H}_2\text{SO}_4} \geq 0.25 \text{ M}$ and cannot be extracted with chloroform. Form *Ic* existing in strongly alkaline medium as well as form *Ib* existing in the pH region of 7—11 is extractable with chloroform. The different extractibility indicates that form *Ia*, in contrast to forms *Ib* and *Ic*, is endowed with a charge. In order to confirm the

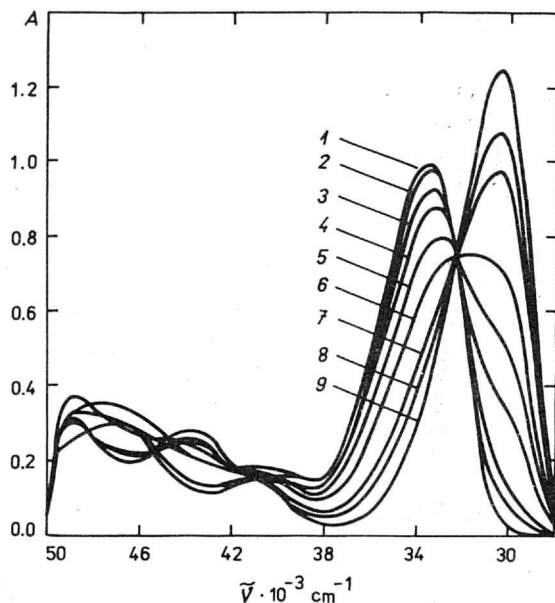


Fig. 1. Absorption curves of compound *I* at varying pH of the medium (acid and neutral region).

$$c_i = 3.5 \times 10^{-5} \text{ M}, d = 2 \text{ cm.}$$

1. pH 0.92; 2. pH 1.85; 3. pH 2.17; 4. pH 2.58; 5. pH 2.85; 6. pH 3.13; 7. pH 3.47; 8. pH 3.89; 9. pH 7.0.

assumption that form *Ic* was not an enolate anion of compound *I*, we investigated the dependence of the equilibrium between forms *Ib* and *Ic* on the content of ethanol at a constant concentration of NaOH. The result of these measurements is shown in Fig. 3. Since we cannot suppose in this case that an increase in the content of ethanol, *i.e.* a decrease in polarity of the medium, is able to favour dissociation and in spite of this fact the band of form *Ic* increases in the same manner as it increases with concentration of NaOH at a constant concentration of ethanol, we may assume that form *Ic* is the nondissociated enol form which is stabilized by hydrogen bond. The probability of formation of the hydrogen bond increases with decreasing polarity of the medium, owing to which an increase in the content of ethanol shifts the equilibrium in favour of the enol form. The measurement of the height ratio of the absorption maxima of forms *Ib* and *Ic* at varying concentration of compound *I* has shown that this ratio is constant in the concentration range 1×10^{-5} — 50×10^{-5} M, which eliminates the possibility of occurrence of intermolecular hydrogen bond. The assumption that form *Ic* is the nondissociated enol form of compound *I* stabilized by intramolecular hydrogen bond is confirmed by the observation that the product of this compound with Hg^+ [8] and form *Ic* give the corresponding band in the u.v. spectrum at equal position.

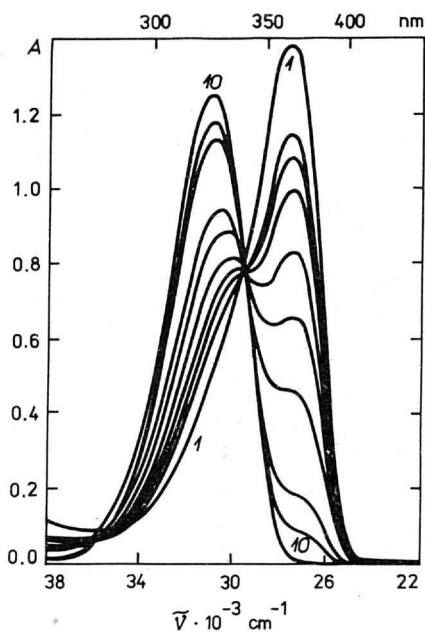


Fig. 2. Absorption curves of compound *I* at varying c_{NaOH} .

$$c_I = 3.5 \times 10^{-5} \text{ M}, d = 2 \text{ cm.}$$

c_{NaOH} : 1. 5×10^{-1} M; 2. 3×10^{-1} M; 3. 2.5×10^{-1} M; 4. 2×10^{-1} M; 5. 1.5×10^{-1} M; 6. 1×10^{-1} M; 7. 5×10^{-2} M; 8. 2×10^{-2} M; 9. 1×10^{-2} M; 10. 0 M.

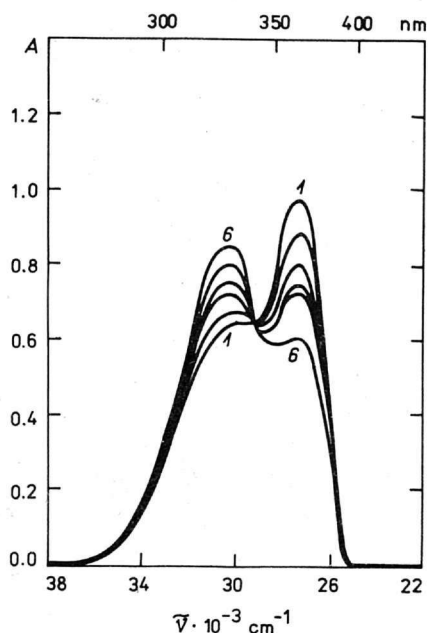


Fig. 3. Absorption curves of compound *I* at varying content of ethyl alcohol and constant concentration of NaOH.

$$c_I = 3.5 \times 10^{-5} \text{ M}, c_{\text{NaOH}} = 10^{-1} \text{ M}, d = 2 \text{ cm.}$$

$c_{\text{C}_2\text{H}_5\text{OH}}$ in volume %: 1. 80%; 2. 70%; 3. 60%; 4. 50%; 5. 40%; 6. 0%.

The spectrophotometric study of compound *II* at varying pH value of the medium has shown that only one equilibrium between forms *IIa* and *IIb* exists in the region from 1 M- H_2SO_4 to 1 M-NaOH. Form *IIa* alone exists in a medium with $c_{\text{H}_2\text{SO}_4} \geq 1$ M. Form *IIb* is present alone in a medium with $\text{pH} > 4$. The absorption curves of compound *II* are identical in the medium of pH 4 and in the medium of 1 M-NaOH. Compound *III* is also present in two forms in the investigated pH range. But the absorption curves of compound *III* are identical in the medium of 1 M- H_2SO_4 and pH 5. Compound *IV* occurs in equal form both in the medium of 1 M- H_2SO_4 and 1 M-NaOH. It is subject to a gradual irreversible change in alkaline medium while the decrease in its absorption band is accompanied with an increase in the band which corresponds to form *IIIb*. The spectrophotometric characteristics of individual acid-base forms of compounds *I*–*IV* as well as the delimitation of the region of their existence, pK value, and data on extractibility with chloroform are given in Table 1. The acid-base equilibria between forms

Table 1

Characteristics of the acid-base forms of compounds I—IV

Compound	Region of existence	pK	$\tilde{\nu}_{\max}$	ϵ_{\max}	Extractibility with chloroform
<i>Ia</i>	$c_{\text{H}_2\text{SO}_4} \geq 0.25 \text{ M}$	3.00 ± 0.05	33 700	14 300	—
<i>Ib</i>	$7 \leq \text{pH} \leq 11$		30 640	18 000	+
<i>Ic</i>	$c_{\text{NaOH}} > 0.5 \text{ M}$		27 400	19 700	+
<i>IIa</i>	$c_{\text{H}_2\text{SO}_4} \geq 1 \text{ M}$	2.35 ± 0.04	32 400	16 000	—
<i>IIb</i>	$\text{pH} > 4$		29 000	20 200	+
<i>IIIa</i>	$\text{pH} < 5$	7.04 ± 0.05	33 400	11 400	+
<i>IIIb</i>	$\text{pH} > 9$		30 100	16 300	—
<i>IV</i>	1 M- H_2SO_4 — 1 M- NaOH	—	35 000	10 000	+

Ia—Ib, *IIa—IIb*, and *IIIa—IIIb* are characterized by the pH curves in Fig. 4. The dissociation constants of forms *Ia*, *IIa*, and *IIIa* presented in Table 1 have been calculated from the equation

$$\text{pK} = \text{pH} + \log (A_{\nu,z} - A_{\nu}) - \log (A_{\nu} - A_{\nu,K})$$

where ν corresponds to the maximum absorbance of the pertinent deprotonated form, $A_{\nu,z}$ is the absorbance at ν provided only deprotonated form is present in the solution, $A_{\nu,K}$ is the absorbance at ν provided only protonated form is present in the solution, and A_{ν} is the absorbance of the solution at ν for varying pH value. In

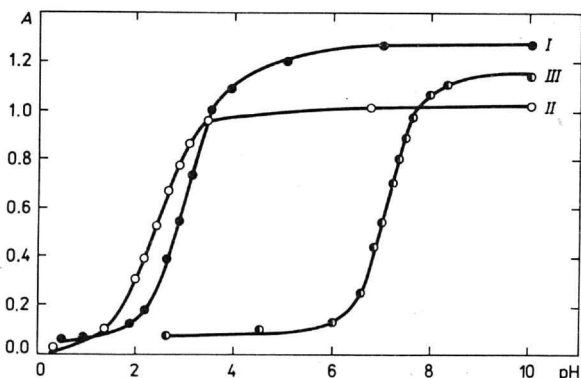


Fig. 4. Variation of the absorbance of compounds *I*, *II*, and *III* with pH in aqueous medium.

$$c_I = 3.5 \times 10^{-5} \text{ M}, I = 2, \tilde{\nu} = 30\,640 \text{ cm}^{-1}.$$

$$c_{II} = 2.5 \times 10^{-5} \text{ M}, I = 2, \tilde{\nu} = 29\,000 \text{ cm}^{-1}.$$

$$c_{III} = 3.5 \times 10^{-5} \text{ M}, I = 2, \tilde{\nu} = 30\,100 \text{ cm}^{-1}.$$

The cell pathlength $d = 2 \text{ cm}$.

contrast to forms *IIIa* and *IV*, forms *IIa* and *Ia* are able to exist in high concentrations in the absence of organic solvent in acid aqueous solution and are nonextractible with chloroform. On alkalization, they separate in the form of a precipitate which can be extracted with chloroform. Forms *Ib*, *Ic*, *IIB*, *IIIa*, and *IV* are extractible with chloroform. In contrast to forms *Ic*, *IIB*, and *IV*, form *IIIb* is able to exist in high concentration in the absence of organic solvent in alkaline aqueous solution and is not extractible with chloroform. On acidifying the alkaline aqueous solution, it separates in the form of a precipitate which can be extracted with chloroform.

If we compare the results concerning the number of acid-base forms of individual compounds, regions of their existence, and their behaviour towards different polar solvents with the possible theoretical acid-base forms of compounds *I—IV*, we may state that forms *Ia* and *IIa* are once protonated, forms *Ib*, *Ic*, *IIB*, *IIIa*, and *IV* are electroneutral, and form *IIIb* is a dissociated form.

If we compare the constants of deprotonation of forms *Ia* and *IIa*, we can see that form *Ib* accepts a proton more easily than form *IIIb*. Considering the intensity of electron-donating effect of the particular substituents, this result is unexpected. If we do not suppose that the decrease in basicity of form *IIIb* with respect to form *Ib* is of steric character, the only explanation in agreement with [1] but at variance with [3] is the assumption that form *Ib* is the iminothiazoline form. This assumption would be also consistent with a quite higher stability of hydrazo compounds on the base of 7-oxo-5,5-dimethyl-4,5,6,7-tetrahydrobenzothiazole in comparison with analogous hydrazo compounds of indandione, dimedone, and barbituric acid. In the first case, the height of polarographic wave of azo group corresponds to a two-electron reduction in the whole pH range [7] but in other cases, it corresponds to a four-electron reduction because of rapid disproportionation of the arising hydrazo compounds.

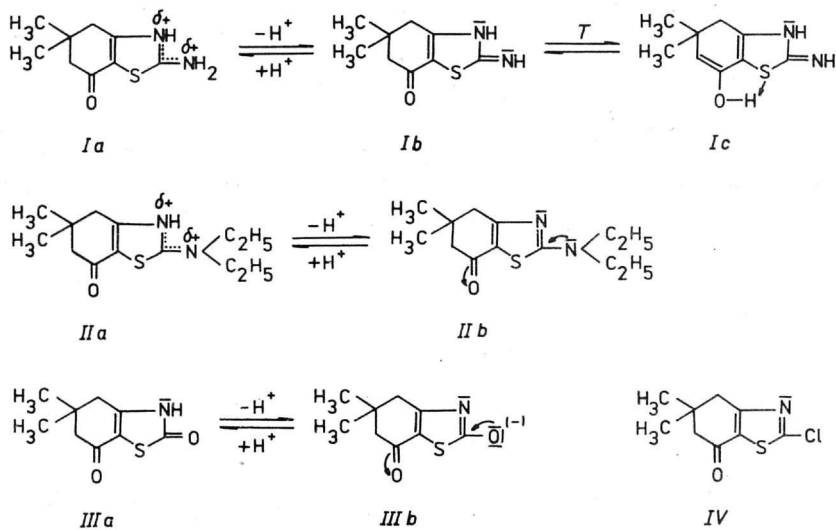
According to [2], compound *III* in nondissociated state *IIIa* represents a tautomeric equilibrium of the hydroxythiazole form and oxothiazoline form.

The polarographic study of compounds *I—IV* has shown that, in contrast to compounds *I*, *II*, and *IV*, compound *III* is polarographically inactive over the whole concentration range. We have proved in [8] that the $-\text{C}=\text{N}-$ group is the reducible group of compounds *I*, *II*, and *IV*. Therefore, the hydroxythiazole structure of form *III* should be reduced more easily than e.g. compound *II*. The reducibility of the isolated carbonyl group of the oxothiazoline form cannot be expected. The polarographic nonreducibility of compound *III*, therefore, evidences a considerable shift in tautomeric equilibrium in favour of the oxothiazoline form.

Form *IIIb* is a dissociated form of compound *III*. If we consider that compound *III* dissociates fairly easily ($\text{p}K = 7.04 \pm 0.05$) and compounds *I*, *II*, and *IV* are not able to dissociate even in the medium of 1 M-NaOH, we can state that the deprotonation concerns only the hydroxyl group.

Compound IV is not able to undergo either protonation in the medium of 1 M-H₂SO₄ or dissociation in the medium of 1 M-NaOH.

On the basis of the results and observations discussed above, the acid-base equilibria of compounds I—IV may be described by Scheme 1

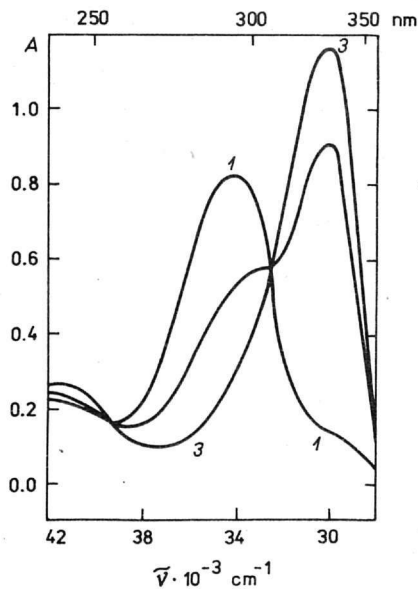


Scheme 1

Fig. 5. Transformation of compound IV into compound III in alkaline aqueous alcoholic medium.

The samples were taken from the reaction mixture containing 1.8 g of the compound in 100 ml, 1 M-NaOH, 40% C₂H₅OH, diluted in the ratio 1:2000 and measured in a cell ($d = 1$ cm) during the reaction.

1. 5 min after preparation; 2. 11/2 h after preparation; 3. 3 h after preparation.



Compound *IV* is subject to irreversible change in alkaline medium, owing to which form *IIIb* comes into existence. The spectrophotometric investigation of this change in dependence on time has shown that the absorption curves intersect in a distinct isosbestic point, which means that the sum of the concentrations $c_{IV} + c_{III}$ remains constant. Compound *III* arises from compound *IV* quantitatively and unambiguously.

The method of preparation of compound *III* from compound *IV* described in [2] requires: *a*) 11/2 hours' boiling in the aqueous medium of HCl (1 : 1), yield 70%; *b*) 2 hours' boiling in the aqueous medium of 10% NaOH, yield 50%. These conditions of preparation, owing to which some side reactions contaminating the product and reducing the yield take place, are necessary because of the insolubility of compound *IV* in aqueous medium. If we used the aqueous alcoholic medium of 1 M-NaOH, compound *III* arose from compound *IV* quantitatively and unambiguously in the course of 3 h at laboratory temperature (Fig. 5). The working procedure is described in Experimental.

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