

# Thione-Disulfide Interchange of some Heterocyclic Tautomeric Thiones and their Symmetrical Disulfides

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**Summary.** The UV/Vis spectroscopic properties of some symmetrical disulfides derived from potentially tautomeric thiones are investigated. Reversed thione-disulfide transformation is observed, and the influence of several factors including the nature of solvent, concentration, and UV irradiation, is studied. Possible implication of the tautomeric thiol form and the importance of this thione-disulfide redox system in biological aspects is suggested. A general scheme including monomer-dimer equilibrium, thione-thiol tautomeric equilibrium, and reversible thiol-disulfide redox behaviour is proposed in order to explain the factors affecting the overall thione-disulfide transformation.

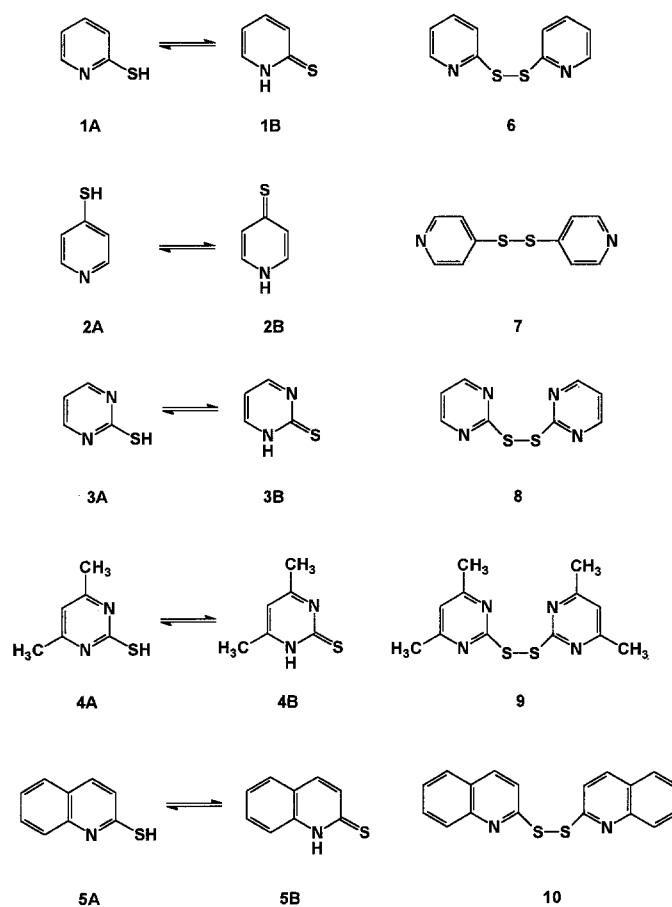
**Keywords.** Pyridine and pyrimidine derivatives; Symmetrical disulfides; Thiol-disulfide interchange; Thione-thiol tautomerism; UV/Vis spectroscopy.

## Thion-Disulfid-Umwandlung einiger heterocyclischer tautomerer Thione und ihrer symmetrischen Disulfide

**Zusammenfassung.** Die UV/Vis-spektroskopischen Eigenschaften einiger symmetrischer Disulfide, die als Derivate von potentiell tautomeren Thionen auftreten, wurden untersucht. Es wurde eine reversible Thion-Disulfid-Transformation beobachtet. Der Einfluß einiger Faktoren wie Natur des Lösungsmittels, Konzentration und UV-Bestrahlung wurden erforscht. Die Bedeutung des untersuchten Redoxsystems in biologischer Hinsicht wird diskutiert. Um die Auswirkung der einzelnen Faktoren auf die Umsetzung zu erklären, wird ein allgemeines Schema vorgeschlagen (Monomer-Dimer-Gleichgewicht, Thion-Thiol-Gleichgewicht, reversibles Thiol-Disulfid-Redoxsystem).

## Introduction

N-containing 6-membered heterocyclic thiones (**1–5**) are fundamentally tautomeric systems, and their properties have been the subject of systematic theoretical and experimental studies [1–9]. Various external factors (temperature, solvent, concentration, phase, *etc.*) influence the position of this tautomeric equilibrium [8, 10–12]. It is generally accepted [1, 13, 14] that in solution both pyridine and pyrimidine substituted at positions 2 and 4 by the potentially tautomeric SH-group exist in their thione rather than in their thiol form (Scheme 1).



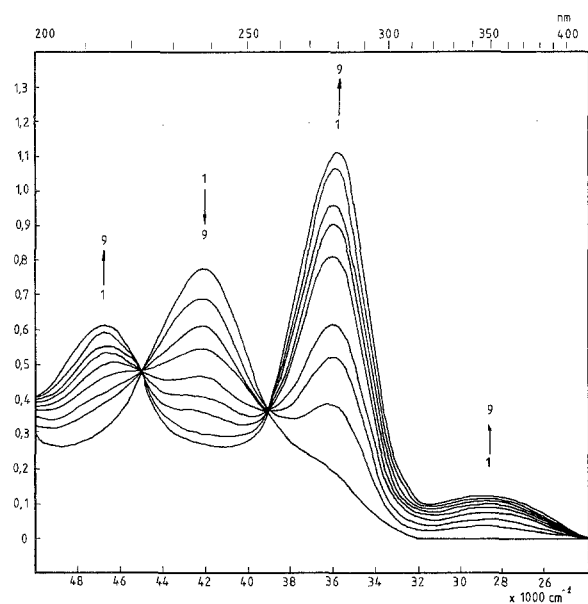
Scheme 1

On the other hand, the more active thiol group can easily be oxidized to the corresponding symmetrical disulfide. The disulfides in turn can easily be reduced to the initial thiols [15, 16].

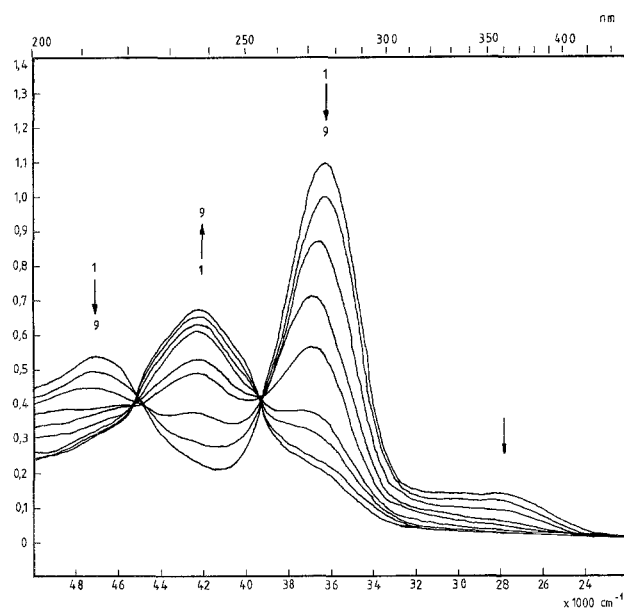
In our previous study [17] it was found that on standing at ambient laboratory conditions the thiones **1B–4B** are converted almost completely to the corresponding disulfides **6–9** (Scheme 1). Additional standing in the dark affords the initial thiols. This thione-disulfide redox system could be of some importance in biological aspects – in hormones, enzymes, proteins, pharmacologically active polypeptides, *etc.*, and may be pertinent to many aspects of their action [18, 19]. Therefore, the aim of this investigation is to study in detail the spectroscopic properties of the symmetrical disulfides and possible implications of the thiol form in the overall process of thione-disulfide transformation.

## Results and Discussion

The absorption spectra of disulfides **6–9** in water were monitored with time in order to follow the changes when the solutions were kept in dark. In all cases the spectral changes observed could be explained by a reduction of the initial disulfide to the



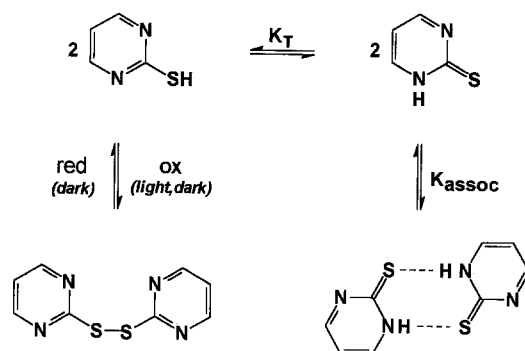
**Fig. 1.** Absorption spectra of **8** in water;  $c = 3.33 \times 10^{-5} M$ ,  $l = 1$  cm, recorded in the dark; 1: initial solution; 9: after 25 days



**Fig. 2.** Absorption spectra of **3** in water;  $c = 6.25 \times 10^{-5} M$ ,  $l = 1$  cm, exposed at indirect sunlight; 1: initial solution; 9: after 25 days

corresponding thione (Fig. 1), *i.e.* a process opposite to that observed with the initial thiones [17] exposed to indirect sunlight in the same solvent (Fig. 2).

Thus, solution of a thione is oxidized to the corresponding disulfide; on the other hand, a solution of a disulfide is reduced to the corresponding thione in the dark. It is important to note that upon changing the conditions (dark, light) the process can be reversed. This reversible thione-disulfide transformation can be represented by the following Scheme (Scheme 2).



According to Scheme 2, the thiol form is involved in the overall process of thione-disulfide transformation as a result of the thione-thiol tautomerism. Due to the greater reactivity of the thiol SH-group [15, 16] and the fast tautomeric transition [23], the relatively stable final forms – thiones or disulfides – are usually observed in the absorption spectra. The transformation in water is represented by a complex system composed of the following equilibria:

- thione monomer-dimer equilibrium,
- thione-thiol tautomeric equilibrium,
- reversible thiol-disulfide transformation.

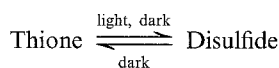
Taking into account the existence of these equilibria, it is possible to explain the observed concentration dependence in the thione-disulfide transformation. The oxidation process thione  $\rightarrow$  disulfide is strongly concentration dependent, whereas the reverse process is only weakly influenced. The self-association of thiones [10] is essential for the interpretation of the observed concentration dependence [17] of the thione-disulfide oxidation. Upon dilution, the monomer-dimer equilibrium (Scheme 2) is shifted from the dimeric species where only the thione dimer is observed to the monomeric ones where both tautomeric forms are possible. As the thiol-disulfide oxidation proceeds, all thione molecules are finally oxidized to the corresponding disulfide. In the opposite case, *i.e.* the disulfide-thione reduction, the rate of reduction in water has a tendency to increase with increasing of concentration, following the mass action law. The corresponding rate constants  $K_{\text{obs}}$  for the first order kinetics [24] of **6–9** and for the second order kinetics [24] of **1–4** in water calculated by the least-squares method are presented in Table 1.

In the polar solvent water the initial thione form dominates, but upon standing in dark the thione-disulfide oxidation takes place. This process is accelerated when the water solutions are exposed to indirect sunlight. The opposite is true for the disulfide-thione reduction, *i.e.* in the dark an almost complete transformation to thione takes place, whereas at indirect sunlight the reaction does not proceed. When the initial disulfide **7** is allowed to stay in the dark in water, an almost complete transformation to the thione **2B** is observed. Additional standing at indirect sunlight induces reversion to the initial disulfide **7** (Fig. 3).

**Table 1.** Rate constants of thione-disulfide transformations in water, measured at the long wavelength maxima of the thione forms

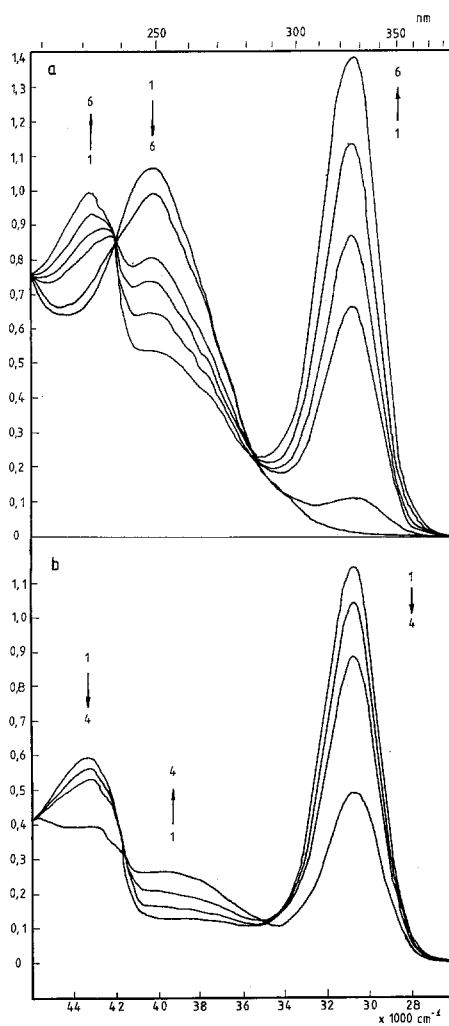
	$c$ (mol·l <sup>-1</sup> )	$K_{\text{obs}}$	$\tau_{1/2}$ (h)
<b>1</b> $\xrightarrow{\text{light}}$ <b>6</b>	$7.65 \times 10^{-5}$	$2.5 \pm 0.07 \times 10^{-2}$ (l·mol <sup>-1</sup> ·s <sup>-1</sup> )	143.98
<b>6</b> $\xrightarrow{\text{dark}}$ <b>1</b>	$1.36 \times 10^{-5}$	$4.66 \pm 0.02 \times 10^{-7}$ (s <sup>-1</sup> )	412.91
<b>2</b> $\xrightarrow{\text{light}}$ <b>7</b>	$5.95 \times 10^{-5}$	$4.40 \pm 0.1 \times 10^{-2}$ (l·mol <sup>-1</sup> ·s <sup>-1</sup> )	101.27
<b>7</b> $\xrightarrow{\text{dark}}$ <b>2</b>	$3.45 \times 10^{-5}$	$4.37 \pm 0.1 \times 10^{-7}$ (s <sup>-1</sup> )	439.65
<b>3</b> $\xrightarrow{\text{light}}$ <b>8</b>	$6.25 \times 10^{-5}$	$3.60 \pm 0.06 \times 10^{-2}$ (l·mol <sup>-1</sup> ·s <sup>-1</sup> )	123.17
<b>8</b> $\xrightarrow{\text{dark}}$ <b>3</b>	$3.33 \times 10^{-5}$	$3.69 \pm 0.02 \times 10^{-7}$ (s <sup>-1</sup> )	520.44
<b>4</b> $\xrightarrow{\text{light}}$ <b>9</b>	$5.33 \times 10^{-5}$	$3.50 \pm 0.1 \times 10^{-3}$ (l·mol <sup>-1</sup> ·s <sup>-1</sup> )	1484.75
<b>9</b> $\xrightarrow{\text{dark}}$ <b>4</b>	$2.60 \times 10^{-5}$	$1.65 \pm 0.02 \times 10^{-7}$ (s <sup>-1</sup> )	1167.30

Moreover, when almost all initial thione molecules of **2B** are converted to the corresponding disulfide **7**, additional standing in the dark leads to the formation of 40% of the initial thione form after 30 days. The estimated rate constants  $K_{\text{obs}}$  (Table 1) are in accordance with these observations, and the overall process can be represented as given below (Scheme 3).

**Scheme 3**

It should be noted that the thiol form is involved in the overall reversible process (Scheme 2), implying possible importance in biological systems where the cell thiol-disulfide redox system is present in various hormones, enzymes, proteins, and pharmacologically active polypeptides [16].

In order to clarify the factors affecting the overall thione-disulfide transformation in water, the acidity and basicity constants  $pK'_a$  and  $pK_a$  of the thiones **1B–5B** and the  $pK_a$  values of their corresponding disulfides **6–9** were determined (Table 2).

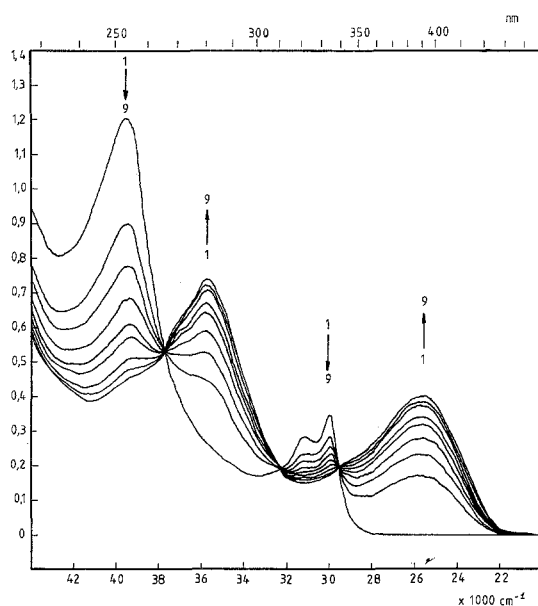


**Fig. 3.** a) Absorption spectra of **7** in water, recorded in the dark;  $c = 3.45 \times 10^{-5} M$ ,  $l = 2$  cm; 1: initial solution; 6: after 8 days; b) absorption spectra of disulfide **7**, converted in the dark to thione **2B** after exposure to indirect sunlight;  $l = 1$  cm; 1: thione **2B** (degree of conversion 88%); 4: after 17 days

**Table 2.**  $pK_a$  and  $pK'_a$  values of the investigated compounds

	proton gained		proton lost	
	$pK'_a$ (exp)	$pK'_a$ (lit)	$pK_a$ (exp)	$pK_a$ (lit)
<b>1B</b>	$-1.07 \pm 0.02$	$-1.07 \pm 0.07$ [6]	$9.87 \pm 0.03$	$9.97 \pm 0.03^a$ [6]
<b>2B</b>	$1.50 \pm 0.05$	$1.43 \pm 0.07$ [6]	$8.87 \pm 0.03$	$8.83 \pm 0.02$ [6]
<b>3B</b>	$1.31 \pm 0.02$	$1.35 \pm 0.03$ [7]	$7.21 \pm 0.01$	$7.14 \pm 0.05$ [7]
<b>4B</b>	$2.86 \pm 0.02$	$2.80^a$ [8]	$8.54 \pm 0.02$	$8.50^a$ [8]
<b>5B</b>	$-1.53 \pm 0.02$	$-1.44 \pm 0.09$ [6]	$10.16 \pm 0.03$	$10.21 \pm 0.04$ [6]
<b>6</b>	$2.46 \pm 0.03$	—	—	—
<b>7</b>	$4.40 \pm 0.04$	—	—	—
<b>8</b>	b	—	—	—
<b>9</b>	b	—	—	—
<b>10</b>	c	—	—	—

<sup>a</sup> Potentiometric determination; <sup>b</sup> protonated thione form is produced immediately; <sup>c</sup> insoluble in water



**Fig. 4.** Absorption spectra of **10** in EtOH recorded after polychromatic UV irradiation; 1:1 initial solution (time of irradiation: 10 s)

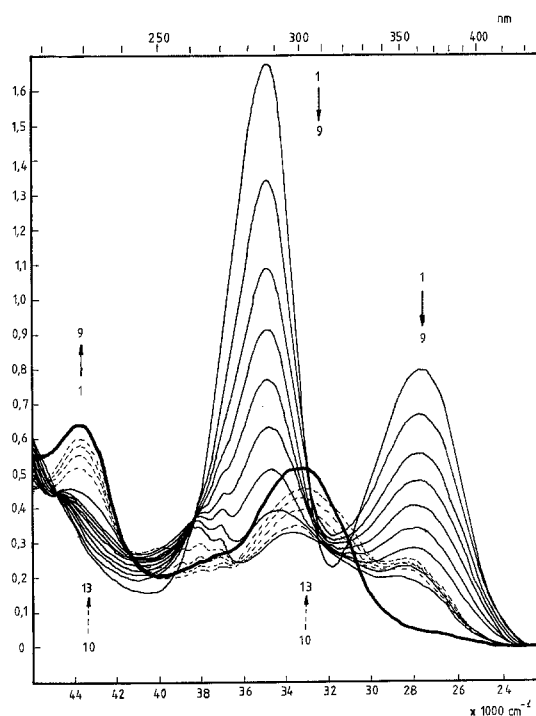
It was not possible to determine the  $pK'_a$  values for the disulfides **6–9** (**10** is not soluble in water), since in all cases the corresponding ionized thiones are formed immediately in alkaline medium. It is interesting to note that in acidic medium the disulfides **8** and **9** are also immediately converted to the corresponding protonated thiones **3B** and **4B** (cf. their absorption spectra). The observed reduction of the disulfides to the corresponding thiones in water is relevant with respect to the scission of the -S-S-bridge. Most probably, it is possible to observe this reversible thione-disulfide transformation due to the amphoteric character of water [25]. In all other solvents used in this study (EtOH, CH<sub>3</sub>CN, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>), the thiones are oxidized to the corresponding symmetrical disulfides to a greater or smaller extent, whereas the reverse process (reduction) is not observed. The oxidation process depends on the existence of the dissolved O<sub>2</sub> whose concentration in water is approximately 10<sup>-3</sup> M [26]. To verify this assertion, analogous experiments were carried out with degassed solutions of thiones. Here, the oxidation process does not proceed within 60 days.

In order to investigate the influence of polychromatic UV irradiation upon the thione-disulfide transformations, the absorption spectra of thiones **1B–5B** and their disulfides **6–10** in different solvents were examined before and after UV irradiation.

In EtOH, initial UV irradiation of disulfides **6–10** leads to formation of about 30–50% of the theoretically estimated thione concentration (Fig. 4), whereas irradiation of thiones **1B–5B** leads to complex products of photochemical degradation.

Only in the case of **1B** in EtOH it was possible to estimate the final product of the photochemical transformation (Fig. 5).

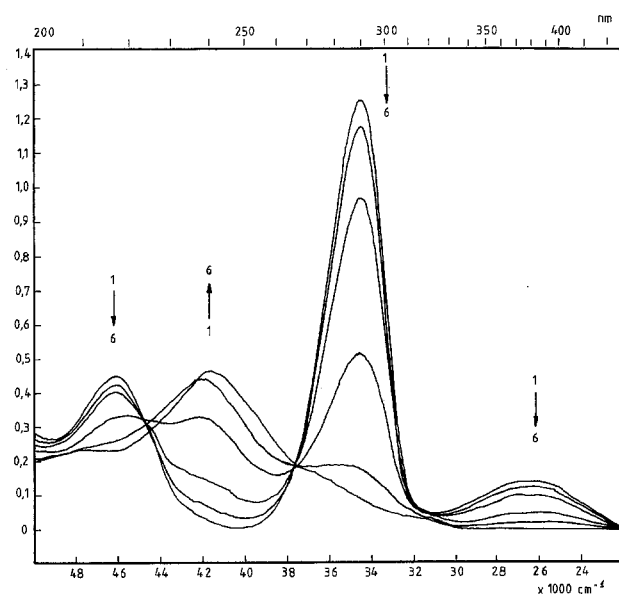
Initially, a decrease of the absorption maxima of the thione form at 287 and 364 nm and the appearance of vibrationally structured bands around 260 nm are observed. Further UV irradiation leads to formation of two new absorption maxima at 228 and 300 nm, corresponding very well to the absorption spectrum of 2-



**Fig. 5.** Absorption spectra of **1B** in EtOH;  $c = 6.73 \times 10^{-5} M$ ,  $l = 2$  cm; recorded after UV irradiation (time of irradiation: 60 s)

oxopyridine in EtOH. This is a direct experimental evidence that in solution 2-pyridinethione **1B** could be transformed to its O-analogue 2-oxopyridine after UV irradiation. It should be noted that 2-oxopyridine exists in its keto form in solution [1, 4, 7, 9], *i.e.* this transformation most probably proceeds *via* its enol form.

The observed changes of the investigated disulfides after UV irradiation in water are similar, but not as distinct as in the case of EtOH. Most probably, the initial step



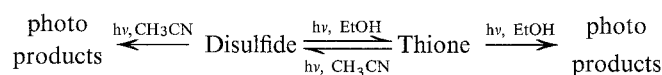
**Fig. 6.** Absorption spectra of **3B** in  $CH_3CN$  recorded after polychromatic UV irradiation; 1: initial solution (time of irradiation: 180 s)



of the photochemical transformation of the disulfides **6–9** is the formation of the corresponding thione. Further irradiation of the thione form, however, leads to its degradation, making the overall picture rather complex. Therefore, the UV irradiation of thiones **1B–5B** in different solvents could be pertinent for the elucidation of the possible photochemical transformations.

In CH<sub>3</sub>CN, initial UV irradiation of the thiones **1B–5B** leads to formation of the corresponding disulfides, most distinctly in pyrimidine derivatives **3B** and **4B** (Fig. 6).

Irradiation of disulfides **6–10** in CH<sub>3</sub>CN leads to a complex mixture of photo products, and their spectra are almost identical with those obtained after further irradiation of the thiones. These findings are opposite to the observations in EtOH and could be explained by Scheme 4:



Scheme 4

In the lower polar solvent dichloroethane, UV irradiation of **1B** and **2B** and their disulfides **6** and **7** leads to absorption spectra almost identical with those of the protonated disulfides. These observations are not unexpected, since the disulfides **6** and **7** are rather strong bases (Table 2). Most probably, the observed protonation in dichloroethane is due to its ability to produce photo radicals and consequently HCl upon UV irradiation [27]. In the case of thiones **3B–5B**, UV irradiation leads to the formation of their corresponding disulfides **8–10**.

The low solubility of the investigated thiones **1–5** in cyclohexane restricts most of the experiments, but it should be mentioned that UV irradiation of **1B** leads to formation of its disulfide **6**.

This investigation of the influence of UV irradiation on the thione-disulfide interchange is considered as preliminary. Further photochemical studies to clarify the nature of these transformations are in process.

## Experimental

For the purposes of the present investigation, the disulfides **6–10** were obtained from the corresponding thiones *via* oxidation with equimolar amounts of H<sub>2</sub>O<sub>2</sub> in water and recrystallized from aqueous ethanol. Elemental analyses melting points, [20, 21], and <sup>1</sup>H NMR spectra for compounds **6–10** are in accordance with those expected [17].

Pyridine-2-thione, pyrimidine-2-thione, 4,6-dimethylpyrimidine-2-thione (Fluka), chinoline-2-thione, and pyridine-4-thione (Aldrich) were purified following the procedures described to obtain analytically pure materials [20, 22]. The IR, NMR and absorption properties were consistent with those expected for the assigned structures.

UV/Vis absorption spectra were obtained at room temperature on Specord and PE Lambda 17 UV/Vis spectrophotometers with cells ranging from 0.1 to 5 cm. Spectroscopic grade solvents were used as received for all measurements.

## Acknowledgements

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