

Investigation of 8-mercaptoquinoline (thiooxine) and its derivatives

CXX. Synthesis and physicochemical properties of 6-methylthio-8-mercaptoquinoline

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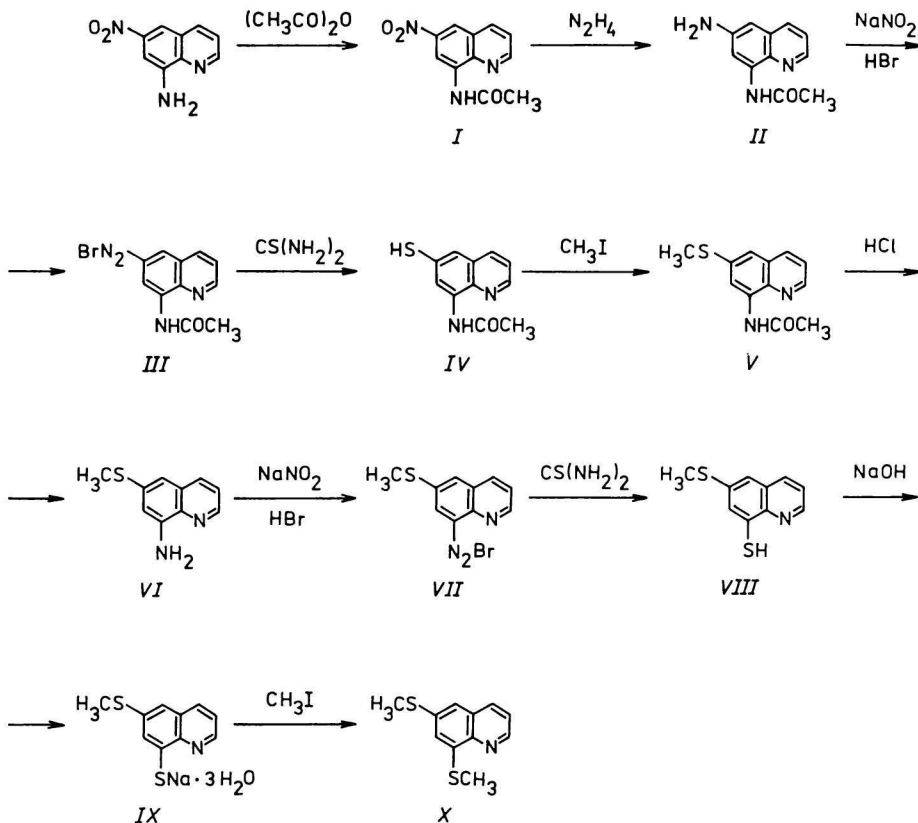
A new derivative of 8-mercaptoquinoline, 6-methylthio-8-mercaptoquinoline (*VIII*), has been synthesized and its electronic absorption spectra, ionization constants, as well as the extraction by organic solvents were investigated. The maxima in the electronic absorption spectra of *VIII* in comparison with 8-mercaptoquinoline (and especially with 6-methoxy-8-mercaptoquinoline) are shifted bathochromically. The main properties of the nitrogen atom in *VIII* are less pronounced than in 8-mercaptoquinoline, and also in 4-, 5-, and 7-methylthio derivatives. As regards the value of the constants of distribution between the organic solvents and water, *VIII* falls behind 2- and 5-, but surpasses 4- and 7-methylthio derivatives.

2-, 4-, 5-, and 7-methylthio derivatives of 8-mercaptoquinoline were synthesized earlier and their physicochemical properties have been investigated [1—3]. In continuation of these studies we concentrated on the investigation of 6-methylthio-8-mercaptoquinoline (*VIII*) the synthesis of which has not been described so far.

For the preparation of *VIII* 6-methylthio-8-aminoquinoline (*VI*) is necessary. Quite a complicated method of its synthesis from 6-chloro-8-aminoquinoline with the yield of 10 % is reported in [4]. One of the stages of synthesis is carried out in hydrogen atmosphere at the increased pressure.

For the preparation of *VI* we have developed a new method of synthesis from 6-nitro-8-aminoquinoline. In comparison with the above-mentioned procedure the number of stages was reduced and the yield increased to 33 %.

6-Methylthio-8-mercaptoquinoline (*VIII*) was obtained according to Scheme 1. At the preparation of *VI*, the amine group must be protected by means of acetylation. In the end of the synthesis the acetylamine group is hydrolyzed with 6 M hydrochloric acid.



Experimental

Absorption spectra of the reagents were recorded on a Specord UV—VIS spectrophotometer. Measurements of absorbance of solutions in connection with the determination of molar absorption coefficients and ionization constants were performed on a spectrophotometer SF 16. The concentration of hydrogen ions was measured using the pH-meter of the type M-25 (Radiometer, Copenhagen).

Organic solvents were distilled before use. The other applied reagents were of high purity or anal. grade quality.

6-Nitro-8-acetylaminoquinoline (I)

6-Nitro-8-aminoquinoline (10 g; 52.9 mmol) is dissolved on heating in chloroform (400 cm³), 7 cm³ of acetic anhydride are added and the solution is evaporated to *ca.*

150 cm³ The colour of the solution changes from red to yellow. The solution is cooled and the formed yellow precipitate is filtered off and dried in air. Yield = 11 g (95 %), m.p. = 237 °C. For C₁₁H₉N₃O₃ w_i(calc.): 57.14 % C, 3.92 % H, 18.17 % N; w_i(found): 57.47 % C, 3.80 % H, 18.40 % N.

6-Amino-8-acetylaminoquinoline (II)

The compound *I* (11 g; 47.6 mmol) is suspended in ethanol (250 cm³), ca. 2 g of the catalyst (palladium on charcoal) are added, as well as hydrazine hydrate (7.5 cm³), and it is kept simmering for 5 h. The solution is cooled, filtered off and diluted with water to 1 dm³ The formed compound *II* is filtered off, washed with water and dried in air. Yield = 7 g (75 %), m.p. = 166 °C. For C₁₁H₁₁N₃O w_i(calc.): 65.66 % C, 5.51 % H, 20.88 % N; w_i(found): 66.01 % C, 5.65 % H, 20.80 % N.

6-Methylthio-8-acetylaminoquinoline (V)

The compound *II* (7 g; 34.8 mmol) is dissolved in hydrobromic acid (50 cm³, 40–48 %), ice chippings are added (ca. 100 g) and the mixture is diazotized by adding 22.24 g of NaNO₂. After 10 min of stirring the solution of the diazonium salt *III* is poured into a solution of thiourea (14 g in 100 cm³ of water), which has been heated to 50 °C. The solution is stirred till the evolution of nitrogen is finished (ca. 15 min), then it is cooled and made alkaline with 20 % solution of NaOH to pH 9–10, heated till dissolution of the precipitate and filtered off. To the obtained solution of the sodium salt of 6-mercapto-8-acetylaminoquinoline (*IV*) the solution of methyl iodide (4.1 g) in ethanol (50 cm³) is added. The formed emulsion is extracted with chloroform, the extract is separated and the chloroform is evaporated on a steam bath. The yield of the dark, thick oil-like liquid was 6 g (70 %). For C₁₂H₁₂N₂SO w_i(calc.): 12.1 % N, 14.2 % S; w_i(found): 12.4 % N, 14.1 % S.

6-Methylthio-8-aminoquinoline (VI)

To the compound *V* (6 g; 25.8 mmol) obtained in the previous stage, concentrated hydrochloric acid (25 cm³) is added, heated till dissolution of the formed yellow precipitate and allowed to boil for 1–2 min, then the solution is cooled. The formed crystals of 6-methylthio-8-aminoquinolinium chloride are filtered off, washed with 3 cm³ of hydrochloric acid and dried in air. Yield = 4.0 g (70 %). For C₁₀H₁₁N₂SCl w_i(calc.): 52.98 % C, 4.89 % H, 12.35 % N; w_i(found): 52.70 % C, 5.01 % H, 12.11 % N.

Free *VI* obtained by hydrolysis of the chloride has m.p. = 75 °C (Ref. [4] gives m.p. = 76–78 °C).

6-Methylthio-8-mercaptoquinoline (VIII)

The chloride of *VI* (4 g; 17.6 mmol) is dissolved in hydrobromic acid (30 cm³) and is diazotized on cooling by ice through addition of 1.05 g of NaNO₂. After 10 min the solution of the diazonium salt *VII* is added into a heated solution of thiourea (6 g in 100 cm³ of water). The solution is heated and kept at 60 °C till the evolution of nitrogen ceases, then it is cooled and neutralized by 20 % NaOH to pH 9, warmed up to dissolution of the precipitate, filtered off and neutralized by 6 M-HCl to pH 5. Thus red crystals of *VIII* are formed. These are filtered off and dried in vacuum. Yield = 2.0 g (20 % relative to 6-nitro-8-aminoquinoline), m.p. = 99 °C. For C₁₀H₈NS₂ w_i(calc.): 57.94 % C, 4.38 % H, 6.76 % N, 30.93 % S; w_i(found): 57.60 % C, 4.40 % H, 6.90 % N, 30.66 % S.

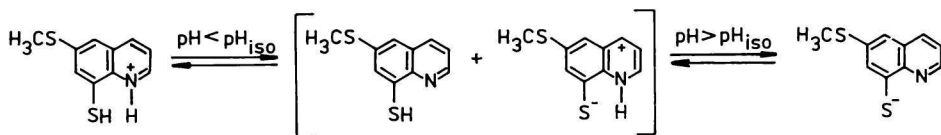
6,8-Dimethylthioquinoline (X)

The compound *VIII* (2 g; 9.6 mmol) is dissolved on heating in a minimum amount of ethanol, then made alkaline by 20 % solution of NaOH till a yellow solution is obtained and filtered off while hot. On cooling yellow crystals of the sodium salt of 6-methylthio-8-mercaptoquinoline (*IX*) precipitate, which are filtered off, washed with ethanol, chloroform and dried in air. The yield is 80 %. For C₁₀H₈NS₂Na · 3 H₂O w_i(calc.): 42.39 % C, 4.98 % H, 4.94 % N, 22.63 % S, 19.07 % H₂O; w_i(found): 42.55 % C, 4.60 % H, 5.10 % N, 22.85 % S, 18.50 % H₂O.

The compound *X* with m.p. = 103 °C is obtained by methylation of the aqueous solution of *IX* by methyl iodide. For C₁₁H₁₁NS₂ w_i(calc.): 60.12 % C, 5.10 % H, 6.17 % N, 29.07 % S; w_i(found): 60.12 % C, 5.20 % H, 6.70 % N, 29.30 % S.

Discussion

Physicochemical properties of 6-methylthio-8-mercaptoquinoline (*VIII*) have been studied. This compound exists in aqueous solutions in dependence on pH, in the protonated (RH₂⁺), neutral (RH and RH^{+·}) and ionized (R⁻) forms (Scheme 2).



Scheme 2

Electronic absorption spectra

In Fig. 1 the absorption spectra of various forms of *VIII* in aqueous solutions are shown. These spectra of the protonated and ionized form are characterized

by two absorption maxima, the neutral forms by four ones. A large bathochromic shift is observed in comparison with 8-mercaptoquinoline and many of its derivatives ([5], p. 50). It is explained by conjugation of the methylthio group with the quinoline ring, which results in diminishing of the excitation energy of the π -electron system. Conjugation increases on protonation of the nitrogen atom, which leads to an especially large bathochromic shift of the absorption maxima in the spectrum of the protonated form of *VIII* in comparison with 8-mercaptoquinoline. As regards the value of the bathochromic shift of the absorption maxima, *VIII* is surpassed only by the 5-alkyl derivatives of 8-mercaptoquinoline.

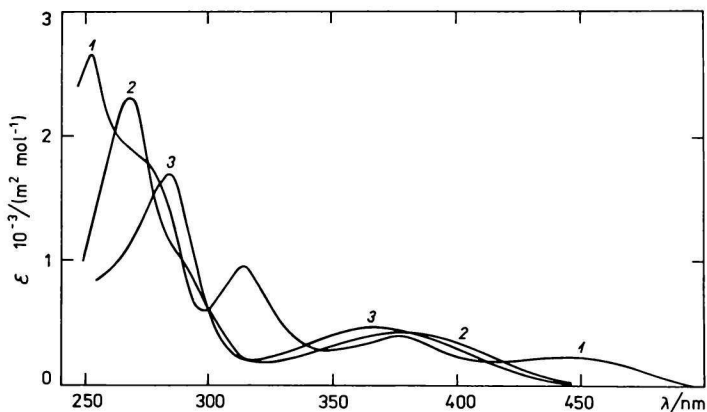


Fig. 1. Absorption spectra of 6-methylthio-8-mercaptoquinoline in aqueous solutions. 1. pH 4.9; 2. 2 M-HCl; 3. 1 M-NaOH.

Table 1

Absorption maxima and molar absorption coefficients of various forms of 6-methylthio-8-mercaptoquinoline in aqueous solutions

Form	Medium	λ_{max} nm	ϵ $\text{m}^2 \text{mol}^{-1}$
R^-	1 M-NaOH	284	1690
		367	470
RH_2^+	3 M-HCl	267	2310
		386	390
$\text{RH} + \text{RH}^{+-}$	pH 5	252	2650
		314	960
		372	385
		443	220
RH^{+-}	pH 5	443	226

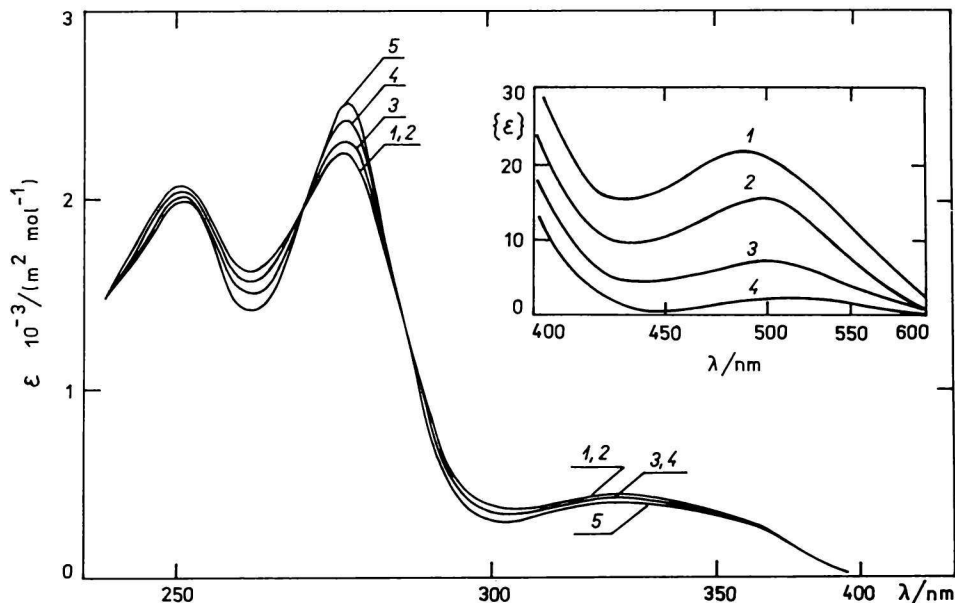


Fig. 2. Absorption spectra of 6-methylthio-8-mercaptoquinoline in organic solvents. 1. Methanol; 2. ethanol; 3. 1-propanol; 4. 1-butanol; 5. chloroform.

The molar absorption coefficients of the absorption maxima for VIII (Table 1) are lower than those of other 6-substituted derivatives of 8-mercaptoquinoline.

In the absorption spectra of VIII in nonpolar organic solvents, in which the reagent exists in the thiol form [6], three absorption maxima are present (Fig. 2). In the polar organic solvents (in aliphatic alcohols) together with the maxima of the thiol form a low-intensity absorption maximum of the zwitter-ionic form

Table 2

Absorption maxima (λ_{\max}/nm) and molar absorption coefficients ($\epsilon/(\text{m}^2 \text{mol}^{-1})$) of 6-methylthio-8-mercaptoquinoline in organic solvents

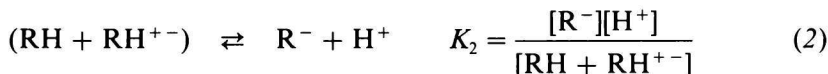
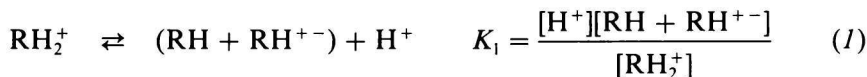
Solvent	λ_{\max}	ϵ	λ_{\max}	ϵ	λ_{\max}	ϵ	λ_{\max}	ϵ
Chloroform	252	2040	274	2540	324	430		
Hexane	253	2040	276	2300	326	450		
Methanol	252	2030	274	2280	323	460	486	22
Ethanol	252	2050	274	2290	325	455	496	16
1-Propanol	252	2000	275	2400	326	440	500	7.5
1-Butanol	252	2100	275	2470	326	430	504	2.5

(RH^{+-}) appears. The band in the range of $\lambda = 320\text{--}370$ nm is greatly blurred due to the fact that it consists of overlapping α - and p -bands.

The position of the absorption maxima of *VIII* in the organic solvents (Table 2) approximately coincides with the absorption maxima of other investigated 6-substituted derivatives of 8-mercaptoquinoline, nevertheless, the molar absorption coefficients are by 10–30 % lower.

The ionization constants

The protolytic equilibria existing in the aqueous solutions of *VIII* are characterized by the ionization constants K_1 and K_2



The ionization constants K_1 , K_2 , and those of the 8-methylthio derivative $K_{\text{NH}^+}^{\text{SCH}_3}$ are determined spectroscopically. The individual ionization constants are calculated (K_A , K_B , K_C , K_D), as well as the tautomerization constant K_t (Table 3).

Table 3

Total and individual ionization constants and the tautomerization constant of 6-methylthio-8-mercaptoquinoline. $\theta = 20^\circ\text{C}$, $I = 0.01 \text{ mol dm}^{-3}$, content (RH^{+-}) = 97.2 %

$\text{p}K_1$	$\text{p}K_2$	$\text{p}K_A$	$\text{p}K_B$	$\text{p}K_C$	$\text{p}K_D$	$\text{p}K_{\text{NH}^+}^{\text{SCH}_3}$	pH_{iso}	K_t
1.64	8.16	1.65	3.19	8.15	6.61	3.19	4.90	34.5

The main properties of the nitrogen atom in the molecule of *VIII* are less pronounced than in the molecules of 6-methyl-8-mercaptoquinoline ($\text{p}K_1$ 2.11, $\text{p}K_2$ 8.49, $\text{p}K_A$ 2.32, $\text{p}K_B$ 3.86, $\text{p}K_C$ 8.56, $\text{p}K_D$ 7.01 [7]) and 6-methoxy-8-mercaptoquinoline ($\text{p}K_1$ 1.95, $\text{p}K_2$ 8.56, $\text{p}K_A$ 1.96, $\text{p}K_B$ 3.76, $\text{p}K_C$ 8.55, $\text{p}K_D$ 6.75 [8]), however they are more pronounced than in the molecules of 6-chloro-8-mercaptoquinoline ($\text{p}K_1$ 1.14, $\text{p}K_2$ 7.52, $\text{p}K_A$ 1.15, $\text{p}K_B$ 2.70, $\text{p}K_C$ 7.51, $\text{p}K_D$ 5.96 [9]) and 6-bromo-8-mercaptoquinoline ($\text{p}K_1$ 1.15, $\text{p}K_2$ 7.58, $\text{p}K_A$ 1.16, $\text{p}K_B$ 2.75, $\text{p}K_C$ 7.57, $\text{p}K_D$ 5.98 [10]). The acidic properties of the sulfhydryl group in the molecule of *VIII* are more expressive than in the molecules of 6-methyl- resp.

6-methoxy-8-mercaptoquinoline and less expressive than in the molecules of 6-chloro- resp. 6-bromo-8-mercaptoquinoline. It points to the fact that the negating effect of the methylthio group manifests itself between the methyl and methoxy groups and the negating effect of the halogen atoms.

On increasing ionic strength of the aqueous solution the ionization constants of *VIII* change in the manner shown in Fig. 3.

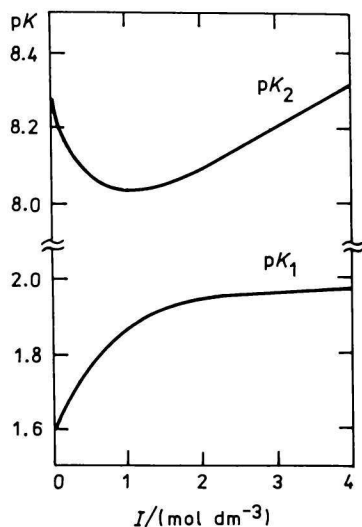


Fig. 3. Dependence of ionization constants of 6-methylthio-8-mercaptoquinoline on the ionic strength of the solution.

The extraction by organic solvents and the distribution constants

In Fig. 4 the dependence of the extractability of *VIII* by some organic solvents upon the hydrogen ion concentration in the aqueous phase is shown which increases in the order hexane, benzene, chloroform.

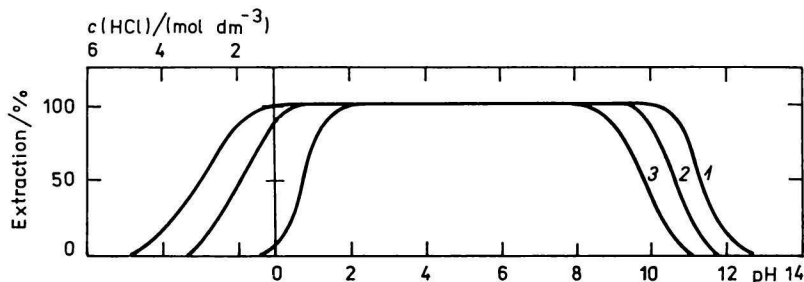


Fig. 4. Extraction of 6-methylthio-8-mercaptoquinoline by organic solvents in dependence on the acidity of the aqueous phase. 1. Chloroform; 2. benzene; 3. hexane.

The distribution constants of VIII in organic solvents and water have been found using ionization constants of the reagent in the aqueous solution and in the two-phase system ([5], p. 97)

$$K_D = \frac{K_2}{K'_2} \quad \text{where} \quad K'_2 = \frac{[H^+]_w[R^-]_w}{[RH]_o} \quad (3)$$

K'_2 being the two-phase ionization constant.

Table 4

pH ranges of the maximum extraction and the distribution constants
of 6-methylthio-8-mercaptoquinoline
 $\theta = 20^\circ\text{C}$, $I = 0.1 \text{ mol dm}^{-3}$

	Chloroform—water	Benzene—water	Hexane—water
pH	0—10.0	1.0—9.0	2.0—8.0
K_D	1380	262	47

The distribution constants of VIII (Table 4) are considerably higher than those of 8-mercaptoquinoline ([5], p. 98). The values of the distribution constants of the methylthio derivatives of 8-mercaptoquinoline decrease in the sequence: 2-, 5-, 6-, 4-, 7-methylthio. Diminishing of the distribution constants in this sequence is explained by the increase of the concentration of the zwitterionic form of the reagents, the K_1 of which is equal to 2, 11.9, 34.5, 12.2, 700, respectively. The zwitterionic form of the reagents lowers the distribution constants because it hydrates greatly and hinders the transition of molecules into the aqueous phase.

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