A STUDY OF 8-MERCAPTOQUINOLINE (THIOOXINE) AND ITS DERIVATIVES

XXXIX. Absorption Spectra, Ionization Constants, and Some Other Properties of 5-Fluoro-8-mercaptoquinoline*

Yu. A. Bankovskii, M. R. Buka, G. P. Mezharaups, A. F. Ievin'sh, and
M. Ya. Abolinya

Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 1, pp. 144–151, 1968

UDC 547.831.7'78:543.422.6:541.132

The absorption spectra of 5-fluoro-8-mercaptoquinoline in aqueous solutions at various pH values have been studied. The ε_{max} values of the 5-fluoro-8-mercaptoquinolinium ion and also of the 5-fluoro-8-mercaptoquinolate ion, and the apparent molar absorption coefficient of the hydrated form have been determined. In the hydrated form, a molecule of water is connected by hydrogen bonds both with the nitrogen and with the mercapto group. The presence of the fluorine atom in positions 5 of the molecule of the 8-mercaptoquinoline increases the acidic properties of the mercapto group and decreases the basic properties of the nitrogen, in comparison with those in 8-mercaptoquinoline. The dissociation constants of 5-fluoro-8-mercaptoquinoline are $pK_{SH} = 7.49 \pm 0.02$ (thermodynamic) and $pK_{NH} = 1.97 \pm 0.02$ (concentration). The isoelectric point is at pH 4.70.

8-Mercaptoquinoline and some of its derivatives are promising analytical reagents. A study of the influence of various substituents in the molecule of 8-mercaptoquinoline is important for increasing our knowledge in the field of the theory of the action of organic analytical reagents. In the present work we have studied the influence of a fluorine atom in position 5 on the properties of the molecule of 8-mercaptoquinoline.

The 5-fluoro-8-mercaptoquinoline [1] was used as the sodium salt $C_9H_5FNSNa \cdot 2H_2O$, which forms lemon yellow crystals. All the salts used in the work (the components of the buffer mixtures) were freed from traces of heavy metals, solutions of alkalis were freed from carbonate, and the acids and solvents were redistilled.

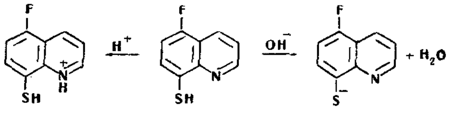
The spectrophotometric measurements were carried out in 1-cm quartz cells on SF-4 and SFD-1 spectrophotometers. The solvent was placed in the comparison cell. Potentiometric titrations were carried out on a "Radiometer" (Denmark) automatic recording apparatus. A TTT 1 automatic titrator with a TTA 2 titrating device fitted with a 0.5-ml plunger microburette with an accuracy of delivery of 0.0002 ml was used. The titration curves were recorded on a SBR 2/SBU 1 automatic titrigraph. The speed of the paper strip was 1 cm per 0.5 pH unit, which gave an accuracy of recording of ±0.03 pH unit. Both instruments were previously calibrated by means of a compensation pH meter of the PHM-4 type ("Radiometer") with an instrumental error of ±0.002 pH unit. However, the instruments were calibrated with an accuracy of ±0.02 pH unit (buffer solutions or tablets with pH 4.01 ± 0.02, 6.50 ± 0.02, and 9.20 ± 0.02) because of the absence of more accurate pH standards. Glass electrodes of types G 202B, G 202C, and G 200B were used as indicator electrodes; these possess a small sodium error in the alkaline region, which was taken into account. We used K-100 saturated calomel electrodes of the flow type as comparison electrodes. The TTT_1 titrator has a linear scale in the pH range from 1 to 12 and the PHM-4 in the range from 0 to 14.

The experiments described below were carried out at 20° C. The concentration of ethanol in the solutions is given in percentages by weight in all cases.

ABSORPTION SPECTRA OF 5-FLUORO-8-MERCAPTOQUINOLINE IN AQUEOUS SOLUTIONS AT VARIOUS pH VALUES

Weighed samples of the sodium salt of 5-fluoro-8-mercaptoquinoline were dissolved in buffer mixtures ($\mu = 0.1$) with the required pH value. In the case of strongly acid or strongly alkaline solutions, hydrochloric acid or alkali of the necessary concentration was used. The solvent was placed in the comparison cell. The absorption curves of 0.0001 M solutions are given in Fig. 1, from which it can be seen that there are six isobestic points in the absorption spectra of 5-fluoro-8-mercaptoquinoline: at 253, 270, 297, 330, 400, and 427 nm. The absorption curves form two groups of greatly differing intensity. The absorption maxima to the left of the isobestic point at 297 nm are due to the quinoline nucleus and are apparently caused by π-π* transitions. The maxima to the right of the isobestic point (297 nm) are probably due to a n-π* transition as a result of the interaction of the unshared electron pair of the nitrogen atom with the C═N double bond.

5-Fluoro-8-mercaptoquinoline is an amphoteric compound. At a pH below the isoelectric point it forms 5-fluoro-8-mercaptoquinolinium ions (λ_{max} 245, 316, and 345 nm); at a pH above the isoelectric point it forms 5-fluoro-8-mercaptoquinolinate ions (λ_{max} 261 and 378 nm).



At the isoelectric point (see below) in aqueous solutions 5-fluoro-8-mercaptoquinoline forms a hydrate giving yellow-orange solutions (λ_{max} 279 and 470 nm).

---

*For part XXXVIII, see [4].

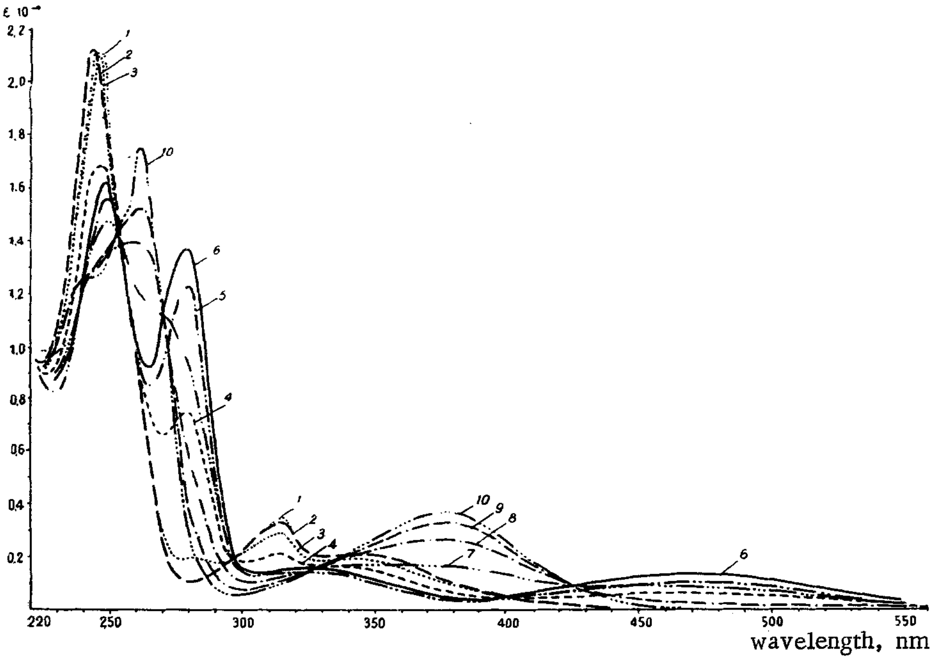


Fig. 1. Absorption spectra of aqueous solutions of 5-fluoro-8-mercaptoquinoline at various concentrations of hydrogen ions: 1 — 6 N HCl; 2 — pH 0; 3 — pH 0.9; 4 — pH 1.9; 5 — pH 2.65; 6 — pH 4.0; 7 — pH 7.1; 8 — pH 7.6; 9 — pH 8.3; 10 — pH 13.

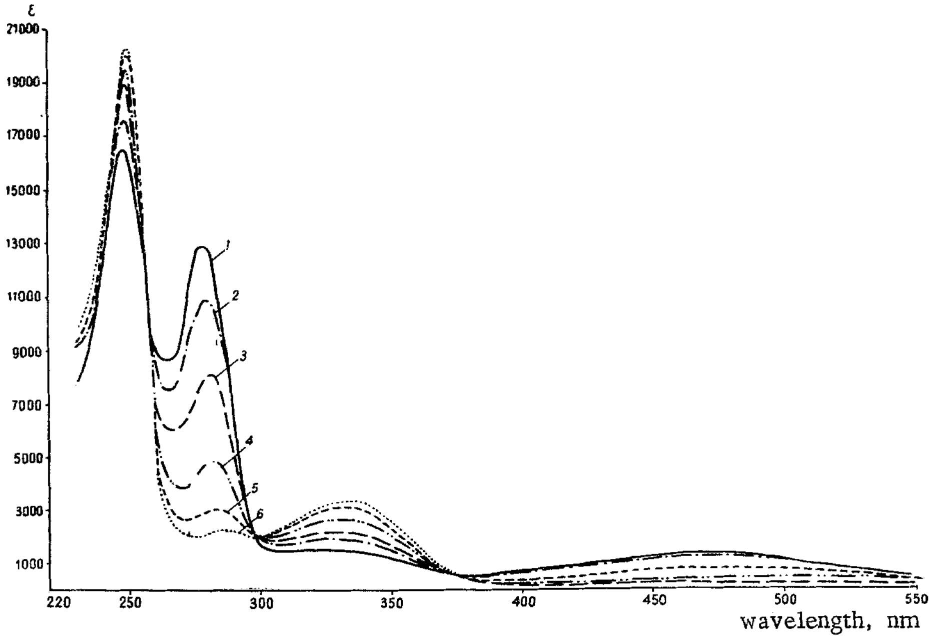


Fig. 2. Absorption spectra of 5-fluoro-8-mercaptoquinoline in mixtures of water and ethanol: 1) aqueous solution, pH 4.70; 2) 10% ethanol, pH 4.75; 3) 20% ethanol, pH 4.80; 4) 30% ethanol, pH 4.80; 5) 40% ethanol, pH 4.80; 6) 50% ethanol, pH 5.10.

The capacity for decomposition of the hydrate at pH values above and below the isoelectric point and the fact that 5-fluoro-8-methylthioquinoline is incapable of forming a hydrate shows that in the hydrate the molecule of water is connected both to the nitrogen atom and to the mercapto group. In agreement with the structure of the hydrate of 8-mercaptoquinoline established previously [2], the hydrate of the fluoro derivative also has a cyclic structure.

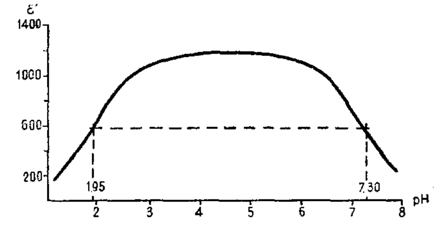
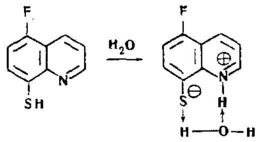


Fig. 3. Formation of hydrated 5-fluoro-8-mercaptoquinoline as a function of the pH of an aqueous solution. The measurements were carried out at the absorption maximum of the hydrated form at 470 nm.



As can be seen from the absorption curves of 5-fluoro-8-mercaptoquinoline in mixtures of water and ethanol (Fig. 2), an increase in the concentration of ethanol in the aqueous phase leads to an increase in the absorption maximum at 331 nm and a decrease in those at 279 and 470 nm, i. e., the concentration of the neutral anhydrous form increases and that of the hydrated molecules decreases. This indicates that the absorption maximum at 331 nm in aqueous solutions at the isoelectric point of 5-fluoro-8-mercaptoquinoline is due to the anhydrous neutral form.

Table 1

Molar Absorption Coefficients of the Ions $C_9H_5FNS^-$ and $C_9H_6FSNH^+$ and the Hydrated Forms of 5-Fluro-8-mercaptoquinoline in Aqueous Solutions at the Absorption Maxima

Form of the reagent in the solution	Medium	λ_{max}, nm	ε
$C_9H_5FNS^-$	pH 14	261 378	17400±200 3650±10
$C_9H_6FSNH^+$	6 *N* HCl	245 316 345	21300±150 3440±20 2070±40
$C_9H_6FNS \cdot H_2O$	pH 4.7	279 331 470	13200±100* 1410±100* 1230±80*

*The apparent molar absorption coefficients were calculated from the total concentration of the reagent in the solution.

The molar absorption coefficients for the $C_9H_9FNS^-$ and $C_9H_6FSNH^+$ ions and the apparent molar absorption coefficients of the hydrated form (calculated from the total concentration of the reagents in the solution) are given in Table 1.

The solubilities of 5-fluoro-8-mercaptoquinoline in water at the isoelectric point (acetate buffer solution with μ = 0.2 and pH 4.7) and in isooctane were found spectrophotometrically: $2.67 \cdot 10^{-3}$ mole/*l* and 0.34 mole/*l*, respectively.

Table 2

Determination of pK_{SH} of 5-Fluoro-8-mercaptoquinoline by the Spectrophotometric Method

pH	$[R_{tot}] \cdot 10^4$	$[RH \cdot H_2O] \cdot 10^4$	$[R^-] \cdot 10^4$	pK_{SH}
7.00	5.90	3.90	2.00	7.44
7.20	6.61	3.26	3.35	7.43
7.40	7.11	3.24	3.87	7.43
7.40	7.58	3.42	4.16	7.43
7.60	7.01	2.58	4.63	7.45

Mean $pK_{SH} = 7.44 \pm 0.02$

IONIZATION CONSTANTS OF 5-FLUORO-8-MERCAPTOQUINOLINE

a) Dependence of the formation of the hydrate on the pH of the aqueous phase, and the graphical spectrophotometric method for determining pK_{SH} and pK_{NH}. Because of its existence in aqueous solutions in the form of the colored hydrate, with a change in the pH the reagent behaves as an indicator. The intensity of the absorption maximum of the hydrated form ($RH \cdot H_2O$) changes linearly with a change in the pH of the solution. At a pH above the isoelectric point the practically un-ionized hydrated form is present in equilibrium with 5-fluoro-8-mercaptoquinolinate ions (R^-) and at a pH below the isoelectric point it is in equilibrium with 5-fluoro-8-mercaptoquinolinium ions (RH_2^+). Figure 3 shows the formation of hydrated 5-fluoro-8-mercaptoquinoline as a function of the pH of an aqueous solution. It is possible to evaluate the ionization constants and the isoelectric point of the reagent from the curve of the formation of the hydrate with adequate reliability. The point of intersection of the mean line (between the horizontal axis of coordinates and the maximum formation of hydrate) with the curve of the optical density as a function of the pH corresponds to the pH at which $[R^-] = [RH_2^+] = [RH \cdot H_2O]$. Under these conditions, as is well known,

Table 3

Determination of pK_{NH} of 5-Fluoro-8-mercaptoquinoline by the Spectrophotometric Method

pH	$[R_{tot}] \cdot 10^4$	$[RH \cdot H_2O] \cdot 10^4$	$[RH_2^+] \cdot 10^4$	pK_{NH}
2.06	6.16	3.38	2.78	1.97
1.93	6.21	3.02	3.19	1.96
1.97	6.75	3.35	3.40	1.98
1.77	6.88	2.68	4.20	1.97
1.58	7.47	2.18	5.29	1.97
2.20	8.16	5.19	2.97	1.96

Mean $pK_{NH} = 1.97 \pm 0.02$

pH = pK. It can be seen from Fig. 3 that $pK_{SH} \approx 7.30$ and $pK_{NH} \approx 1.95$. The mean intercept on the pH scale in the pH range from 1.95 to 7.30 is the isoelectric point, which is $pH_{isoel} = 4.8$.

The ionization constants can be determined more accurately [3] if the light-absorption measurement is carried out at the considerably stronger maximum of the $C_9H_5FNS^-$ or $C_9H_6FSNH^+$ ions. For example, the value of pK_{SH} obtained by this method for 5-fluoro-8-mercaptoquinoline at λ_{max} 378 nm is 7.34.

b) Spectrophotometric method with a calibration graph. The above-described variant of the spectrophotometric method can be used more accurately if the determination of the concentration of the hydrated form is carried out from a previously plotted calibration graph. This is possible in the present case since at the wavelength corresponding to the absorption maximum of the neutral particle $RH \cdot H_2O$, as can be seen from Fig. 1, the R^- and RH_2^+ ions have practically no absorption. The calibration graphs are plotted by using acetate buffers with pH_{isoel} (see above) and an ionic strength of 0.01. The measurements of the optical density of the solutions were carried out at the absorption maximum of $RH \cdot H_2O$.

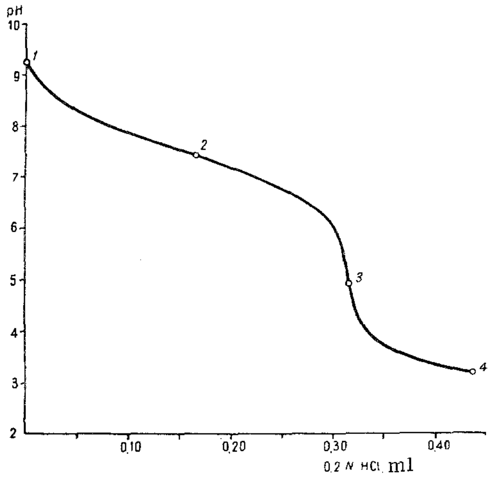


Fig. 4. Potentiometric titration curve of 5-fluoro-8-mercaptoquinoline.

At pH values above and below the isolectric point, the hydrated form and the anhydrous form (RH) (which are practically undissociated) are in equilibrium with the ionized and protonated forms of the reagents. Since the ratio $[RH \cdot H_2O]/[RH]$ for dilute solutions can be regarded as constant and independent of the pH and ionic strength of the solution, the concentration of the anhydrous form of the reagent need not be taken into account.

The acid dissociation constant of the protonated form of the reagent is

$$K_{NH} = \frac{[RH \cdot H_2O] \cdot [H^+]}{[RH_2^+]}, \tag{1}$$

or in the logarithmic form

$$pK_{NH} = pH - \log \frac{[RH \cdot H_2O]}{[RH_2^+]}. \tag{2}$$

To calculate $[R^-]$ and $[RH_2^+]$ it is sufficient to determine the concentration of the hydrated form $[RH \cdot H_2O]$, alone. At a known total concentration of the reagent

$$[R^-] = C_{tot} - [RH \cdot H_2O] \text{ at } pH > pH_{isoel}, \tag{3}$$

$$[RH_2^+] = C_{tot} - [RH \cdot H_2O] \text{ at } pH < pH_{isoel}. \tag{4}$$

To determine pK_{SH} by the spectrophotometric method, a weighed sample of the sodium salt of the reagent was dissolved in 2 ml of water and made up to 50 ml in a measuring flask with a buffer solution having the required pH and an ionic strength of 0.01.

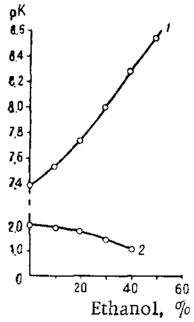


Fig. 5. Ionization constants of 5-fluoro-8-mercaptoquinoline as functions of the concentration of ethanol: 1) pK_{SH}; 2) pK_{NH}.

Acetate, borate, or HCl-KCl buffer mixtures were used, depending on the pH. The light absorption of the solution at the absorption maximum of the hydrate approximately in the center of the fall of the curve of the formation of the hydrate was measured and the concentration of the hydrated (neutral) form was determined from the above-mentioned calibration graph. The concentrations $[R^-]$ and $[RH_2^+]$ were calculated from Eqs. (3) and (4). The pH of the solution was checked potentiometrically after the optical density had been measured. The results of the determinations are given in Tables 2 and 3.

Table 4

Distribution Coefficients of 5-Fluoro-8-mercaptoquinoline between Organic Solvents and Water ($\mu = 0.1$) and the Isoelectric Point (Temperature 20 ± 0.5° C).

Solvent	Dielectric constant	K_{dist}
Isooctane	1.94	130±10
CCl_4	2.24	~ 700
C_6H_6	2.28	~1300
$CHCl_3$	5.05	~1500

c) Potentiometric method. A weighed sample of the sodium salt of 5-fluoro-8-mercaptoquinoline (10–15 mg) was dissolved in 26 ml of water and titrated with 0.2–0.4 N hydrochloric acid using the apparatus

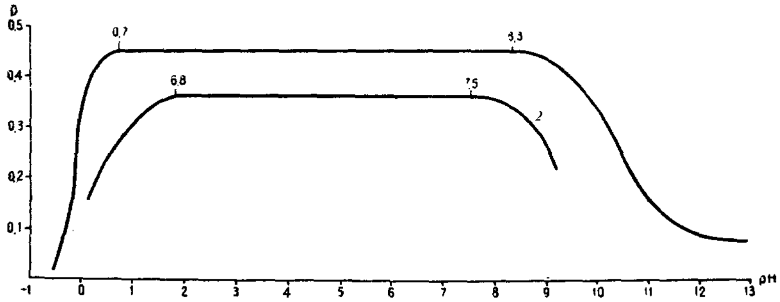


Fig. 6. Extractability of 5-fluoro-8-mercaptoquinoline with organic solvents as a function of the pH of the aqueous phase: 1) benzene; 2) isooctane.

mentioned above. The titration curve is shown in Fig. 4. Between points 1 and 2, the 5-fluoro-8-mercaptoquinolinium ion is being titrated. The yellow color of the solution gradually becomes orange because of the conversion of the ion $C_9H_5FNS^-$ (R^-) into the hydrate $C_9H_5FNSH \cdot H_2O$ ($RH \cdot H_2O$). At point 3, the $C_9H_5FNS^-$ ion has been completely destroyed. This point is the isoelectric point where the reagent exists in the form of the hydrate in equilibrium with the anhydrous form. In the range from point 3 to point 4, the formation of the ion $C_9H_6FSNH^+$ (RH_2) takes place and the solution gradually becomes yellow again. At point 2, half the $C_9H_5FN^-$ ion is neutralized, i.e., half the amount of 5-fluoro-8-mercaptoquinoline taken is present in the form of $C_9H_5FNS^-$ and half in the neutral form (hydrate plus anhydrous form), so that pK_{SH} = pH. In addition to the graphical method, a numerical method was also used in the range of the buffer region. Numerous determinations gave $pK_{SH} = 7.41 \pm 0.03$.

To calculate the thermodynamic ionization constant with respect to the mercapto group, we must take into account the activity of the ions at the ionic strengths of the solution under the experimental conditions

$$pK_{SH}^{t} = pK_{SH} + \log \gamma_{R^-}. \tag{5}$$

To extrapolate the ionic strength to zero, i.e., to calculate the correction factor for the activity of the R^- ions at a given ionic strength, we may use the Debye-Hückel formula (provided that μ does not exceed 0.01).

$$\log \gamma = \frac{0.506\sqrt{\mu}}{\mu}. \tag{6}$$

The spectrophotometric determinations were carried out in buffer solutions with $\mu = 0.01$. Calculation by the Debye-Hückel formula gives a correction factor of 0.05. Thus, the logarithm of the thermodynamic ionization constant is

$$pK_{SH}^{t} = 7.44 + 0.05 = 7.49 \pm 0.02.$$

The thermodynamic value of pK_{NH} cannot be calculated because of the necessity of an ionic strength of the aqueous solution greater than 0.01.

The isoelectric point is

$$pH_{isoel} = \frac{pK_{SH} + pK_{NH}}{2} = \frac{7.44 + 1.97}{2} = 4.70.$$

These results are in good agreement with those obtained from the range of formation of the hydrate of 5-fluoro-8-mercaptoquinoline.

The influence of the concentration of ethanol on the ionization constants pf 5-fluoro-8-mercaptoquinoline is shown in Fig. 5. The values of pK_{SH} at various concentrations of ethanol were determined potentiometrically and those of pK_{NH} spectrophotometrically.

Dependence of the extractability of 5-fluoro-8-mercaptoquinoline by organic solvents on the pH of the aqueous phase. Two milliliters of an aqueous solution of the sodium salt of 5-fluoro-8-mercaptoquinoline was added to a separating funnel containing 20 ml of buffer solution and the mixture was extracted with 10 ml of benzene or isooctane with vigorous shaking for 4 min. After filtration through a wad of cotton wool, the extract was measured photometrically at the absorption maximum (in benzene 338 nm, in isooctane 341 nm). As can be seen from Fig. 6, the range of quantitative extraction (horizontal sections of the curves) is greater in the case of benzene (pH 0.7–8.3) than in the case of isooctane (pH 1.8–7.5) because of the better solubility and higher distribution coefficient of the reagent in benzene. The center of the section of quantitative extraction on the pH scale is the isoelectric point. From the range of extraction with benzene, a value $pH_{isoel} = 4.5$ was obtained, and in the case of isooctane a value $pH_{isoel} = 4.65$. These figures agree satisfactorily with the value calculated from the ionization constants.

Distribution in aqueous phase—organic solvent systems. As has been mentioned above, in aqueous solutions at the isoelectric point 5-fluoro-8-mercaptoquinoline exists to a considerable extent in the hydrated form. However, in water immiscible organic solvents the reagent passes into the anhydrous form.

Aqueous solutions of the reagent contain not only the anhydrous form [RH] and the hydrated form [RH · H_2O] but also the ions [RH_2^+] and [R^-]. The distribution coefficient is expressed by the equation

$$K_{dist} = \frac{[RH]_0}{\Sigma [R]_{H_2O}},$$

where $[RH]_0$ is the molar concentration of 5-fluoro-8-mercaptoquinoline in the organic solvent and $\Sigma[R]_{H_2O}$ is the sum of the molar concentrations of all the forms mentioned in the aqueous phase [RH · H_2O] + [RH] +

$+ [RH_2^+] + [R^-]$. Solutions of 5-fluoro-8-mercaptoquinoline in buffer mixtures (μ = 0.15) with pH_{isoel} were shaken vigorously for 5 min with organic solvents. Because of the high value of K_{dist}, a ratio of aqueous phase to extractant of 5:1 was used, and the light absorption of the aqueous phase after extraction was measured at the maximum at 279 nm. At large values of K_{dist}, considerable variations in the individual experiments were found. The results given in Table 4 are the means of several determinations. It may apparently be deduced from the results obtained that the distribution coefficient increases with an increase in the polarity of the organic solvent and is also greater for solvents having π-bonds or atoms with unshared electron pairs (halogens).

REFERENCES

1. Yu. A. Bankovskii, Z. V. Misulovina, A. F. Ievin'sh, and M. R. Buka, Izv. AN Latv SSR, ser. khim., no. 1, 141, 1962.

2. Yu. A. Bankovskii, L. M. Chera, and A. F. Ievin'sh, ZhAKh, 18, 668, 1963.

3. H. Irwing, J. A. D. Ewart and J. T. Wilson, J. Chem. Soc., 2672, 1949.

4. Yu. A. Bankovskii, D. E. Zaruma, G. P. Mezharaups, Ya. V. Ashaks, and A. F. Ievin'sh, Izv. AN Latv SSR, ser. khim., no. 2, 173, 1966.

16 December 1965

Institute of Inorganic Chemistry,
AS Latvian SSR, Riga