ELECTRONIC ABSORPTION SPECTRA AND ACIDITY OF NEW CONDENSED SYSTEMS OF URACIL-DERIVATIVES OF 1,3-DITHIOLO[4,5-d]PYRIMIDINE

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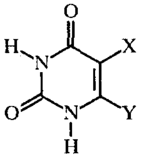
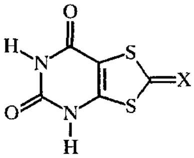
The first and second ionization constants of certain halouracils and a series of derivatives of a new condensed heterocyclic system — (4H,6H)-1,3-dithiolo[4,5-d]pyrimidine-5,7-dione — were evaluated spectroscopically. Substituents at the 2-position of this system were discovered to have considerable influence on the NH-acidity, which increases in the series of 2-O=, 2-S=, 2-Se=, 2-[$(C_2H_5)_2N$=]$^+$. The stability of the spectrum at pH ~ 14 for the 2-S= and 2-Se= derivatives indicates their unusual stability toward hydrolysis, compared with the 2-O= derivative. The mono- and diionization considerably influence the absorption of the dithiolthione and dithiolselenone system, causing bathochromic shifts.

Uracil (Ia) and its 5- and 6-substituted derivatives are dibasic NH-acids and their acid-base equilibria, acidity constants, and electronic absorption spectra have been much studied [1-11]. These investigations mainly concerned the 5- and 6-halo- and alkyl(aryl)-substituted uracils. Derivatives of uracil with sulfur-containing substituents have not yet been investigated.



Ia-i

Ia X=Y=H; b X=F, Y=H; c X=Cl, Y=H;
d X=I, Y=H; e X=PhI$^+$OTs$^-$, Y=H;
f X=H, Y=F; g X=H, Y=Cl; h X=Y=Cl;
i X=I, Y=Cl



IIa-d

IIa X= N$^+$Et2ClO4$^-$; b X=O;
c X=S; d X=Se

We synthesized in our laboratory new condensed sulfur-containing systems of uracil-derivatives of 1,3-dithiolo[4,5-d]pyrimidine (IIa-d). Perchlorate IIa was obtained by cyclization of 5-diethylaminothiocarbonylthiobarbituric acid in a concentrated H_2SO_4 solution, followed by separation of the corresponding acid sulfate and treatment of the latter with ammonium perchlorate in an aqueous solution. Thione IIc and selenone IId were obtained by the reaction of perchlorate IIa with sodium sulfide and selenide in an aqueous solution with subsequent cyclization of the intermediate product in the presence of an acid, as described previously in [12]. Compound IIb was synthesized by an oxidative rearrangement-cyclization of 1,3-dithiol-2-one-4,5-dicarboxylic acid diamide with phenyliodosyl(hydroxy)tosylate. A detailed description of the methods of synthesis of these compounds will be the subject of future publications.

The aim of the present work was to evaluate spectroscopically the first and second ionization constants of compound II and to clarify the influence of the 1,3-dithiol grouping variably substituted at the 2-position. For comparison, we also evaluated the ionization constants of halogen-substituted uracils Ig-i by the same method. The known first ionization constant of these uracils was measured potentiometrically [1]. The results obtained by us and also the literature data on the ionization constants of uracil and its derivatives (Ib-i) are given in Table 1.

A complex problem for compounds of the uracil series is the path of ionization and the structure of the monoanion, i.e., the ionization of N—H bond occurring at the $N_{(1)}$ or $N_{(3)}$ atoms. In general, it takes place at both atoms, since the ionization constants are similar and in the solution a mixture of two monoanions is obtained [7-9, 11]. Their ratio is determined by both the substituents and the solvent [8, 9]. To find their ionization path, electronic absorption spectra are used, since the shifts of the absorption maximum and its intensity during the ionization at the $N_{(1)}$ atom differ sharply from the changes occurring during the ionization at the $N_{(3)}$ atom [7, 11]. In the first case, a large bathochromic shift (20-25 nm) and an increase in the intensity are observed, while in the second case, there is virtually no shift, and the intensity decreases.

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TABLE 1. Acidity Constants of Uracil Ia, Its Derivatives Ib-i, and Also of 2-Substituted 5,7-Dioxo(4H,6H)-1,3-dithiolo[4,5-d]pyrimidines IIa-d in Aqueous Solutions

Compound	pK_1	pK_2	ΔpK
Ia	9,5 [2]; 9,63 [3]	>13 [2]; 13,36 [3]	3,73
Ib	7,98 [2]	~13 [2]	~5
Ic	7,95 [2]	~13 [2]	~5
Id	8,25 [2]; 8,50 [3]	~13 [2]; 13,14 [3]	4,64
Ie	6,04±0,07 [5]	11,04±0,07 [5]	5
If	4,03 [8]		
Ig	5,90±0,04	12,88±0,04	6,98
	5,75±0,07 [1]*		
Ih	4,77±0,04	11,67±0,04	6,90
	4,74±0,04 [1]*		
Ii	4,95±0,05	12,40±0,05	7,45
	5,04±0,01 [1]*		
IIa	3,33±0,03		
IIb	5,53±0,03		
IIc	5,09±0,04	11,66±0,05	6,57
IId	4,84±0,04	12,19±0,1	7,35

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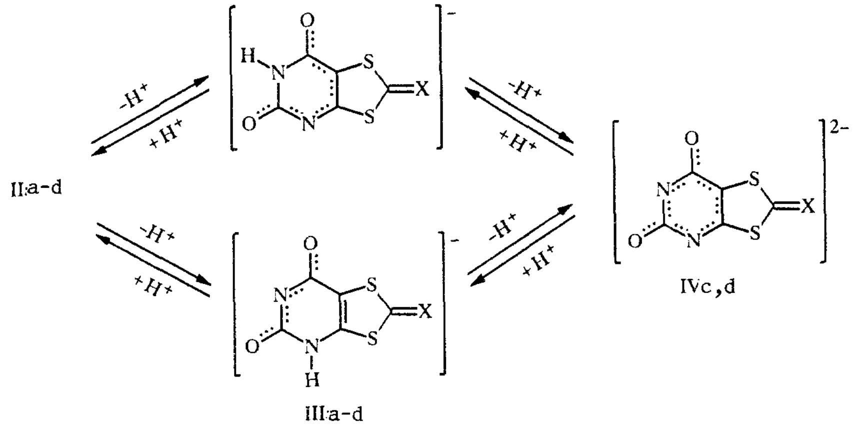
*The constant was determined by potentiometric titration.



Data are given in Table 2 on the electronic absorption spectra of compounds Ia-i and IIa-d. These data show that during the ionization of an unsubstituted uracil a bathochromic shift of the absorption maximum takes place, while the intensity decreases. During the ionization of its 5-fluoro derivative, its bathochromic shift is inappreciable, its intensity strongly decreases, and a second absorption maximum is observed in the form of an inflection. During the ionization of 6-chlorouracil Ic, a considerable bathochromic shift of the absorption maximum and an increase in the absorption intensity are observed. Uracil is ionized to approximately an equal degree at both the $N_{(1)}$ and $N_{(3)}$ atoms [7], while in the case of fluorouracil the ionization at the $N_{(3)}$ atom is twice as great [9]. 6-Halo-substituted uracils (If, g) are ionized mainly at the $N_{(1)}$ atom [1, 8].

The ratio of the ionization paths is directly dependent on the ionization constants of the $N_{(1)}$—H and $N_{(3)}$—H bonds which, in turn, depend on the electronic effects of the substituents at the 5- and 6-positions. The effect on the $N_{(3)}$—H bond is effected mainly by the inductive mechanism, both by the substituent in the 5-position and by the substituent at the 6-position, but much more weakly in the latter case because of the greater distance. The influence of the substituent in the 5-position on the $N_{(1)}$—H bond is effected by both inductive and a mesomeric mechanism, while the substituent in the 6-position has a strong inductive effect on it. Therefore, all the substituents having an electron-acceptor mesomeric effect, as well as an inductive effect, promote the ionization of the $N_{(1)}$—H bond. The phenyliodonium is also such a substituent [5]. Dihalouracils are ionized mainly at the $N_{(1)}$—H bond [1].

The ionization of the monoanion with the formation of dianion proceeds with considerably more difficulty and requires high pH values (see Table 2). Thus the influence of the substituents on the pK_2 is much lower and therefore the difference, ΔpK, increases on transition from an unsubstituted uracil ($\Delta pK = 3.73$) to its 5-substituted electron-acceptor substituents IIb-e ($\Delta pK \sim 5$) and further to 6-substituted Ic, g and disubstituted Ih, i derivatives ($\Delta pK = 6.6$-7.5).

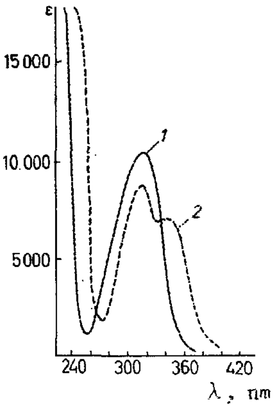


Fig. 1

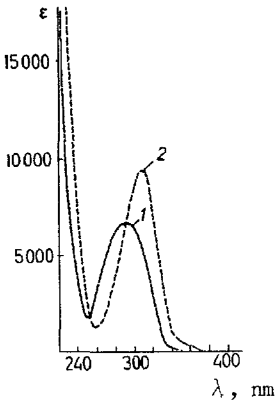


Fig. 2

Fig. 1. Electronic absorption spectrum of compound IIa in an aqueous solution: 1) pH = 1.0 (nonionized); 2) pH = 6.45 (inner salt.

Fig. 2. Electronic absorption spectrum of compound IIb in an aqueous solution: 1) pH = 2.0 (nonionized); 2) pH = 6.9 (monoanion).

TABLE 2. Electronic Absorption Spectra of Uracil Ia, Its Derivatives Ib-i, and 2-Substituted 5,7-Dioxo(4H,6H)-1,3-dithiolo[4,5-d]pyrimidines IIa-d in Aqueous Solutions

Compound	Nonionized molecule (pH < 2)	Monoanion	Dianion (pH > 13)
Ia	259,5(8150) [1]	284(6170) [1]	276,5 [8]
	209,258 [10]		
Ib	268(7000) [2]	270(4100) [2,8]	286(6900) [2]
		305 (inflection)	
Ic	275(7060) [2]	300(6300) [2]	289(7100) [2]
Id	285(6150) [2]	305(7100) [2]	295,5(6400) [2]
Ie	270(12100) [5]	295(14400) [5]	290(8700) [5]
			310 (inflection)
If	248(8500) [1]	267(13200) [1]	258(7800) [8]
Ig	262(9780)	284(13300)	274(8920)
	261(9150) [1]	283(11700) [1]	275(8100) [8]
Ih	275(9200)	298(12200)	287(8600)
	273(8150) [1]	296(11500) [1]	
Ii	283(7200)	227(11500)	230(11500)
	226(4250)	303(10400)	285(7400)
	278(5900) [1]	230(7750)	
		300(8700) [1]	
IIa	221(23300)	217...218(22500)	Rapid splitting at pH >10
	315(10600)	315(8900)	
		343(7200)	
IIb	217(19000)	223(23000)	Splitting at pH > 10
	295(6700)	310(9300)	
IIc	223(15200)	230(18300)	226(19800)
	264(7300)	290(12000)	295(9600)
	330(3650)	323(4400)	422(12900)
	384(18500)	402(14000)	
IId	227(14460)	232(17700)	230(18900)
	280(5000)	308(8100)	304(5700)
	425(17300)	438(16300)	447(12450)

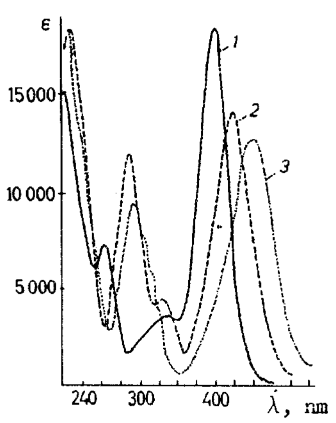


Fig. 3

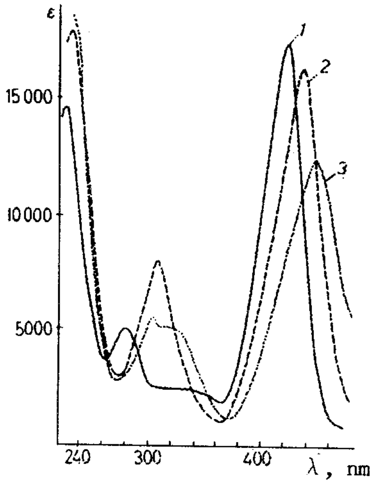


Fig. 4

Fig. 3. Electronic absorption spectrum of compound IIc in an aqueous solution: 1) pH = 2.25 (nonionized); 2) pH = 6.85 (monoanion); 3) pH = 13.9 (dianion).

Fig. 4. Electronic absorption spectrum of compound IId in an aqueous solution: 1) pH = 2.0 (nonionized); 2) pH = 6.75 (monoanion); 3) pH = 13.9 (dianion).

The 2-substituted 5,7-dioxo(4H,6H)-1,3-dithiolo[4,5-d]pyrimidines IIa-d studied behave similarly to disubstituted electron-acceptor derivatives of uracil Ih, i.

A special position is taken by 2-diethylammonio(4H,6H)-1,3-dithiolo[4,5-d]pyrimidine-5,7-dione perchlorate (IIa), which was found to be a very strong NH-acid (see Table 1).

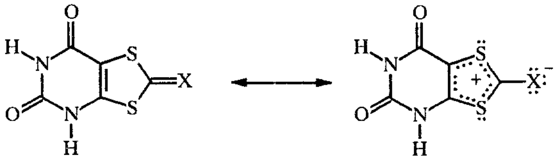
Judging from the changes in the electronic spectra (Fig. 1, Table 2), during the formation of monoanion IIIa (in this case an inner salt), the ionization is effected at both the $N_{(4)}$—H bond and the $N_{(6)}$—H bonds, with the latter predominating. The formation of dianion IV could not be observed, since already at pH ~ 10 the spectrum changes with time: the intensity of the maximum at 343 nm decreases, while, on the contrary, the intensity of the maximum at 315 nm increases, and a hypsochromic effect of this maximum is observed. At pH = 10.75, the absorption at about 345 nm decreases by 20% in the course of 30 min. The compound is unstable in an alkaline medium because of hydrolytic splitting.

(4H,6H)-1,3-Dithiolo[4,5-d]pyrimidine-2,5,7-trione (IIb) is an NH-acid, which can be compared in its strength with 6-chlorouracil and is ionized mainly at the $N_{(4)}$—H bond with an admixture of another anion (judging from the asymmetry of the absorption band with a maximum at 310 nm, Fig. 2). At pH = 10.8, the intensity of the absorption at 310 nm increases slowly, at pH = 12 it increases by 10% after 30 min, and the absorption in the 340-360 nm range also increases. Hydrolytic splitting of compound IIb takes place, but the spectrum of the splitting product is different from that in the case of compound IIa.

The yellow-colored 5,7-dioxo(4H,6H)-1,3-dithiolo[4,5-d]pyrimidine-2-thione (IIc) is a stronger NH acid than compound IIb and, judging from the changes in the electronic spectra (Fig. 3), is ionized mainly at the $N_{(4)}$—H bond. The compound is also stable at pH ~ 14, which makes it possible to evaluate the second ionization constant, which is approximately equal to pK_2 of 5,6-dichlorouracil Ih. There is an intense maximum at 400 nm in the spectrum of IIc, which is characteristic for the 1,3-dithiol-2-thione system. On transition from the neutral molecule to monoanion IIIc and dianion IVc, significant bathochromic shifts of 20 nm are observed for this compound (see Fig. 3).

The red-colored 5,7-dioxo(4H,6H)-1,3-dithiolo[4,5-d]pyrimidine-2-selenone (IId) is a stronger acid than thione IIc, is comparable with acetic acid, and is ionized mainly at the $N_{(4)}$—H bond (Fig. 4). The compound is stable at pH ~ 14. The second ionization constant shows that the proton is split off with more difficulty from monoanion IIId than in the case of thione IIIc. Compound IId absorbs intensely at 430 nm, which is characteristic for 1,3-dithiol-2-selenone system; bathochromic shifts of 10-15 nm are observed in the spectrum for this maximum on transition to monoanion IIId and dianion IVd (see Fig. 4).

A unique fact is that the acidity increases in the series of "one" IIb, "thione" IIc, and "selenone" IId. The stability to alkaline hydrolysis increases also in the same series. This may be explained by the electron density distribution changing on transition from an oxygen atom to the sulfur and selenium atoms: the "fraction" of the bipolar dithiolic form increases in this series.



X = O, S, Se

EXPERIMENTAL

The electronic absorption spectra were run on a Specord-Vis spectrophotometer. The pH values were determined on a pH-340 pH meter. The aqueous solutions of the compounds at a concentration of $5 \cdot 10^{-4}$ mole/liter were diluted by buffer solutions, prepared from phosphoric and acetic acids and sodium hydroxide. In the case of compounds IIb-d, which are sparingly soluble in water, the required solutions were prepared from crystalline monohydrates of their Na-salts, while the latter were obtained by treating IIb-d with an aqueous methanolic solution of NaOH. The pK values were calculated according to the formula

$$pK = pH + \lg \frac{D_A - D}{D - D_{AH}} + \frac{0{,}505 \sqrt{\mu}}{1 + 1{,}6 \sqrt{\mu}} ,$$

where D_{AH} is the optical density of a nonionized particle; D_A is the optical density of an ionized form; D is the optical density of an equilibrium mixture; μ is the ionic strength of the solution. The pH values at which the D_{AH} and D_A were measured are shown in the figures. Solutions at the following pH were used for the determination of pK: 3.2 (IIa), 5.45 (IIb), 4.53 (IIc for pK_1), 11.5 (IIc for pK_2), 4.3 (IId for pK_1), 12.05 (IId for pK_2). The measurements were carried out at 10-12 different wavelengths.

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