INVESTIGATION OF HETEROCYCLIC QUINONES

XXV.* TAUTOMERIC AND COVALENT HYDRATION IN THE QUINAZOLINEQUINONE SERIES

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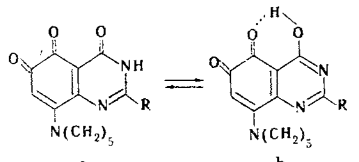
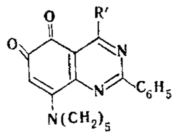
The tautomeric forms of 2-phenyl-4-hydroxy-8-piperidinoquinazoline-5,6-quinone were determined quantitatively by means of UV spectroscopy. It is shown that quinazolinequinones are not capable of covalent hydration.

Information regarding the electronic spectra of quinazoline-5,6-quinones and quinazoline-5,8-quinones is absent in the literature.



a I, II b



III, IV

I $R=C_6H_5$; II $R=N(CH_2)_5$; III $R'=H$; IV $R'=OCH_3$

It is well known that 4-quinolones and 4-quinazolones exist in the oxo form [2]. However, some 4-quinolone-5,6-quinones [3] and 4-quinazolone-5,6-quinones [4] are found primarily in the hydroxy form stabilized by an intramolecular hydrogen bond. A comparison of compounds I and II shows that the strength of the hydrogen bond depends substantially on the substituent attached to C_2 (compare the effect of substituents attached to C_2 on the carbonyl frequency in the spectra of quinoline-5,6-quinones [5]). Quinone II exists exclusively in hydroxy from IIb in both the solid state and in solutions owing to transmission of the mesomeric effect of the piperidine residue attached to C_2 through the pyrimidine ring; this leads to an increase in the basicity of the $C_5{=}O$ oxygen atom and reinforcement of the chelate hydrogen bond. In contrast to II, the IR spectrum of quinone I in the solid state at 1600-1800 cm^{-1} contains three maxima; this constitutes evidence in favor of the oxo form [2, 4]. The group of bands at 3000 cm^{-1} cannot be unambiguously assigned to associated ν_{OH} or ν_{NH} bands, but deuteration of I confirms the quinazolone structure of the compound in the solid state, inasmuch as the band at 1552 cm^{-1}, which is related to δ_{NH}, undergoes a low-frequency shift, and ND bands appear at 2176 and 2282 cm^{-1}. The IR spectrum of a chloroform solution of I contains only two carbonyl bands; this can be explained by predominance of the hydroxy form. The addition of ethanol leads to destruction of the intramolecular hydrogen bond and to a shift in the equilibrium to favor the oxo form, the presence of which is attested to by the appearance of a third $\nu_{C=O}$ band at 1712 cm^{-1}.

The UV spectra of III and IV have four principal absorption maxima (Table 1). Judging from the in-

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* See [1] for communication XXIV.

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TABLE 1. Absorption Maxima in the Spectra of Quinazoline-5,6-quinones

Compound	Solvent	Concn, mole/liter · 10^{-5}	$\pi \to \pi^*$ band No. 1		$\pi \to \pi^*$ band No. 2		$\pi \to \pi^*$ band No. 3		Band No. 4		$n_p \to \pi^*$ band No. 5	
			λ, nm	lg ε	λ, nm	lg ε	λ, nm	lg ε	λ, nm	lg ε	λ, nm	lg ε
I	Ethanol	2,95	238	4,25	293	4,06			378	3,88	504 528*	2,97 3,05
	Chloroform	4,46			276	4,03	311	4,11	369	3,96	555 578*	3,15 3,04
	Dioxane	3,00			270	4,07	307	4,11	360	3,93	510 510*	3,02 3,11
	10% Chloroform in cyclohexane	3,13			273	4,07	306	4,10	365	4,00	514	3,14
II	Ethanol	2,57	247	4,33	290	4,12	397	4,31			530 530*	3,19 3,25
	Chloroform	4,12	248	4,28	296 318	4,17 3,88	386 403 420	4,20 4,30 4,22			520 524*	3,21 3,08
III	Ethanol	1,99	231	4,20	282	4,28	328	4,28	—	—	508	3,57
IV	Ethanol	3,37	218	4,33	273	4,21	310	4,23	360	4,09	510	3,51
	Chloroform	3,98			273	4,27	311	4,28	358	4,15	500	3,56
	Dioxane	2,90			273	4,33	309	4,26	348	4,09	480	3,49
	10% Chloroform in cyclohexane	2,80			273	4,31	306	4,26	350	4,15	483	3,50

* The concentration was increased by a factor of 10 in the measurement of the spectra.

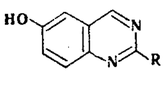
tensity and position in various solvents, bands 1-3 are due to $\pi \to \pi^*$ transitions [2, 6]. The introduction of an electron-donor substituent at C_4 is accompanied by the appearance of an additional absorption band (band 4) [6].

The presence of carbonyl groups in quinazoline-5,6-quinones makes it possible to observe satisfactorily distinguishable singlet $n_p \to \pi^*$ transitions due to the unshared electron pair of the oxygen atom (band 5).

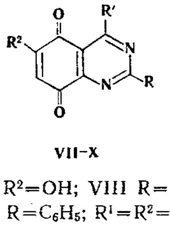
The electronic spectrum of II differs from the spectra of III and IV. A strong intramolecular hydrogen bond leads to the formation of a quasi-aromatic ring, as a result of which a strong bathochromic shift of the principal $\pi \to \pi^*$ bands is observed. Moreover, band 3 completely masks the other low-intensity transitions.

The UV absorption spectra of solutions of I in chloroform, dioxane, and cyclohexane–chloroform (9:1) are similar to the spectrum of model compound IV; this is due to the existence of the quinazolinequinone in the hydroxy form. However, only two bands that characterize the allowed $\pi \to \pi^*$ transition are present in the spectrum of an ethanol solution of I. Their position and intensity provide evidence for changes in the system of conjugated bonds through the pyrimidine ring and confirm the previously drawn conclusion regarding the existence of I in the oxo form. An isopiestic point at 296 nm is observed for the spectra of I in chloroform–ethanol mixtures. It was shown by a known method [7] that, depending on the percentage of ethanol in chloroform, the amount of hydroxy form Ib present in a $3 \cdot 10^{-5}$ M solution at 24° is as follows: 0(96),5 (92),10 (81),20 (68),40 (48),60 (29),and 80 (6) [volume percent of ethanol (percent of the hydroxy form), average of two parallel measurements]. The results obtained correlate well with respect to the IR spectra.

Quinazolines are hydrated at the $C_4{=}N_3$ bond in acidic media, and this causes a hypsochromic shift of the long-wave maximum in the UV spectrum [8]. The introduction of electron-acceptor substituents into the 5-8 positions leads to an increase in the degree of hydration [9].



V, VI



VII-X

V R=H; VI $R{=}C_6H_5$; VII $R{=}N(CH_2)_5$; $R^1{=}H$; $R^2{=}OH$; VIII $R{=}C_6H_5$; $R^1{=}H$; $R^2{=}OH$; IX $R{=}C_6H_5$; $R^1{=}H$; $R^2{=}OCH_3$; X $R{=}C_6H_5$; $R^1{=}R^2{=}OCH_3$

TABLE 2. UV Spectra of 6-Hydroxyquinazolines (V,VI) and Quinazoline-5,8-quinones (VII-X)

Substance	Solvent	Band 1		Band 2		Band 3	
		λ, nm	lg ε	λ, nm	lg ε	λ, nm	lg ε
V	H_2O	233	4,58	260	3,62	340	3,58
	0,05 N HCl	—	—	277	4,12	342	2,65
VI	H_2O	258	4,59	290	4,17	348	3,81
	0,05 N HCl	236	4,22	250	4,18	290	4,23
VII	H_2O			242	4,33	338	4,42
	0,05 N HCl			242	4,35	324	4,33
	0,05 N NaOH			242	4,33	338	4,41
VIII	H_2O			244	4,20	312	4,41
	0,05 N HCl			246	4,20	298	4,30
	0,05 N NaOH			244	4,24	312	4,36
IX	H_2O			254	4,14	298	4,22
	0,05 N HCl			254	4,10	298	4,32
X	H_2O			268	4,23	310	4,19
	0,05 N HCl			—	—	292	4,35

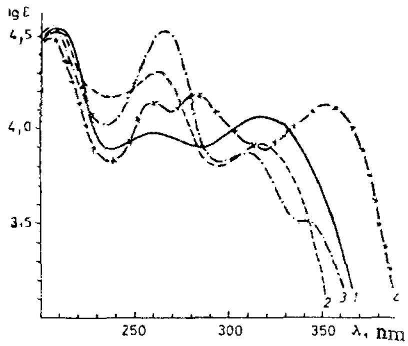
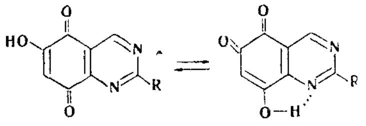


Fig. 1. UV spectra of 2-phenyl-6-hydroxyquinazoline in water (1) and in 0.05 N HCl (2) and of 2-phenyl-6-hydroxyquinazoline-5,8-quinone in water (3) and in 0.05 N HCl (4).

A comparison of the UV spectra of 6-hydroxyquinazolines V and VI and quinazolinequinones VII-X in neutral and acidic media (Table 2 and Fig. 1) shows that 6-hydroxyquinazoline (V) [10] and 2-phenyl-6-hydroxyquinazoline (VI), which are unhydrated in neutral solution, add water during protonation. In contrast to them, quinazolinequinones VII-IX do not display the changes in the UV spectra that are characteristic for covalent hydration on passing from neutral to acid solutions.

The UV spectra of VII and VIII in neutral and alkaline media do not differ, and they consequently cannot be hydrated in the form of neutral molecules. The hypsochromic shift of the long-wave maximum in acidic media of V, VII, and VIII of 14 nm is apparently explained by the tautomeric conversions XI ⇌ XII, inasmuch as this equilibrium depends on the pH of the medium. The UV spectrum of IX, which is incapable of tautomeric transformations, does not change on passing from neutral to acid solutions.



XI XII

The fact that the spectra of VII and VIII in neutral solution do not differ from the spectra of IX and X also constitutes evidence in favor of the existence of the XI ⇌ XII equilibrium. Compound X was used as the standard, inasmuch as it is known that it is not hydrated at the $C_4{=}N_3$ bond.

Thus quinazolinequinones VII-IX are incapable of covalent hydration. This probably depends on steric and polar effects leading to migration of the electrophilic center of quinazoline-5,6-quinones from C_4 to C_2 [1].

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EXPERIMENTAL

The investigated substances were previously synthesized in [4]. The IR spectra of mineral-oil suspensions and solutions in chloroform and in a 10% solution of chloroform in ethanol (sample concentration 0.1 mole/liter, cuvette thickness 0.6 mm) were recorded with a UR-20 spectrometer. Compounds I and II were deuterated by means of D_2O for 7 days with periodic removal of the heavy water in vacuo and addition of new portions. The UV spectra were measured with a Specord UV-vis spectrophotometer.

Measurement of the Percentages of the Hydroxy Form of I. The solution concentration was $3 \cdot 10^{-5}$ M. The measurements were made at 311 nm (the absorption maximum of the hydroxy form). On the basis of the IR spectral data, it was assumed that the extinction of the substance in ethanol corresponds only to the oxo form and that the extinction in chloroform corresponds only to the hydroxy form; the formula for the calculation therefore was in the form

$$\% \text{ of the hydroxy form} = \frac{(\varepsilon-\varepsilon_0)\cdot 100}{\varepsilon_h-\varepsilon_0}.$$

where ε is the extinction of the substance in chloroform–ethanol, ε_0 is the extinction of the substance in ethanol, and ε_h is the extinction of the substance in chloroform.

The percentage of the hydroxy form in chloroform was determined from the extinction of model compound IV at the absorption maximum (311 nm). The ratio of the extinction of IV and I in chloroform and in chloroform–cyclohexane (1 : 9) was 1.46 at this wavelength. The extinction for 100% of the hydroxy form was calculated from these data.

The covalent hydration of 6-hydroxyquinazolines and quinazoline-5,8-quinones was detected from the change in the UV spectra of samples in alcohol–water (1 : 1) and in alcohol–0.1 N hydrochloric acid (1 : 1) because of the inadequate solubilities of the substances in water ($3 \cdot 10^{-5}$ M). Preliminary experiments showed that the spectra of 6-hydroxyquinazoline in water and in 50% alcohol are practically the same. The UV spectra of VII and VIII in alcohol–0.1 N sodium hydroxide (1 : 1) were recorded; under these conditions, IX and X were saponified.

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