BENZODIAZINES

XIII. ACID-BASE PROPERTIES OF SOME QUINAZOLINES*

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The ionization constants of 2-R-4-quinazolones (where R = H, CH_3, phenyl, N-pyrrolidinyl, or γ-pyridyl), and of 4-R-2-quinazolones (where R = H, phenyl, and N-pyrrolidinyl), have been measured. The polarographic reduction potentials of the corresponding 2-R-4-chloroquinazolines and 4-R-2-chloroquinazolines have been determined. A satisfactory relation between the $E_{1/2}$ of 2-R-4-chloroquinazolines and the pKa for the removal of a proton from 2-R-4-quinazolones has been found.

We have described in previous communications [2, 3] the synthesis and reactions of some 2,4-disubstituted quinazolines. In the course of this work, we repeatedly observed differences in behavior related to the substituents in the 2- and 4-positions. These observations led us to examine in detail the effects of substituents in the quinazoline system. For this purpose, we measured the ionization constants of the quinazolones and the polarographic reduction potentials of the chloroquinazolines. The influence of the substituents, as related to their donor-acceptor properties, is seen with particular clarity in the 4-quinazolone series, which is dealt with more fully than the corresponding 2-quinazolone series (in view of the difficulty of synthesizing some compounds of this series).

In a series of 2-R-4-quinazolones, the substituents are arranged in the following order with respect to their effect on proton elimination (in order of increasing acidity): N-pyrrolidinyl, methyl, phenyl, and γ-pyridyl. The unsubstituted compound (R = H) occupies a position between the methyl and phenyl derivatives. Comparison of the pK_a values (see Table 1) shows that, in the removal of a proton, the N-pyrrolidinyl group stands out as a +M substituent, methyl as a +I, phenyl as a −I, and γ-pyridyl as a −I and perhaps a −M substituent. In the loss of a proton from the 2-quinazolones, the effect of substituents (N-pyrrolidinyl and phenyl) on the pK_a values is similar.

These substituents have a somewhat different effect on the addition of a proton. The pK_a of 4-quinazolone (proton addition) is 2.10, and of 2-phenyl-4-quinazolone 2.43, i.e., higher than the pK_a of the unsubstituted 4-quinazolone. Thus the phenyl group here behaves as a weak +M substituent. The pK_a of 2-γ-pyridyl-4-quinazolone is 3.33, and of 2-N-pyrrolidinyl-4-quinazolone, 4.68. In these cases, both the nitrogen atom of the quinazolone ring, and also the nitrogen of the substituents, can function as basic centers. The pK_a values of 2-quinazolone and of 4-phenyl-2-quinazolone are 1.34 and 1.87, respectively, and the values for 4-N-pyrrolidinyl-2-quinazolone are 2.11 and 7.44. From the chemical properties of 4-N-pyrrolidinyl-2-quinazolone (it forms a salt with acetic acid), we may assume that the pK_a value of 7.44 relates to the addition of a proton, and the pK_a of 2.11, to the addition of a second proton. Thus, the value of 7.44 doubtless relates to the addition of a proton to the nitrogen of the pyrrolidine ring, while the value of 2.11 refers to protonation of the nitrogen in the quinazolone ring.

We clearly see the effects of the substituents on the values of the half-wave potentials in the polarographic reduction of the 2- and 4-chloroquinazolines. The chloroquinazolines were obtained from the quinazolones [2, 4] by treatment with phosphoryl chloride [5]. The heterocycle in these compounds has the

*For part XII, see [1].

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TABLE 1. Quinazolones

Formula	Substituent	pK_a		IR spectra, cm^{-1}			Chlorides		
		$+H^+$	$-H^+$	C=O	free	bound		Substituent	$E_{1/2}$
4-R-2-Quinazolones	N-Pyrrolidinyl	2.11±0.03 7.44±0.02	(12.5—13)*	1696 v w (sh) 1620 s sharp	3330 v s, sharp	3212 v w	4-R-2-Chloroquinazolines	N-Pyrrolidinyl	1,47
	H	1.34±0.06 1.30[6]	10.69±0.06 10.69[6]	1689 v s	3430 s	3275 v s		H	1,07
	Phenyl	1.87±0.03	10.57±0.05	1760 v w 1658 v s, broad	—	3134 v w 3100		Phenyl	0,95
2-R-4-Quinazolones	N-Pyrrolidinyl	4,68±0.06	10.74±0.06	1690 v s 1677 broad	(3329 v w	3263 v w 3129 med	2-R-4-Chloroquinazolines	N-Pyrrolidinyl	1,19
	Methyl	3.15±0.02	10.51±0.06	1688 v s 1678	3319 w	3169 3122		Methyl	1,00
	H	2.10±0.06 2.12[6]	9.86±0.03 9.81[6]	1706 v s	—	3205 med 3159 s 3134		H	0,96
	Phenyl	2.43±0.04	9.49±0.01	1671 v s, broad	3328 v w	3199 med 3170		Phenyl	0,93
	γ-Pyridyl	3.33±0.04	8.52±0.04	1767 v w 1682 v s	3480 v w	3164 w		γ-Pyridyl	0,83

*The exact determination of this value was rendered difficult by the low solubility of the compound, and by the small change in optical density over the whole frequency range in this pH interval.

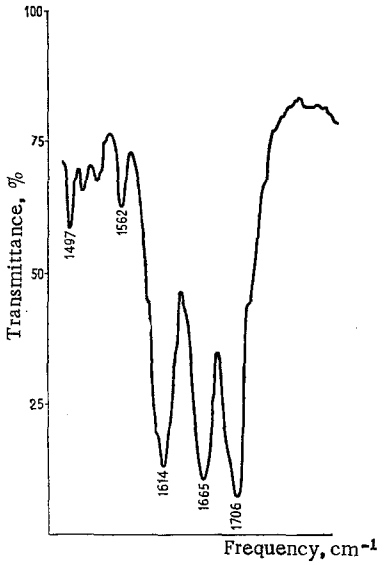

Fig. 1. IR spectrum of 4-quinazolone in the 1490-1700 cm^{-1} region.

pyrimidine structure. The relative ability to undergo reduction depends on the value of the δ^+ charge on the carbon atom bearing the chlorine atom. If the substituents are arranged according to their ability to move the reductive potential of the chloro compounds toward negative values, they have the following order: γ-pyridyl, < phenyl < H < methyl < N-pyrrolidinyl. It is interesting that the value of $E_{1/2}$ for the 2-R-4-chloroquinazolines correlates satisfactorily with the value of the pK_a for the process of proton removal from the 2-R-4-quinazolones, the correlation coefficient r being 0.93, with scatter value s = 0.442. The correlation between values of the pK_a for the 4-quinazolones (proton removal) and the half-wave potentials for the 4-chloroquinazolines is explicable in terms of the removal of a proton from the quinazolones, and the addition of electrons in the polarographic reduction of the chloro compounds, being in the final analysis dependent on the value of the δ^+ charge on the fourth carbon atom of the quinazoline ring.

We see from Table 1 that the 2-quinazolones are both weaker bases and weaker acids than the corresponding 4-quinazolones. The isomeric 2(4)-quinazolones differ in that, in the 4-quinazolones, the C = O group is adjacent to the benzene ring and is conjugated with both the ring and the nitrogen atom, while in the 2-quinazolones the oxygen atom and the two nitrogen atoms occupying the 1 and 3 positions are next to one another and form a resonance-stabilized system with the participation of both the nitrogen atoms in the conjugation. This conjugation is probably also the reason for the weakening of both the basic and acidic properties of the 2-quinazolones. IR spectroscopy should be a method of definitely confirming this. Because of the low solubility of the quinazolones in the appropriate organic solvents, the IR spectra were taken in the crystalline state, and, therefore, interpretation of the bands is only qualitative. Nevertheless, the absence of bands in the 3600-3500 cm^{-1} region, and the presence in all the compounds of a very strong, broad band (at 1700-1650 cm^{-1}) leaves no doubt that all the compounds, in the crystalline state, possess to a greater or lesser extent the polarized amide structure rather than a hydroxy structure. (In addition to this band, the spectrum also shows both a high intensity amide band at 1650 cm^{-1}, and a band due to the $-C=N-$ group at 1610-1590 cm^{-1}. See Fig. 1.) The spectrum of 2-quinazolone shows a clear band at 3430 cm^{-1} which may be assigned to the free NH group, which is not hydrogen bonded. Bands due to the bound NH group are also present. Bands due to the free NH group are not seen in 4-quinazolone, i.e., in the crystals of 4-quinazolone the molecules are associated through hydrogen bonds to a greater extent than in 2-quinazolone. This is perhaps connected with the greater degree of polarization of the amide group in 4-quinazolone in comparison with 2-quinazolone. This is also shown in the spectrum of 4-quinazolone by the presence of weak bands at 2700-2600 cm^{-1}. Similar, but very weak bands also appear in the substituted 2-quinazolones, indicating the polarizing effect of the substituents. Comparison of the IR data for the quinazolones with the polarographic reduction potentials for the chloroquinazolines shows that, as expected, the greater polarization of the C=O bond in 4-quinazolone, compared with 2-quinazolone, results in greater ease of reduction of the 4-chloro compound.

The unusual effect of the phenyl substituent of the acid-base properties of both the quinazolone isomers should be noted. In 2-phenyl-4-quinazolone and 4-phenyl-2-quinazolone, both the acidic and the basic properties are increased in comparison with the corresponding unsubstituted compounds. The reason for the change in the direction of the mesomeric effect is, apparently, that in the acid or the conjugate quinazolone base, the electron-acceptor properties of the quinazoline ring are substantially increased.

EXPERIMENTAL

The pK_a values of the quinazolones were measured spectrophotometrically in aqueous solution at a concentration of $4 \cdot 10^{-5}$ M on an SF-4 spectrophotometer. The pK_a values for unsubstituted 2- and 4-quinazolones were obtained from the literature [6]. These compounds were used as checks. We see from Table 1 that the agreement between our results and those given in the literature is fully satisfactory.

Polarographic reduction of the chloroquinazolines at the dropping mercury electrode was carried out in dimethylformamide solution, using tetraethylammonium iodide as the base, at a chloroquinazoline concentration of $2 \cdot 10^{-3}$ M relative to the mercury background. The polarogram was obtained on an LP-60 polarograph.

The IR spectra were taken on an IKS-14 spectrophotometer as pastes in Vaseline oil (NaCl prisms), and in perfluorocarbon oils (LiF prisms).

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