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REACTIVITIES OF 4,5-BRIDGED QUINAZOLINES

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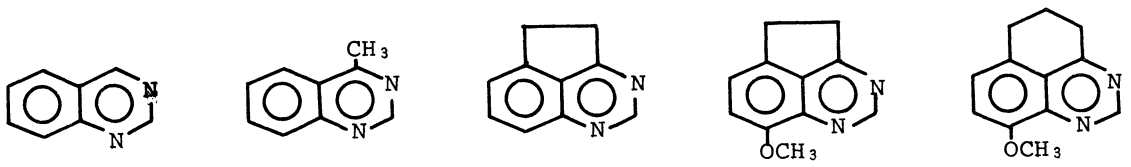
Introduction of the 4,5-bridged five-membered ring to quinazoline derivatives enhanced the rate of the acid-catalized hydrolysis of the quinazoline ring in the derivatives due to a steric effect caused by the presence of the bridged ring. This steric effect also reflected in their pKa values and polarografic half-wave potentials.

The X-ray diffraction study has revealed that the naphthalene ring in acenaphthene is strained in bond angles.[1] This strain apparently arises from the presence of the peri-bridged five-membered ring in acenaphthene. However, the effect of this sort of ring strain on chemical reactivities has little been elucidated. We now wish to report the results that the rates of the acid-catalyzed hydrolysis and some other properties of quinazolines are appreciably influenced by introduction of the 4,5-bridged five-membered ring.

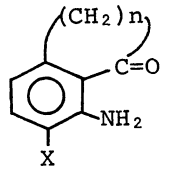
The compounds chosen for this investigation are shown in Chart 1.

Chart 1.



(1) (2) (3a) (3b) (4)

The new compounds, 3,5-diazaacenaphthene (3a), 6-methoxy-3,5-diazaacenaphthene (3b), and 7-methoxy-2,3-dihydro-4,6-diazaphenalene (4), were synthesized from the corresponding amino-ketones (5a-c) and formamidine acetate by the method of Taylor and Ehrhart.[2] The compound (5a) was prepared from 4-nitro-1,3-indandione via 4-nitro-1,3-indandione-1-ethylene thioacetal.[3] The compounds (5b) and (5c) were prepared according to the methods reported in the literature.[4,5] The structures of (3a), (3b), and (4) were confirmed by the elemental analyses and spectral data: (3a), mp 92-95°C; IR(KBr) 1610, 1570, 1480, 1355, 840 and 780 cm^{-1}; NMR($CDCl_3$) δ 3.40 (bs, 4H, H_1, H_2), 7.50-8.00 (m, 3H, H_6, H_7, H_8), and



(5a); X=H, n=2
(5b); X=OCH_3, n=2
(5c); X=OCH_3, n=3

9.21 ppm (s, 1H, H_4); Mass m/e 157 (M^++1), 156 (M^+), and 155 (M^+-1); UV (H_2O, pH 7.0) λmax (log ε) 227 (4.53), 273 (3.42), and 316 nm (3.49); UV (H_2O, pH 1.0) λmax (log ε) 241 (4.46), 273 (3.53), and 337 nm (3.51). (3b), mp 115-119°C; IR(KBr) 1620, 1610, 1575, and 845 cm^{-1}; NMR($CDCl_3$) δ 3.37 (bs, 4H, H_1, H_2), 4.10 (s, 3H, $-OCH_3$), 7.29 (d, J=8.1 Hz, 1H, aromatic H), 7.38 (d, J=8.1 Hz, 1H, aromatic H), and 9.30 ppm (s, 1H, H_4); Mass m/e 186 (M^+) and 185 (M^+-1); UV (H_2O, pH 7.0) λmax (log ε) 221sh (4.21), 242 (4.47), and 332 nm (3.59); UV (H_2O, pH 1.0) λmax (log ε) 221 (4.21), 256 (4.43), 329 (3.35) and 370 nm (3.42). (4), mp 70-72°C; IR(KBr) 1610, 1565, and 825 cm^{-1}; NMR($CDCl_3$) δ 2.14 (pentuplet, J=6.1 Hz, 2H, H_2), 3.05 (t, J=6.1 Hz, 2H, H_1), 3.18 (t, J=6.1 Hz, 2H, H_3), 4.09 (s, 3H, $-OCH_3$), 7.16 (d, J=8.1 Hz, 1H, aromatic H), 7.30 (d, J=8.1 Hz, 1H, aromatic H), and 9.25 ppm (s, 1H, H_5); Mass m/e 200 (M^+) and 199 (M^+-1); UV (H_2O, pH 7.0) λmax (log ε) 245 (4.58) and 338 nm (3.58); UV (H_2O, pH 1.0) λmax (log ε)258 (4.57), 330 (3.39), and 386 nm (3.40).

The acid-catalyzed hydrolyses of (1-4) were carried out in a buffered aqueous solution (HCl-KCl) of pH 1.0 at 35°C. The compounds (3a) and (3b) were rapidly hydrolyzed respectively to the 7-formylamino-1-indanone derivatives (6a) and (6b) (for the structures, see Scheme 1), then to (5a) and (5b). The products (6a) and (6b) could be isolated by interrupting the reaction after a short period of time. The structures of (6a) and (6b) were established by comparisons of the IR and UV spectra with those of the respective authentic samples which were prepared by the formylation of (5a) and (5b).

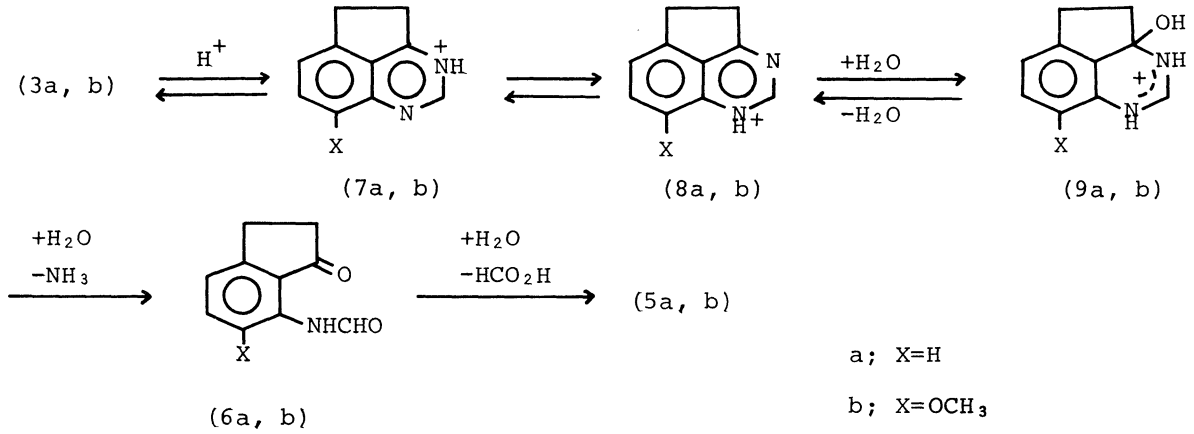
In contrast to (3a) and (3b), the compounds (1), (2) and (4) were not appreciably hydrolyzed even after a long period of reaction time under the same conditions as those employed above: (4) was recovered unchanged quantitatively after standing for one year in an aqueous solution of pH 1.0 at room temperature. The rates of the hydrolysis of (3a) and (3b) to (6a) and (6b) in the buffered solution of pH 1.0 at 35°C were then measured by monitoring the change in absorbances at 260 nm for (3a) and at 255 nm for (3b). In both cases, the absorbance changed linearly with progress of the reaction. The linear relationships between the absorbances and the reaction times continued until 50% of the starting materials was hydrolyzed. From the slopes of the straight lines thus obtained, the pseudo 1st-order rate-constants were calculated. The results are summarized in Table 1.

The predominant forms of these compounds were then investigated. Some quinazolines have been shown to undergo a covalent hydration in acidic aqueous solutions, and the degree of the hydration depends on the substituents. For example, (1) hydrates at the 4-position and exists predominantly in the hydrated form (~100%), but (2) exists almost exclusively in the non-hydrated form (81%) in an aqueous solution of pH 1.0.[6] A pKa value has been shown to be a good measure of the degree of covalent hydration.[7] Thus, we determined the pKa values of (1)-(4) in 57% (v/v) aqueous ethanol by the potentiometric titration. The pKa's of (3a), (3b) and (4) were very close to the pKa of (2), although their values were significantly smaller than the pKa of (1). This observation suggests that (3a), (3b) and (4) as well as (2) exist predominantly in non-hydrated forms in an acidic aqueous solution. A support for this suggestion was provided by the examination of their UV spectra. The UV spectrum of (1) greatly changes by changing a medium from neutral to acidified water, because of an appreciable hydration in an acidic medium.[8] On the other hand, the UV spectrum of (2), which does not undergo an effective covalent-hydration,

exhibits a bathochromic shift by changing the medium from neutral to acidified water.[8] In the UV spectra of (3a), (3b) and (4), the absorption maxima shifted to longer wave lengths, and the spectral patterns remained almost unchanged upon changing the medium from neutral water to the buffered aqueous solution of pH 1.0. This observation substantiates that (3a), (3b) and (4) exist predominantly in non-hydrated forms in acidic aqueous solutions.

On these grounds, we deduced a possible mechanism for the acid-catalyzed hydrolyses of (3a) and (3b), which is illustrated in Scheme 1.

Scheme 1.



The high reactivity of (3a) and (3b) in the hydrolysis may be attributed to a ring strain involved in the intermediates (9a) and (9b): a steric instability of (9a) and (9b) enhances the rate of decomposition to (6a) and (6b).

The possibility that (9a) and (9b) suffered a steric instability was secured from the examination of polarographic reduction-potentials. Rieke and coworkers[9] have found that in a series of substituted 1,4-naphthoquinones, the half-wave reduction-potentials shift toward more positive potentials by introduction of the 2,3-bridged four-membered ring which brings about a ring strain to the naphthoquinone ring. The half-wave reduction-potentials of the quinazolines were measured in aqueous solutions buffered at pH 7.0 and in DMF at room temperature. The results are also included in Table 1. Quinazoline (1) in an aqueous solution is reduced to 3,4- dihydroquinazoline at the 1st half-wave potential, and then to 1,2,3,4-tetrahydroquinazoline at the 2nd half-wave potential.[10] The wave-patterns of (2-4) in the polarograms were found to be very similar to the wave-pattern of (1). Consequently, we presumed that (2-4) were reduced through the pathways similar to the one taken by (1).

As shown in Table 1, the 1st half-wave potentials in the aqueous solutions shifted to more negative potentials in the order of (1) < (2) < (3a) ≃ (4) < (3b). This order can reasonably be explained in terms of the electron-donating power of the substituents attached to the quinazoline ring. The polarograms of (1-4) in DMF showed only the 1st reduction-wave because of the absence of a proton source. The tendency of the shifts of the half-wave potentials for these compounds in DMF was almost same as that in aqueous solution as shown in Table 1.

On the other hand, the 2nd half-wave potentials in the aqueous solutions shifted to more negative potentials in the order of (3a) < (3b) < (1) < (4) ≃ (2). It is important to note that considerably large positive-shifts were observed in the 2nd half-wave potentials of (3a) and (3b). These large positive-shifts could be explained by assuming that 2a,3-dihydro-3,5-diazaacenaphthenes, the compounds to be reduced at the 2nd half-wave potentials, are constrained by the presence of the peri-bridged five-membered ring. If this assumption is correct, it is reasonable to assume that (9a) and (9b) are also strained by the presence of the peri-bridged ring so that the decompositions to (6a) and (6b) are facilitated.

Table 1.
Properties of The Quinazoline Derivatives

Compd	k, min^{-1} [a]	pKa [b]	$-E_{1/2}$ [c] 1st wave	$-E_{1/2}$ [c] 2nd wave	$-E_{1/2}$ [d]
(1)	——	3.13	0.95	1.51	2.35
(2)	——	2.47	1.08	1.54	2.48
(3a)	2.8×10^{-2}	2.59	1.14	1.44	2.56
(3b)	2.7×10^{-2}	2.49	1.21	1.46	2.62
(4)	——	2.49	1.14	1.53	2.61

a) The pseudo 1st-order rate-constants in the buffered aqueous solutions of pH 1.0 at 35°C.

b) The pKa's (±0.02) in 57% (v/v) C_2H_5OH-H_2O at 30°C.

c) The half-wave reduction-potentials (volts vs. SCE) in a buffered aqueous solution ($Na_2HPO_4 \cdot 12H_2O$-citric acid$\cdot H_2O$) of pH 7.0.

d) The half-wave reduction potentials (volts vs. Ag/0.1 M $AgClO_4$) in DMF containing 0.1 M Tetraethylammonium perchlorate.

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