ACETALS OF LACTAMS AND ACID AMIDES

XXVIII.* IONIZATION CONSTANTS OF 4-PYRIDONES CONDENSED WITH PYRROLIDINE, PIPERIDINE, AND HEXAHYDROAZEPINE RINGS

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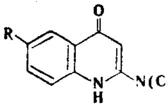
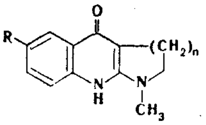
The ionization constants of 4-quinolone, pyrrolo-, pyrido-, and azepinoquinolines, pyrido[2,3-d]pyrimidine, and pyrrolo-, pyrido-, and azepino[2,3-b]pyrido[2,3-d]pyrimidines were measured. The effect of the size of the condensed saturated azaheteroring on the acidities and basicities of the examined systems is discussed.

A large number of studies have been devoted to the problem of the dependence of the properties of cyclic systems on the ring size [2]. The difference in the properties of such compounds is determined by the ring strain, steric factors, and various polar effects. In 1930 Mills and Nixon [3] advanced a theoretical substantiation of their observed experimental fact of a change in the direction of bromination as a function of whether the benzene ring is fused with a five- or six-membered ring [3]. Although the interpretation of these authors presently can hardly be considered to be satisfactory [4], there is no doubt about the effect of the ring size on the properties of the molecules (which has come to be known as the Mills–Nixon effect). A rational explanation of this phenomenon can be found in a number of cases. From this point of view the concept of I strain, which has recently been extended to systems that include more than one sp^2 atom in the ring [6], developed by Brown and coworkers [5] is extremely attractive. However, in many cases (for example, see [7]) the interpretation of the results also currently being obtained is fraught with difficulties.

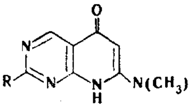
The aim of the present research was to measure the ionization constants of derivatives of 4-quinolone (I), pyrrolo-, pyrido-, and azepinoquinolines (II-IV), pyrido[2,3-d]pyrimidine (V), and pyrrolo-, pyrido-, and azepino[2,3-b]pyrido[2,3-d]pyrimidines (VI) and an examination of the effect of the size of the condensed saturated azaheteroring on the acidities and basicities of the examined systems.



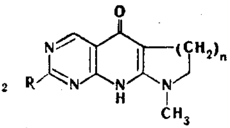
I a-c



II-IV a-c



V a, b



VI-VIII a, b

I–VIIIa R=H; I–IVb R=Cl; c $R=NO_2$; V–VIIIb $R=SCH_3$; I, II, VI n=1; III, VII n=2; IV, VIII n=3

It is apparent from the data presented in Table 1 that the effect of substituents on the ionization constants corresponds to the expected effect: The introduction of a chlorine atom in the benzene ring lowers the basicity by ~ 0.5 of an order of magnitude and increases the acidity of the compounds by ~ 0.5 of an order of magnitude. A nitro group in the 6 position of the quinoline ring increases the acidity even more (by ~ 1.5 orders of magnitude), and replacement of the benzene ring by a pyrimidine ring leads to the development of distinctly expressed acidic properties in the corresponding compounds (V-VIII, $pK_a \sim 6.6$-7.7).

The interpretation of the dependence of the ionization constants on the size of the condensed saturated ring is considerably more complex.

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[*] See [1] for communication XXVII.

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TABLE 1. Ionization Constants of I-VIII

Compound *	pK_a (addition of a proton)	pK_a (detachment of a proton)	Compound *	pK_a (addition of a proton)	pK_a (detachment of a proton)
Ia	5,49±0,06	11,92±0,06	IIIc	—	10,50±0,02
IIa	5,60±0,05	12,55±0,07	IVc	—	10,51±0,05
IIIa	5,31±0,06	12,65±0,07	Va	—	7,24±0,03
IVa	4,97±0,06	12,70±0,06	VIa	—	6,60±0,04
Ib	4,90±0,04	11,40±0,08	VIIa	—	7,56±0,1
IIb	5,01±0,06	11,68±0,07	VIIIa	—	7,54±0,05
IIIb	4,67±0,06	12,02±0,08	Vb	—	7,27±0,05
IVb	4,41±0,04	12,01±0,07	VIIb	—	7,58±0,05
Ic	—	10,28±0,08	VIIIb	—	7,68±0,04
IIc	—	10,40±0,07			

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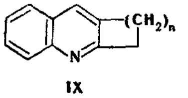
*The pK_a values of I-IV were measured in 70% aqueous dimethylformamide (DMF) and the pK_a values of V-VIII were measured in 10% aqueous DMF.

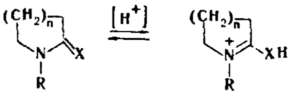
There are data [7] that provide evidence for the appreciable effect of the size of such a ring on the pK_a values of the heterocyclic compounds. Thus the basicities of condensed quinolines (IX) increase successively as the size of the condensed ring increases from a four-membered system to a six-membered system (for comparison, the pK_a value of 2,3-dimethylquinoline is 5.99) [7].



IX

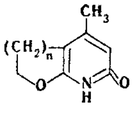
n=1 pK_a=4.55
n=2 pK_a=5.45
n=3 pK_a=6.41

This phenomenon has been explained [7] by the increased electron-acceptor effect of small rings as compared with a six-membered ring. It is also known that in a number of systems, the protonation of which proceeds at the exocyclic O, N, and C atoms – in lactams, amidines, and enamines – six-membered compounds are the most basic systems, and five-membered compounds are the least basic systems [8-12].



n = 1-3; X = O, N<, C<

The interpretation of these data is based on the assumption of destabilization of the ionized forms of these systems in the case of five- and seven-membered rings because of the additional strain that arises as the double bond migrates to the endocyclic position.



X

	pK_a Proton detachment	pK_a Proton addition
n=1	8.92	1.95
n=2	10.17	1.94

Measurements of the ionization constants of condensed 2-pyridones (X) show that the compound with a five-membered ring has substantially greater acidity than its six-membered analog, whereas the basicities of these compounds are equal [7].

To explain these facts, Spinner and Yeoh [7] invoke the Miller–Nixon effect (during which they also use the essential features of the concept in [3]) and the concept of the greater electron-acceptor strength (in this case the smaller electron-donor effect) of the five-membered ring as compared with the six-membered ring.

Two-ring systems X have a certain similarity to the systems studied in the present research: Their protonation also takes place at the exocyclic oxygen atom,* and a proton is detached from the nitrogen atom of the pyridine ring.

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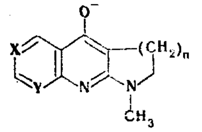
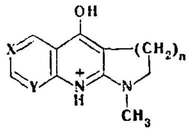
*It has been shown [13] that the tetrafluoroborate salt of IVa has the 1-methyl-6-hydroxy-2,3,4,5-tetrahydroazepino[2,3-b]quinolinium tetrafluoroborate structure, i.e., the site of protonation of IV is the oxygen atom of the carbonyl group in the 6 position.

It follows from an examination of the results presented in Table 1 that the basicities of the investigated compounds decrease in the order II > I > III > IV, i.e., quinoline derivatives condensed with a five-membered ring are the most basic compounds, and quinoline derivatives condensed with a seven-membered ring are the least basic compounds. Two-ring systems I have the highest acidities among the quinoline derivatives, and thereafter the acidities decrease in the order $5 > 6 \approx 7$ as a function of the size of the condensed saturated ring. The order of acidity of the three-ring derivatives is retained for the series of pyridopyrimidine derivatives, i.e., the pK_a values of the compounds with six- and seven-membered rings are close to one another, and pyrrolopyridopyrimidine VIa is a substantially stronger acid (its acidity is even higher than the acidity of two-ring system Va).

Proceeding from general considerations, during an examination of the polar effects one should direct greater attention to the final states of the investigated equilibria (the protonated form and the anion), since transmission of these effects is more pronounced in the ionized form. If one assumes that conjugation of the nitrogen atom in the 2 position of the quinoline or pyridopyrimidine system is realized most fully in the case of a six-membered saturated ring, the above-indicated order of the change in the acidities in the three-ring systems can be interpreted by starting from the polar effects.


A

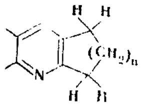

B

In fact, anion A will be less destabilized, the smaller the degree to which the electron-donor effect of the third saturated ring is expressed, i.e., pyrroline derivatives IIa, IIb, IIc, and VIa should have higher acidities than piperidine derivatives IIIa, IIIb, IIIc, and IIa. However, this explanation does not answer the question as to why two-ring compounds Ia, Ib, Ic, and Va are stronger acids than three-ring systems with a condensed six-membered ring. In addition, in the case of an approach of this type it remains unclear why the basicities of five-membered compounds IIa and IIb are actually higher than the basicities of their six-membered analogs.

With respect to cations of the B type an examination of the polar effects should lead to the reverse pattern: The high degree of conjugation of the unshared electron pair of the nitrogen atom in the case of the six-membered ring should ensure the highest stabilization in this series of cations and, correspondingly, the highest basicities of piperidinoquinoline derivatives IIIa, b. The explanation of the data obtained on the basis of an examination only of the electronic effects is consequently inadequate.

In this connection, we made an attempt to examine the observed changes in the ionization constants from the point of view of the possibility of solvation of the anionic and cationic centers of A and B as a function of the size of the saturated azaheteroring. It appears that the degree of effectiveness of solvation in this case should be determined to a greater extent by the steric effect than by the polar effect.

The literature contains data that show that the five-membered ring in compounds of the XI type shields the 1 and 4 positions of the pyridine ring to a substantially lesser extent than the six-membered ring, which in turn creates somewhat less steric hindrance to attack at these positions than the seven-membered ring [14].


XI
n = 1–3

If these data are applied to the systems under investigation in this paper, it becomes possible to explain all of the results obtained.

Let us examine the results of measurement of the basicities. In the case of IIa steric hindrance to solvation is a minimum, and this factor turns out to be more important than the electronic effect. Hence IIa has the maximum basicity of all the remaining representatives of this series. In the case of seven-membered IVa the steric and polar effects act in the same direction and cause a decrease in its basicity as compared with piperidine analog IIIa.

The comparison of the data obtained for chloro derivatives Ib, IIb, IIIb, and IVb is completely analogous.

In examining the acidities of quinoline derivatives I-IV one should bear in mind that the negative charge in the anion is concentrated to the greatest extent on the oxygen atom of A and that the possibility of solvation of precisely this atom plays a principal role. It is clear that the steric hindrance to solvation is expressed to a lesser extent in two-ring systems Ia-c and compounds with a five-membered ring (IIa-c). In conformity with this, the former are the strongest acids in the series of compounds I-IV, followed by II, while the acidities of substances with piperidine (IIIa-c) and hexahydroazepine (IVa-c) rings are close to one another.

As we have already pointed out (see also Table 1), the strongest acid among pyrido[2,3-d]pyrimidine derivatives V-VIII is pyrrolino[2,3-b]pyrido[2,3-d]pyrimidine VIa. This phenomenon is evidently due to the fact that the presence of an electron-acceptor pyrimidine ring gives rise to a substantial increase in the role of the polar effect as compared with the solvation effect. In the case of VIa these effects act in the same direction (see above), and this also determines its increased acidity as compared with two-ring systems Va, b, six-membered systems VIIa, b, and seven-membered analogs VIIIa, b.

EXPERIMENTAL

Compounds I-VIII were previously described in [1, 13, 15, 16]. The dissociation constants were determined by potentiometric titration by means of a PHM-26 pH meter (Radiometer, Denmark) with glass (G 2222) and calomel electrodes. The pH meter was adjusted by means of aqueous buffer solutions.

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