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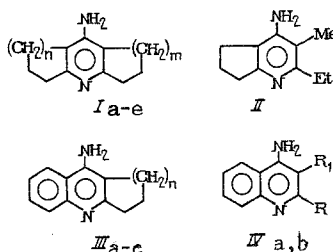
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The role of ionization in the appearance of biological activity in different classes of organic compounds is quite significant: for example, ionization can facilitate the appearance of selectivity of action of biologically active compounds, substantially affect their adsorption on the receptor surface, the permeability through the biological membranes, etc. [1]. So it is quite important to know the degree of ionization of biologically active compounds in studying their biological effect and to accordingly measure the ionization constants of these substances and their analogs.

In this paper, we have measured the pK_a values of the drugs amiridin [5] and tacrine [15], and also a number of structurally similar compounds.

Another aspect of our investigation was a continuation of the study of the effect of the size of the saturated ring on the ionization constants of aminopyridine derivatives, which was done with other systems earlier in [3, 16].

As the compounds to study, we selected bicyclic and tricyclic derivatives (Ia-e), (II), (IIIa-c), and (IVa, b).



I: $n=m=1$ (a), $n=1$, $m=2$ (b), $n=1$, $m=3$ (c), $n=m=2$ (d),
 $n=2$, $m=3$ (e); III: $n=1$ (a), $n=2$ (b, tacrine), $n=3$ (c); IV: $R=$
 $=Me$, $R'=H$ (a), $R=Et$, $R'=Me$ (b).

In the first stage of the work, using UV spectroscopy we studied the protonation site of the derivatives under investigation. It is well known that 4-aminopyridine and 4-aminoquinoline are protonated at the cyclic nitrogen atom [8]. Upon going from the neutral molecule (N) and the cation (C), in the spectrum of 4-aminopyridine we observe a bathochromic shift of the short-wavelength band with a small change in the position of the long-wavelength band and an increase in the intensity of both bands. As a result of these changes, for the cation we observe a single absorption maximum. Comparison of the effect of protonation for 4-aminopyridine and the compounds Ia-e, II shows (Table 1) that annelation of saturated rings, like substitution in the 2,3 positions by alkyl groups, does not change the overall pattern and we can unambiguously say that protonation of these compounds also occurs at the cyclic pyridine nitrogen atom. The UV spectral data suggest that we observe the same pattern also for compounds III and IV.

The studied compounds were synthesized by reaction of enaminonitriles (V) or anthranylonitrile (VI) with the corresponding ketones in the presence of $ZnCl_2$:

TABLE 1. Characteristic Absorption Bands in UV Spectra of Neutral Molecules (N) and Cations (C)

Compound	Form of compound	λ_{\max} , nm (lg ϵ)			
4-Amino-pyridine	N	264(3,43)	243(4,13)		
Ia	C		263(4,30)		
	N	264(3,73)	246(3,99)		
	C		267(4,26)		
Ib	N	264(3,71)	246(3,93)		
	C		267(4,24)		
Ic	N	265(3,62)	243(3,96)		
	C		267(4,20)		
Id	N	264(3,71)	248(3,88)		
	C		268(4,17)		
Ie	N	264(3,55)	243(3,94)		
	C		267(4,17)		
II	N	264(3,58)	244(3,92)		
	C		267(4,20)		
IIIa	N		308(3,86)	235(4,52)	
	C	331(4,03)	319(4,06)	239(4,56)	
IIb	N		317(3,88)	237(4,57)	
	C	335(4,02)	324(4,07)	240(4,62)	
IIIc	N		312(3,83)	236(4,49)	
	C	331(4,02)	320(4,04)	240(4,54)	
IVa	N		307(3,82)	231(4,40)	
	C	330(3,96)	319(4,03)	236(4,43)	
IVb	N		308(3,86)	234(4,55)	
	C	331(4,06)	321(4,09)	238(4,60)	

*Absorption bands for neutral molecules (N) off 4-aminopyridine, Ia, IIIa-c, IVa,b in 0.01 N KOH; for compounds Ib-e, II in 0.01 N KOH; for cations (C), in water at pH 6.5.

TABLE 2. Ionization Constants of Compounds I-IV

Compound	λ_a , nm	C_m/l 10^{-5}	pKa	Error in determination
Ia	267	2,0	9,47	0,06
Ib	267	3,0	10,10	0,01
Ic	267	3,0	9,85	0,04
Id*	268	3,0	10,96	0,04
Ie	267	3,0	10,70	0,03
II	267	3,0	10,17	0,06
IIIa	331	4,0	9,00	0,05
IIIb†	335	4,0	9,82	0,03
IIIc	331	4,0	9,55	0,06
IVa	319	6,0	9,63	0,05
IVb‡	331	4,0	9,80	0,02

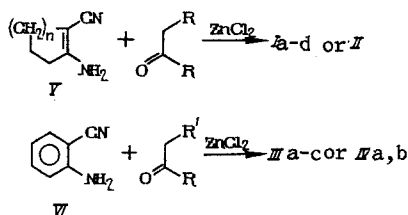
Lit. data for pKa:

*10.76 [9], 11.0 [13].

†9.85 [9].

‡9.59 [9].

** λ_a are the analytical wavelengths.



The ionization constants of compounds I-IV, determined spectrophotometrically, are presented in Table 2.

As we see from these data, all the compounds obtained are strong bases, which might be expected from the rather high basicity of 4-aminopyridine ($pK_a = 9.17$ [8]) and 4-aminoquinoline ($pK_a = 9.17$ [8]). From the experimental data obtained it follows that the most characteristic feature of the studied compounds is the clear dependence of the magnitudes of the ionization constants on the size of the condensed saturated rings. This corresponds to the familiar idea that the annelated cycloalkyl fragments affect the physicochemical and chemical properties of different heterocycles [2]. The observed dependence on the whole can be summed up as follows: the presence of a condensed five-membered ring leads to reduction of the basicity compared with compounds having a six-membered saturated ring or compounds with acyclic alkyl fragments in the 2,3 positions of the pyridine ring. Compounds with an annelated seven-membered ring are intermediate in basicity. Three major factors affect the pK_a values in the studied compounds. First of all, introduction of alkyl or cycloalkyl substituents should probably lead to some increase in the basicity as a result of their positive induction effect. Secondly, the best conditions for solvation of the cation are realized in the case of a condensed five-membered ring (for steric reasons); the worst conditions occur in the case of a seven-membered ring. Thirdly, according to the Streitwiser-Finnegan concept [10, 14], the presence of a strained ring (in this case, this refers only to five-membered compounds) condensed with an aromatic (pyridine) nucleus leads to a reduction in the electron density at the α -position of the pyridine ring, i.e., at the cyclic nitrogen atom, which is the protonation site. This in turn is responsible for destabilization of the cations of the correspond-

ing compounds (for example, Ia, II, IIIa) and consequently reduction in their basicity. While the first factor has hardly any substantial effect on the pK_a values of the studied systems, the basicity series we obtained for compounds I-IV can be explained by superposition of the second and third factors: $6 \approx \text{acyclic substituents} > 7 > 5$.

Thus our data show that amiridin, tacrine, and related drugs are completely ionized at physiological pH values, which should be considered when interpreting the mechanism of their biological action.

EXPERIMENTAL

The ionization constants were determined spectrophotometrically at a temperature of 25°C. The UV spectra and the optical densities at the analytical wavelengths were measured on the Specord M40 spectrometer (West Germany). The pH of the buffer and working solutions was measured on the I-155 pH meter. The starting solution of the test compound was prepared in a 50 ml volumetric flask by dissolving a weighed amount in 25 ml 96% ethanol and diluting with water. The working solutions were prepared in 50 ml volumetric flasks by diluting 1 ml of the starting solution with the buffer solutions. The pK_a value was determined for a series of seven working solutions in the pH range of $pK_a \pm 0.6$. The analytical wavelengths, the concentrations of the working solutions, and the accuracy of the pK_a determination are presented in Table 2. The IR spectra were obtained in vaseline on the Specord IR 75 instrument (West Germany); the mass spectra were recorded on the MKh 1321A instrument for an ionization energy of 30 eV with direct injection of the sample into the ion source. In the mass spectra of the compounds obtained, the molecular ion peaks correspond to the computed molecular masses.

The melting points were determined on the PTP apparatus.

The course of the reaction and the purity of the compounds obtained were monitored by TLC (Silufol UV-254, benzene-absolute ether-ammonia, 40:9:1; CHCl_3 -MeOH-ammonia, 70:30:1).

Compound 16 was obtained from the drug amiridin.

Polymethylene-4-aminopyridines (I, II). 0.01 moles enamionitrile V, 0.02 moles ketone, and 1.5 g anhydrous ZnCl_2 in 25 ml dry xylene were boiled with a reflux condenser for 2-8 h and cooled. The xylene solution was decanted and the gummy residue was ground in 25 ml 5 N KOH. The residue was filtered off and washed with water, suspended in hot CHCl_3 , and filtered. The CHCl_3 was driven off, the residue was chromatographed on a column (diameter 3 cm, length 20 cm) with silica gel L 100/250 μ first in CHCl_3 , then in the system benzene-absolute alcohol-ammonia, 40:9:1. The major fraction was concentrated and the substance was crystallized from aqueous alcohol. By this method we obtained: Ia $\cdot\text{H}_2\text{O}$, m.p. 201-202°C (198-200°C [7]); Ic, m.p. 213-214°C (213-214°C [7]); Id, m.p. 218-220°C (218-219°C [4]); Ie, yield 25%, m.p. 216-217°C. IR spectrum, ν_{max} , cm^{-1} : 3480, 8300, 3160, 1630, 1560. Found, %: C 78.17; H 9.40; N 13.10; M^+ 216. $\text{C}_{14}\text{H}_{20}\text{N}_2$. Calculated %: C 77.73; H 9.32; N 12.96; II $\cdot\text{H}_2\text{O}$, yield 25%, m.p. 150-151°C. Found, %: N 14.46, M^+ 176. $\text{CH}_{11}\text{H}_{18}\text{N}_2\text{O}$. Calculated, %: N 14.42. IR spectrum, ν_{max} , cm^{-1} : 3440, 3360, 3220, 1660, 1570.

(Polymethylene(dialkyl)-4-aminoquinolines (III, IV). 0.01 moles anthranilonitrile VI, 0.03 moles ketone, and 1.5 g anhydrous ZnCl_2 were boiled with a reflux condenser for 2-15 h and cooled. 20 ml ether was added and the residue was filtered off and dried in air. 25 ml 5 N KOH was added to the residue, stirred, and allowed to stand overnight. The residue was filtered off, washed with water, and dried on the filter. 50 ml alcohol was added to the residue, boiled for 20-30 min, and filtered. The alcohol was driven off and the residue was crystallized from aqueous alcohol. By this method we obtained: IIIa $\cdot\text{H}_2\text{O}$, m.p. 179.5-180.5°C (176°C [11]); IIIb, m.p. 181-182°C (183-184°C [12]); IIIc m.p. 205-206°C (176-177°C [6]), M^+ 212; IVa, m.p. 167.5-168.5°C (169-170°C [12]); IVb, m.p. 145-146°C (144-146°C [19]).

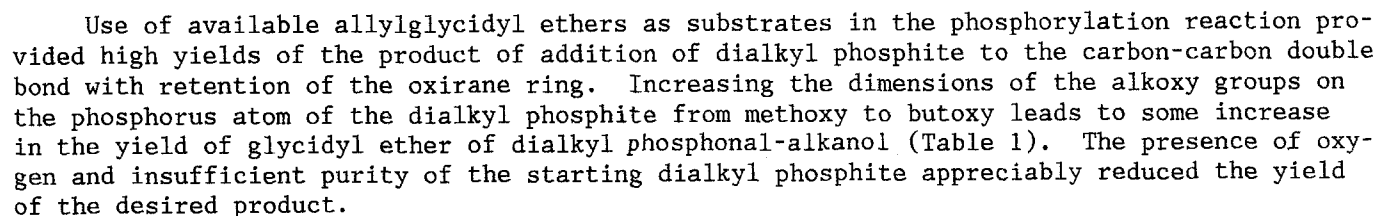
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- SYNTHESIS AND STUDY OF THE TOXIC AND PSYCHOTROPIC PROPERTIES
-
- OF 3-DIALKOXYPHOSPHORYLPROPYLGLYCIDYL ETHERS

UDC 547.466.6:615.225.2

The synthesis of 3-dialkoxyphosphorylpropylglycidyl ethers was brought about by homolytic phosphorylation of allylglycidyl ether by the corresponding dialkyl phosphite [1] in the presence of tert-butylbenzoyl peroxide as initiator at a temperature of 140-170°C and a molar ratio of dialkylphosphite: allylglycidyl ether: peroxide of 3.0-4.0:1.0:0.02-0.03 according to the scheme:



The ^1H NMR spectra were registered on a Tesla BS-567 A (100 MHz) instrument in the FT regime using 10-15% solutions in deuteroacetone at 20-25°C sample temperature, and with hexa-

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