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BASIC AND ACIDIC CHARACTERISTICS OF COMPOUNDS OF THE 3-AMINO-1-IMINO-1H-ISOINDOLE SERIES

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The basic and acidic characteristics of N,N'-diaryl- and N,N'-dimethyl-substituted 3-amino-1-imino-1H-isoindoles, which are determined by electronic factors related to the nature of the substituents at the exocyclic nitrogen atoms, were studied. Electron-donating alkyl groups lead to an increase in the basicity of these compounds. The introduction of aryl groups containing electron-withdrawing substituents (NO_2, COMe) at the p-positions leads to significant weakening of the basic characteristics and strengthening of the acidic characteristics. The protonation and deprotonation and also methylation processes in the series of compounds were studied.

Keywords: N,N'-diaryl- and N,N'-dimethyl-substituted 3-amino-1-imino-1H-isoindoles, deprotonation, methylation, protonation, spectral characteristics.

As shown earlier [1, 2], the 1,3-diimino derivatives of 1H-isoindole generally exist in two tautomeric forms – 3-amino-1-imino-1H-isoindole (**a**) and 1,3-diimino-2,3-dihydro-1H-isoindole (**b**). The position of the tautomeric equilibrium is determined primarily by the electronic nature of the substituents at the exocyclic nitrogen atoms. In the series of diaryl-substituted derivatives the ratio of the tautomers depends on the substituents in the aromatic ring. In addition, they exhibit *Z,E*-isomerism in relation to the C=N bonds.

The aminoimino derivatives of 1H-isoindole are unique amidines with a N=C–N=C–N pentad. They contain three potential basicity centers, two of which in the tautomeric form **b** are degenerate. It seemed interesting to study the direction of their protonation since this aspect has been inadequately covered in the literature [3, 4]. In the investigated N,N'-diaryl-substituted 1H-isoindoles **1-12** (Table 1), to judge from the experimental data, it takes place at one of the exocyclic nitrogen atoms with the formation of structures that are derivatives of the 3-amino-1-imino-1H-isoindole asymmetric tautomeric form **a**.

Such direction of the proton attack is probably due, first, to the higher basicity of the exocyclic imine nitrogen atom and, second, to the formation of a cation of type **c**, in which effective delocalization of charge is possible. In the electronic spectra of compounds **1-12** (Table 1) the most long-wave maxima are in the region between 300 and 471 nm. For compounds **8-12**, which contain substituents at the *p*-positions of the N-aryl rings, they lie in a region of longer wavelengths than in the isomeric *o*-substituted derivatives as a result, clearly, of the higher degree of planarity in their molecules.

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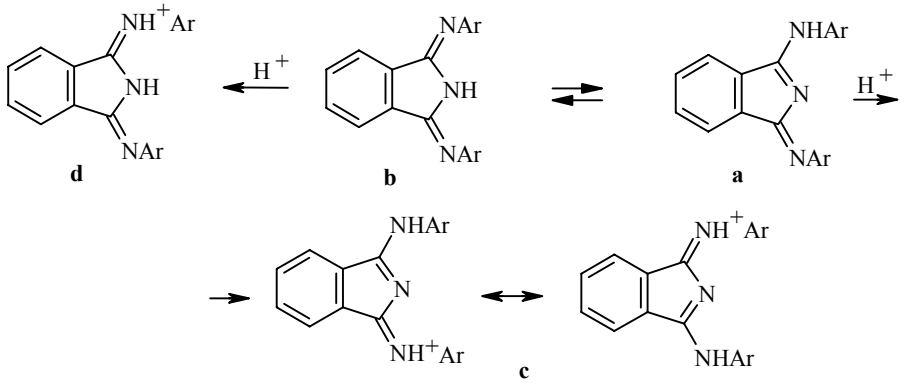
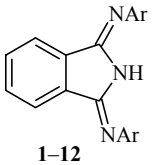


With the addition of acid to ethanol solutions of compounds **7**-**12** the absorption maxima in their electronic spectra are shifted significantly toward the longwave region, and the molar absorption coefficients are at the same time increased (Table 1). The largest bathochromic shift is observed in the *p*-dimethylamino-substituted **10** (112 nm). Such increase in λ_{max} can be explained by the existence of the protonated compounds in form **c**, since the length of the conjugation chain here is increased in comparison with the neutral molecule or the alternative structure **d**.

The conclusions made on the basis of the electronic spectra are supported by the data from the ^{1}H NMR spectra. The ^{1}H NMR spectrum of the salt **13** solution (from the 4-methylphenyl-substituted 1H-isoindole **8**) in DMSO-d_6 at 293 K consists of a singlet for the protons of the methyl groups at the *p*-positions of the N-aryl rings (2.35 ppm), a symmetrical AA'BB' multiplet for the *o*- and *m*-protons of the N-aryl rings (8.00 and 7.35 ppm), a symmetrical multiplet of the AA'BB' type for the 4- and 7- protons of the H-isoindole ring

TABLE 1. The Characteristics of the Absorption Bands in the Electronic Spectra of 1,3-Di(arylimino)-2,3-dihydro-1H-isoindoles **1**-**12** in Ethanol

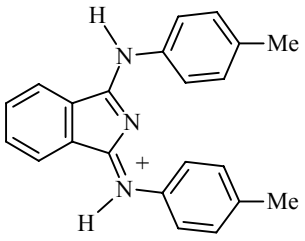


1–**12**

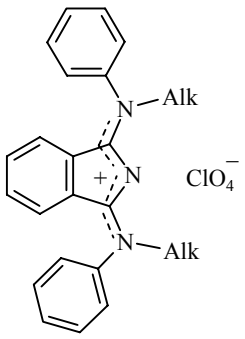
Com-pound	Ar	λ_{max}, nm ($\varepsilon \cdot 10^{-4}$)	
		Neutral form	Protonated form
1	2-MeC_6H_4	264 (2.18), 308* (1.02)	
2	2,4-$Me_2C_6H_3$	340 (0.68)	
3	2,4,6-$Me_3C_6H_2$	267 (2.10), 303* (0.82)	
4	2-$MeOC_6H_4$	348 (0.78)	
5	2-ClC_6H_4	264 (2.09), 307* (1.01)	
6	2-BrC_6H_4	265 (2.23), 307* (0.54)	
7	C_6H_5	308 (0.88)	354 (1.55), 424 (1.29)
8	4-MeC_6H_4	360 (0.84)	365 (1.38), 433 (1.24)
9	4-$MeOC_6H_4$	405* (0.93), 384 (0.97)	410 (1.42), 360 (1.48)
10	4-$Me_2NC_6H_4$	471 (1.29)	351 (1.29), 583 (0.47)
11	4-$MeC(O)C_6H_4$	285 (0.62), 315* (1.07)	
12	4-$O_2NC_6H_4$	310 (2.33)	358* (1.08)

* Inflection

($\delta_{4\text{-H},7\text{-H}}$ 8.71, $\delta_{5\text{-H},6\text{-H}}$ 7.78 ppm), and a broad signal for the two protons of the NH groups in the region of 13.5 ppm. The symmetrical pattern of the signals of the aromatic protons and the singlet for the protons of the methyl group make it possible to conclude that such a type of spectrum corresponds to structure **13** with a protonated exocyclic nitrogen atom. In contrast to the quaternary immonium salts of type **e** [5] and the free base with the *Z*,*Z*- and *Z*,*E*-configuration for the N-aryl substituents [1], the salt **13** has the *Z*,*Z*-configuration, as demonstrated by the downfield shift of the signals of 4- and 7-H (8.71 ppm) compared with the signal of the same protons in the corresponding immonium salts of type **e** (6.5-6.7 ppm).



13 (*Z*,*Z*)



e (*E*,*E*)

If the temperature of the sample is increased to 373 K, only the signals of the 4-H and 7-H protons of the isoindole ring and the *o*- and *m*-protons of the N-aryl rings in its ^{1}H NMR spectrum are broadened. Such changes are probably due the deprotonation–protonation process, reflected primarily in the signals of the protons situated in direct proximity to the exocyclic nitrogen atoms.

A more complex pattern is typical of 3-(N-methyl)amino-1-(N-methyl)imino-1H-isoindole (**14**), which (as shown in [1]) exists preferentially in the unsymmetrical tautomeric form **a**.

Spectrophotometric investigations of this compound showed that there are two ranges of pH in which the positions of the absorption maxima and their intensities change, i.e., at pH ~1 and in the range of 7-10 (Fig. 1). It was possible to estimate quantitatively the ability of compounds of the investigated series to be deprotonated by the Comar method [6].

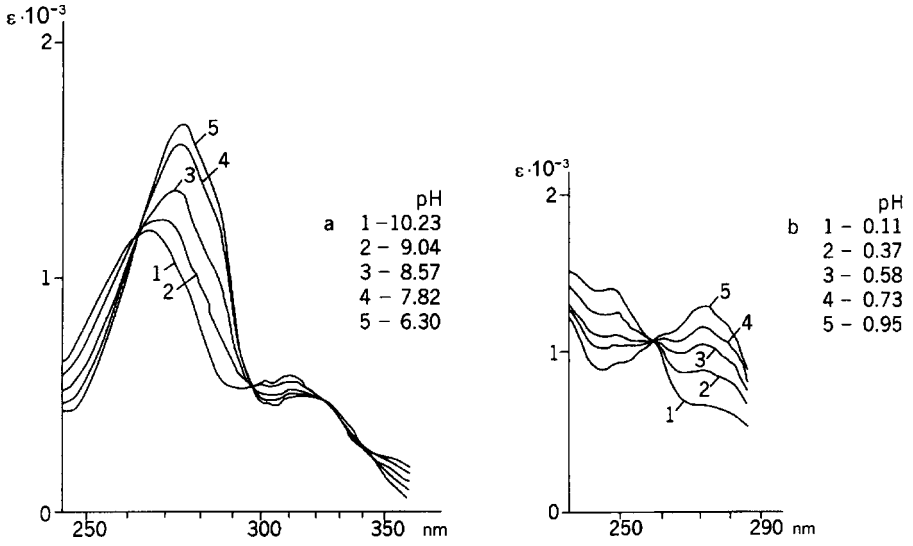
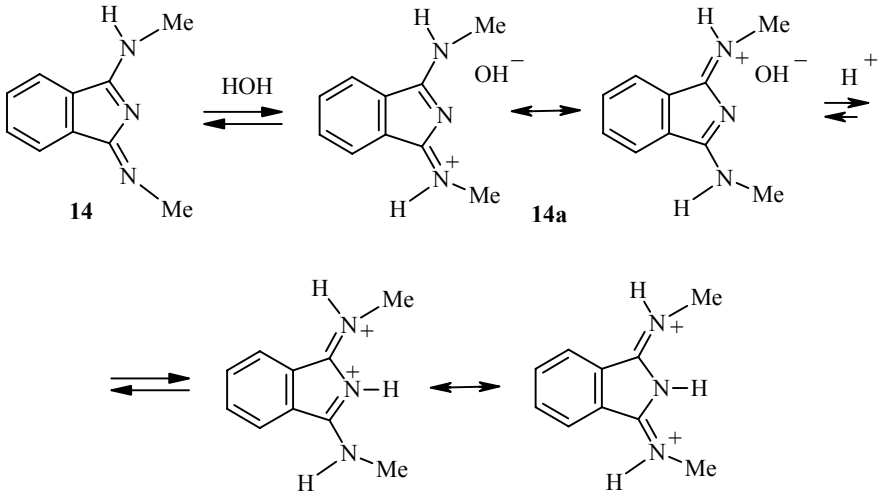


Fig. 1. The dependence of the electronic spectra of compound **14** on the pH of the medium (ethanol–water, 1:1): a) $c = 5.8 \cdot 10^{-4}$; b) $c = 2.9 \cdot 10^{-4}$.

In acidic and neutral water–ethanol (1:1) solutions of compound **14** its absorption spectra are identical and have two maxima at 273 and 310 nm. At pH values of 7-10 the absorption curve changes: The maximum at 273 nm undergoes a hypsochromic shift to 265 nm with a simultaneous decrease in intensity. The more longwave but weaker maximum (310 nm) also undergoes a slight hypsochromic shift.

The identical form of the absorption curves in the acidic and alkaline media (up to pH 10) is probably due to the fact that compound **14** in water–alcohol solutions exists in the hydrated form, which was isolated in the individual state [1]. It can be supposed that this hydrate is in equilibrium with the ionic hydroxide **14a**.

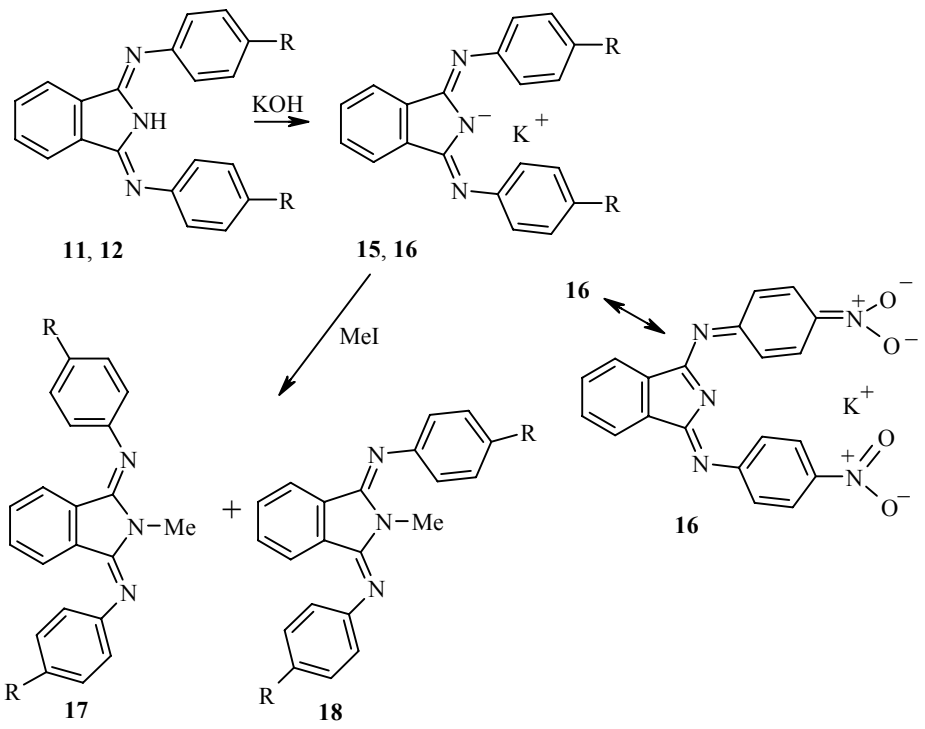
The nature of the absorption curve only changes in a strongly acidic medium (pH 0.1-1.0); λ_{max} 273 gradually disappears, which can be explained by the protonation process. The deprotonation constant determined for this region of pH values is 0.8. Such a value is probably explained by the fact that its hydrated form and not the neutral molecule undergoes protonation:



The second transition at pH values between 7 and 10 can characterize the deprotonation of form **14a** and the displacement of the equilibrium toward the neutral molecule. The deprotonation constant, determined from measurements at the given pH values, amounts to 8.69±0.02 and characterizes compound **14** as a strong base. For comparison it should be noted that the pK_a value determined for unsubstituted 3-amino-1-imino-1H-isoindole by electrometric titration amounts to 7.47 [7].

With the introduction of electron-withdrawing groups into the molecules of N-aryl-substituted 1H-isoindoles their basicity is substantially reduced, and they begin to exhibit the characteristics of weak NH acids. The capacity for deprotonation shows up particularly clearly with the introduction of such electron-withdrawing groups as acetyl (compound **11**) and nitro (compound **12**) at the *p*-position of the phenyl rings in the molecules of the N,N'-disubstituted 1,3-diimino-1H-isoindoles. The action of aqueous ammonia, an aqueous solution of potassium hydroxide, or sodium methoxide on compounds **11** and **12** leads to the formation of the deeply colored salts **15** and **16**. For the 4-nitro derivative it was possible to isolate its potassium salt **16** and recrystallize it from a strongly alkaline alcohol solution.

The UV spectra of the neutral molecules of compounds **11** and **12** in water–alcohol (1:1) solutions contain one longwave absorption maximum in the near UV region: 280 (**11**) and 334 nm (**12**). In the UV spectra of these compounds at pH 11 and 9 the maxima in the near UV region disappear, and there are two longwave absorption maxima, one of which is in the visible region: 335 and 440 (**11**); 380 and 500 nm (**12**) (Fig. 2). The appearance of these bands is due to the presence of the deprotonated forms in the alkaline solutions, in which a high degree of delocalization of the negative charge in the organic anion is possible as, for example, in compound **16**.



15, **17** (*E*,*E*) R = COMe; **16**, **18** (70% *E*,*E*, 30% *Z*,*E*) R = NO_2

The large bathochromic shift of λ_{max} (60 nm) in the *p*-nitro derivative **12** compared with its acetyl analog **11** is clearly due to the stronger electron-withdrawing characteristics of the nitro group.

The pH values at which the transition from the neutral form to the deprotonated form takes place most clearly were selected by measuring the absorption spectra of compounds **11** and **12**. For the diacetyl derivative **11** (c $2.55 \cdot 10^{-4}$) such a transition is observed at pH 11.1-12.4 (Fig. 2). From the spectra recorded in this range the deprotonation constant pK_a 12.0±0.1, which characterizes this substance as a weak NH acid, was obtained.

For the *p*-nitro-substituted **12** it was possible to determine only the approximate value of the deprotonation constant (pK ~ 9.0), which demonstrates the more clearly defined acid function of this compound. It was not possible to determine the exact pK_a value of compound **12** by the employed method, since this substance is unstable in alkaline water–alcohol solutions.

The ease of removal of a proton during the action of bases is confirmed by its substitution by an organic residue. The potassium salts of compounds **11** and **12** react with methyl iodide in a reaction of the Gabriel type, forming good yields of 2-methyl-substituted 1,3-diarylimino-1H-isoindoles **17** and **18**. Methylation takes place, as described earlier for the methyl-substituted 1H-isoindoles **1**, **8** [1], at the endocyclic nitrogen atom, as follows from the ^{1}H NMR spectra of the derivatives **17**, **18**. The substituents have the *E*,*E*-configuration in relation to the C=N bonds, as shown by the upfield shift of the signals of the 4-H and 7-H nuclei. However, in the case of the 4-nitro-substituted **18** in the ^{1}H NMR spectra of solutions in DMSO-d_6 and deuterochloroform there are additional signals belonging, probably, to the *Z*,*E*-isomer, the content of which is not greater than 30%.

Thus, it can be concluded that the basic and acidic characteristics of the investigated compounds of the 3-amino-1-imino-1H-isoindole series are determined predominantly by electronic factors related to the nature of the substituents at the exocyclic nitrogen atoms. Electron-donating alkyl groups lead to increase in the nucleophilicity of the nitrogen atoms and accordingly the basicity of these compounds. The introduction of aryl groups containing electron-withdrawing substituents (NO_2, COMe) at the *p*-positions leads to significant weakening of the basic and strengthening of the acidic characteristics.

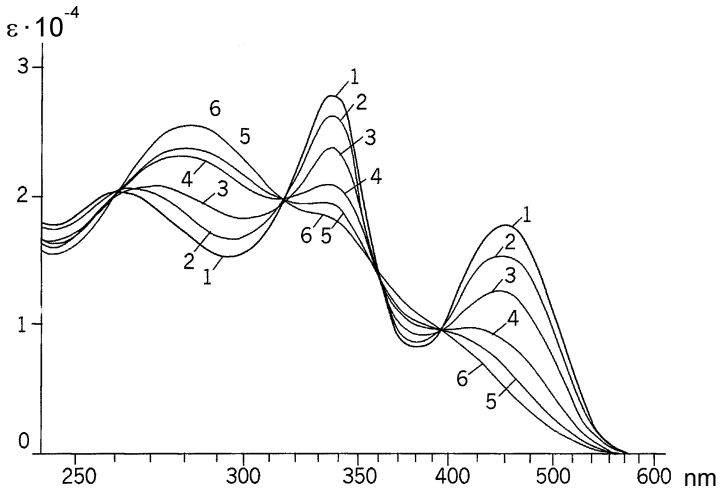


Fig. 2. The dependence of the electronic spectra of 1,3-di(acetylphenylimino)-2,3-dihydro-1H-isoindole (**11**) on the pH of the medium (ethanol–water, 1:1, *c* $2.55 \cdot 10^{-4}$ M): 1) 12.40; 2) 12.20; 3) 11.95; 4) 11.60; 5) 11.30; 6) 11.10.

EXPERIMENTAL

The spectral investigations were carried out on a Bruker HX-90E spectrometer (90 and 100 MHz) in the pulse mode with Fourier transformation and with TMS as internal standard. The absorption spectra were recorded on a Specord UV-Vis instrument.

The aminoimino-1H-isoindoles **1-12**, **14** were obtained from 1,1,3-trichloro-1H-isoindole according to the procedure in [5].

The Potassium Salt of 1,3-Di(4-nitrophenyl)imino-2,3-dihydro-1H-isoindole (16). A suspension of compound **12** (3.87 g, 10 mmol) was refluxed for 1 h with aqueous solution of potassium hydroxide (20 ml). The precipitate here became dark-red. The solution was decanted, ethanol was added to the hot suspension until the precipitate had completely dissolved, and the solution was filtered while hot. After cooling the product **16** in the form of dark needles with a metallic luster was filtered off, washed with an alkaline water–alcohol (1:1) solution, and dried. Yield 3.82 g (90%); mp >310°C. Found %: N 15.82. $C_{20}H_{12}KN_5O_4$. Calculated %: N 16.46.

1,3-Di[N-(4-acetylphenyl)]imino-2-methyl-2,3-dihydro-1H-isoindole (17). To a suspension of compound **11** (1.3 g, 3.4 mmol) in absolute ethanol (20 ml) with stirring we added potassium hydroxide (0.2 g, 3.4 mmol). The mixture was then heated to boiling. To the obtained solution we added methyl iodide (0.5 ml, 7.5 mmol). A yellow precipitate immediately appeared. The reaction mixture was refluxed for 2 h and kept at room temperature for ~16 h. The precipitate was filtered off, washed with ethanol and with water, and recrystallized from ethanol. Yield 1.0 g (78%); mp 232°C. ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz): 2.60 (3H, s, $COCH_3$); 3.46 (3H, s, N–CH_3); 6.70 (2H, dd, 4-, 7-H); 7.03 (4H, dd, J_{HH} = 8, *m*-H); 7.10 (2H, dd, 5-, 6-H); 7.98 (4H, dd, J_{HH} = 8, *o*-H). Found %: N 10.68. $C_{25}H_{21}N_3O_2$. Calculated %: N 10.63.

1,3-Di[N-(4-nitrophenyl)]imino-2-methyl-2,3-dihydro-1H-isoindole (18). To a suspension of compound **12** (0.64 g, 1.65 mmol) in absolute ethanol (50 ml) with stirring we added granulated potassium hydroxide (0.1 g, 2 mmol). The mixture was heated to boiling, and all the precipitate dissolved. To the dark-red solution we added methyl iodide (0.3 ml, 0.67 g, 4.69 mmol). Crystals soon appeared, and the solution became yellow. The reaction mixture was kept at room temperature for ~16 h. The yellow crystals were then filtered off, washed with 5 ml of ethanol and with water, and dried. Yield 0.36 g (86%); mp 297°C. ^{1}H NMR spectrum (deuterochloroform), δ, ppm, *J* (Hz). *E*,*E* isomer (70%): 3.49 (3H, s, N–Me); 6.77 (2H, dd, J_{HH} = 3, 4-, 7-H);

7.10 (4H, d, J_{HH} = 9, *m*-H); 7.30 (2H, m, 5-, 6-H); 8.29 (4H, d, J_{HH} = 9, *o*-H). *Z*,*E* isomer (30%): 3.72 (3H, s, N–Me); 6.12 (1H, d, J_{HH} = 9, 4-H); 7.10 (4H, d, J_{HH} = 9, *m*-H); 7.56 (2H, m, 5-, 6-H); 8.02 (1H, d, J_{HH} = 9, 7-H); 8.29 (4H, d, J_{HH} = 9, *o*-H). Found %: N 17.36. $C_{21}H_{15}N_5O_4$. Calculated %: N 17.45.

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