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PROTONATION OF DERIVATIVES OF PYRROLO(1,2-a)PYRAZINE AND PYRROLO(1,2-a)-PYRIMIDINE

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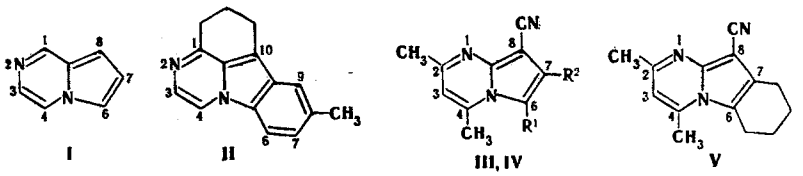
Study of the protonation of derivatives of 5- and 7-azaindoles [1, 2] has shown that the structure of the monocations of these compounds corresponds to a significant contribution of the quinonoid structure with transfer of the positive charge from the cation center – the nitrogen atom of the pyridine fragment, $N_{(5)}$ and $N_{(7)}$ respectively – to the pyrrole nitrogen atom $N_{(1)}$. Earlier [3] the predominance (~ 90%) of the para-quinonoid structure with transfer of the positive charge from the exocyclic amino group to the 4-aminopyridine cation has been established. The results of subsequent studies of the structure of the mono- and dications of the imidazo(4,5-b)pyrazines [4] compared with the results for the protonation of purine [5] suggested that the perturbation of the cation aromatic system, linked with delocalization of the positive charge, makes a considerable contribution to the stabilization energy of the protonated forms and to a significant degree determines the position of the mono-protonation center in polybasic heteroaromatic systems. From this point of view data relating to the structure of the protonated forms of ambi- and polydentate bases of the indolizine type and its aza analogs are of special interest.

We have studied the protonation of pyrrolo(1,2-a)pyrazine (I), 1,10-trimethylene-8-methylpyrazino(1,2-a)indole (II) and the 2,4-dimethyl-8-cyanopyrrolo(1,2-a)pyrimidines (III-V). Previously it has been established [6] that in CF_3COOH protonation of derivatives of pyrrole(1,2-a)pyrimidine, structurally analogous to compounds III-V, but not carrying sub-



I II III, IV V

III $R^1=R^2=CH_3$; IV $R^1=CH_3$, $R^2=C_2H_5$

stituents at $C_{(8)}$, occurs exclusively at $C_{(6)}$. The formation of cations, corresponding to proton addition to the carbon atom of the pyrrole ring in the α- and β'-positions to the bridgehead nitrogen, was also discovered when derivatives of pyrrolo(1,2-a)pyridazine were protonated under similar conditions [7, 8]; at the same time it was shown that only the α-form of the conjugate acid is thermodynamically stable in solution [8]. Moreover it is known that in a series of aza analogs of indolizine, containing a nitrogen atom of the "pyridine" type in the five-membered ring, N-protonation is always observed [9, 10]. These results suggest three possible structures of the conjugate acid of pyrrolo(1,2-a)pyrazine (I):

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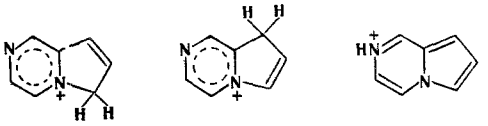


α-form β'-form N-form

With the object of establishing the protonation centers of compounds I and II the PMR spectra of the neutral molecules and of the cations in various media were measured. In the spectrum of the neutral molecule I there were clearly resolved a broad signal due to 1-H and a doublet of quartets due to 4-H situated at low field with spin–spin interaction (SSI) constants of J_{34} = 4.9, J_{14} = 1.6, J_{48} = 0.9 Hz (Tables 1 and 2). The doublet at 7.4-7.5 ppm with a SSI constant of 4.9 Hz was assigned to 3-H. In CH_2Cl_2 in the same region of the spectrum a signal due to 6-H was present. On passing to more polar media (CH_3CN, $(CD_3)_2CO$) the signal due to 6-H undergoes a small shift towards low field and is observed at 7.54-7.64 ppm as an octet with interaction constants J_{67} = 2.2-2.3, J_{68} = 1.4-1.5, J_{61} ≈ 0.6 Hz. The signals due to the protons in positions 7 and 8, which are observed in the spectrum of the neutral molecule as an overlapping multiplet in the interval 6.7-6.9 ppm, are separated in the spectrum of the protonated form.

Measurement of the spectra of pyrrolopyrazine (I) in mixtures of CF_3COOH/CH_2Cl_2 with various concentrations of the acid showed that the greatest changes in the chemical shifts and the SSI constants of the protons of the bicyclic compound were observed when the acid concentration was increased from 0 to 6-10 mole %. Further increase of the concentration of CF_3COOH in CH_2Cl_2 was accompanied by relatively small changes in the chemical shift and had practically no effect on the character of the multiplicity of the spectral lines and the values of the SSI constants (Tables 1 and 2), which indicates a shift of the protolytic equilibrium in the direction of the monocation. Over the whole examined region of change in acidity of the medium, signals were not observed to appear in the region 4-6 ppm, which are characteristic for the CH-conjuate acids [6-8]. From these results it follows that the base I forms only one mono-protonated form, the structure of which corresponds to the addition of a proton to the atom $N_{(2)}$. The position of the protonation center in molecule I was unequivocably established from the change in the character of the multiplicity of the signals from the protons of the six-membered ring due to spin–spin interaction with the proton $N_{(2)}$–H. Thus in the spectrum of the cation I^+ the signal due to 1-H was observed as a doublet with a constant J_{12} = 7.4 Hz, the components of which were split due to SSI with the protons at positions 3, 4 and 6. The signal due to 3-H had the form of a split quartet with constants J_{23} = 5.2 and J_{34} = 5.8 Hz. The additional splitting is due to the increase of the SSI constants of the meta-protons in positions 1 and 3 on passing from the neutral molecule I ($J_{13} \approx 0$) to the cation I^+ (J_{13} = 0.9 Hz). A similar effect of N-protonation on the value of the SSI constants for the protons in the α,α'-positions to the cation center has also been detected in other systems, for example, in the diazines [11]. The effect of protonation also results in an increase in the SSI constants for the ortho-protons in the α- and β-positions to the cation center J_{34} by 0.8-0.9 Hz and the emergence of the constant J_{24} = 0.9 Hz. Similar changes in PMR spectrum parameters were also observed in the protonation of 1,10-trimethylene-8-methylpyrazino(1,2-a)indole (II). Analogous spectra measured in acetic (pK_a = 4.76), α-bromobutyric (pK_a = 2.85) and trifluoroacetic (pK_a = 0.23) acids indicated that compound II also forms one mono-protonated form. Assignment of the proton signals of the two six-membered rings of the aromatic fragment of the neutral molecule II and the cation II^+ (Table 1) was made on the basis of the character of the multiplicity of the spectral lines. The proton signals of the pyrazine ring were readily assigned from the value of the constant J_{34}, which was close to the value of the analogous constant in pyrrolopyrazine I, but markedly different from the constant J_{67} for the ortho-protons of the benzene fragment (Table 2). As in the spectrum of pyrrolopyrazine, the signal due to 3-H was shifted towards high field relative to the 4-H signal. The 6-H and 7-H signals were observed as split doublets ($J_{69} \approx 0.5$, J_{79} = 1.7 Hz). The high value of the SSI constant for the meta-protons of the benzene ring permitted assignment of the signal situated at high field to 7-H. Additional splitting of the signals due to 3-H (J_{23} = 4.8 Hz) and 4-H (J_{24} = 0.7 Hz), observed in the spectrum of the cation II^+, indicates the addition of a proton to $N_{(2)}$. At the same time the J_{34} constant is increased by 0.6-0.8 Hz. In the spectra of the cations I^+ and II^+, independently of the acid concentration in solution and strength of the proton donor, the appearance with time of signals corresponding to the conversion of the N-form into the α- and β'-forms of the CH-acids was not observed, as was detected in the series of derivatives of

TABLE 1. Chemical Shifts in the PMR Spectra of the Bases and Conjugate Acids (ppm)

Compound	Medium	Position							
		1	2	3	4	6	7	8	9
I	CH_2Cl_2	8,76	—	7,43	7,74	7,4—7,5	6,7—6,9		—
	CH_3CN	8,74	—	7,40	7,98	7,54	6,7—6,9		—
	$(CD_3)_2CO$	8,60	—	7,43	8,13	7,64	6,7—6,9		—
I+	10% CF_3COOH/CH_2Cl_2	9,05	—	7,55	8,28	8,11	7,42	7,69	—
I+	CF_3COOH	8,97	—	7,50	8,40	8,22	7,60	7,80	—
II	CCl_4	—	—	7,15	7,60	7,54	7,02	2,49	7,43
	$CDCl_3$	—	—	7,27	7,75	7,69	7,17	2,55	7,56
	CH_2Cl_2	—	—	7,24	7,77	7,70	7,15	2,52	7,55
	CH_3CN	—	—	7,20	7,88	7,75	7,14	2,43	7,51
II+	CD_3COOD	—	—	7,39	8,41	7,97	7,44	2,53	7,65
	$C_2H_5CHBrCOOH$	—	—	7,42	8,39	7,99	7,53	2,57	7,71
	CF_3COOH	—	—	7,20	8,35	7,99	7,67	2,64	7,84
Hydrochloride II	CF_3COOH	—	—	7,20	8,45	7,99	7,67	2,64	7,83
III	CH_2Cl_2	—	2,43	6,28	2,77	2,60	2,24	—	—
III+	CF_3COOH	—	2,88	7,01	3,23	2,88	2,48	—	—
IV	CH_2Cl_2	—	2,43	6,29	2,78	2,62	1,19 2,65	—	—
IV+	CF_3COOH	—	2,86	7,01	3,21	2,86	1,33 2,93	—	—
V	CH_2Cl_2	—	2,42	6,30	2,75	—	—	—	—
V+	CF_3COOH	—	2,87	7,02	3,18	—	—	—	—

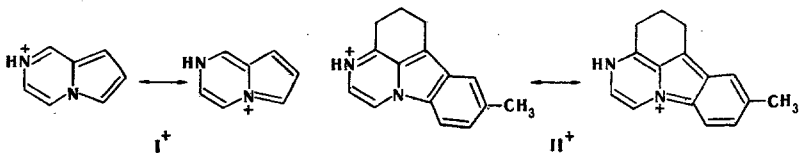
TABLE 2. SSI Constants in the PMR Spectra of the Bases and Conjugate Acids, J, Hz

Compound	Medium	12	13	14	16	23	24	34	48	67	68	78
I	CH_3CN	—	—	1,6	0,6	—	—	4,9	0,8	2,2	1,4	—
I+	CF_3COOH	7,4	0,9	0,9	0,9	5,2	0,9	5,8	0,9	2,5	1,0	4,8
II	CH_3CN	—	—	—	—	—	—	5,2	—	8,6	—	—
II+	CF_3COOH	—	—	—	—	4,8	0,7	6,0	—	8,8	—	—
Hydrochloride II	CF_3COOH	—	—	—	—	5,0	0,7	5,8	—	8,9	—	—
III—V	CH_2Cl_2	—	—	—	—	—	—	0,9*	—	—	—	—

*$J_{3\text{-}H,4\text{-}CH_3}$.

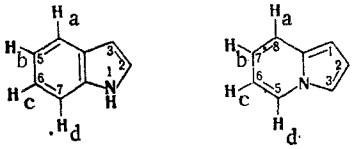
pyrrolo(1,2-a)pyridazine [8]. Consequently of the three possible structures for the conjugate acid of pyrrolopyrazine I and its analog II the N-form is thermodynamically the most favored.

In the bases and conjugate acids of the compounds I and II the proton chemical shifts are very dependent on the nature of the solvent. However in all the studied media, addition of a proton to $N_{(2)}$ of pyrrolo(1,2-a)pyrazine caused much greater descreening of the protons of the pyrrole fragment ($\Delta\delta$ = 0.6-1.0 ppm) compared with the protons of the six-membered ring, present in the α-($\Delta\delta_1$ = 0.2-0.4 ppm; $\Delta\delta_3$ = 0.07-0.1 ppm) and β-($\Delta\delta_4$ = 0.3-0.7 ppm) positions to the cation center. Similar changes in the chemical shifts of the protons of the pyrazine ring ($\Delta\delta_3$ = −0.1 — +0.2 ppm, $\Delta\delta_4$ = 0.5-0.8 ppm) were observed with protonation of pyrazinoindole II. At the same time signals due to the protons at the benzene fragment of the molecule II which are more removed from the cation center undergo comparable in magnitude low field shifts ($\Delta\delta_6$ = 0.2-0.4 ppm, $\Delta\delta_7$ = 0.3-0.6 ppm, $\Delta\delta_9$ = 0.1-0.4 ppm). This indicates a considerable delocalization of the positive charge from the cation center $N_{(2)}$ onto the bridgehead nitrogen atom with an increase in the contribution of the para-quinonoid type structure:



I^+ II^+

TABLE 3. Changes in the Chemical Shifts of the ^1H of the Six-Membered Ring on Protonation of Azaindoles and Azaindolizines

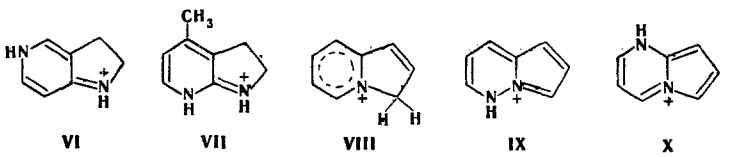


Compound	Protonation center	Medium*	Δδ, ppm				Literature reference
			H_a	H_b	H_c	H_d	
5-Azaindole	$N_{(5)}$	CH_2Cl_2/CF_3COOH	0,03	—	0,02	0,57	1
5-Azaindoline	$N_{(5)}$	CH_2Cl_2/CF_3COOH	−0,30	—	−0,15	0,25	1
4-Methyl-7-azaindole	$N_{(7)}$	CH_2Cl_2/CF_3COOH	—	0,53	0,01	—	Present work
4-Methyl-7-azaindoline	$N_{(7)}$	CH_2Cl_2/CF_3COOH	—	0,31	−0,27	—	2
Indolizine	$C_{(3)}$	CCl_4/CF_3COOH	0,89	1,97	1,53	1,22	14, 15
2-Methyl-7-carbethoxy-indolizine	$C_{(3)}$	CCl_4/CF_3COOH	0,55	—	1,37	1,37	16
2,6-Dimethyl-5-azaindolizine(2,6-dimethyl)pyrrolo(1,2-a)pyridazine	$C_{(3)}$	$CDCl_3/CF_3COOH$	0,76	1,97	—	—	8
2,3,5,7-Tetramethyl-8-azaindolizine(2,4,6,7-tetramethyl)pyrrolo(1,2-a)pyrimidine	$C_{(3)}$	$CDCl_3/CF_3COOH$	—	—	1,53	—	6
7-Azaindolizine[pyrrolo(1,2-a)pyrazine]	$N_{(7)}$	CH_2Cl_2/CF_3COOH	0,21	—	0,07	0,66	Present work

*The media given are those in which the PMR spectra of the neutral molecule and the cations were measured.

From the results of the effect of protonation of the aza analogs of indole and indolizine under the same conditions on the changes in the chemical shifts of the protons of the six-membered ring (Table 3) it follows that the observed effects are determined in the main not by the nature and position of the cation center but by changes in the aromatic system of the ion compared to the neutral molecule. In the cations of the 5- and 7-azaindoles transfer of charge from the protonation center to the pyrrole nitrogen atom leads to a decrease in ring current effects in the six-membered ring [1] which to a considerable degree compensates for the descreening effect, due to the development of a positive charge in the molecule. This explains the very much smaller changes in the chemical shifts of the protons in the α- and β-positions to the cation center in the azaindoles ($\Delta\delta_\alpha$ = 0.01-0.03 ppm, $\Delta\delta_\beta$ = 0.53-0.57 ppm) in comparision with the changes observed on protonation of pyridine under analogous conditions ($\Delta\delta_\alpha$ = 0.35 ppm, $\Delta\delta_\beta$ = 1.04 ppm) [12, 13]. The difference from pyridinium ions is apparent to a still greater degree in the case of 5- and 7-azaindolines: the predominant contribution of the quinonoid type structure (VI, VII) to the protonated forms of these compounds results in a shift of the α-proton signals towards high field by 0.15-0.30 ppm.

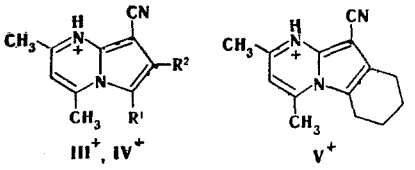
Protonation of derivatives of indolizine and its 5- and 8-azaanalogs — derivatives of pyrrolo(1,2-a)pyridazine and pyrrolo(1,2-a)pyrimidine — at the $C_{(3)}$ atom is coupled with an opposite transition to structures of the "pyridine" type (VIII) in the CH acids. This leads to an increase in the ring currents and a considerable increase in the descreening effect of the six-membered ring protons (Δδ = 0.6-2.0 ppm). N-protonation of pyrrolo(1,2-a)pyrazine (7-azaindolizine) causes very much less perturbation of the aromatic ring of the bicyclic compound: transfer of the positive charge from the cation center to the bridgehead nitrogen atom in cation I^+ is coupled only with a change in the relative contributions of the ortho- and para-quinonoid structures. Corresponding with this, the low field shifts of the signals



VI VII VIII IX X

of the six-membered ring protons on passing from the neutral molecule I to the cation ($\Delta\delta$ = 0.2-0.7 ppm) decrease by a factor of 2-3 compared with the values of $\Delta\delta$ for the indolizines, but exceed the descreening effects observed on protonation of the azaindoles and azaindolizines.

Thus perturbation of the aromatic system in the protonated forms of the pyrroloazines, due to transfer of the positive charge from the cation center to the nitrogen atom, participating in the conjugated system as the donor of an electron pair, is clearly apparent in the PMR spectra. The results of studying the structure of the cations of the aza analogs of indolizine indicate that this effect exerts a considerable influence on the relative basicity of the different centers in compounds of this type. The increase in the basicity of the "pyridine" type nitrogen atom in pyrrolo(1,2-a)pyrazine compared with pyrrolo(1,2-a)pyridazine and pyrrolo(1,2-a)pyrimidine is explained apparently by the fact that transfer of charge to the cation I^+ results in a predominant contribution of the para-quinonoid structure which is energetically more favorable compared with the ortho-quinonoid structures, possible for N-protonated forms of the pyrrolopyridazine and pyrrolopyrimidine (IX, X). Therefore for the two last-named systems N-protonation is not energetically favored, but formation of the CH-acid is. The steric effect of alkyl groups in the pyrrole ring does not result in a change in the protonation center in the pyrrolo(1,2-a)pyrimidines [6]. Formation of the N-protonated forms is observed only when a strong electron acceptor substituent is introduced into the pyrrole ring. This conclusion follows from examination of the PMR spectra of the bases and the conjugate acids of the 2,4-dimethyl-8-cyanopyrrolo(1,2-a)pyrimidines (III)-(V) (Table 1). Assignment of the signals in the spectra of the neutral molecules was made on the basis of the character of the multiplicity of the spectral lines (Table 2) and comparison with the spectra of the previously studied derivatives of pyrrolo(1,2-a)pyrimidine [6]. In the spectra of the conjugate acids III^+-V^+ signals are not observed in the region of 4-6 ppm nor is there a change in the multiplicity of the signal of the methyl group at $C_{(6)}$. These data permit the possibility of addition of the portion to the carbon atoms of the pyrrole ring to be excluded. On passing from the neutral molecules to the cations all the signals are shifted towards low field. At the same time the changes in the chemical shifts of 3-H ($\Delta\delta_3$ = 0.72-0.73 ppm) are close to the values of $\Delta\delta$, for protons in the β-position to the cation center which are observed during N-protonation of compounds I and II under analogous conditions. This result corresponds to protonation of compounds III-V at the nitrogen atom of the six-membered ring $N_{(1)}$.



EXPERIMENTAL

The studied compounds were synthesized and characterized as described previously [17, 18]. In view of the chemical instability of pyrrolo(1,2-a)pyrazine the compound was synthesized and purified immediately before measurement of the PMR spectra. Measurement of the spectra was carried out using 0.1-0.2 M solutions of the studied substances in various solvents (Table 1) on the C-60 HL spectrometer, using TMS as internal standard.

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