MASS SPECTRA AND STRUCTURES OF ISOMERIC PHENYLAMINOPYRAZOLES

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UDC 543.51:547.772

The processes involved in the dissociative ionization of isomeric phenylaminopyrazoles under the influence of electron impact were studied. The pathways of fragmentation of the molecular ion (M^+) were proved rigorously by means of the spectra of the metastable ions. The empirical compositions of the fragment ions were confirmed by the high-resolution mass spectra. It was established on the basis of the mass spectra of the amino-group-deuterated analogs that M^+ exists exclusively in the amide from. A rearrangement leading to the formation of benzodiazepine cation radicals precedes fragmentation of M^+. The elimination of an HCN particle in the first step of the fragmentation of M^+ does not involve the amino group. The pK_a values are presented for all of the investigated phenylaminopyrazoles.

The influence of electron impact on some dihetaryl systems has been previously described [1-3]. In the present research we investigated the mass spectra of isomeric phenylaminopyrazoles (Table 1) in order to search for analytical criteria that make it possible to identify compounds of this type in the reaction mixtures (UV, IR, and PMR spectroscopy are not always effective in this case) and to evaluate the possibility of amino–imine tautomerism for the molecular ions (M^+) in the investigated models [4].

In addition to the ordinary mass spectra, we used high-resolution mass spectrometry (Table 2) and the mass spectra of the metastable ions obtained by the DADI technique [5, 6].

It has been demonstrated by optical spectroscopy methods [4, 7] that all of the aminopyrazoles exist in the amino form. Assuming that the amine–imine equilibrium is realizable in the excited state of M^+, we recorded the spectra of deuterium-labeled samples IIa and IIIa (Table 1), which showed that the initial processes in the fragmentation of M^+ – elimination of $H^\cdot$, C_2H_2, and HCN – do not involve the NH_2 group. This fact excludes the presence of the imine form of M^+ in the spectra of I-VI.

However, a study of the spectra of the metastable ions formed in a second fieldless space with an apparatus with "inverse" geometry showed that HCN (for I, IV, and VI), N_2H and $C_2H_2N_2$ (for V), and $NHCNH_2$ (for VI) particles are eliminated directly from M^+; this constitutes evidence for the occurrence of rearrangement processes in M^+. Studies with deuterium-labeled samples IIa and IIIa showed that these rearrangements do not involve the amino group and completely exclude migration of the phenyl group bonded to the pyrazole ring (as evidenced also by the high-resolution mass spectra presented in Table 2) [8].

It has recently been shown [9] that the N–N bond in the hydroxypyrazole ring is sufficiently polar and dissociates readily under the influence of electron impact. In this case one can link the isomerization of M^+ with the formation of the corresponding amine of the 1,4-benzodiazepine series (the M_2^+ form) [10]. Migration of hydrogen from the ortho position of phenyl substituent R to the nitrogen atom in the 1 position of the pyrazole ring is assumed for the realization of such rearrangement processes.

The dissociative ionization of benzodiazepines has been studied [11, 12]. The M_2^+ and M_3^+ forms of the molecular ions of I-VI exclude structural blocking of the particles listed above, and their elimination in the initial stages of the fragmentation leads to the development of the general characteristics of the ion peaks (fragmentography) for the investigated class of compounds.

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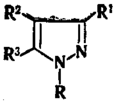
0009-3122/78/1410-1123$07.50

TABLE 1. Mass Spectra of Isomeric Phenylaminopyrazoles*



Compound	R	R¹	R²	R³	m/e values (relative intensities of the ion peaks in % relative to the maximum peak)
1	2	3	4	5	6
I	C_6H_5	NH_2	H	H	50 (6,0), 51 (23,6), 52,5 (9,4), 54 (4,9), 55 (4,2), 63 (4,1), 64 (4,5), 65 (4,9), 77 (32,3), 78 (6,8), 79,5 (6,0), 89 (4,6), 90 (5,3), 91 (5,2), 92 (15,7), 93 (3,0), 104 (14,8), 105 (5,0), 117 (3,9), 119 (3,6), 131 (14,2), 132 (5,1), 133 (3,9), 158 (27,8), 159 (100,0), 160 (12,1)
II	C_6H_5	H	NH_2	H	50 (14,2), 52 (40,6), 53 (8,0), 56 (6,0), 57 (3,2), 63 (4,2), 64 (3,4), 66 (3,2), 74 (3,3), 76 (7,3), 77 (62,4), 78 (21,0), 79,5 (3,0), 103 (3,0), 104 (100,0), 105 (19,1), 131 (32,0), 132 (29,3), 133 (3,5), 158 (3,3), 159 (72,8), 160 (9,5)
IIa	C_6H_5	H	ND_2	H	50 (13,7), 52 (39,8), 53 (6,0), 54 (6,8), 56 (6,6), 57 (3,3), 63 (4,4), 64 (3,3), 66 (3,3), 74 (3,0), 75 (3,0), 76 (7,3), 77 (54,0), 78 (14,4), 79,5 (3,6), 80,5 (3,0), 103 (3,0), 104 (56,2), 105 (100,0), 106 (13,8), 131 (12,7), 132 (13,4), 133 (19,3), 134 (17,6), 159 (29,1), 160 (3,0), 161 (43,7), 162 (5,2)
III	C_6H_5	H	H	NH_2	50 (9,2), 51 (41,1), 52 (23,4), 53 (13,1), 54 (9,0), 56 (3,8), 63 (7,9), 64 (10,0), 65 (12,7), 66 (6,5), 67 (4,9), 76 (3,8), 77 (54,6), 78 (13,1), 79,5 (3,3), 89 (4,2), 90 (5,8), 91 (25,1), 92 (5,5), 103 (3,0), 104 (21,6), 105 (7,6), 117 (3,6), 119 (6,7), 130 (4,5), 131 (17,2), 132 (7,3), 133 (5,8), 158 (23,0), 159 (100,0), 160 (13,1)
IIIa	C_6H_5	H	H	ND_2	50 (8,3), 51 (39,6). 52 (25,6), 53 (8,9), 54 (8,8), 56 (3,0), 63 (8,1), 64 (11,3), 65 (13,0), 66 (6,8), 67 (5,3), 76 (4,3). 77 (55,3), 78 (14,6), 80,5 (4,0), 89 (4,4), 90 (6,1), 91 (14,8), 92 (6,0), 104 (7,5), 105 (14,5), 106 (5,3), 117 (4,0), 121 (5,2), 131 (3,5), 133 (14,0), 134 (5,8), 135 (4,6), 158 (4,0), 159 (20.0), 160 (20,4), 161 (100.0), 162 (12,0)
IV	H	C_6H_5	H	NH_2	50 (6,2), 51 (12,8), 52 (5.2), 63 (3,4), 75 (3,2), 76 (4,9), 77 (28,0), 78 (3,0), 90 (3,0), 102 (10,6), 103 (10.9), 104 (6,2), 105 (12,3), 117 (3,8), 128 (5,4), 130 (21,2), 131 (4,2), 159 (100,0), 160 (11,0)
V	4-NH_2—C_6H_4	H	H	H	50 (4,0), 51 (4,0), 52 (10,4), 63 (4,3), 64 (3,0), 65 (22,7), 66 (7,4), 77 (3,9), 78 (5,0), 79 (5,0), 79,5 (3,6), 80 (5,6), 92 (12,2), 93 (3,6), 104 (9,0), 105 (8,8), 107 (5,4), 118 (5,0), 119 (10,9), 130 (6,1), 131 (19,1), 132 (10,2), 133 (4,3), 158 (9,5), 159 (100,0), 160 (10,6)
VI	C_6H_5	C_6H_5	H	NH_2	50 (6,0), 51 (14,3), 52 (4,4), 53 (3,0), 63 (7,1), 64 (8,8), 65 (9,1), 66 (4,0), 76 (3,0), 77 (28,9), 78 (3,0), 89 (3,2), 91 (6,7), 92 (9,2), 102 (7,5), 104 (13,6), 105 (5,6), 113 (4,5), 117,5 (4,5), 131 (8,6), 132 (3,3), 133 (3,0), 180 (3,0), 192 (3,7), 206 (3,0), 207 (16,5), 208 (3,0), 234 (29,5), 235 (100,0), 236 (17,5)

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*The ion peaks with intensities ≥ 3% of the maximum peak are presented.

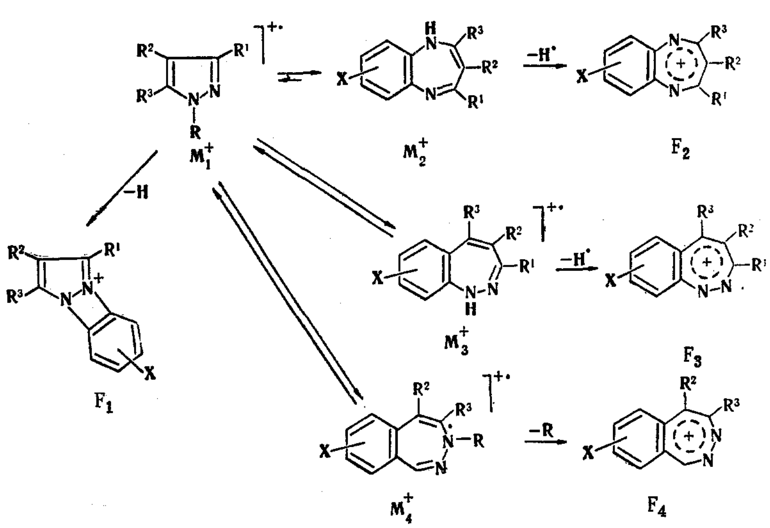
TABLE 2. Elementary Compositions of Some Ions Determined by Means of the High-Resolution Mass Spectra for I-VI ($M/\Delta M$ = 30,000; with perfluorinated kerosene as the standard)

Compound	Ion	Proposed structure of the fragment	*m/e*		Empirical formula
			determined	ealc.	
I	A	2-Aminobenzimidazole	133,0661	133,0640	$C_7H_7N_3$
	B	2(3)-Aminoindole	132,0680	132,0687	$C_8H_8N_2$
				132,0562	$C_7H_6N_3$
II	C		105,0539	105,0453	$C_6H_5N_2$
				105,0578	C_7H_7N
III	D	Benzoimidazolinium cation	119,0593	119,0609	$C_7H_7N_2$
IV	E	Benzopyridazinium or benzopyrimidinium cation	131,0642	131,0735	C_9H_9N
				131,0609	$C_8H_7N_2$
	F	Quinolinium or isoquinolinium cation	130,0657	130,0657	C_9H_8N
	G		128,0487	128,0501	C_9H_6N
	D^1	Benzopyrazolinium cation	119,0600	119,0609	$C_7H_7N_2$
	H	Indole	117,0560	117,0578	C_8H_7N
	I	Diazonium cation	105,0483	105,0453	$C_6H_5N_2$
	J		104,0523	104,0500	C_7H_6N
	K	$C_6H_5CH{=}\overset{+}{C}H$	103,0523	103,0548	C_8H_7
	L	Phenylacetylene	102,0472	102,0469	C_8H_6
V	A	5-Aminobenzimidazole	133,0673	133,0640	$C_7H_7N_3$
				133,0765	$C_8H_9N_2$
	B	5-Aminoindole	132,0679	132,0687	$C_8H_8N_2$
	E^1		131,0610	131,0609	$C_8H_7N_2$
	M		130,0649	130,0656	C_9H_8N
	N		119,0606	119,0609	$C_7H_7N_2$
	O		107,0592	107,0609	$C_6H_7N_2$
	P		106,0580	106,0531	$C_6H_6N_2$
				106,0656	C_7H_8N
	C^1		105,0510	105,0453	$C_6H_5N_2$
				105,0578	C_7H_7N
	J^1		104,0481	104,0500	C_7H_6N
VI	B^1	1-Phenyl-2-aminoindole	208,0946	208,1000	$C_{14}H_{12}N_2$
	Q	Phenylbenzopyridazinium or benzopyrimidinium cation	207,0919	207,0922	$C_{14}H_{11}N_2$
				207,1047	$C_{15}H_{13}N$
	R		206,0899	206,0846	$C_{14}H_{10}N_2$
	S		192,0806	192,0812	$C_{14}H_{10}N$
	T	Phenanthridinium cation	180,0812	180,0815	$C_{13}H_{10}N$
	A		133,0657	133,0640	$C_7H_7N_3$
				133,0765	C_8H_9N
	B		132,0682	132,0687	C_8H_8N
	C		105,0569	105,0578	C_7H_7N
	J		104,0497	104,0500	C_7H_6N
	L		102,0465	102,0467	C_8H_6

TABLE 3. Stabilities of the Molecules with Respect to Electron Impact (W_M), Intensities (in percent relative to the total ion current), and Ratios of the Intensities of the Peaks of the Characteristic Ions in the Mass Spectra of I-VI Recommended for Use in Their Identification

Characteristic ions and ratios of the intensities of the peaks	Compounds					
	I	II	III	IV	V	VI
W_M	26,4	15,0	23,8	31,8	29,4	30,8
$[M-H]^+$	7,4	0,7	5,5	0,5	2,8	8,8
$[M-C_2H_2]^+$	1,0	0,7	1,4	0,5	1,3	—
$[M-HCN]^+$	1,4	6,0	1,7	0,5	3,0	0,8
$[M-H_2CN]^+$	3,8	6,6	4,1	1,3	5,6	4,9
$[M-H_2CN]^+/[M-HCN]^+$	2,7	1,1	2,4	2,6	1,9	6,1
$[M-N_2H]^+$	0,7	0,3	1,1	6,7	1,8	3,0
$[M-C_2H_2N]^+$	1,0	—	1,6	0,7	3,2	0,5
$[M-H_2CN_2]^+$	1,0	—	0,8	1,2	—	0,4
105^+	1,3	4,0	1,7	3,9	2,6	1,7
104^+	4,0	20,7	5,2	2,0	2,6	4,0
$105^+/104^+$	0,3	0,2	0,3	2,0	1,0	0,4
103^+	0,6	0,6	0,7	3,5	—	0,6
102^+	—	—	—	3,4	—	2,2
92^+	4,2	—	6,0	—	3,6	2,7

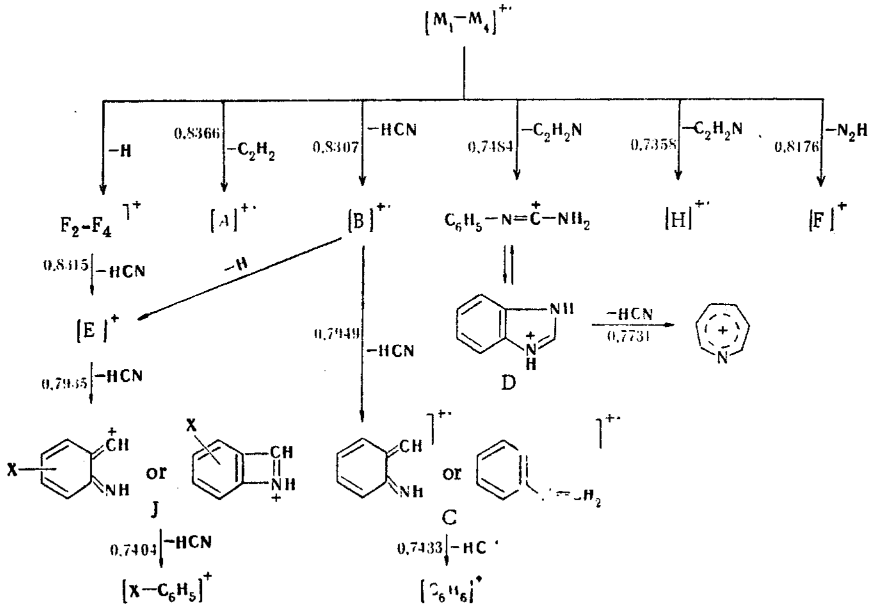
The rearrangement of the M^+ ion peak of IV is evidently associated with cleavage of the C_3–C_4 bond in the pyrazole ring (M_4^+).



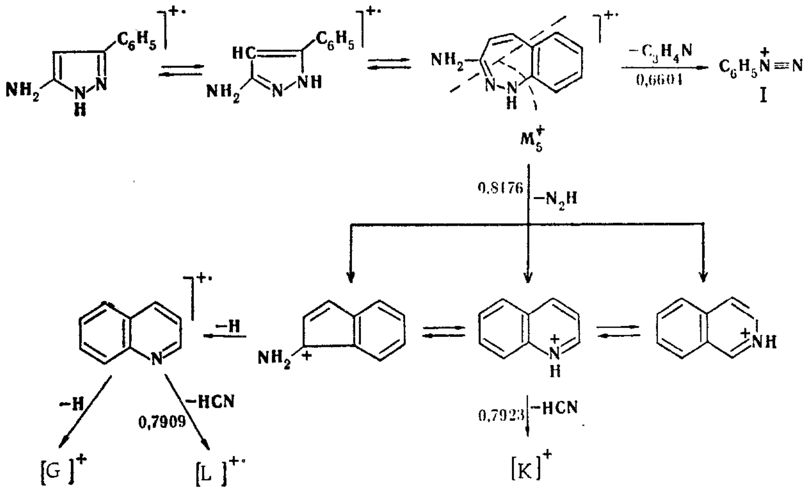
$R = C_6H_5$, $4\text{-}NH_2C_6H_4$; X=H or NH_2

As demonstrated above, the process $M^{+\cdot} \xrightarrow[*]{-H^\cdot} [M-H]^+ \xrightarrow[*]{-HCN} [M-H_2CN]^+$, detected by means of the spectra of the metastable ions, constitutes evidence in favor of the existence of M^+ in the form of benzodiazepine cation radicals (M_2-M_4^+). In fact, it has been previously shown [2, 3, 13] that the M^+ ions of phenyl-substituted N-heterocyclic bases with a coplanar orientation of the rings primarily undergoes cyclization with elimination of a hydrogen atom and the formation of a bond through the heteroatom (F_1); however, elimination of an HCN particle is impossible in this case (the NH_2 substituent does not participate in this act; see IIa and IIIa in Table 1), whereas, detachment of a hydrogen atom from the M_2^+-M_4^+ ions leads to stable benzoazatropylium structures F_2-F_4, respectively [12]. Depending on the orientation of the R^1-R^3 substituents, subsequent detachment of an HCN molecule leads to the corresponding benzopyridazinium, benzopyrimidinium, or quinoxalinium cations [11].

An analysis of the high-resolution spectra (Table 2) introduced substantial corrections in the interpretation of the fragmentation of the molecular ions and revealed that there is a difference in the elementary compositions of some of the ions with identical mass numbers for the investigated isomers I-V. The set of data obtained by means of high-resolution mass spectrometry and the spectra of the metastable ions enabled us to describe the fragmentation of the M^+ of I-VI in the general case by the scheme*



The fragmentation of the M^+ ion of IV differs somewhat from the scheme presented above. The processes associated with the formation of the F_4, A, B, D (the benzopyrazolinium cation is formed in this case), and H ions are realized to a much smaller extent (see Table 3). On the other hand, elimination of the N_2H group, which leads to the formation of a quinolinium or isoquinolinium cation (E), is an extremely energetic process. The appearance of K, G, and L daughter ions in the spectrum constituted indirect proof for the existence of this ion (Table 2) [14].



Precise measurement of the mass of the ion with m/e 105 (I) showed that its empirical composition corresponds to the structure of a diazonium cation (Table 2) rather than to the ion with structure C. The spectrum of the metastable ions showed that this ion is formed directly from M^+ by detachment of a C_3H_4N particle. This fragmentation pathway suggests that the character of the isomerization of M^+ differs somewhat. Rearrangement in this case evidently leads ultimately to the benzoazepine structure.

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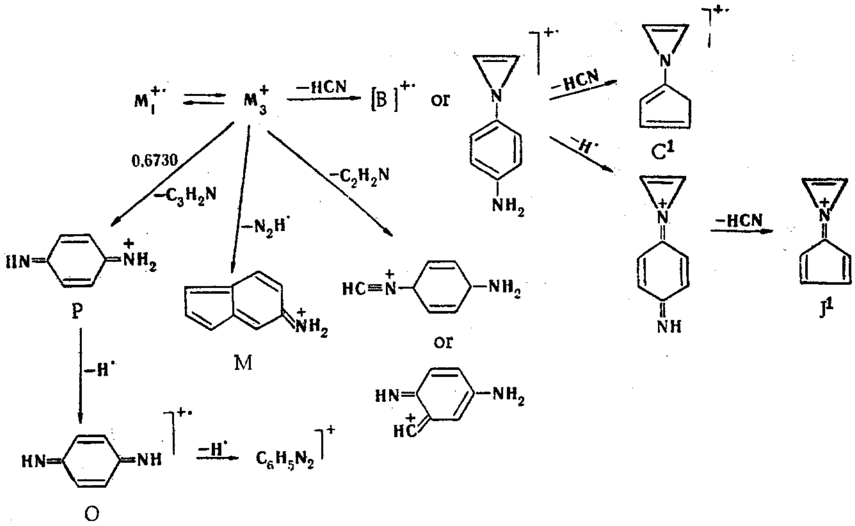
*The numbers next to the arrows, which indicate the direction of fragmentation, show the magnitude of the E_i/E_0 ratio, where E_0 is the constant value of the deflecting voltage (506.6 V) of the electrostatic sector of the mass spectrometer affiliated with the focused parent ion with mass m_0, and E_i is the measured deflecting voltage affiliated with the focused daughter (fragment) ion with mass m_i. The spectrum of the metastable ions was calculated from the formula $m_i = (E_i/E_0)m_0$.



In the case of V the M^+ ions exist primarily in the M_3^+ form, since the greatest overall contribution of the fragmentation processes is due precisely to this form (Table 3). In addition to the fragmentation pathways that are common to I-IV and lead to the formation of pseudomolecular 5-aminobenzimidazole (A) and 5-aminoindole (B) ions, respectively, structures of different fragment ions with masses equal to those of the A, B, C, D, F, H, and J ions are formed. This follows from the peculiarities of the structure of isomer V.

The chief distinctive feature in the fragmentation of the M^+ ion of this compound is elimination of a C_3H_2N fragment from M_3^+. The P fragment evidently has a quinoid structure, which suggests its subsequent dehydrogenation (Table 2).

The presence of two phenyl substituents in the aminopyrazole ring (VI) actually does not change the overall pattern of the fragmentation of M^+. Instead of processes involving the elimination of C_2H_2 or HCN, which lead to the formation of ions A and B, respectively, processes associated with elimination of $C_6H_5C\equiv CH$ and C_6H_5CN particles, which lead to the same ions, are realized. The detachment of HCN is evidently due to the existence of M^+ in the M_4^+ form, since other isomeric forms hinder detachment of this molecule. The resulting B^1 ion, which has the 1-phenyl-2-aminoindole structure (Table 2), subsequently undergoes fragmentation via the general scheme with the successive splitting out of two hydrogen atoms (ions Q and R) or an HCN molecule from the $[B^1 - H]^+$ ion to give fragment F, which evidently has a phenanthridinium cation structure. In addition to the indicated peculiarity, an $NHCNH_2$ fragment is split out (to give fragment S) from the M^+ ion of the M_2^+ form. It may be assumed that an azatropylium ion condensed with two phenylene rings is formed in this case. All of the indicated processes are confirmed by the spectra of the metastable ions and the high-resolution mass spectrum.

The above-noted peculiarities of the fragmentation of the M^+ ions of I-VI are presented in Table 3. A comparison of the intensities of the peaks of the individual ions or their ratios makes it possible to unambiguously identify any of the investigated compounds.

EXPERIMENTAL

The low-resolution mass spectra and the spectra of the metastable ions were obtained with a Varian MAT-311 spectrometer. The technique of direct introduction of samples into the ion source was used with the following conditions: the accelerating voltage was 3 kV, the cathode emission current was 300 µA, the ionizing voltage was 70 V, and the temperature of the ion source was 35-50°C. The reproducibility of the spectra was 2-3 rel. %. The high-resolution mass spectra were obtained under similar conditions with a Varian MAT-731 spectrometer.

The purity of the substances was monitored by thin-layer chromatography (TLC) on activity II (Brockmann scale) Al_2O_3 in a benzene—methanol system (25:1) with development by iodine.

The pK_a values of the conjugate acids were obtained with a Yanagimoto PT-3 automatic titrator in 80% Methylcellosolve by titration with 0.1 N HCl solution.

1-Phenyl-3-aminopyrazole (I) was obtained by the method in [15] and had mp 91°C (from benzene—petroleum ether), R_f 0.30, and pK_a 4.28. 1-Phenyl-4-aminopyrazole (II) was obtained by the method in [16] and had mp 101-102°C (from benzene—hexane), R_f 0.28, and pK_a 5.23. 1-Phenyl-5-aminopyrazole (III) was obtained by the method in [17] and had mp 44-45°C (from benzene—hexane), R_f 0.25, and pK_a 4.54. 3-Phenyl-5-aminopyrazole (IV) was obtained by the method in [18] and had mp 125-126°C (from ethyl acetate), R_f 0.25, and pK_a 5.51.

1-(p-Aminophenyl)pyrazole (V). A three-necked flask equipped with a reflux condenser, mechanical stirrer, and a dropping funnel was charged with 93 g (1.8 mole) of hydrazine hydrate, a threefold volume of propyl alcohol, and 0.1 g of Raney Ni, and the mixture was heated to the boiling point and treated with a solution of 9.8 g (0.05 mole) of 1-(p-nitrophenyl)pyrazole (obtained by the usual method from tetraethoxypropane and p-nitrophenylhydrazine) in 100 ml of propyl alcohol in the course of 1 h. The mixture was then refluxed for 3 h, after which it was cooled and filtered to remove the nickel. The clear filtrate was evaporated, and the residue was distilled to give 7.7 g (85%) of pyrazole V with mp 180-181°C (9 mm), mp 43-54°C (from hexane), R_f 0.32, and pK_a 5.23. UV spectrum (in isopropyl alcohol), λ_{max} (log ε): 270 nm (4.24); in dioxane: 274 nm (4.31). IR spectrum (KBr): 3450 (N—H) and 810 and 850 cm^{-1} (two adjacent protons of the benzene ring). Found: C 67.9; H 5.8; N 26.3%. $C_9H_9N_3$. Calculated: C 67.9; H 5.7; N 26.4%.

1,3-Diphenyl-5-aminopyrazole (VI). This compound was obtained by the method in [19] and had mp 128-129°C (from benzene—petroleum ether), R_f 0.35, and pK_a 3.81.

Deuteration of II and III. A weighed sample of the corresponding pyrazole was refluxed with a tenfold molar amount of D_2O in a flask equipped with a reflux condenser for 30 min, after which the excess D_2O was removed with a rotary evaporator. This process was repeated twice, and the resulting sample was dried in a vacuum desiccator over alkali. Compounds II and III contained 62 and 81% IIa and IIIa, respectively (according to the mass-spectral data and the intensity of the ν_{NH} band at 3540 cm^{-1} in the IR spectrum).

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