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NEGATIVE ION MASS SPECTRA AND STRUCTURE OF 4-SUBSTITUTED 1-PHENYL-3-METHYL-5-PYRAZOLONES*

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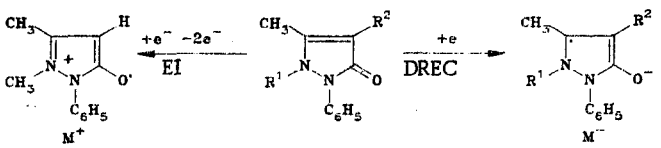
This is the first study of the electron capture dissociative resonance (ECDR) mass spectra of 4-substituted 1-phenyl-3-methyl-5-pyrazolones. The major features of the fragmentation of these compounds under ECDR conditions were found relative to their substituent properties. After loss of the methyl group from the nitrogen atom, the pyrazolone ring isomerizes to a pyrazole ring with localization of the negative charge on the oxygen atom of the carbonyl group. The intensity of the $[M - CH_3]^-$ fragment depends on the substituent properties.

Negative ion mass specta electron capture dissociative resonance (ECDR) spectra of 1-phenyl-3-methylpyrazolone derivatives have not yet been studied, although the behavior of these compounds upon electron impact has been investigated in detail [2-5].

We should expect that the interaction of pyrazolone derivatives with low-energy electrons should result in localization of the negative charge in the molecular radical-anion (M^-) predominantly on the carbonyl group since the oxygen atom of the carbonyl group is more electronegative than the heterocycle nitrogen. The behavior of pyrazolones upon electron impact [2] indicates that the positive and negative molecular ions M^+ and M^- should be given by the formal structures shown in Scheme 1.

SCHEME 1



The electron redistribution in M^- should facilitate the decomposition of pyrazolone derivatives by various energy channels with loss of substituents and breakage of the ring bonds. Upon electron impact (EI), the loss of substituents as radical species is not observed [2, 3] since their splitting off from M^+ would apparently lead to a breakdown in

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 0009-3122/85/2112-1368$09.50

TABLE 1. Mass Spectra of I and II [peak intensities (electron energies at the ion yield maximum) characteristic for specific spectra of I and II aregiven in % relative to the total ion current for each resonance]

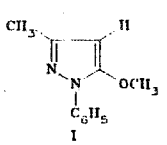
m/z	Ion	Resonance a	Resonance b	Resonance c
		Characteristic ions		
187	$[M-H]^-$	10,1 (0,6)	0,3 (4,4)*	14,0 (8,1)
		—	3,7 (3,2)	20,0 (8,1)
173	$[M-CH_3]^-$	88,0 (0,6)	3,4 (4,5)	6,0 (9,0)
		99,0 (0,7)	20,0 (4,2)	—
172	$[M-H-CH_3]^-$	—	—	6,0 (8,5)
		—	—	17,0 (8,9)
157	$[M-CH_3O]^-$	1,0 (0,5)	6,5 (3,5)	3,0 (8,0)
		0,7 (0,7)	—	1,0 (8,0)
132	$[M-HC\equiv C-OCH_3]^-$	1,0 (0,5)	3,4 (3,9)	—
			8,8 (4,7)	9,0 (8,2)
111	$[M-C_6H_5]^-$	—	2,0 (4,7)	13,0 (8,7)
		—	1,3 (4,4)	4,8 (8,7)
96	$[M-HN-C_6H_5]^-$	—	2,0 (4,3)	39,0 (8,2)
		—	26,0 (4,3)	—
92	$[C_6H_5HN]^-$	—	—	0,1 (9,0)
		—	8,8 (5,5)	7,5 (9,0)
91	$[C_6H_5N]^-$	—	—	—
		—	26,0 (4,8)	—
		Specific ions Compound I		
160	$[M-H-HCN]^-$	—	8,6 (3,5)	3,0 (8,5)
141	$[M-C_2H_7O]^-$	—	37,6 (4,7)	—
116	$[M-C_3H_6NO]^-$	—	24,0 (4,4)	15,7 (8,7)
74	—	—	12,0 (2,6)	—
		Compound II		
147	$[M-CH=CO]^-$	—	—	6,2 (8,3)
119	$[M-C_4H_7N]^-$	—	1,6 (5,0)	15,2 (9,1)
118	$[M-C_4H_6O]^-$	—	2,0 (5,5)	10,5 (9,0)
94	—	—	1,5 (5,7)	8,5 (9,0)

*The first line gives the value for compound I while the second gives the value for compound II

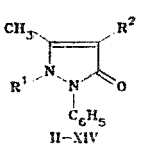
the energetically favorable ring structure. Thus, we expected that a study of the ECDR mass spectra would permit a more profound study of the fragmenation of substituted pyrazolones relative to the nature of their substituents and the energy of the captured electrons.

For these purposes, we studied the ECDR spectra of I-XIV with different substituents at $C_{(4)}$.

The study of the ECDR spectra of derivatives I-XIV also holds practical interest since II and XIV are used as drugs and IV, VI, XI, XII and VIII-X are intermediates and by-products in drug synthesis. ECDR mass spectrometry is an efficient method for structural and analytical studies [6] and thus may be used for control of the quality and purity of drug preparations.



I



II-XIV

II $R^1 = CH_3$, $R^2 = H$; III $R^1 = CD_3$, $R^2 = H$; IV $R^1 = R^2 = H$; V $R^1 = D$, $R^2 = H$; VI-XIV $R^1 = CH_3$; VI $R^2 = NO$; VII $R^2 = NO_2$; VIII $R^2 = HNCHO$; IX $R^2 = N(CH_3)CHO$; X $R^2 = OH$; XI $R^2 = NH_2$; XII $R^2 = NHCH_3$; XIII $R^2 = NDCH_3$; XIV $R^2 = N(CH_3)_2$.

TABLE 2. Mass Spectra of IV, VI-XII and XIV [peak intensities (electron energies at the ion yield maximum) given in % relative to the most intense peak in one of the resonances]

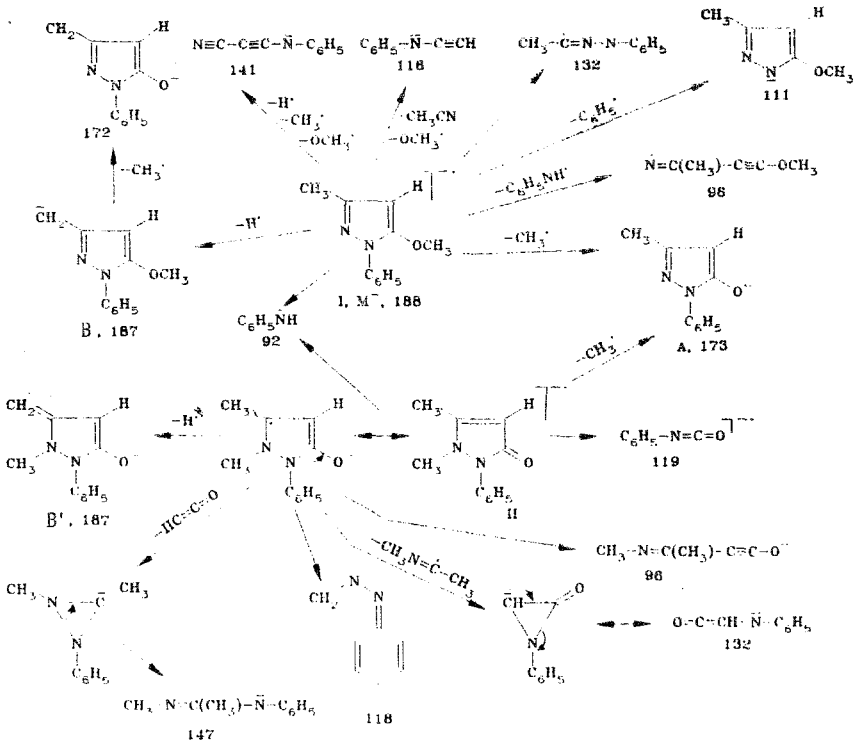
Compound	Ion	m/z	Resonance		
			a	b	c
IV	$[M-H]^-$	173	100 (1,1)	3,2 (5,2)	—
	$[M-CH_2CO]^-$	132	—	4,9 (4,6)	—
	$[M-C_6H_5-H_2]^-$	95	2,0 (0,4)	0,3 (3,6)	—
VI	M^-	217	4,4 (0,5)	—	—
	$[M-CH_3]^-$	202	23,0 (0,6)	—	—
	$[M-OH]^-$	200	13,0 (0,9)	—	—
	$[M-NO]^-$	187	1,5 (1,0)	—	—
	$[M-C_3H_6N]^-$	145	80,0 (0,9)	—	—
	$[M-C_2H_6NO_2]^-$	141	—	100 (4,6)	23,3 (7,0)
VII	$[M-H]^-$	232	0,25 (0,5)	—	—
	$[M-CH_3]^-$	218	100,0 (0,2)	2,2 (3,3)	—
	$[M-CHO]^-$	203	4,9 (0,1)	—	—
	$[M-NO_2]^-$	186	10,0 (0,3)	—	—
	$[M-CHO-NO_2]^-$	158	3,0 (0,1)	—	—
	$[M-C_3H_6NO_2]^-$	145	2,5 (0,1)	—	—
	$[M-NO_2-C_6H_5]^-$	110	6,4 (0,2)	—	—
VIII	M^-	231	31,2 (0,2)	—	—
	$[M-H]^-$	230	35,0 (0,8)	46,5 (1,4)	—
	$[M-CH_3]^-$	216	100,0 (0,7)	8,0 (3,5)	0,3 (0,9)
	$[M-H-CH_3]^-$	215	1,1 (0,5)	1,7 (5,4)	0,4 (8,2)
	$[M-CHO]^-$	202	2,3 (0,2)	4,8 (1,9)	1,4 (6,0)
	$[M-H-CH_2O]^-$	200	0,7 (0,1)	0,7 (4,7)	0,2 (9,2)
	$[C_6H_5-NH]^-$	92	—	37,7 (5,0)	—
IX	M^-	245	100,0 (0,6)	—	—
	$[M-H]^-$	244	—	—	1,0 (8,2)
	$[M-CH_3]^-$	230	84,0 (0,9)	4,0 (4,2)	0,4 (9,3)
	$[M-CO]^-$	217	5,2 (0,5)	—	—
	$[M-CHO]^-$	216	—	5,2 (4,8)	—
	$[M-CH_3-CHO]^-$	201	—	1,4 (5,2)	0,2 (9,3)
	$[M-H-CH_3-CHO]^-$	200	—	1,1 (5,2)	0,1 (9,5)
	$[M-N(CH_3)-CHO]^-$	187	—	0,3 (5,0)	0,1 (8,7)
X	M^-	204	100,0 (0,0)	—	—
	$[M-H]^-$	203	7,4 (0,0)	12,2 (1,1)	1,0 (5,3)
	$[M-CH_3]^-$	189	8,7 (0,5)	8,8 (3,4)	—
	$[M-C_7H_{10}]^-$	110	—	4,5 (5,4)	7,3 (8,5)
	$[C_6H_5-NH]^-$	92	—	41,8 (4,4)	—
XI	$[M-H]^-$	202	—	6,6 (3,2)	4,7 (7,4)
	$[M-CH_3]^-$	188	—	38,6 (2,0)	—
	$[M-NH_2]^-$	187	—	1,6 (3,7)	1,0 (7,9)
	$[M-CO]^-$	175	—	2,0 (3,7)	0,8 (8,2)
	$[M-C_3H_6N]^-$	147	—	—	2,9 (7,1)
	$[M-C_6H_5-OH]^-$	109	—	6,7 (3,5)	4,8 (8,0)
	$C_6H_5H^-$	92	—	100,0 (4,2)	24,2 (8,5)
XII	M^-	217	36,5 (0,1)	—	—
	$[M-H]^-$	216	32,3 (0,3)	67,8 (4,6)	36,8 (9,0)
	$[M-CH_3]^-$	202	—	100,0 (3,6)	—
	$[M-NHCH_3]^-$	187	2,6 (0,7)	12,3 (4,9)	5,2 (9,5)
	$[M-C_3H_6N]^-$	161	—	67,8 (4,4)	—
	$[M-C_4H_{10}N]^-$	145	5,8 (0,5)	22,1 (2,1)	4,8 (9,6)
	$[M-C_6H_5]^-$	140	—	2,6 (4,8)	8,1 (9,6)
	$[M-C_6H_5-OH]^-$	123	—	12,1 (5,0)	10,0 (9,3)
	$[C_6H_5NH]^-$	92	—	6,3 (4,7)	1,7 (8,6)
XIV	M^-	231	54,2 (0,2)	—	—
	$[M-H]^-$	230	—	—	9,3 (8,0)
	$[M-CH_3]^-$	216	—	100,0 (2,8)	—
	$[M-H-CH_3]^-$	215	—	5,2 (3,8)	1,3 (9,0)
	$[M-C_2H_7]^-$	200	—	10,4 (4,0)	2,2 (9,1)
	$[M-N(CH_3)_2]^-$	187	—	1,3 (3,9)	—
	$[M-H-N(CH_3)_2]^-$	186	0,9 (1,4)	0,4 (3,3)	1,7 (8,3)
	$[M-C_4H_6NO]^-$	147	—	—	1,4 (8,4)
	$[M-C_5H_{12}N]^-$	145	5,2 (1,6)	—	—
	$[M-C_2H_7C_6H_5]^-$	123	—	17,8 (4,1)	—
	$[C_6H_5NH]^-$	92	—	20,9 (4,7)	—

Comparison of the ECDR mass spectra of the structural isomers I and II with pyrazole and pyrazolone rings revealed fragment ions $[M - H]^-$ (187)*, $[M-CH_3]^-$(173), $[M-H, CH_3]^-$(172), $[M-OCH_3]^-$(157), $[M-CH_3-N=C-CH_3]^-$ (132), $[M-C_6H_5]^-$ (111), $[M-NH-C_6H_5]^-$ (96), $[C_6H_5NH]^-$(92), and $[C_6H_5N]^-$ (91) which are, characterististically observed in the decompositon of both compounds. They are recorded in three captured electron energy ranges: 0-1.2, 2.0-4.7 and 7.5-9.0 eV. These resonances are termed a, b and c, respectively (Table 1).

M^- peaks were not observed in the spectra of analogs I and II since their lifetime is apparently less than 10^{-6} sec [6]. The maximum-intensity peaks in the spectra of I and II given in % relative to the total ion current of the corresponding resonance are related to $[M - CH_3]^-$ ions. These ions are observed in low-energy resonance a. The spectrum of the deuteroanalog III shows that the loss of the CD_3 radical observed under the same conditions as the elemination of the methyl radical occurs exclusively from $N_{(2)}$.

The intensity and electron energy at the ion current yield maximum in this resonance which corresponds to a vibrationally excited Feschbach resonance are virtually identical, which is evidence for identical structure of these ions. This permits the assignment of structure A with a pyrazole ring for the $[M - CH_3]^-$ fragment (Scheme 2).

SCHEME 2



The ease of the loss of methyl groups from nitrogen and oxygen atoms is presumably a consequence of the formation of an even-electron fragment with aromatic structure and charge on the oxygen atom. This tendency is characteristic for the decomposition of the pyrazolone compounds studied in this work.

Comparison of the energy characteristics of the ions in Table 1 also indicates that not all the fragments characteristic for I and II have identical structure. The $[M - H]^-$ ions in resonances a and b apparently have different structures (B and B') (scheme 2). On the other hand, these ions in the electronically excited state (resonance c) likely isomerize and have identical structure. It is interesting to note that the $[M-CH_3]^-$ ion in the electronically excited state is not observed in the decomposition of II. The loss of a methyl group directly from M_{II}^- in this case is apparently suppressed by the competitive reaction with ring opening and the formation of anions 132, 92, 91 and a series of other anion observed in resonance c.

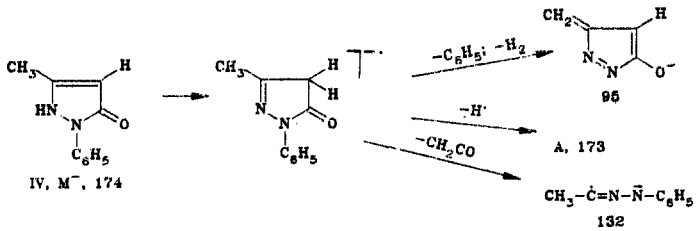
Fragments 141 and 116 are formed upon ring opening and are characteristic for the decomposition of methoxypyrazole I. Anions 119 and 132 are specific only for analog II. The

*Here and subsequently, the number characterizing the ion gives the m/z value.

decomposition processes of II are supported by the spectrum of deuteroanalog II, in which the ions at 187, 147, 118 and 96 are shifted to higher masses (190, 150, 120 and 99, respectively). No shifts are found in the mass numbers for the ions at 173, 172, 132, 92 and 91.

The electron impact mass spectrum of IV [2, 5] indicates that this compound exists in the gas phase predominantly in the CH_2 form (Scheme 3).

SCHEME 3



This significantly facilitates the formation of aromatic fragments 173 and 95 due to loss of hydrogen atoms and the substituent from $N_{(1)}$ (Scheme 3). The greatest intensity in the ECDR spectrum of this compound is found for the $[M - H]^-$ ion which is observed in resonances a and b (Table 2). Relatively low intensity (< 10%) is found for the $[M - CH_2CO]^-$ ion. The loss of ketene is observed in the decomposition of IV upon electron impact [2, 5]. The peaks for fragments 173 and 174 and for fragments 95 and 96 have equal intensities in the spectrum of deuteroanalog V due to tautomerism. There is no shift in the mass number of fragment 132.

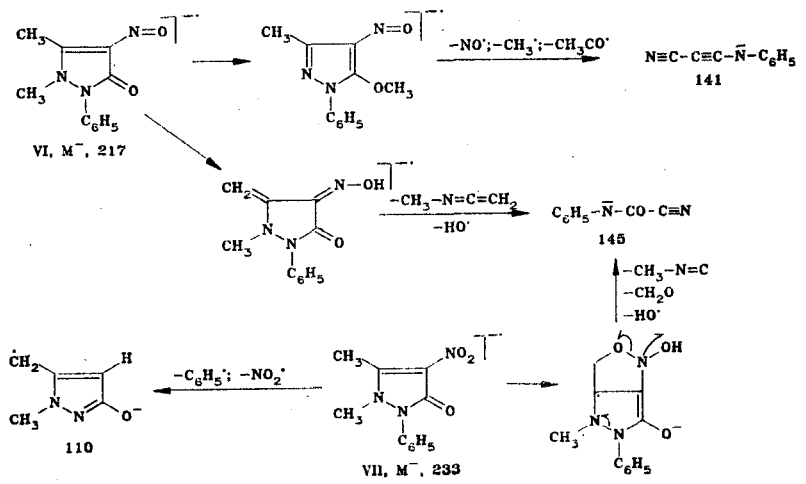
The fragmentation mechanisms of the pyrazolone derivatives under ECDR conditions were studied relative to the nature of the substituents at $C_{(4)}$ in the series VI-XIV. The electron-withdrawing nitro and nitroso groups do not stabilize the ring. The spectra of VII and VIII have fragments formed upon ring opening. In this case, the M^- peaks have low intensity, which are typical for nitroso and nitro compounds [6].

The negative charge is apparently delocalized both on the carbonyl group and the electron-withdrawing substituents, which creates conditions for the loss of the substituents and various rearrangements involving ring opening (Scheme 4).

Greatest intensity is found for the peaks of ions 145 and 141 and $[M - CH_3]^-$, $[M-OH]^-$ and $[M- NO]^-$ in the spectrum of VI. The peaks with the greatest intensity in the spectrum of nitro derivative VII correspond to the $[M - CH_3]^-$ and $[M - NO_2]^-$ fragments.

The formyl and N-methylformyl substituents in VIII and IX enhance the stability of M^- relative to decomposition and their peaks are extremely intense. The lifetimes of the M^- ions of VIII and IX are 40 and 240 μsec, respectively. Although these substituents lead to additional channels for the decomposition of the pyrazolone ring, the intensities of the peaks for the $[M - CHO]^-$, $[M - CO]^-$, $[M - CH_3, - CHO]^-$ and other fragments do not exceed 3-5% relative to the maximum peak. The most intense peaks in the ECDR spectra of VIII and IX correspond to the molecular anion M^- and fragments $[M - H]^-$ and $[M - CH_3]^-$.

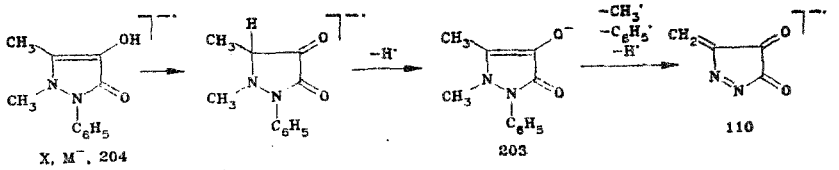
SCHEME 4



The longest lifetime for the M^- ion is found for 4-hydroxypyrazolone X (500 μsec). These lifetimes are typical for dicarbonyl compounds [6]. Hence, X in the gas phase apparently exists in the diketo form (scheme 5).

This explains the low intensities of the peaks of the characteristic $[M - H]^-$ and $[M - CH_3]^-$ ions. Interest is found in the formation of odd-electron ion 110 by the loss of three radical species (scheme 5).

SCHEME 5

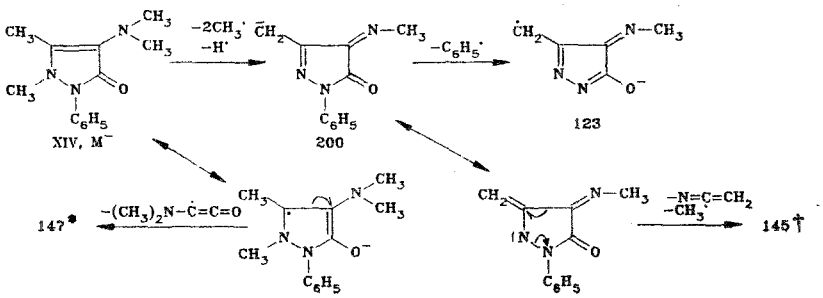


The presence or absence of M^- peaks and their intensity in the ECDR spectra of XI, XII and XIV are a factor of the electron-donor properties of their substituents. For $R^2 = H_2N$, M^- is unstable and is not detected. On the other hand, the intensities of the M^- peaks in the spectra of the compounds with methylamino and dimethylamino groups are 36 and 54%, respectively relative to that for the $[M - CH_3]^-$ ion peak which has the greatest intensity. The strongest peak in the spectrum of XI corresponds to rearrangement fragment 92 (Table 2) which is also observed in the decomposition of XII and XIV.

Some decomposition process holding interest for the ECDR mass spectrometry of pyrazolone derivatives are shown in scheme 6 in the case of the decomposition of XIV.

In contrast to compounds with electron-withdrawing substituent, the major contribution to the total ion current in the decomposition of XII and XIV is made by the $[M-H]^-$ and $[M - CH_3]^-$ fragments. The presence of strong M^- peaks in the spectra of XII and XIV also indicates the stabilizing effect of substituents with strong electron-donor properties. Apparently, the migration of the $C_{(3)}=C_{(4)}$ double bond to the $C_{(4)}=C_{(5)}$ position and localization of the negative charge on the carbonyl group oxygen atom is facilitated in the case of these substitutents. As a result, the decomposition of these compounds largely proceeds along two pathways with the loss of hydrogen atoms and of the methyl group.

SCHEME 6



*See scheme 2.
†See scheme 4.

Thus, we have carried out the first study of the major features in the behavior of pyrazolone derivatives upon electron capture dissociative resonance relative to the type of substituent at $C_{(4)}$. The $[M - CH_3]^-$ ion is characteristic for the decomposition of N-methyl-substituted derivatives. The stability of this ion relative to subsequent decomposition may be attributed to the aromatic structure formed after the loss of the substituent by isomerization of the pyrazolone ring to a pyrazole system with localization of the charge on the carbonyl group oxygen atom. The intensity of the $[M - CH_3]^-$ fragment peak in the spectra of compounds with electron-donor and electron-withdrawing substituents is large determined by a single factor, namely, the existence of competing processes with ring opening

and rearrangement involving the substituent at $C_{(4)}$. These results are used in the quality control of pyrazolone drugs and establishing the structure of new compounds in this class.

EXPERIMENTAL

The mass spectra were taken on an MKh-1303 mass spectrometer modified for taking ECDR spectra [6]. The ion lifetimes were measured according to Kosyanovskii et al. [9]. The electron energies at the ion current yield maxima were measured to ±0.2 eV. The error in the determination of the ion lifetimes was ±5 μsec.

Derivatives II, IV, VI, VII, XI and XII are starting materials and intermediates in the preparation of the drug, amidopyrine, while VIII-X are side-products in the synthesis of this drug.* Prior to taking the specta, the compounds were crystallized from organic solvents or water according to reported procedures [7]. Derivative I was synthesized according to Benary [8]. Its physical constants corresponded to the literature values. Deuteroanalog was obtained by the methylation of phenylmethylpyrazolone IV by the deuterated methyl ester of benzenesulfonic acid, $CD_3OSO_2C_6H_5$. The deuteroanalog and V and XIII were synthesized by heating IV and XII in CD_3OD at reflux twice.

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