IODONIUM DERIVATIVES OF HETEROCYCLIC COMPOUNDS

I. PHENYLIODONIUM SALTS AND BETAINES OF PYRAZOLES

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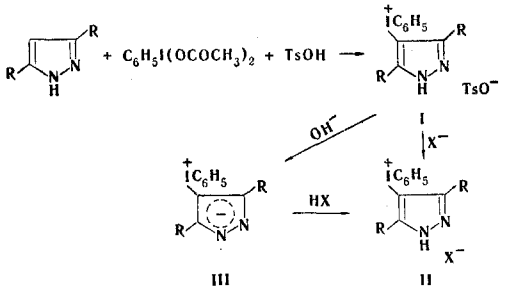
A method for the preparation of phenyliodonium derivatives of pyrazoles was developed. The reaction of pyrazole and 3,5-dimethyl- and 3,5-diphenylpyrazoles with phenyl iodosoacetate in the presence of p-toluenesulfonic acid gives pyrazole-4-phenyliodonium tosylates, which are converted to pyrazole-4-phenyliodonium betaines on treatment with alkali. The tosylates are converted to pyrazole-4-phenyliodonium chlorides, bromides, and iodides by exchange reactions, and pyrazole-4-phenyliodonium fluorides and borofluorides are obtained by reaction of the betaines with hydrofluoric and fluoboric acids. The ionization constants for a number of phenyliodonium derivatives of pyrazoles were calculated on the basis of the electronic absorption spectra. The 4-phenyliodonium grouping increases the acidity of pyrazoles by 4.5-5 orders of magnitude.

Up until now, mainly aryliodonium derivatives of β-dicarbonyl compounds have been studied in investigations of the aryliodonation of an active methylene group [1]. Since several groups of heterocyclic compounds – pyrrole, indole, pyrazole, imidazole, triazole, and others – are analogs of enol ethers and enamines of β-dicarbonyl compounds, we have assumed that they may be suitable nucleophlic components in aryl iodonation reactions.

In the present study we have investigated the possibility of the production of aryliodonium derivatives of pyrazoles. As demonstrated in [2], one of the limiting factors of the aryliodonation reaction is the insufficient nucleophilicity of the carbon atom, which can be characterized by the density of the frontal electrons on this atom: the higher this density, the easier the formation of a carbon–iodine bond. Calculations by the Hückel MO LCAO method have demonstrated that there is an extremely high density of frontal π electrons in pyrazole on the carbon atom in the 4 position [2]. This makes it a very reactive component in the reaction with aryliodoso compounds.



R = H, CH_3, C_6H_5; X = Cl, Br, I, F, BF_4; Ts = p-$CH_3C_6H_4SO_2$

We have investigated the phenyliodonation of pyrazole and 3,5-dimethyl- and 3,5-diphenylpyrazoles. We found that these compounds are very readily phenyliodonated by phenyl iodosoacetate in the presence of p-toluenesulfonic acid to give the corresponding pyrazole-4-phenyliodonium tosylates (Ia-c, Table 1).

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TABLE 1. Pyrazole-4-phenyliodonium Salts

Comp.	X	R	mp (dec.), °C	Empirical formula	Found, %		Calc., %		Yield, %
					N	I	N	I	
Ia	TsO	H	209—210[a,c]	$C_{16}H_{15}IN_2O_3S$[b]	6,4	28,6	6,3	28,7	70
Ib	TsO	CH_3	118—120[c]	$C_{18}H_{19}IN_2O_3S$[d]	5,5	26,9	5,9	27,0	94
Ic	TsO	C_6H_5	222—224[a]	$C_{28}H_{23}IN_2O_3S$[e]	4,7	21,4	4,7	21,4	75
IIa	Cl	H	210—211[c]	$C_9H_8ClIN_2$	9,2	41,6	9,1	41,4	77
IIb	Br	H	200—201[a]	$C_9H_8BrIN_2$	7,9	36,3	8,0	36,2	63
IIc	I	H	173—174[a]	$C_9H_8I_2N_2$	6,8	64.0	7,0	63,8	93
IId	Cl	CH_3	218—220[c]	$C_{11}H_{12}ClIN_2$	8,1	38,1	8,4	38,0	90
IIe	Br	CH_3	203—204[c]	$C_{11}H_{12}BrIN_2$	7,4	33,6	7,4	33,6	98
IIf	I	CH_3	174—176[a]	$C_{11}H_{12}I_2N_2$	6,5	59,5	6,6	59,6	97
IIg	Cl	C_6H_5	198—199[a]	$C_{21}H_{16}ClIN_2 \cdot H_2O$	5,9	26,6	5,9	26,6	87
IIh	Br	C_6H_5	193—195[a]	$C_{21}H_{16}BrIN_2$	5,3	25,1	5,6	25,2	60
IIi	I	C_6H_5	159—160[a]	$C_{21}H_{16}I_2N_2$	4,6	46,0	5,1	46,1	91
IIj	F	H	158—160[f]	$C_9H_8FIN_2$		43,6		43,7	51
IIk	F	CH_3	146—148[f]	$C_{11}H_{12}FIN_2$		39,8		39,9	83
IIl	F	C_6H_5	162—163[f]	$C_{21}H_{16}FIN_2$		28,8		28,7	84
IIm	BF_4	CH_3	205—208[f]	$C_{11}H_{12}BF_4IN_2$		33,1		32,9	97
IIn	BF_4	C_6H_5	223—224[f]	$C_{21}H_{16}BF_4IN_2$		24,7		24,9	77

[a] From ethanol. [b] Found, %: S 7.2. Calculated, %: S 7.2. [c] From water. [d] Found, %: S 6.1. Calculated, %: S 6.8. [e] Found, %: S 5.3. Calculated, %: S 5.4. [f] From ethanol–ether.

TABLE 2. pK_a Values of Pyrazole Derivatives

Compound	pK_a	
	water	50% ethanol
3,5-Dimethylpyrazole-4-phenyliodonium betaine (IIIb)	—	11,04±0,06
3,5-Dimethylpyrazole-4-phenyliodonium chloride (IId)	10,79±0,09	11,11±0,07
3,5-Dimethylpyrazole-4-phenyliodonium tosylate (Ib)	10,88±0,07	11,02±0,06
Pyrazole-4-phenyliodonium chloride (IIa)	—	10,00±0,06
3,5-Diphenylpyrazole-4-phenyliodonium bromide (IIh)	—	9,31±0,07
4-Bromo-3,5-dimethylpyrazole	12,92±0,08	13,70±0,08
Pyrazole	14[7, 8]	~14,7
3,5-Dimethylpyrazole	—	~15,7
3,5-Diphenylpyrazole	—	14,0

The reaction with 3,5-dimethyl- and 3,5-diphenylpyrazoles proceeds at room temperature in a few minutes, but brief heating of the reaction mixture is required to accelerate the reaction with unsubstituted pyrazole.

A number of other pyrazole-4-phenyliodonium salts – chlorides, bromides, and iodides (IIa-i) – were obtained by reaction of tosylates Ia-c with alkali metal salts.

Treatment of tosylates Ia-c with alkali solution readily gives compounds of the inner salt type – pyrazole-4-phenyliodonium betaines (IIIa-c) – as colorless crystalline substances with rather high decomposition temperatures. These compounds are, however, less stable than pyrazole-4-phenyliodonium salts; they gradually become rose-colored on prolonged storage in light. Compounds III are extremely thermally stable – they can be crystallized from hot water or ethanol.

Pyrazole-4-phenyliodonium fluorides and fluoborates (IIj-n) were obtained from III by reaction with hydrofluoric and fluoboric acids. Pyrazole-4-phenyliodonium fluorobrate could not be isolated in crystalline form, since it is very hygroscopic. The characteristics of I, II, and III are given in Table 1.

The iodonium derivatives of the pyrazoles were characterized by the electronic absorption spectra of aqueous and aqueous ethanol solutions at various pH values (Figs. 1-3). The literature [3-6] contains data on the electronic absorption spectra of several other pyrazole derivatives. The introduction of a phenyliodonium grouping into the 4 position of pyrazole and 3,5-dimethylpyrazole increases the absorption intensity and causes a bathochromic shift (Figs. 1 and 2). In the case of 3,5-diphenylpyrazole, the phenyliodonium grouping causes a hypsochromic shift of the chief absorption maximum (Fig. 3). The ionization constants for a number of iodonium derivatives of pyrazoles (Table 2) were calculated on the basis of the electronic absorption spectra. There are no accurate data in the literature regarding the acidity of pyrazole itself in aqueous and aqueous ethanol media [7, 8]. There are some data [5, 6] on the pK values of acyl derivatives of pyrazoles. Because of the weak acidity of pyrazoles, we were able to accurately determine the pK value only for 3,5-diphenylpyrazole. From the results, one can judge that the introduction of a phenyliodonium grouping into the 4 position of pyrazoles increases the acidity of the latter by about 4.7-5 orders of magnitude. This sort of large effect of the phenyliodonium grouping also is exerted on the OH

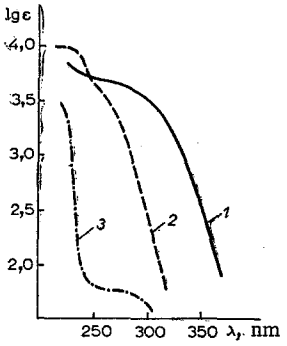

Fig. 1

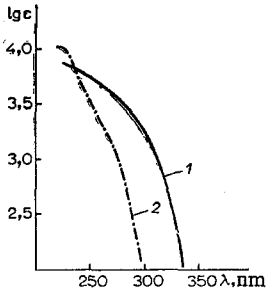

Fig. 2

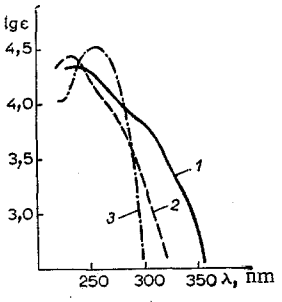

Fig. 3

Fig. 1. UV spectra in 50% ethanol: 1) 3,5-dimethylpyrazole-4-phenyliodonium betaine (IIIb) in 0.1 N KOH; 2) IIIb in acidic medium; 3) 3,5-dimethylpyrazole.

Fig. 2. UV spectra of pyrazole-4-phenyliodonium chloride (IIa) in 50% ethanol: 1) in 0.25 N KOH; 2) pH 3.

Fig. 3. UV spectra in 50% ethanol: 1) 3,5-diphenylpyrazole-4-phenyliodonium bromide (IIh) in 0.25 N KOH; 2) IIh in acidic medium (pH ~ 5); 3) 3,5-diphenylpyrazole.

acidity of β-dicarbonyl compounds [9]. The acidity constants of pyrazole itself and dimethylpyrazole in 50% ethanol can be approximately established from the pK values of the iodonium derivatives of pyrazole and dimethylpyrazole.

EXPERIMENTAL

Pyrazole [10], 3,5-dimethylpyrazole [11], 3,5-diphenylpyrazole [12], and phenyl iodosoacetate [13] were synthesized by methods described in the literature.

The spectroscopic measurements were made with an SFD-2 spectrometer. The acidity constants were determined by a spectrophotometric method [14]. The pH values of buffer solutions were measured with an LPM-60M pH meter by means of a glass electrode coupled with a flow-type silver–silver chloride electrode.

Pyrazole-4-phenyliodonium Tosylates (Ia-c). A 0.01-mole sample of the appropriate pyrazole was added to a solution of 1.9 g (0.01 mole) of p-toluenesulfonic acid monohydrate in 10 ml of ethanol, after which 0.01 mole of phenyliodosoacetate was added gradually with stirring. The mixture was allowed to stand at room temperature for 30 min, after which, in the case of Ia, the mixture was refluxed for 5 min, the hot solution was filtered, and the filtrate was allowed to stand for crystallization. In the case of Ib, the solution was diluted with 50 ml of ether and allowed to stand for crystallization. In the case of Ic, the mixture was heated to the boiling point, the hot solution was filtered, and the filtrate was allowed to stand for crystallization.

Tosylates Ia-c were colorless, stable, crystalline substances that were moderately soluble in water and ethanol.

Pyrazole-4-phenyliodonium Betaine (IIIa). A total of 35 ml of 15% aqueous sodium hydroxide solution was added to a hot solution of 4.4 g (0.01 mole) of Ia in 20 ml of water. The mixture was then cooled, and the precipitated IIIa was removed by filtration to give a product with mp 144-147° (from water) in 90% yield. Found,%: I 46.8; N 10.7. $C_9H_7IN_2$. Calculated,%: I 47.0; N 10.4.

3,5-Dimethylpyrazole-4-phenyliodonium Betaine (IIIb). A 4.7-g (0.01 mole) sample of Ib was added to 35 ml of 15% aqueous sodium hydroxide, and the mixture was allowed to stand at room temperature for 1 h and then at 0-5° for 2 h. The precipitated IIIb was removed by filtration to give a product with mp 170-172° (dec., from ethanol–ether) in 90% yield. Found,%: I 42.4; N 8.0. $C_{11}H_{11}IN_2$. Calculated,%: I 42.6; N 9.4.

3,5-Diphenylpyrazole-4-phenyliodonium Betaine (IIIc). A hot solution of 2.2 g (0.05 mole) of sodium hydroxide in 50 ml of ethanol and 15 ml of water was added to a hot solution of 5.9 g (0.01 mole) of Ic in 120 ml of ethanol. Colorless crystals of IIIc began to precipitate immediately. The mixture was cooled, and

the crystals were removed by filtration to give a product with mp 196-199° (dec.) in 94% yield. Found,%: I 28.9; N 6.3. $C_{21}H_{15}IN_2$. Calculated,%: I 28.7; N 6.6.

Pyrazole-4-phenyliodonium Fluorides (IIj-l). A 0.01-mole sample of IIIa-c was dissolved at room temperature in 20 ml of a 41% solution of hydrochloric acid in ethanol (1:100). After 0.5 h, the solution was diluted with 100 ml of ether, and the precipitated fluoride was removed by filtration.

Pyrazole-4-phenyliodonium Fluoborates (IIm, n). A 0.001-mole sample of IIIb,c was dissolved at room temperature in 3 ml of a 1 N solution of fluoboric acid in ethanol (prepared from 19 g of 41% hydrofluoric acid and 6 g of boric acid in 100 ml of ethanol), and the mixture was allowed to stand at room temperature for 30 min, after which it was diluted with 10 ml of ether and allowed to stand at 0-5° for crystallization.

Pyrazole-4-phenyliodonium Chloride, Bromide, and Iodide (IIa-c) (Table 1). A 0.001-mole sample of Ia was dissolved in 5 ml of hot ethanol, and a solution of 0.002 mole of sodium chloride, sodium bromide, or potassium iodide in 2 ml of water was added. The mixture was cooled, and IIa-c were removed by filtration.

3,5-Dimethylpyrazole-4-phenyliodonium Chloride, Bromide, and Iodide (IId-f) (Table 1). These compounds were prepared by the method used for IIa-c, but 3 ml of acetic acid at room temperature was taken as the solvent for Ib.

3,5-Diphenylpyrazole-4-phenyliodonium Chloride, Bromide, and Iodide (IIg-i) (Table 1). These compounds were prepared by the method used for IIe-f but hot acetic acid was used as the solvent.

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