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RESEARCH ON AMINOMETHYLENE DERIVATIVES OF AZOLES. 23.* SYNTHESIS AND STRUCTURE OF FORMYL DERIVATIVES OF 1-PHENYL-5-HYDROXY(MERCAPTO)-IMIDAZOLES

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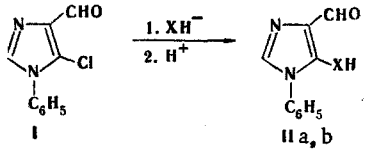
UDC 547.783.07

1-Phenyl-4-formyl-5-hydroxy(mercapto)imidazoles were obtained by replacement of the chlorine atom in 1-phenyl-4-formyl-5-chloroimidazole by hydroxy and mercapto groups, and their physicochemical properties and structures were studied. It was shown by a comparison of the electronic and IR spectra (and the PMR spectra in the case of the sulfur-containing compound) with the spectral characteristics of compounds that model the various possible tautomeric forms that 1-phenyl-4-formyl-5-hydroxy(mercapto)imidazoles exist primarily in the mesoionic form; this is associated with their high acidities and the presence of a sufficiently basic ring nitrogen atom.

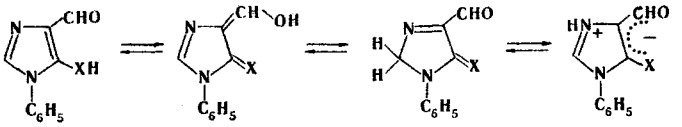
In a continuation of our studies of the tautomeric transformations of 4-formyl-5-hydroxypyrazoles [2] and 4-formyl-5-mercaptopyrazoles [3] it seemed of interest to study their corresponding imidazole derivatives. The latter were obtained from 1-phenyl-4-formyl-5-chloroimidazole (I) by replacement of the chlorine atom by hydroxy and mercapto groups.



I IIa, b

IIa X=O; b X=S

Compounds IIa, b are rather strong acids and have pK_a values of 5.68 ± 0.03 (X = O) and 4.63 ± 0.03 (X = S). These compounds, like 1-phenyl-3-R-4-acyl-5-pyrazolones [2] and 2-phenyl-4-acyl-5-oxazolones [4], may exist in several tautomeric forms:



A B C D

Because of the low solubilities of the investigated compounds in nonpolar solvents, their structures were investigated primarily by comparison of the data from the electronic and IR spectra with the data for compounds that model the most important tautomeric forms, viz., the hydroxy aldehyde (structure A, IIIa, b), hydroxymethylene (structure B, IVa, b), and mesoionic (structure D, Va, b) forms. Compound IIIa was obtained by replacement of the chlorine atom by a methoxy group, while IIIb was obtained by alkylation of imidazole IIb with methyl iodide. 1-Phenyl-4-dimethylaminomethylene-5-imidazolone (IVa)

*See [1] for Communication 22.

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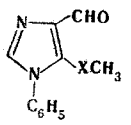
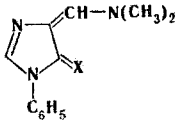


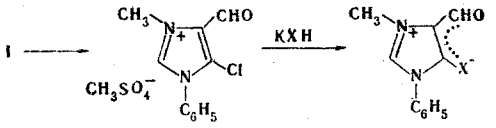
IIIa, b



IVa,b

and its sulfur analog (IVb), which were obtained by reaction of IIa and IIb with dimethylamine, were used as model compounds for structure B.

The mesoionic structure was synthesized by replacement of the chlorine atom by the appropriate group in the quaternary salt of I:



Va, b

The spectral and physical properties of the compounds with the mesoionic structure (Va, b) are similar to those of the previously described ketones of azoles obtained in [5, 6].

Intense absorption bands at 1690 (C=O) and 1570-1610 cm^{-1}, which include the vibrations of the C=C and C=N bonds of the imidazole ring are observed in the IR spectrum of IIa (Fig. 1 and Table 1). A comparison of the IR spectra of IIa with the IR spectra of model compounds IIIa, IVa, and Va shows that its structure is closer to the structure of the mesoionic form. A similar picture is also observed for sulfur-containing compounds, and in this case the character of the IR spectrum of 1-phenyl-4-formyl-5-mercaptoimidazole is similar to that of the spectrum of Vb but differs from that of the IR spectra of the remaining compounds (Fig. 1, curve 3'). Unfortunately, because of the limited solubilities of IIa and IIb we were unable to record their IR spectra in nonpolar solvents and were also unable to study the concentration dependences; in addition, the intramolecular interactions between the strongly polar groups are, of course, superimposed.

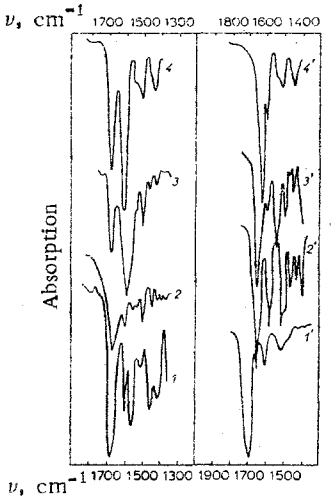


Fig. 1. IR spectra at 1500-1700 cm^{-1} (for KBr pellets): 1) 1-phenyl-4-formyl-5-methoxyimidazole (IIIa); 2) 1-phenyl-3-methyl-4-formyl-5-imidazolium dehydrooxide (Va); 3) 1-phenyl-4-formyl-5-hydroxyimidazole (IIa); 4) 1-phenyl-4-dimethylaminomethylene-5-imidazolone (IVa); 1') 1-phenyl-4-formyl-5-methylmercaptoimidazole (IIIb); 2') 1-phenyl-3-methyl-4-formyl-5-imidazolium dehydrothiooxide (Vb); 3') 1-phenyl-4-formyl-5-mercaptoimidazole (IIb); 4') 1-phenyl-4-dimethylaminomethylene-5-imidazolethione.

TABLE 1. Spectral Characteristics of 1-Phenyl-4-formyl-imidazole Derivatives

Compound	Tautomer	λ_{max}, nm (lg ε)		Principal bands in the IR spectra in the 1300-1700 cm^{-1} region (KBr)	δ, ppm (dimethylacetamide)		
		ethanol	chloroform		CHO	R-H	CH
IIa		225 (4,1), 315 (4,2)	327 (3,9)	1690 s, 1610—1570 br s, 1540 sh, 1510, 1470 w, 1425 w, 1390 w, 1320 s, 2700—2500 br			
IIIa	A	226 (4,0), 275 (4,1)	277 (4,1)	1690, 1680 s, 1600, 1570 s, 1505, 1450 s, 1410 s, 1355 s, 1320	9,96	7,94	
IVa	B	230 (3,9), 260 (4,1), 336 (4,4)	260 (4,1), 340 (4,3)	1685 s, 1630 sh, 1605 s, 1560 w, 1510 s, 1450 s, 1410, 1320 s,		7,7*	7,6—7,3
Va	D	228 (3,9), 313 (3,6)	330 (3,5)	1680—1660 s, 1600 s, 1555, 1530, 1500 s, 1445, 1420, 1325			
IIb		297 (3,6), 363 (3,9)	303 (3,7), 385 (3,5)	1645 s, 1595, 1540, 1500, 1465, 1445, 1410, 1340 s,	9,92	9,35	
IIIb	A	252 (4,1), 294 пл (3,7)	253 (4,0), 290 (3,9)	1695 s, 1600, 1510	10,18	8,38	
IVb	B	277 (4,2), 407 (4,1)	280 (4,3), 420 (4,2)	1630 s, 1600, 1550 sh, 1510, 1445 m, 1380, 1360 s, 1340 s		8,05*	7,5—7,3
Vb	D	302 (3,6), 272 (3,9)	315 (3,8), 382 (3,9)	1655 s, 1600, 1580 s, 1510 s 1490, 1460, 1415, 1390, 1340 s	10,0	9,4†	
I	A	267 (4,1)	268 (4,2)	1692 s, 1600, 1520 s, 1395, 1355 s	10,3‡	7,9‡	

*The signal of the proton of the CH group falls in the aromatic proton region of 7.3-7.6 ppm; δNCH_3 3.6 and 3.25 (X = O, 6H); 3.67 and 3.33 (X = S, 6H). †δNCH_3 4.1 (3H). ‡In $CDCl_3$.

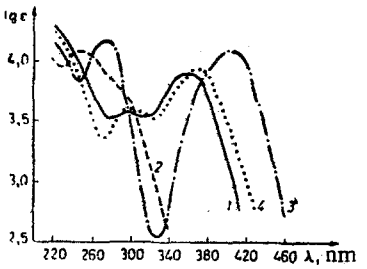


Fig. 2

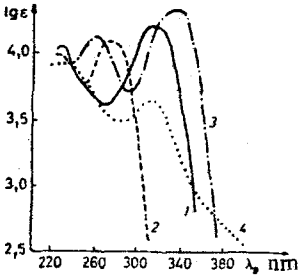


Fig. 3

Fig. 2. Electronic absorption spectra in ethanol: 1) 1-phenyl-4-formyl-5-hydroxyimidazole (IIa); 2) 1-phenyl-4-formyl-5-methoxyimidazole (IIIa); 3) 1-phenyl-4-dimethylaminomethylene-5-imidazolone (IVa); 4) 1-phenyl-3-methyl-4-formyl-5-imidazolium dehydrooxide (Va).

Fig. 3. Electronic absorption spectra in ethanol: 1) 1-phenyl-4-formyl-5-mercaptoimidazole (IIb); 2) 1-phenyl-4-formyl-5-methyl-mercaptoimidazole (IIIb); 3) 1-phenyl-4-dimethylaminomethylene-5-imidazolethione (IVb); 4) 1-phenyl-3-methyl-4-formyl-5-imidazolium dehydrooxide (Vb).

We were able to obtain a great deal of information on the structures of the investigated compounds by comparison of the electronic spectra recorded both in ethanol and in chloroform. It is apparent from Fig. 2 (for the compounds with X = O) and Fig. 3 (for the compounds with X = S) that the curves of the absorption spectra of IIa and IIb are similar in character to the curves of the absorption spectra of the fixed structures of mesoionic form D but differ significantly from the electronic spectra of the other model compounds. A similar conclusion can also be drawn on the basis of a comparison of the absorption spectra in chloroform (Table 1). Thus an examination of the IR and electronic spectra of IIa

and IIb of the model compounds provides evidence for their primary existence in the mesoionic form. This conclusion is confirmed by the data from the PMR spectra, which we were able to record only for the sulfur-containing compounds in dimethylacetamide (DMA) (IIa is only slightly soluble in this solvent). We judged the structure of IIb from the position of the signal of the proton in the 2 position of the imidazole ring. It is apparent from the data in Table 1 that the signal of this proton is shifted to weak field ($\Delta\delta \sim 1$ ppm) as compared with the 2-H signal for IIIb and IVb; this may be due to the inductive effect of the quaternized nitrogen atom in mesoionic structure D. The same position of the signal of this proton is observed for model compound Vb. In this case it should be noted that the signal of the proton of the $H-N^+$ group in the PMR spectrum of IIb is broadened markedly, and, considering the low solubilities of IIa and IIb in organic solvents as compared with their N-methylated analogs, it may be assumed that they are stabilized due to the formation of an intermolecular hydrogen bond, evidently of the $^+NH...O{=}CH-$ type. Thus an examination of the spectral and other properties of the formyl derivatives of 5-hydroxy(mercapto)-imidazoles shows that, in contrast to the corresponding pyrazole [2] and oxazole [4] derivatives, they exist primarily in the mesoionic form as a consequence of their high acidities and the presence of a sufficiently basic ring nitrogen atom.

EXPERIMENTAL

The electronic spectra of the compounds were recorded with an SF-8 spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a Perkin–Elmer 60 spectrometer. The pK_a values were determined with a pH-340 potentiometer with a DL-02 adapter in 50% aqueous ethanol at 20°C by the method in [7].

1-Phenyl-4-formyl-5-hydroxyimidazole (IIa). A 0.01-mole sample of 1-phenyl-4-formyl-5-chloroimidazole (I) [8] was added to a solution of 2.8 g (0.06 mole) of potassium hydroxide in 40 ml of aqueous ethanol (1:1), and the mixture was heated at 50-60°C for 2 h and refluxed for 30 min. The solvent was then removed by vacuum distillation, and the residue was dissolved in the minimum amount of water. The undissolved material was removed by filtration, and the filtrate was acidified with formic acid. The resulting precipitate was removed by filtration, washed with water, and dried to give 1.8 g (90%) of product. Two reprecipitations from sodium carbonate solution by the addition of formic acid and recrystallization from water–ethanol gave a product with mp 283-285°C (mp 284-285°C [8]).

1-Phenyl-4-formyl-5-mercaptoimidazole (IIb). A mixture of 2.1 g (0.01 mole) of I, 2.1 ml (0.015 mole) of a 50% aqueous solution of potassium hydrosulfide in 40 ml of ethanol was refluxed for 3 h, after which the solvent was removed by distillation, and the residue was dissolved in the minimum amount of water. The aqueous solution was acidified with formic acid to give 2 g (98%) of IIb. Two reprecipitations from sodium carbonate solution by the addition of formic acid gave a product with mp 203-204°C (mp 203-204°C [8]).

1-Phenyl-4-formyl-5-methoxyimidazole (IIIa). A 2.1-g (0.01 mole) sample of I was dissolved in 50 ml of absolute methanol containing 2.4 g of sodium ethoxide, and the solution was allowed to stand at room temperature for 10 h. The solvent was removed by distillation, and the residue was washed several times with water and removed by filtration. The yield of IIIa was 1.3 g (63%). Column chromatography (on silica gel with elution by benzene) gave a product with mp 93-94°C (from n-heptane). Found: N 13.9%. $C_{11}H_{10}N_2O_2$. Calculated: N 13.9%.

1-Phenyl-4-formyl-5-methylmercaptoimidazole (IIIb). A 0.4-g (0.002 mole) sample of IIb was dissolved in 20 ml of ethanol containing 0.14 g of sodium ethoxide, 0.4 g (0.0025 mole) of methyl iodide was added, and the mixture was allowed to stand at room temperaure for 3 h. The solvent was then removed by distillation, and the residue was washed with water and removed by filtration. The yield was 0.35 g (80%) and the product had mp 75-76°C (from aqueous ethanol). Found: N 12.7; S 14.8%. $C_{11}H_{10}N_2OS$. Calculated: N 12.8, S 14.7%.

1-Phenyl-4-dimethylaminomethylene-5-imidazolone (IVa). A 1.7-g sample of IIa was dissolved in a 20-fold excess of a 25% aqueous solution of dimethylamine, and the solution was heated to the boiling point. It was then cooled, and the resulting precipitate was removed by filtration, washed with water, and dried. The yield of product with mp 218-219°C (from benzene–petroleum ether) was 1.7 g (80%). Found: N 19.7%. $C_{12}H_{13}N_3O$. Calculated: N 19.5%.

1-Phenyl-4-dimethylaminomethylene-5-imidazolethione (IVb). This compound was similarly obtained from IIb and an aqueous solution of dimethylamine. The product was obtained

in 68% yield and had mp 181-182°C (from benzene–petroleum ether). Found: N 18.1; S 13.9%; M (ebullioscopic) 228. $C_{12}H_{13}N_3S$. Calculated: N 18.2; S 13.8%; M 231.

1-Phenyl-3-methyl-4-formyl-5-imidazolium Dehydrooxide (Va). A 0.9-g (4.5 mole) sample of I was heated with 0.42 ml (4.5 mmole) of dimethyl sulfate at 140-150°C for 2 h, after which the mixture was cooled, and the solid material was pulverized and dissolved at room temperature in an aqueous solution of sodium hydroxide (9 mole). The resulting precipitate was removed by filtration, washed with water, and precipitated twice from ethyl acetate by the addition of petroleum ether. The yield of product with mp 178-180°C was 0.14 g (15%). Found: N 13.8%. $C_{11}H_{10}N_2O_2$. Calculated: N 13.9%.

1-Phenyl-3-methyl-4-formyl-5-imidazolium Dehydrothiooxide (Vb). This compound was similarly obtained by treatment of methylated I with an aqueous solution of potassium hydrosulfide. Two reprecipitations from ethyl acetate by the addition of petroleum ether gave a product with mp 237-239°C. The yield was 0.66 g (67%). Found: N 13.1; S 14.9%. $C_{11}H_{10}N_2OS$. Calculated: N 12.9; S 14.7%.

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NEW REACTION FOR THE DIRECT INCORPORATION OF PURINES IN NUCLEOPHILIC ORGANIC COMPOUNDS

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UDC 547.857.07

The direct incorporation of purine and theophylline residues in indole, oxindole, and pyrazolone rings was accomplished in the presence of acylating agents.

Very little is known regarding reactions involving the replacement of a hydrogen atom of the purine ring, and those that have been reported pertain mainly to electrophilic substitution [1]. Almost no study whatsoever has been devoted to the quaternary salts of purine and their reactions with nucleophiles. It is known that purine itself is a weak base and that the most nucleophilic center of the molecule is the N_1 atom of the pyrimidine ring. Protonation [2] and the formation of N-oxides [3] take place at this atom. It might have been assumed that purine in acylating agents would be capable of forming N-acyl salts, which in situ, in analogy with other N-acyl heteroaromatic cations [4], would serve as electrophilic agents for the incorporation of purine in nucleophilic organic compounds.

In fact, in the case of the reaction of purine with 1-methylindole, oxindole, and 1-phenyl-3-methyl-5-pyrazolone in acetic anhydride we obtained the corresponding N_1-acetyl heterocyclic derivatives of 1,6-dihydropurine (I-III):

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