PYRAZOLES

LXIV. The Protonation of Pyrines*

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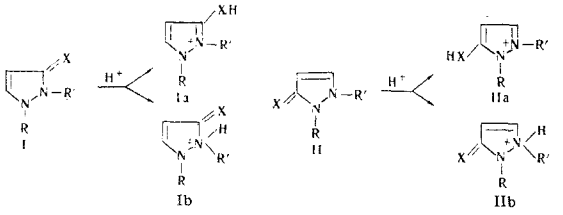
The IR, UV, and NMR spectra of 3- and 5-pyrines, and of their thio, seleno, and imino analogs, are examined, and their pK_a values measured. On the basis of the results, it is suggested that protonation in these systems takes place at the exocyclic heteroatom.

We have previously investigated the dipole moments [1] and complex formation in the pyrine system [2]. Since it proved impossible to determine unequivocally the course of complex formation in thio and seleno pyrines (i.e., at the exocyclic heteroatom or a ring nitrogen atom), the present investigation was undertaken. LCAO-MO calculations indicate very high electron densities at the exocyclic heteroatoms in all 3- and 5-pyrine systems (I and II, respectively), but of course this does not exclude the possibility of protonation at a ring nitrogen atom, with the formation of **IIb** and **Ib**.



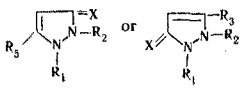
IR Spectra. The IR spectra of 3- and 5-antipyrines (table, nos. 1–3, 6, 11, 12) show strong absorption bands in the 1670–1640 cm^{-1} region, which are assigned to the valency vibrations of the carbonyl group. (cf. Figs. 1 and 2). The absorption bands at 1500 and 1600 cm^{-1}, which are observed in all the pyrines, are due to benzene ring vibrations, since they are absent from the spectrum of compound 6. The absorption due to the pyrine ring proper either occurs at much lower frequencies, or it corresponds to the low intensity bands at 1520 and 1600 cm^{-1} (as a shoulder on the C=O band for compound 6- see Fig. 2). The high integral intensity of the carbonyl band (for example, $A_{\nu C=C} = 7.4$ $mole^{-1} \cdot \cdot l \cdot cm^{-2}$ for compound 3 in $CHCl_3$) excludes a bipolar structure for the antipyrines, as we have known [1], but it indicates extremely high polarization of the exocyclic C=O bond. The introduction of a methyl group in the 3- or 5-position of the antipyrine ring results in the disappearance of the band at 1545 cm^{-1}, apparently as a result of an increase in the "pseudosymmetry" of the ring. The exocyclic C=NH bond appears clearly at 1625–1622 cm^{-1} in the 3- and 5-iminopyrines (see Fig. 2).

The assignment of the C=S and C=Se bands in thio- and selenopyrines is very difficult. The assignment of these bands in the few papers on the IR spectroscopy of thio and seleno amides is very inconsistent [2]. In the most comprehensive paper, Jensen [2], although giving assignments for 7 characteristic bands in a series of thio and seleno amides, does not examine compounds with strongly polarized exocyclic C=S and C=Se bonds. In an article [3] on thioamide complexes, the difficulty of assigning the C=S bonds as a result of superimposition of the C–N bond is pointed out. Examination of the spectra of the thiopyrazolones 4 and 9 (cf. Fig. 3, 3 and Fig. 4, 3), permits the assignment of the bands at 1360–1370 cm^{-1} to the thioamide C–band, after Jensen [2]; for the seleno analogs it must be lower by 10–15 cm^{-1} [2], and in fact for the selenopyrines 5 and 10 (cf. Fig. 3, 5 and Fig. 4, 5) it is observed to lie at 1347–1351 cm^{-1}.

The assignment of the other bands has, unfortunately, proved still more difficult. A great similarity exists between the IR spectra of all the thio- and seleno pyrines (nos. 4, 5, 9, and 10), irrespective of the replacement of Se

*For part LXIII, see [8].

Physicochemical Properties of 3- and 5-Pyrines, and Their Thio and Seleno Analogs



Compound No.	R_1	R_2	R_3	R_5	X	pK_a, in water	UV Spectra, λ_{max}, nm/lg			NMR Spectra, chemical shift, δ scale, ppm					
										H_4		Phenyl protons		Other protons	
							in water	в CH_3OH	in conc HCl	in $(CH_3)_2SO$	in D_2O : : D_2SO_4 (3 : 1)	in $(CH_3)_2SO$	in D_2O : : D_2SO_4 (3 : 1)	in $(CH_3)_2SO$	in D_2O : D_2SO_4 (3 : 1)
1	C_6H_5	CH_3	H	—	O	2.42	264/3.98	276/4.02	237/3.96	5.97	—	7.98	—	H_3—8,57	—
2	C_6H_5	CH_3	—	H	O	2.40	268/4.10	280/4.16	—	—	—	—	—	—	—
3	C_6H_5	CH_3	CH_3	—	O	2.85	242, 254/ 3.96, 3.92	250, 242/ 3.98, 3.96	—	—	—	—	—	—	—
4	C_6H_5	CH_3	CH_3	—	S	2.49	282/4.01	302/4.06	249/4.00	6.28	6.14	7.7—7.8	7.9—7.3	—	2-CH_3 3.20 3-CH_3 2.02
5	C_6H_5	CH_3	CH_3	—	Se	2.64	292/3,96	314/3.99	2.60, 4.20/ 3.35, 2.45	6.48	6.01	7.7—7.8	7.4—8.0	—	2-CH_3 3.25 3-CH_3 2.06
6	CH_3	CH_3	CH_3	—	O	—	—	—	—	5.10	—	—	—	1-CH_3—3.33 2-CH_3—3.24 3-CH_3—2.31	
7	C_6H_5	CH_3	CH_3	—	NH	10.4	—	261/3.93	—	5.42	—	7.5—7.6	—	NH—4.29	—
8	C_6H_5	CH_3	—	CH_3	NH	10.6	—	260/3.98	—	5.74	—	7.6—7.7	—	NH—4.47	—
9	C_6H_5	CH_3	—	CH_3	S	2.29	282/4.02	302/4.07	—	—	—	—	—	—	—
10	C_6H_5	CH_3	—	CH_3	Se	2.42	292/4.01	312/4.10	—	—	—	—	—	—	—
11	C_6H_5	CH_3	—	CH_3	O	2.49	258/4.02	269/4.14	—	—	6.07	—	7.6—7.8		3-CH_3 2.89 2-CH_3 3.16
12	$C_6H_5CH_2$	CH_3	CH_3		O	—	—	256/3.88	230/3.76	—	6.10	—	7.05—7.15		2-CH_3 3.12 3-CH_3 2.30 CH_2 5.51
13*	C_6H_5	H	CH_3		O	—	258/4.05	268/4.11	230/3.98	—	6.20	—	7.4—7.6		3-CH_3 2.17

*Pyrazolone

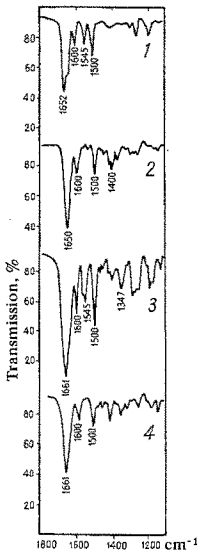


Fig. 1. IR Spectra of antipyrines in $CHCl_3$: 1) 1-phenyl-2-methyl-3-pyrazolone (c 0.01 M; layer thickness 0.17 mm); 2) 1-phenyl-2, 5-dimethyl-3-pyrazolone (c 0.02 M, layer thickness 0.25 mm); 3) 1-Phenyl-2-methyl-5-pyrazolone (c 0.02 M, layer thickness 0.17 mm); 4) 1-phenyl-2, 3-dimethyl-5-pyrazolone (c 0.02 M, layer thickness 0.25 mm).

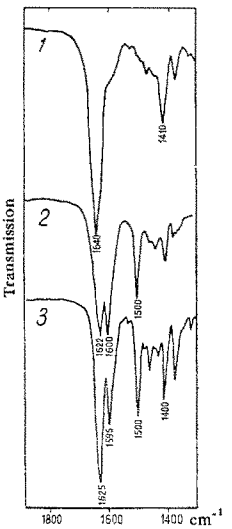


Fig. 2. IR Spectra in $CHCl_3$ (c 0.05 M, layer thickness 0.25 mm): 1) 1, 2, 3-trimethyl-5-pyrazolone; 2) 1-phenyl-2, 5-dimethyl-3-iminopyrine.

by S, or of the position of the heteroatom in the ring (Fig. 5).

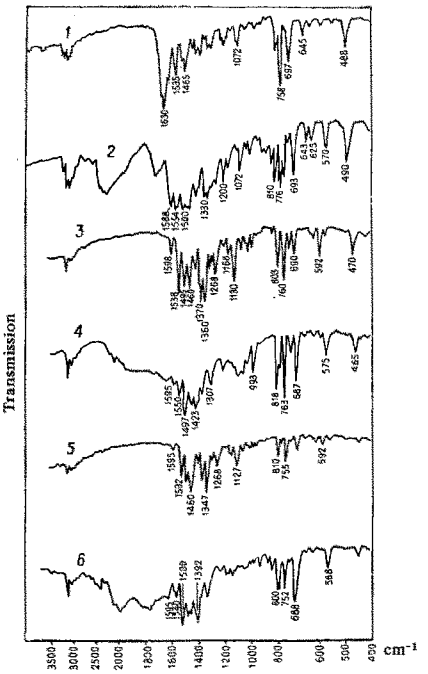
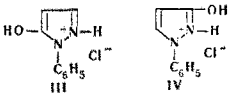


Fig. 3. IR Spectra in the crystalline state (in vaseline oil): 1)1-phenyl-2-methyl-5-pyrazolone; 2) its hydrochloride; 3) 1-phenyl-2, 3-dimethyl-5-thiopyrine; 4) its hydrochloride; 5)1-phenyl-2, 3-dimethyl-5-selenopyrine; 5) its hydrochloride.

Examination of the IR spectra of the protonated forms of these molecules (the crystalline hydrochlorides) showed that the carbonyl absorption band had virtually disappeared (see Fig. 3, 2 and Fig. 4, 2), while strong, wide bands due to hydrogen bonding of the hydroxyl group (2250–2300, 2580, 2690, 2400 cm^{-1}), and two new bands at 1565–1580 and 1523–1547 cm^{-1}, appear (see also [4, 5]). These bands were assigned by comparing the IR spectra of the hydrochlorides of 1-phenyl-5-hydroxy- (III) and 1-phenyl-3-hydroxypyrazole (IV), which have a positive charge on the ring nitrogen atom in the 2-position (cf Fig. 6)



III IV

The spectra of the latter contained bands at 1578 and 1550 cm^{-1} which were assigned to the oscillations of the protonated pyrazole ring. On the whole, the spectra resembled closely those of the protonated antipyrines. A similar observation made previously [6] was interpreted differently, but in special experiments using solutions of the antipyrines in HCl, conversion into 1-phenyl-3-methyl-5-chloropyrazole methochloride was not observed.

Jensen [2] observed that, on changing from the $\rangle N-\overset{|}{C}=S(Se)$ grouping to $\rangle \overset{+}{N}=\overset{|}{C}-S-$, the C-band underwent a small shift to higher frequencies. On protonation of the thio-and selenopyrines, we also oberved a shift of these bands, from 1370 to 1423 cm^{-1} (compounds 4, Fig. 3, curves 3, 4); from 1347 to 1392 cm^{-1} (compound 5, Fig. 3, curves 5, 6); from 1367 to 1395 cm^{-1} (compound 10, Fig. 4, curves 5, 6). These results make it reasonably certain that protonation in the thio-and selenopyrines, also occurs at the exocyclic heteroatom, forming structures Ia and IIa. In the imino pyrines, protonation occurs without any doubt at the exocyclic nitrogen atom, since the extremely high basicity constants of the imino analogs (some 7 orders of magnitude greater than those of any of the other compounds, see table) clearly lead to such a conclusion.

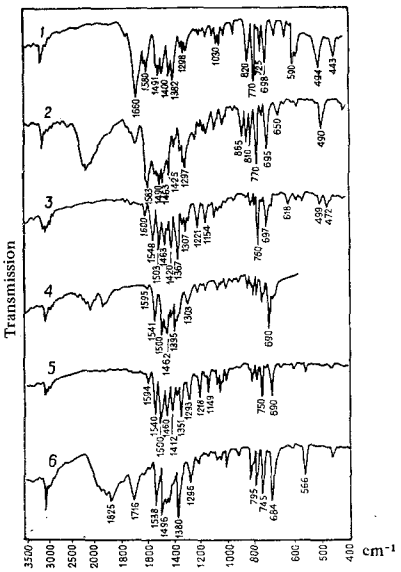


Fig. 4. IR Spectra in the crystalline state (in vaseline oil): 1) 1-phenyl-2, 5-dimethyl-3-pyrazolone; 2) its hydrochloride; 3) 1-phenyl-2, 5-dimethyl-3-thiopyrine; 4) its hydrochloride; 5) 1-phenyl-2, 5-dimethyl-3-selenopyrine; 6) its hydrochloride.

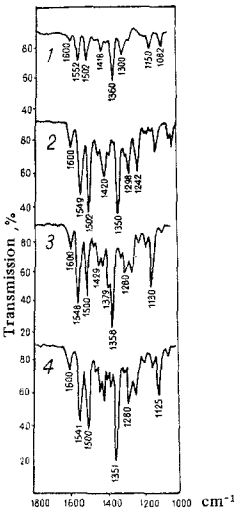


Fig. 5. IR Spectra of thio and seleno pyrines in $CHCl_3$: 1) 1-phenyl-2, 5-dimethyl-3-thiopyrine (c 0.015 M, layer thickness 0.4 mm); 2) 1-phenyl-2, 5-dimethyl-3-selenopyrine; 3) 1-phenyl-2, 3-diemthyl-5-thiopyrine; 4) 1-phenyl-2, 3-dimethyl-5-selenopyrine (for 2–4, c 0.1 M, layer thickness 0.17 mm).

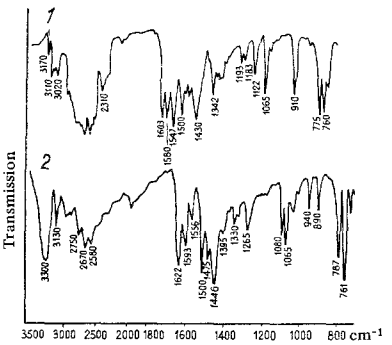


Fig. 6. IR Spectra in the crystalline state: 1) 1-phenyl-5-hydroxypyrazole hydrochloride; 2) 1-phenyl-3-hydroxy-pyrazole hydrochloride.

In hydroxylic solvents, antipyrines, for example compounds 1 and 2, show a very large shift of the carbonyl band towards lower frequencies, by 80–100 cm^{-1} (Figs. 1 and 7). Such a large shift is not surprising in view of the very high polarization of the C=O bond, and its large dipole moment. The low basicity (see table) means that this effect cannot be explained in terms of ionization, but can only arise from the formation of simple hydrogen bonds between the hydroxyl groups of the solvent and the C=O group. For the 5-antipyrine (compound 1), the frequency lies at 1684 (in dioxane), 1659 (in $CHCl_3$), 1630 (in C_2H_5OD), 1586 (in D_2O), and in the crystalline state, at 1670 cm^{-1}, respectively, while for the 3-antipyrine (compound 2), they are found at 1680 (in dioxane), 1650 (in $CHCl_3$), 1622 (in D_2O), 1590 (in C_2H_5OD), and in the crystalline state, at 1660 cm^{-1}.

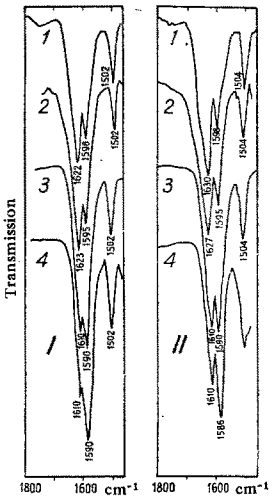
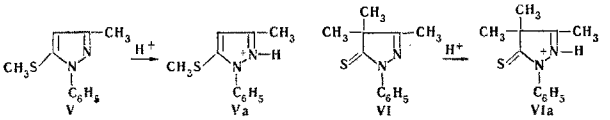


Fig. 7. IR Spectra: I) 1-phenyl-2-methyl-3-pyrazolone; II) 1-phenyl-2-methyl-5-pyrazolone [c 0.2 M, layer thickness 0.046 mm; 1) in C_2H_5OD; 2) in a mixture of C_2H_5OD–D_2O (4:1); 3) in a mixture of C_2H_5OD–D_2O (2:3); 4) in D_2O].

UV Spectra. Since the determination of the course of the protonation of thio- and selenopyrines from their IR spectra was inconclusive, we attempted to resolve this problem by UV spectroscopy. The K-absorption band for all the antipyrines was found at 255–268 nm, with an intensity of about 10,000. On changing to the thio, then to the seleno derivatives, a bathochromic effect of about 30 nm was observed (see table). As model compounds, we used 1-phenyl-3-methyl-5-methylthiopyrazole (V) and 1-phenyl-3, 4, 4-trimethyl-5-thiopyrazolone (VI), the protonation of which clearly gives salts Va and VIa, respectively, without any doubt as to their structure. With these compounds, we observed only a very small change in the UV spectra (see table).



The UV spectra of all the antipyrines and their thio and seleno analogs in HCl solution showed a very large shift to shorter wavelengths (by 25–30 nm), the spectra becoming very similar to those of the protonated pyrazole model compounds (see table). These results, therefore, also support the occurrence of protonation at the exocyclic heteroatom.

NMR Spectra. Attempts to utilize the NMR spectra for the solution of this problem were unsuccessful, as a result of the poor resolution of the spectra, and of the similarity of the chemical shifts both for the protons of the heterocycle and for those of the substituents in the pyrines, and in the pyrazole and pyrazolone compounds (both in their neutral and protonated forms) (see table).

EXPERIMENTAL

The compounds were synthesized by previously described methods [1]. The IR spectra were obtained on a UR-10 spectrophotometer. Alcoholic and aqueous-alcoholic solutions were measured in KRS-5 cuvettes. In the crystalline state, the compounds were examined as pastes in vaseline and polyfluorinated oil. The preparation of the samples was carried out in a specially-dried chamber in a stream of dry nitrogen.

The UV spectra were taken on an SF-4A spectrophotometer.

Potentiometric measurements were carried out in a stream of purified nitrogen on a LP-58 potentiometer. Calculation of pK_a values was carried out using the formula $pK_a = pH - \lg \left\{ \frac{[B]+[H^+]}{[BH^+]-[H^+]} \right\}$, where [B] is the molar concentration of base, $[BH^+]$ the molar concentration of protonated base, and $[H^+]$ the concentration of hydrogen ions [7].

NMR Spectra were recorded on a JNM-2 spectrometer (40 MHz).

REFERENCES

1. A. D. Garnovskii, V. I. Minkin, I. I. Grandberg, and T. A. Ivanova, KhGS [Chemistry of Heterocyclic Compounds], collection 1, 74, 1967.

2. K. A. Jensen and P. H. Nielsen, Acta chem. Scand., **20**, 597, 1966.

3. T. I. Lene, A. Gamaguchi, I. V. Quagliano, I. A. Ryan, and S. Muzushima, J. Am. Chem. Soc., **81**, 3824, 1959.

4. A. I. Busev, B. E. Zaitsev, and V. K. Akimov, ZhOKh, **35**, 1568, 1965.

5. D. Cook, Can. J. Chem., **41**, 2794, 1963.

6. N. A. Valyashko and V. I. Bliznyukov, ZhOKh, **10**, 1280, 1343, 1940; **11**, 24, 559, 1941.

7. I. I. Grandberg, S. V. Tabak, and A. N. Kost, KhGS [Chemistry of Heterocyclic Compounds], 85, 1966.

8. I. I. Grandberg, L. F. Morozova, V. A. Moskalenko, and A. N. Kost, KhGS [Chemistry of Heterocyclic Compounds], 1049, 1969.

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