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# STUDY OF THE STRUCTURES OF INDAZOLES, PYRAZOLO[3,4-b]PYRIDINES, AND PYRAZOLO[3,4-b]PYRAZINE BY IR SPECTROSCOPY

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It is shown on the basis of a study of the IR spectra of indazoles, pyrazolopyridines, and pyrazolopyrazine in the solid state and of their N-deutero-substituted derivatives and hydrochlorides at room temperature and at the temperature of liquid nitrogen that these heterocycles exist in a tautomeric form in which the labile hydrogen atom is localized on the nitrogen atom of the pyrazole ring. It was established that 6-aminopyrazolopyridine exists in the crystalline state in the amino form and that it is protonated at the ring nitrogen atom rather than at the amino group. The applicability of the temperature-shift method for the detection not only of $\gamma_{NH}$ bands but also of $\gamma_{ND}$ bands is demonstrated.

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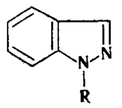
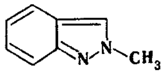
Few data on the IR and UV spectra and the structures of condensed pyrazoles and closely related compounds have been published. In particular, the tautomeric forms of some of them in solution and in the crystalline state have been determined [1-4], and the spectra and structures of natural purines and their derivatives have been studied [5-7]. In [7-9] it was shown that one of the several possible tautomeric forms predominates for many hydroxy, amino, and mercapto derivatives of purines and their salts in the solid state. Some of the regularities found in the spectra of purines can be used for the interpretation of the spectra of condensed pyrazoles.

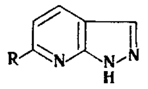
The first results of a study of the IR spectra in the solid state of indazole and its derivatives (I-III), pyrazolo[3,4-b]pyridines (IV-X), and pyrazol[3,4-b]pyrazine (XI), as well as their hydrochlorides (Ia-XIa), are reported below:



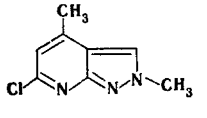
I, II



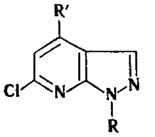
III



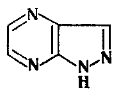
IV-VI



X



VII-IX



XI

I R= H; II R=CH$_3$; IV R=H; V R=NH$_2$; VI R=N(CH$_3$)$_2$; VII R=R′=H;
VIII R=CH$_3$, R′=H; IX R=R′=CH$_3$

The method of temperature shift of the bands of the N-H deformation vibrations [10, 11], deuterium substitution, and a comparison with the spectra of model heterocyclic compounds [12] were used for the interpretation of the IR spectra of the condensed pyrazoles.

The assignment of the frequencies associated with the vibrations of the NH and NH$_2$ groups and the skeleton of the molecules is presented in Table 1.

It is known that the bands of stretching vibrations of CH, NH, $\overset{+}{\mathrm{N}}\mathrm{H}$, ND, NH$_2$, and ND$_2$ groups are found at 2000-3400 cm$^{-1}$. A broad intense absorption band at 2500-3300 cm$^{-1}$, which has a complex structure, is observed in the spectra of all of the investigated compounds. It undoubtedly is related to the NH stretching vibration, and its structure and position constitute evidence for the presence of strong intermolecular hydrogen bonds in crystals of the condensed pyrazoles. The IR spectra of pyrazolopyridine (VI) and its hydrochloride and N-deutero derivative are presented in Fig. 1 as an example.

A broad band with a maximum at about 2500 cm$^{-1}$, which is related to the stretching vibration of the $\overset{+}{\mathrm{N}}\mathrm{H}$ bond, appears, as a rule, in the spectra of the hydrochlorides.

In addition, intense bands at about 3150, 3300, and 3400 cm$^{-1}$, which are shifted on deuteration to 2300 and 2560 cm$^{-1}$, are observed in the spectrum of 6-aminopyrazolo[3,4-b]pyrid-

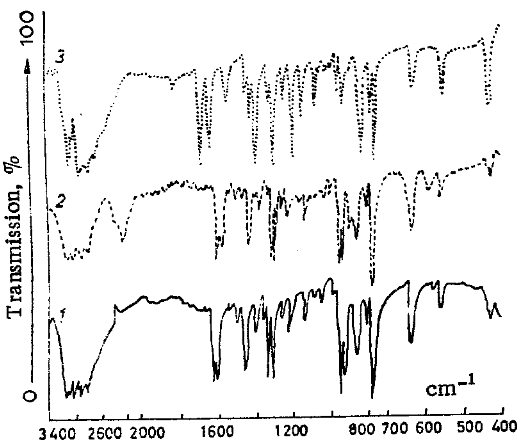


Fig. 1. IR absorption spectra of pyrazolopyridine (1) and its deutero derivative (2) and hydrochloride (3).

TABLE 1. Principal Absorption Bands in the IR Spectra of the Condensed Pyrazoles

| Arbitrary assignment | I | | Ia | II | IIa | III | IIIa | IV | | IVa | V | | Va |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | H* | D | H | H | H | H | H | H | D | H | H | D | H |
| $\omega_{NH_2(ND_2)}$ | — | — | — | — | — | — | — | — | — | — | ~535 (545) | — | 550 (550) |
| $\gamma_{NH(ND)}$ | 785† (802) | 525 (535) | ~808 (812) | — | — | — | — | 810 (825) | 580 (594) | 820 | 725 (731)<br>782 (795) | 510 (522)<br>560 (575) | 780 (784) |
| $\gamma^{+}_{NH}$ | — | — | ~870 (890) | — | ~830 (832) | — | 890 | — | — | 870 | — | — | 825 (827) |
| $\nu_{skel}$ | 1510<br>1625 | 1504<br>1625 | 1530<br>1600<br>1640 | 1500<br>1610 | 1520<br>1540<br>1630 | 1520<br>1625 | 1540<br>1580<br>1640 | 1592<br>1610 | 1592<br>1610 | 1600<br>1640 | 1455<br>1590<br>1623 | 1455<br>1590<br>1613 | 1590<br>1640 |
| $\delta_{NH_2(ND_2)}$ | — | — | — | — | — | — | — | — | — | — | 1655 | 1390 | 1660 |
| $\nu^{+}_{NH}$ | — | — | 2400—2600 | — | 2350—2800 | — | 2500—2750 | — | — | 2400—2600 | — | — | 2600—2800 |
| $\nu_{NH(ND)}$ | 2600—3350 | 2100—2550 | 2600—2700 | — | — | — | — | 2750—3150 | 2200—2400 | 2650—3100 | 2500—3000 | 2000—2500 | 2800—3000 |
| $\nu^{s}_{NH_2(ND_2)}$ | — | — | — | — | — | — | — | — | — | — | 3150 | 2300 | 3080 |
| $\nu^{as}_{NH_2(ND_2)}$ | — | — | — | — | — | — | — | — | — | — | $\left.\begin{matrix}3300\\3400\end{matrix}\right\}$ | 2560 | 3300 |

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*Symbols: H indicates the undeuterated compound, and D indicates the N-deuterated derivative.

†The frequencies observed at −170°C are given in parentheses.

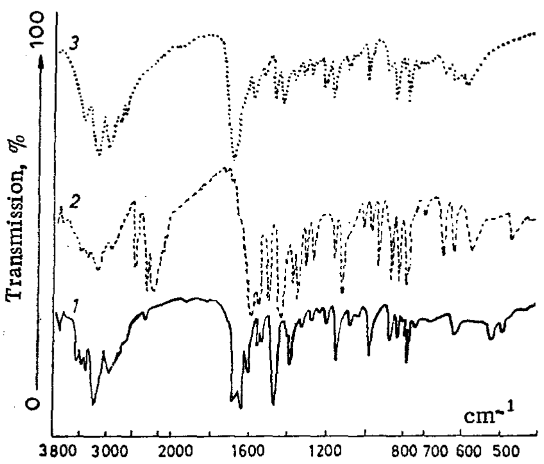


Fig. 2. IR absorption spectra of 6-aminopyrazolopyridine (1) and its deutero derivative (2) and hydrochloride (3).

ine (V) (Fig. 2). Their form and position are characteristic for an amino group participating in the formation of hydrogen bonds [12]. It is difficult to determine the position of the bands of aromatic ring CH stretching vibrations in the spectra of the investigated compounds, since they are overlapped by a strong and broad NH band.

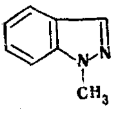
Bands at 2850, 2920, 3060, and 3100 $cm^{-1}$, which are related to the stretching vibrations of the CH bonds of methyl groups and an aromatic ring, can be observed in the spectra of methylated indazole derivatives II and III and pyrazolopyridine derivatives IX and X.

Bands of ring stretching vibrations and in-plane CH, NH, and $NH_2$ deformation vibrations are found at 1000-1700 $cm^{-1}$. The presence of several intense bands at 1400-1700 $cm^{-1}$, which undergo practically no shifting on deuteration and can be assigned to aromatic ring stretching vibrations, is characteristic for all of the investigated compounds. These frequencies increase on passing to the hydrochlorides; this has also been noted for purine hydrochloride [7].

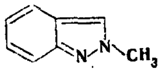
The position of the highest frequency ring vibrations at 1500-1600 $cm^{-1}$ depends on which nitrogen atom is connected to the substituent in the pyrazole ring (II, III, IX, and X in Table 1); this is apparently associated with a transition from the benzenoid structure (A) to the o-quinoid structure (B).

This frequency is 10-12 $cm^{-1}$ higher in the spectra of compounds with structure B than in the spectra of compounds with structure A. An intense band at 1655 $cm^{-1}$, which is shifted to 1390 $cm^{-1}$ on deuteration and is related to the scissors vibration of the $NH_2$ group, is observed above 1600 $cm^{-1}$ in the spectrum of 6-aminopyrazolopyridine (V). The presence of this band and its sensitivity to deuterium substitution serve as a confirmation of the above-expressed assumption that V exists in the amino form in the crystalline state. The invariability of this band on passing to hydrochloride Va provides evidence that protonation takes place at one of the ring nitrogen atoms rather than at the amino group. It has also been established for adenine and adenosine [13] that protonation takes place at the purine ring nitrogen atom rather than at the exocyclic nitrogen atom.

The bands of ring in-plane deformation vibrations, out-of-plane NH, $NH_2$, and CH deformation vibrations, and skeletal out-of-plane deformation vibrations are found at 400-1000 $cm^{-1}$. Most of these vibrations are uncharacteristic: many bonds and valence angles participate in each of them. However, some of these vibrations, namely, the out-of-plane deformation vibrations of NH and $NH_2$ groups, are sufficiently characteristic and, in addition, are sensitive to intermolecular interactions [10, 11]. The bands in the IR spectra that correspond to these vibrations are shifted on deuteration and are also shifted by 10-20 $cm^{-1}$ and undergo a pronounced increase in intensity as the temperature is lowered from +20 to −170°. These peculiar-



A



B

ities of the bands of the NH and $NH_2$ out-of-plane vibrations make it possible in many cases to make a sufficiently unambiguous assignment of the corresponding bands, and the character and number of identical proton-donor groups in the molecule can be determined from the number and position of these bands. This information in turn makes it possible to discern the presence of one or another tautomeric molecular or ionic form in the crystals of a given compound.

The frequencies of the NH out-of-plane vibrations are found over a rather narrow range (725-810 $cm^{-1}$) in the spectra of all of the investigated compounds. The correctness of the assignment is confirmed by the decrease or disappearance of these bands on deuteration and the appearance of bands of ND out-of-plane vibrations at 510-570 $cm^{-1}$. These new bands, like the bands of NH out-of-plane vibrations, are shifted by 10-20 $cm^{-1}$ and undergo a change in intensity as the temperature changes from +20 to −170°. Thus the temperature-shift method is applicable for the detection not only of the $\gamma_{NH}$ bands but also of the $\gamma_{ND}$ bands. As seen from Table 1, the frequencies of the various vibrations of the NH, $NH_2$, and $\overset{+}{N}H$ groups in the spectra of all of the investigated compounds are quite close to one another, from which it can be concluded that these compounds exist in similar tautomeric forms in the crystalline state. It may be assumed that the labile hydrogen atom in the pyrazolopyridine and pyrazolopyrazine molecules (IX-XI) is localized in the pyrazole ring. Evidence for this is provided by the analogous character of the change in the vibrations of the NH groups on deuteration and as the temperature changes (see Table 1), as well as by the similarity in the spectra of IX-XI at 510-570 $cm^{-1}$ and the spectra of indazole I, in which only this orientation of the hydrogen atom is possible. Additional methods must be drawn upon to establish the localization of the hydrogen atoms in the pyrazole ring. Changes in the spectrum in two regions — 500-600 and 700-850 $cm^{-1}$ — were observed during a study of the temperature dependence of the IR spectra of 6-aminopyrazolopyridine (V), for which there is a possibility of amine-imine tautomerism from +20 to −170°. It is known [10, 11] that the frequencies of the fan vibrations of the $NH_2$ group are found at 500-600 $cm^{-1}$. Consequently, the band at 535 $cm^{-1}$ in the spectrum of V, which changes with temperature, can be assigned precisely to this vibration; this is confirmed by its disappearance on deuteration and also by the absence of the corresponding band and, in general, temperature changes at 500-600 $cm^{-1}$ in the spectrum of 6-dimethyl aminopyrazolopyridine (VI). Two bands each, which are shifted on deuteration and whose position depends on the temperature, are observed in the spectra of V and VI; this makes it possible to assign them to $\gamma_{NH}$ vibrations. We were able to detect bands of out-of-plane vibrations at 510-560 $cm^{-1}$ in the spectra of V and VI deuterated at the NH groups. These bands are also sensitive to temperature. The presence of two $\gamma_{NH}$ bands in the spectra of V and VI is difficult to interpret unambiguously. The existence simultaneously in the solid state of two tautomeric forms with a hydrogen atom in different positions is unlikely, although this possibility cannot be completely excluded. The splitting of these bands is most likely due to the presence of different forms of associates characterized by different distributions of the intermolecular hydrogen bonds, to the state of which the NH out-of-plane vibrations are very sensitive.

By way of correlating what we have stated above regarding the IR spectra of the amino and dimethylamino derivatives of pyrazolopyridine (V and VI), it can be asserted that, in conformity with the IR spectral data (in both the high-frequency and low-frequency regions), V exists in the amino form in the crystalline state, whereas the heterocyclic ring contains a hydrogen atom attached to the nitrogen atom of the pyrazole ring. New bands, which in a number of cases can be assigned to the out-of-plane vibrations of the protonated groups, appear in the low-frequency region of the spectrum on passing from the starting condensed pyrazoles to their protonated forms, i.e., to the hydrochlorides. Thus bands at 830 and 890 $cm^{-1}$, respectively, which are assigned to the out-of-plane vibrations of $\overset{+}{N}H$ groups, since there are no $\overset{+}{N}H$ groups in starting II and III, appear in the spectra of the hydrochlorides of methylated IIa and IIIa. We note that the frequencies of the NH out-of-plane vibrations increase when the compounds are protonated.

The bands of NH vibrations remain unchanged in the spectra of a number of compounds on passing to the protonated forms, and above-lying bands of $\overset{+}{N}H$ out-of-plane vibrations, which are shifted as the temperature of the samples changes, simultaneously appear. Consequently, the addition of a proton to the ring nitrogen atoms that do not bear a hydrogen atom rather than to the NH or $NCH_3$ group is characteristic for these compounds. This pertains to indazole I and its N-methyl-substituted derivatives (II and III), pyrazolopyridine (IV), and 6-aminopyrazolopyridine.

We were unable to detect the bands of $\overset{+}{N}H$ out-of-plane vibrations in the spectra of the remaining compounds, possibly because of the weak intensity of these bands; the site of addition of a proton was therefore not determined for them.

## EXPERIMENTAL

The investigated compounds were synthesized by the methods described in [14-17]. The hydrochlorides of these compounds were obtained by dissolving the bases in concentrated hydrochloric acid with subsequent drying in vacuo or passage of dry HCl into solutions of the investigated substances in organic solvents. The N-deuterated investigated compounds were obtained by double exchange with heavy water by refluxing and subsequent vacuum drying over $P_2O_5$.

The IR spectra of KBr pellets of the solid compounds were recorded with a UR-10 spectrometer. The IR spectra at low temperatures were obtained by cooling the KBr pellets with liquid nitrogen in a special cryostat.

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