SYNTHESIS AND STUDY OF THE STRUCTURE OF SOME PYRIDAZINO[4,5-b]QUINOXALINE DERIVATIVES

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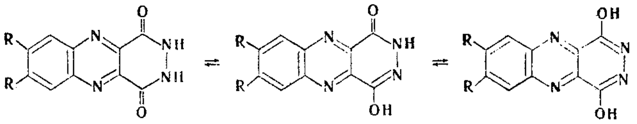
The structures of 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline and some of its methyl derivatives were established by IR and UV spectroscopy.

We have previously [1, 2] described the derivatives of the little-investigated pyridazino[4,5-b]quinoxaline heterocyclic system – 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline (I) and 1-oxo-4-hydroxy-6,7-dimethylpyridazino[4,5-b]quinoxaline (II) – which are potentially capable of lactim–lactam tautomerism with possible tautomeric dioxo (Ia, IIa), oxo-hydroxy (I, II), and dihydroxy (Ib, IIb) forms:



Ia, IIa I, II Ib, IIb

I R=H; II R=CH_3

The structures of a number of compounds that contain a system of $O{=}\overset{|}{C}{-}NH{-}NH{-}\overset{|}{C}{=}O$ bonds were studied by means of physicochemical and, in particular, spectral methods [3, 4]. However, up until now there has been relatively little objective data that would provide the possibility of an unambiguous answer as to whether these different hydroxy derivatives exist in the crystalline state and in solutions in the form of any one of the tautomeric forms or as a mixture of them.

The present communication is devoted to an examination of the state of the tautomeric equilibrium of I and some of its derivatives by means of the absorption spectra in the IR and UV regions.

To solve this problem, we obtained as model compounds that have various fixed tautomeric form the methyl derivatives of I: 1-oxo-2-methyl-4-hydroxy- (III), 1-oxo-2-methyl-4-methoxy- (IV), 1,4-dioxo-2,3-dimethyl- (V) and 1-oxo-4-methoxypyridazino[4,5-b]quinoxaline (VI).

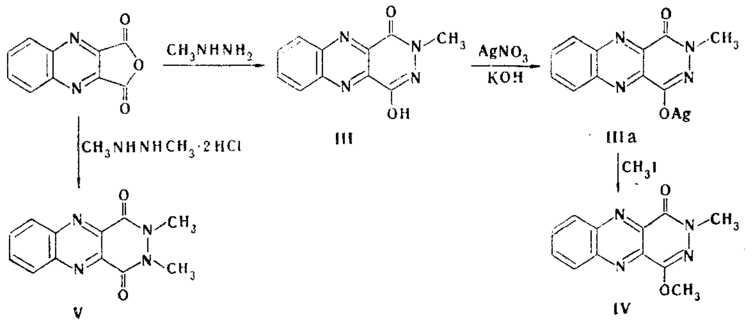


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TABLE 1. Characteristics of the Absorption Bands of I–VI

Compound	ν_{CO}, cm^{-1}	$\nu_{C=C}$ and $\nu_{C=N}$, cm^{-1}	ν_{NH}, cm^{-1}	ν_{OH}, cm^{-1}
I	1660	1495, 1540	3160	3230
II	1670	doublet 1480—1505, 1530, 1600	3180	3335
III	1670	1485, 1530, 1620	—	3330
IV	1670	1485, 1540, 1595, 1615	—	—
V	1690	1500, 1590, 1630	—	—
VI	1660	1490, 1540, 1595, 1615	3170	—

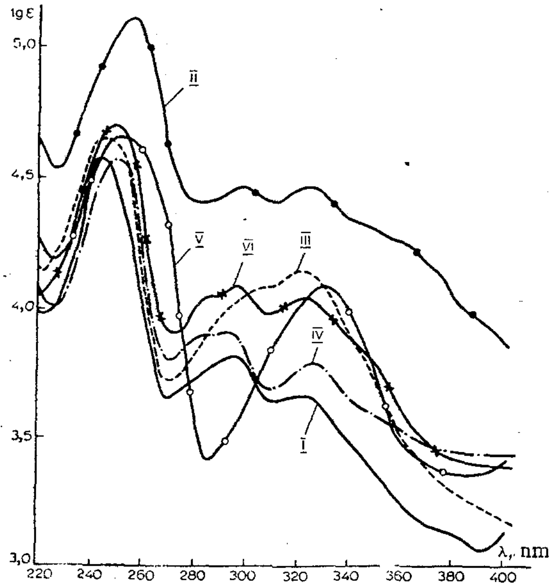
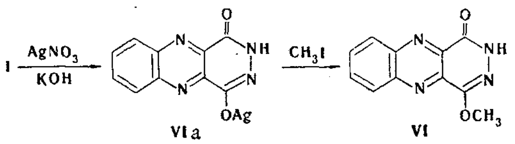


Fig. 1. UV spectra: I) 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline; II) 1-oxo-4-hydroxy-6,7-dimethylpyridazino[4,5-b]quinoxaline; III) 1-oxo-2-methyl-4-hydroxypyridazino[4,5-b]quinoxaline; IV) 1-oxo-2-methyl-4-methoxypyridazino[4,5-b]quinoxaline; V) 1,4-dioxo-2,3-dimethylpyridazino[4,5-b]quinoxaline; VI) 1-oxo-4-methoxypyridazino[4,5-b]quinoxaline.



The reaction of the anhydride of quinoxaline-2,3-dicarboxylic acid [5] with aqueous methylhydrazine in acetic acid gave a dark-violet substance that was converted to a yellow crystalline compound (III) after repeated precipitation from dilute NaOH solution by the addition of concentrated hydrochloric acid.

An attempt to synthesize III from dimethyl quinoxaline-2,3-dicarboxylate and aqueous methylhydrazine and also from the anhydride of quinoxaline-2,3-dicarboxylic acid and methylhydrazine hydrochloride gave products of as yet unestablished structure.

Compound III was used as the starting material for the synthesis of IV. It is known that salts of lactim–lactams are capable of N- and O-alkylation, depending on the nature of the metal and reagent; in this case, the sodium salts are alkylated by alkyl halides primarily at the nitrogen atom, while the silver salts are alkylated primarily at oxygen. We isolated the silver salt of III (IIIa) and found that heating it with methyl iodide in methanol gave IV.

Compound V was synthesized by the reaction of the anhydride of quinoxaline-2,3-dicarboxylic acid with dimethylhydrazine hydrochloride [6].

Methoxy derivative VI was obtained by methylation of the monosilver salt of I (VIa) with methyl iodide by heating in methanol for 1 h.

IR Spectra

As seen from Table 1, the spectrum of I contains an intense band of the stretching vibration of a carbonyl group at 1660 cm^{-1}. The presence of carbonyl absorption excludes the dihydroxy structure Ib for I, and thus dioxo form Ia and the mixed oxo-hydroxy form of I, which is formed during enolization of one carbonyl group, remain possible.

A comparison of the spectra of I and its N,O-dimethyl derivative (IV) demonstrated the presence of the band of a C = O group in both compounds at 1660 cm^{-1}. However, in the spectrum of N,N-dimethyl derivative V the most intense band is that at 1690 cm^{-1}, which attests to the presence of a carbonyl group that has a shift in its frequency to shorter wavelengths; this indicates the absence of conjugation of the C = O group with the π-electron system of the heteroring.

Consequently, the presence of a carbonyl absorption band at 1660 cm^{-1} in the spectra of I and IV makes it possible to assume that the very same system of double bonds and an identical degree of conjugation of the C = O group with the ring double bonds are present in these compounds, and this is possible only if I has mixed oxo-hydroxy structure in the crystalline state and is 1-oxo-4-hydroxypyridazino[4,5-b]-quinoxaline (I). If I had the 1,4-dioxopyridazino[4,5-b]quinoxaline structure, the C = O frequency in its spectrum should have been shifted by ~ 30 cm^{-1} to the short-wave region.

The spectrum of N-methyl derivative III makes it possible to assert that this compound is 1-oxo-2-methyl-4-hydroxypyridazino[4,5-b]quinoxaline, since it has a ν_{CO} band at ~1670 cm^{-1}; this is characteristic for the system of bonds in a molecule with the oxo-hydroxy structure, while the dioxo form should have been characterized by an intense carbonyl band at 1690 cm^{-1}. In this case, the dihydroxy structure is excluded both by the method of synthesis and the presence of a ν_{CO} band in the spectrum. In addition, many of the absorption bands in the spectra of III and IV turn out to be close to one another or coincident; this also confirms the mixed oxo-hydroxy structure of III.

The presence of a C = O band in the spectrum of O-methyl derivative VI at 1660 cm^{-1} makes it possible to assert that it has the 1-oxo-4-methoxypyridazino[4,5-b]quinoxaline form. In addition, the spectrum of VI coincides with the spectrum of IV both with respect to the position of the carbonyl band and with respect to the position of all of the other bands; this attests to the oxo-hydroxy structure of VI.

Thus an examination of the IR spectra of I and its various methyl derivatives makes it possible to judge the structure of the molecule even from the position of the carbonyl band and to conclude that 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline (I) and its methyl derivatives (III, VI) exist in the oxo-hydroxy form in the crystalline state.

Strong absorption at 1500-1630 cm^{-1}, which is related to the in-plane stretching vibrations of the C = C and C = N bonds of the rings, is characteristic for all of the investigated compounds. It is interesting to note that the spectrum of IV, which has a genuine oxo-hydroxy structure, contains a band at 1540 cm^{-1} which is absent in the spectrum of dioxo form V. Consequently, for the type of substances that we studied, one can differentiate between the oxo-hydroxy and dioxo forms from the presence or absence of the indicated absorption band. The band at 1530-1540 cm^{-1}, which is present in the spectra of I, III, and VI, again confirms that these compounds have the oxo-hydroxy structure in the solid state.

Thus an analysis of the position of the frequency of the carbonyl absorption and of the skeletal vibrations at 1600-1630 cm^{-1} makes it possible to distinguish the oxo-hydroxy form from the dioxo structure.

A study of the IR spectrum of II demonstrated that the introduction of two methyl groups into the benzene ring of I affects the $p\pi$ conjugation in the molecule, since the form of the spectrum at 800-1400 cm^{-1} differs somewhat from the spectrum of I with respect to both the position of some absorption bands and their intensities (the presence or absence of a number of bands and doubling or, on the other hand, merging of individual bands). However, the intense band of carbonyl absorption at 1670 cm^{-1} and the position of the bands in the region of the ring vibrations correspond to the oxo-hydroxy structure of II, and it can thus be assumed that the oxo-hydroxy structure is retained in the crystalline state when electron-donor substituents are introduced into I.

The spectra of I-III and VI in the high-frequency region have a characteristic feature that consists of the fact that the bands of the O−H and N−H groups are shifted to the long-wave region as compared with the bands of the free O−H and N−H groups; this means that strong intermolecular hydrogen bonds are present in the crystalline state. Thus the spectrum of I contains a broad absorption band at 2850-3230 cm^{-1} with several maxima. The band at 3160 cm^{-1} can be assigned to the stretching vibrations of bonded N−H groups, since a band at 3170 cm^{-1} is observed in the spectrum of VI, which has only an N−H group. The band at 3230 cm^{-1} can be assigned to the stretching vibrations of the O−H groups that participate in the formation of hydrogen bonds, since there is a band at 3330 cm^{-1} in the spectrum of III, which has only an OH group.

The spectrum of II also has a broad absorption band due to the stretching vibrations of bonded O−H and N−H groups, but it is shifted to the high-frequency side (the stretching vibrations of the bonded N−H groups are found at 3180 cm^{-1}, while those of the O−H groups are found at 3335 cm^{-1}).

A study of the IR spectra of solutions in which the hydrogen bonds are weakened and the substances may have a structure that corresponds to the other possible tautomeric forms proved to be impossible because of the very low solubility of the investigated compounds in solvents that are suitable for the study of IR spectra.

UV Spectra

The spectrum of I (Fig. 1) contains three bands with λ_{max} 245, 294, and 322 nm. This same system of bands is present in the spectrum of III (λ_{max} 246, 305, and 322 nm); the band at 294 nm in the spectrum of I experiences a small bathochromic shift to 305 nm. Absorption at 250, 283, 293, 325 and 250, 284, 296, and 322 nm, respectively, is characteristic for the spectra of IV and VI.

The band at 294-305 nm in the spectra of I and III is split into two bands in the spectra of IV and VI with maxima at 283-284 and 293-294 nm (although it is possible that they merge in other solvents).

The spectrum of II has the same system of bands as in the spectrum of I with λ_{max} 256, 298, and 325 nm, although it should be noted that there is a small bathochromic shift of all of the spectral bands.

Only two absorption bands with λ_{max} 254 and 330 nm appear in the spectrum of V, a compound with a rigidly fixed dioxo structure, and these bands are bathochromically shifted as compared with the corresponding bands in the spectrum of IV, a compound with a fixed oxo-hydroxy structure. In addition, an absorption minimum at 286 nm is observed instead of a maximum in the spectrum of V at 280-300 nm.

The similarity between the electronic spectra of I-IV and VI is clearly seen when they are compared, and this indicates that they have the oxo-hydroxy structure and also indicates the substantial difference in the position of the bands from the spectrum of V, which exists in the dioxo form.

Thus a study of the electronic spectra has confirmed the conclusions that we drew in our examination of the IR spectra – compounds I, II, IV, and VI exist in the mixed oxo-hydroxy form in both the crystalline state and in solution. The methods that we used to investigate these compounds did not show the presence of any other tautomeric form.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrophotometer. The IR spectra of perfluorohydrocarbon pastes of III and VI at 2800-3600 cm^{-1} were recorded with a UR-10 spectrophotometer.

The UV spectra of alcohol solutions ($5 \cdot 10^{-4}$ to $1 \cdot 10^{-5}$ M) of the compounds (layer thickness 0.5 cm) were recorded with a VSU-1 spectrophotometer.

1-Oxo-2-methyl-4-hydroxypyridazino[4,5-b]quinoxaline (III). A mixture of 2 g (0.01 mole) of the anhydride of quinoxaline-2,3-dicarboxylic acid, 30 ml of acetic acid, and 60 ml of aqueous methylhydrazine was refluxed for 1 h to give 0.9 g (40%) of a cherry-red precipitate, which was converted to bright-yellow crystals with mp 300° after repeated precipitation from a dilute NaOH solution by the addition of concentrated HCl. Found: C 57.6; H 3.5; N 25.0%. $C_{11}H_8N_4O_2$. Calculated: C 57.9; H 3.5; N 24.6%.

1-Oxo-2-methyl-4-methoxypyridazino[4,5-b]quinoxaline (IV). A 0.23-g (0.001 mole) sample of III and 0.17 g (0.001 mole) of silver nitrate in 3 ml of water were added with stirring to a solution of 0.056 g (0.001 mole) of KOH in 2 ml of water, and the resulting precipitate was removed by filtration, washed successively with water, alcohol, and acetone, and dried to give 0.33 g of silver salt IIIa. A 0.33 g sample of IIIa was heated with 1 ml of methyl iodide in 10 ml of methanol for 1 h. The mixture was filtered, and the solvent was removed from the filtrate to give 0.1 g (41%) of a yellow substance with mp 240° (from heptane). Found: C 59.0; H 4.1; N 23.4%. $C_{12}H_{10}N_4O_2$. Calculated: C 59.5; H 4.2; N 23.1%.

1,4-Dioxo-2,3-dimethylpyridazino[4,5-b]quinoxaline (V). A mixture of 2 g (0.01 mole) of the anhydride of quinoxaline-2,3-dicarboxylic acid and 1.5 g (0.01 mole) of dimethylhydrazine hydrochloride in 25 ml of water was refluxed with stirring for 3 h, after which it was neutralized with potassium carbonate and extracted with chloroform. The extract was dried with potassium carbonate, and the chloroform was removed by distillation to give 0.17 g (7.3%) of V with mp 198° (from heptane). Found: C 59.2; H 4.1; N 22.9%. $C_{12}H_{10}N_4O_2$. Calculated: C 59.5; H 4.2; N 23.1%.

1-Oxo-4-methoxypyridazino[4,5-b]quinoxaline (VI). A 0.5-g (2.3 mmole) sample of I and 0.4 g (2.3 mmole) of silver nitrate in 3 ml of water were added with stirring to a solution of 0.13 g (2.3 mmole) of KOH in 4 ml of water, and the precipitate was removed by filtration, washed successively with water, alcohol, and acetone, and dried to give 0.75 g of silver salt VIa. A mixture of 0.75 g of VIa and 1 ml of methyl iodide in 30 ml of methanol was heated for 1 h, after which it was filtered. The solvent was removed from the filtrate by distillation to give 0.15 g (30%) of a yellow residue with mp 200° (from heptane). Found: C 57.6; H 3.4; N 25.0%. $C_{11}H_8N_4O_2$. Calculated: C 57.9; H 3.5; N 24.6%.

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