SOME PROPERTIES OF 1-OXO-4-HYDROXYPYRIDAZINO[4,5-b]QUINOXALINE

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The dissociation constants of 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline were measured by potentiometric titration. It is shown that this compound is a dibasic acid. Its reaction with organic bases, acids, alkalis, and oxidizing agents was studied. Its aminomethylation, hydroxymethylation, and cyanoethylation were also investigated.

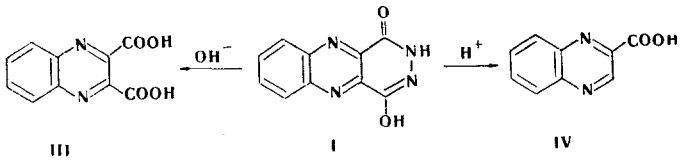
We have previously obtained [1] the structural isomer of one of the benzopteridine derivatives, which are of interest as antimetabolites of vitamins of the B group [2, 3] — 1,4-dihydroxypyridazino[4,5-b]quinoxaline.

The present communication is devoted to the study of some physicochemical properties of 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline (I) and its chemical transformations in order to ascertain the possibilities of chemical modification of the molecule to obtain substances with potential biological activity.

In [4] we showed that I displays acid properties by forming salts with metals. We also obtained salts of this compound (IIa-d) with organic bases such as dimethylamine, diethylamine, morpholine, and piperidine. These salts are quite stable but decompose to the starting compounds at 200-230°C.

We found by means of potentiometric titration that 1-oxo-4-hydroxypyridazino[4,5-b]quinoxaline I is a dibasic acid with dissociation constants $K_1 = 1.77 \cdot 10^{-6}$ (pK_1 5.75) and $K_2 = 1 \cdot 10^{-11}$ (pK_2 11.10). Taking into account data from the potentiometric titration of 1-oxo-4-methoxypyridazino[4,5-b]quinoxaline [5], one may conclude that the hydrogen of the hydroxyl group has the most acidic properties in I.

We investigated the behavior of pyridazino[4,5-b]quinoxaline I with respect to the action of acids, alkalis, and various oxidizing agents. It was established that this compound is resistant to the action of 2 N HCl, CH_3COOH, and H_2SO_4 and 2 N NaOH at room temperature and to the action of hot CH_3COOH. Prolonged heating of I in 2 N HCl, concentrated H_2SO_4, and 2 N NaOH led to opening of the pyridazine ring to give quinoxaline-2,3-dicarboxylic acid (III) under alkaline hydrolysis conditions and quinoxaline-2-carboxylic acid (IV) under acid hydrolysis conditions:



III I IV

Quinoxaline-2,3-dione (V) was obtained by oxidation of 1,4-dihydroxypyridazino[4,5-b]quinoxaline with 30% hydrogen peroxide in both acetic and formic acids. Oxidation of nitrogen-containing heterocyclic compounds with hydrogen peroxide in acetic media usually leads to N-oxides. However, the results of the reaction of I with H_2O_2 constitute evidence that it is not capable of forming N-oxides under the given conditions, probably because of the effect of substituents conjugated with the tertiary nitrogen atoms.

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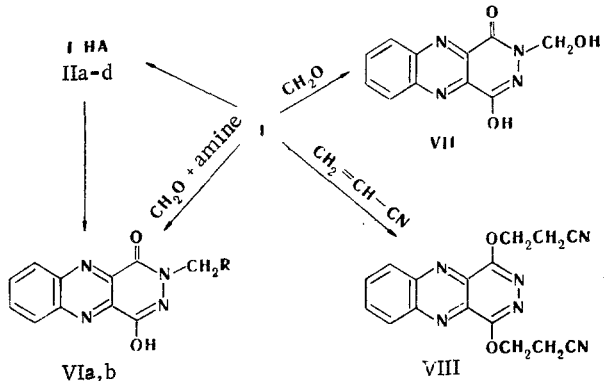
The action of potassium permanganate on 1,4-dihydroxypyridazino[4,5-b]quinoxaline in alkaline media and in acetone gave quinoxaline-2,3-dicarboxylic acid (III).

During a study of aminomethylation we found that I does not react with formaldehyde and secondary amines (morpholine and piperidine) under the conditions usually employed for aminomethylation in the cyclic hydrazide series [6]. This is evidently associated with the low solubility of the starting compound. Compounds VIa,b were obtained either with reaction with excess formaldehyde and amine or by heating salts II with aqueous formaldehyde solution.



IIa A=N(CH$_3$)$_2$; b A=N(C$_2$H$_5$)$_2$; c A= morpholyl d A= piperidyl VIa R= morpholyl b R= piperidyl

Heating I with formalin in a mixture of dimethylformamide (DMF) and alcohol led to hydroxymethyl derivative VII.

Cyanoethyl derivative VIII was obtained by reaction of 1,4-dihydroxypyridazino[4,5-b]-quinoxaline I with acrylonitrile in the presence of a catalytic amount of alkali.

We have previously shown [5] the possibility of using IR and UV spectroscopy for establishing the oxo-hydroxy and dioxo structures of pyridazino[4,5-b]quinoxaline derivatives both in the crystalline state and in solution on the basis of a parallel study of the synthesized compounds and model substances with authentic structures. The structures of VI-VIII were also studied by vibrational and electronic spectroscopy.

The position of the band of carbonyl absorption, the presence in the region of double bond vibrations of a band at 1530-1543 cm^{-1}, which is characteristic for compounds with an oxo-hydroxy structure in this series [5], and the presence in the high-frequency region of a strong broad absorption band due to vibrations of an OH group tied up in hydrogen bonds (Table 1) made it possible to assume that solid VIa,b and VII have the 1-oxo-2-R-4-hydroxy-pyridazino[4,5-b]quinoxaline structure.

The UV spectra of alcohol solutions of VIa,b contain two absorption maxima at λ_{max} 242, 318 and 249, 321 nm, respectively; this is in agreement with the dioxo form. Consequently, in contrast to the crystalline state, in solution the substances exist primarily in the 1,4-dioxo-2-R-3H-pyridazino[4,5-b]quinoxaline form. Spectra of this sort were also obtained for aqueous solutions of these compounds.

On the other hand, three absorption maxima appear at 342, 290, and 325 nm in the UV spectrum of an alcohol solution of VII; this constitutes evidence for the oxo-hydroxy structure of this compound in solution.

Absorption bands of CO, OH, and NH groups are absent in the IR spectrum of cyanoethyl derivative VIII (Table 1); this indicates incorporation of the two cyanoethyl groups at the oxygen atoms and that the product has the 1,4-bis(cyanoethyoxy)pyridazino[4,5-b]quinoxaline structure. The very weak band at 1670 cm^{-1} evidently is related to the stretching vibrations of C=N bonds, as previously demonstrated in [4].

We were unable to study the electronic spectrum of VIII because of its insolubility in both water and organic solvents suitable for measurements.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of alcohol and aqueous solutions were recorded with a VSU-1 spectrophotometer.

TABLE 1. Absorption Bands (cm^{-1}) in the IR Spectra of the Synthesized Compounds

Compound	C=O	C=C and C=N	OH	C≡N
VIa	1665	1490, 1530, 1570	3440	
VIb	1662	1490, 1530, 1570	3450	
VII	1665	1500, 1543	3235	
VIII	—	1460, 1570, 1670	—	2248, 2210

Potentiometric titration was carried out in acidic media with NaOH solution with an LPU-01 potentiometer with a glass electrode in a thermostatted beaker at 25° with stirring.

1-Oxo-4-hydroxypyridazino[4,5-b]quinoxaline Salts with Amines (IIa-d). A 4-ml sample of the amine (dimethylamine, diethylamine, morpholine or piperidine) was added to a suspension of 0.2 g (1 mmole) of I in 20 ml of ethanol, and the mixture was refluxed for 1.5 h. The solvent was removed, and the residue was triturated with acetone. The solid material was removed by filtration and washed with acetone. The salts were light-brown substances that were quite soluble in water and alcohol (except for IIc). Salt IIa [0.2 g (82%] decomposed above 200° [from benzene–alcohol (1:1)]. Found: C 55.9; H 4.8; N 27.3%. $C_{10}H_6N_4O_2 \cdot C_2H_7N$. Calculated C 55.6; H 5.1; N 27.0%; Salt IIb [0.26 g (96.5%)] decomposed above 200° [from benzene–alcohol (1:1)]. Found: C 58.7; H 6.0; N 24.2%. $C_{10}H_6N_4O_2 \cdot C_4H_{11}N$. Calculated C 58.5; H 6.0; N 24.4%. Salt IIc [0.23 g (83.3%)] decomposed above 220° (from aqueous alcohol). Found: C 55.7; H 4.6; N 23.4%. $C_{10}H_6N_4O_2 \cdot C_4H_9NO$. Calculated: C 56.0; H 5.0; N 23.1%. Salt IId [0.26 g (92.6%)] decomposed above 230° [from benzene–alcohol (1:1)]. Found: C 60.4; H 6.0; N 23.1%. $C_{10}H_6N_4O_2 \cdot C_5H_{11}N$. Calculated: C 60.2; H 5.7; N 23.4%.

Alkaline Hydrolysis. A 0.5-g (2.3 mmole) sample of I was refluxed in 150 ml of 2 N NaOH for 6 h, and the resulting dark-brown solution was concentrated in vacuo. The precipitate was removed by filtration and dissolved in water, and the solution was acidified with concentrated HCl. The precipitated substance was crystallized twice from acetic acid to give 0.44 g (87%) of quinoxaline-2,3-dicarboxylic acid (III) with mp 188-189° (dec.) [mp 190° (dec.) [7]]. Found: C 55.2; H 3.2; N 12.6%. $C_{10}H_6N_2O_4$. Calculated: C 55.1; H 2.8; N 12.8%.

Acid Hydrolysis. A) A 0.3-g (1.4 mmole) sample of I was refluxed in 300 ml of 2 N HCl for 50 h, and the resulting solution was concentrated in vacuo and extracted with ether. The ether was removed by distillation to give 0.23 g (97.8%) of a light-brown crystalline substance. Recrystallization from acetic acid gave quinoxaline-2-carboxylic acid (IV) with mp 210°. Found: C 62.2; H 3.3; N 16.4%. $C_9H_6N_2O_2$. Calculated: C 62.1; H 3.5; N 16.1%.

B) A 0.3-g (1.4 mmole) sample of I was heated at 90° in 10 ml of concentrated H_2SO_4 for 15 h, after which the mixture was diluted with an equal volume of water and extracted with ether. The ether was removed by distillation to give 0.22 g (93.7%) of acid IV with mp 210°.

Oxidation of 1-Oxo-4-hydroxypyridazino[4,5-b]quinoxaline. A) With 30% H_2O_2 in glacial acetic acid. A 0.3-g (1.4 mmole) sample of I was dissolved by refluxing in 300 ml of glacial acetic acid, after which the solution was cooled to 70° and 10 ml of 30% H_2O_2 was added to it. The mixture was heated at 70° for 20 h, after which it was concentrated in vacuo to the minimum volume. The resulting precipitate was removed by filtration and crystallized from glacial acetic acid to give 0.13 g (61.8%) of quinoxaline-2,3-dione (V) with mp 386° (dec.) [mp 386-390 (dec.) [9]]. Found: C 59.6; H 3.8; N 17.5%. $C_8H_6N_2O_2$. Calculated: C 59.6; H 3.7; N 17.3%.

B) With 30% H_2O_2 in formic acid. A 0.3-g (1.4 mmole) sample of I was suspended in 35 ml of 85% formic acid, and 8 ml of 30% H_2O_2 was added. The mixture was heated at 60° for 15 h, and the resulting solution was concentrated in vacuo to the minimum volume. The precipitate was removed by filtration and crystallized twice from glacial acetic acid to give 0.13 g (58.9%) of quinoxaline-2,3-dione (V), which was identical to the product described in method A.

C) With potassium permanganate in an alkaline medium. A 2.4-g sample of $KMnO_4$ was added with stirring and heating to a solution of 0.3 g (1.4 mmole) of I in 60 ml of 0.1 N NaOH. After 4 h under these conditions, the mixture was filtered, and the filtrate was concentrated in vacuo. Acidification of the filtrate produced a precipitate, which was crystallized from glacial acetic acid to give 0.1 g (33.7%) of quinoxaline-2,3-dicarboxylic acid III

with mp 188-189° (dec.).

D) With potassium permanganate in acetone. A 2.4-g sample of $KMnO_4$ was added in portions at room temperature with stirring and bubbling in a strong stream of carbon dioxide to a suspension of 0.3 g (1.4 mmole) of I in 500 ml of acetone, after which the mixture was maintained under these conditions for 7 h. It was then filtered, and the filtered solid material was treated several times with hot water. The combined aqueous extracts were acidified with concentrated HCl to precipitate 0.21 g (70.2%) of yellow acid III.

1-Oxo-2-morpholinomethyl-4-hydroxypyridazino[4,5-b]quinoxaline (VIa). A) Formalin (1 ml) was added to 0.15 g (0.5 mmole) of salt IIc in 5 ml of alcohol, and the resulting solution was refluxed for 1 h, after which it was concentrated, and the residue was triturated with acetone. The solid material was removed by filtration and washed with acetone. Crystallization from aqueous acetone gave 0.08 g (50%) of a light-yellow product with mp >300°. Found: C 57.6; H 5.1; N 22.2%. $C_{15}H_{15}N_5O_3$. Calculated: C 57.5; H 4.8; N 22.3%.

B) A mixture of 0.4 g (1.9 mmole) of I, 1.8 ml of morpholine, 8 ml of formalin, and 40 ml of alcohol was refluxed for 1 h, after which the resulting solution was concentrated to the minimum volume, and the residue was dissolved in absolute alcohol. The alcohol solution was saturated with dry hydrogen chloride, the solvent was removed by distillation, and the resinous residue was treated with acetone until a precipitate formed. The precipitate was crystallized from alcohol-acetone to give 0.36 g (45.6%) of the trihydrochloride of VIa with mp 180°. Found: Cl 25.4; N 16.3%. $C_{15}H_{15}N_5O_3 \cdot 3HCl$. Calculated: Cl 25.3; N 16.5%.

1-Oxo-2-piperidinomethyl-4-hydroxypyridazino[4,5-b]quinoxaline (VIb). This compound [0.1 g (62.5%)], with mp 240°, was obtained by the method used to prepare VIa. Found: C 62.0; H 5.1; N 22.9%. $C_{16}H_{17}N_5O_2$. Calculated: C 61.7; N 5.5; N 22.5%. The trihydrochloride of VIb was also obtained under the conditions of the synthesis of the salt of VIa, but the resinous residue was treated with ether–acetone until a precipitate formed. The precipitate was extracted with dichloroethane, after which it was crystallized from alcohol to give 0.2 g (34.5%) of the salt with mp 250° Found: Cl 25.3; N 16.0%. $C_{16}H_{17}N_5O_2 \cdot 3HCl$. Calculated: Cl 25.3; N 16.5%.

1-Oxo-4-hydroxy-2-hydroxymethylpyridazino[4,5-b]quinoxaline (VII). A mixture of 0.3 g (1.4 mmole) of I, 40 ml of DMF, 9 ml of formalin, and 15 ml of alcohol was refluxed for 1 h, after which another 9 ml of formalin was added, and the mixture was refluxed for 2.5 h. The resulting solution was concentrated to the minimum volume, and the residue was triturated with acetone. The solid material was removed by filtration and washed with acetone. Crystallization from aqueous alcohol gave 0.25 g (73.1%) of a light-yellow substance with mp 300°. The product did not decompose during crystallization or on prolonged storage. Found: C 53.8; H 3.4; N 22.7%. $C_{11}H_8N_4O_3$. Calculated: C 54.1; H 3.3; N 22.9%.

1,4-Bis(cyanoethoxy)pyridazino[4,5-b]quinoxaline (VIII). A 0.1-g sample of NaOH was added to a solution of 0.1 g (0.5 mmole) of I in 5 ml of acrylonitrile, and the mixture was heated at 60° for 1 h. The precipitate was removed by filtration and washed with hot water to give 0.145 g (96.6%) of yellow crystals with mp 296° (from aqueous DMF). Found: N 25.9%. $C_{16}H_{12}N_6O_2$. Calculated: N 26.2%.

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