ACID-BASE PROPERTIES OF 1-ACYL-5-HYDROXYPYRAZOLIDINES IN A HYDROGEN BOND

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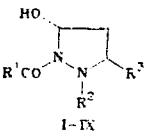
In solutions, 1-acyl-5-hydroxypyrazolidines form only intermolecular hydrogen bonds in which the proton acceptor is the oxygen atom of the hydroxyl group. These compounds are similar to phenols with respect to the acidity in a hydrogen bond.

The hydroxyl group in the 5 position on 1-acylpyrazolidines has a semi-annual nature, making it extremely sensitive to electrophilic as well as nucleophilic agents [1-3]. This circumstance hinders the study of many chemical properties of hydroxypyrazolidines, especially acid-base properties. At the present time, the method of using IR spectroscopy to estimate the acid-base properties of compounds from their ability to form hydrogen bonds, has been well-developed. This method is suitable for labile compounds, and we have used it to investigate the group of hydroxypyrazolidines, I-IX. In the 3600-3200 cm^{-1} the IR spectra of their solutions (c = 100 mmole/liter), absorption bands of "free" hydroxyl groups (3580 cm^{-1}) are observed along with broad absorption bands due to a hydrogen bond.



I-IX

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
I	H	*i*-Pr	H	VI	*p*-Br_6CH_4	CH_2Ph	H
II	Me	Ph	Me	VII	*p*-$NO_2C_6H_4$	CH_2Ph	H
III	Et	Ph	Me	VIII	*p*-$CH_3OC_6H_4$	CH_2Ph	H
IV	Ph	CH_2Ph	H	IX	*p*-$CH_3C_6H_4$	CH_2Ph	H
V	Ph	CH_2Ph	Me				

The presence of a hydroxyl group in the 5 position suggests the possibility of an intramolecular hydrogen bond with the formation of a six-membered cyclic complex. However, the spectra of all of the compounds in solutions with c = 150-3.5 mmole/liter show a clear dependence of the hydroxyl group absorption band on the concentration (see Fig. 1). In other words, there is not a single case of intramolecular hydrogen bonding in the cases under consideration. There are only intermolecular hydrogen bonds, which are also characteristic of the crystalline state of hydroxypyrazolidines, according to x-ray structural analyses [2]. In such a case, a question arises concerning the nature of the hydrogen bond in self-associates of 1-acyl-5-hydroxypyrazolidines I-IX. The determination of the center of gravity of the bound OH group absorption band shows that it is shifted by 180-200 cm^{-1} on formation of a hydrogen bond, and that this is independent of the concentration of the solutions (see Table 1). The carbonyl group has to be excluded from consideration as the electron donating center because the position of the absorption bands (1660 cm^{-1} for I-III and 1620 cm^{-1} for IV-IX) corresponds to the position of the absorption band of a free amido carbonyl and is constant on dilution and a decrease in the amount of associates. The amide $N_{(1)}$ atom has extremely weak donor properties; association through the amine, $N_{(2)}$ atom is highly likely. However, in our case, replacement of an alkyl substituent on the $N_{(2)}$ atom (compound I) with an aryl (compounds II, III) does not lead to a marked change in $\Delta\nu_{OH}$ (and, consequently, in $-\Delta H$) in the self-associates, even

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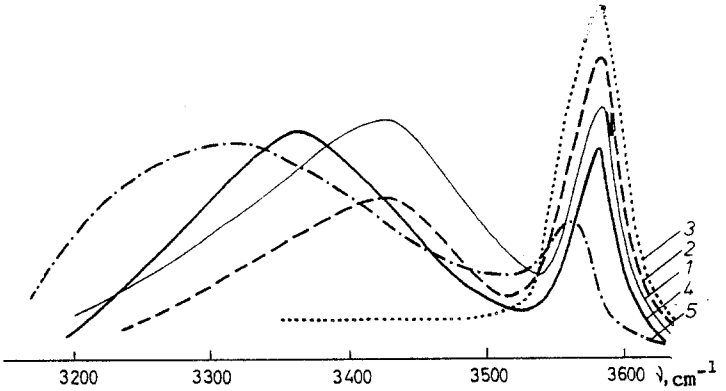


Fig. 1. IR spectra of compounds II and VIII in the ν_{OH} region: 1-3) dependence of the absorption bands of compound II in CH_2Cl_2 on concentration [1) c = 120 mmole/liter, ℓ = 0.5 mm; 2) c = 30 mmole/liter, ℓ = 2 mm; 3) c = 3 mmole/liter, ℓ = 20 mm]; 4) H-complex of hydroxypyrazolidine II with THF; 5) H-complex of hydroxypyrazolidine VIII with THF.

TABLE 1. Spectral and Thermodynamic Characteristics of Self-Associates I-VII and of the Complexes of the Hydroxypyrazolidines with THF

Compound	"Free" ν_{OH}, cm^{-1}	$\Delta\nu_{OH}$, cm^{-1}	$-\Delta H$, kcal/mole	ν_{CO}, cm^{-1}	Complex with THF	$\Delta\nu_{OH}$, cm^{-1}	$-\Delta H$, kcal/mole	p_i
I	3570	190	4,0	1660	I	222	4,45	0,81
II	3570	200	4,2	1650	II	230	4,55	0,83
III	3575	200	4,2	1660	IV	240	4,67	0,85
IV	3560	180	3,9	1620	VI	240	4,67	0,85
V	3550	180	3,9	1620	VII	230	4,55	0,82
VI	3555	175	3,8	1618	VIII	290	5,22	0,95
VII	3555	185	4,0	1630	IX	300	5,32	0,96

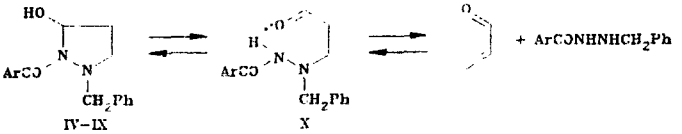
though the unshared pair of electrons on the N(2) atom is conjugated with the aromatic nucleus, as confirmed by UV spectroscopy (λ_{max} 239, 278 nm, log ε 4.15, 4.04 – analogous to the spectrum of aniline). These data show that the donor center is not the N(2) atom, since, according to [4, 5], on the association of phenols with triethylamine and diethylaniline, the values of $\Delta\nu_{OH}$ differ markedly (800 and 260 cm^{-1}, respectively). Therefore, it must be assumed that in solutions of 1-acyl-5-hydroxypyrazolidines, hydrogen bonds form with the proton acceptor being the oxygen atom of the hydroxyl group, analogous to alcohols, while at the same time, dimers form in the crystalline state with hydrogen bonding via the carbonyl group [2].

The acid-base properties of unassociated hydroxypyrazolidines I-IX were measured for dilute solutions (20-30 mmole/liter) in an inert solvent (see Fig. 1). Tetrahydrofuran (THF) was used as the organic base in a concentration of 1 M; such a ratio precluded the possibility of self-associates forming. The relative acidity of compounds in a hydrogen bond is characterized in Iogansen's method [5] by the acidity factor, p_i:

$$p_i = \Delta H_{ij}/(\Delta H_{11}\varepsilon_j),$$

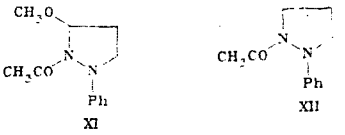
where ΔH_{ij} is the enthalpy of the hydrogen bond; $\Delta H_{11} = 5.3$ (the enthalpy of the standard complex of phenol with diethyl ether, the "acidity" and "basicity" of which are taken as unity); and ε_j, the basicity factor (for THF, ε_j = 1.04 [5]). The thermodynamic characteristics of the hydrogen bond in the compounds studied were calculated from spectroscopic data (Table 1). The acidity factor is, on the average, 0.80-0.95 for our systems; i.e., the sequence of relative "acidities" for the hydroxypyrazolidines is narrow, indicating the predominant role

of the compound class, cyclic semihydrazinal, and the lesser importance of the substituent on the $N_{(1)}$ atom (compare $p_i = 0.6$ for alcohols and $p_i = 1$ for phenol). The "acidity" of the compounds considered is somewhat higher in the case of aroyl derivatives IV-IX, particularly with the introduction of donor substituents: p-OCH_3, p-CH_3 > H; p-Br > p-NO_2. Moreover, the spectra of the aroyl compounds have some special features: the "free: absorption band of the OH group is shifted to 3560 cm^{-1} and narrowed. This could be due to the presence of a weak, intramolecular hydrogen bond through the aromatic ring of the aroyl group [6]. When the spectra were measured in THF, the presence of an insignificant amount of a linear form was revealed, β-hydrazinoaldehyde X*, its condensation products, and possibly oligomers of acrolein.



This required a graphical separation of the partially overlapping absorption bands of hydroxyl groups of the dimers and hydroxypyrazolidines in the 3300-3450 cm^{-1} region. Using the spectrum of methyl-2-(2-benzoyl-1-benzylhydrazino)ethyl ketone as a model compound to identify the spectrum of linear form X, we became convinced that in the spectrum of linear form X, the NH group absorption ("free" ν_{NH}, 3425; bound, 3340 cm^{-1}) is of low intensity, and that there is an intramolecular hydrogen bond through the cabonyl group and an extremely low constant of intermolecular interaction with THF ($\Delta\nu$, 105 cm^{-1}, $-\Delta H$ 2.66 kcal/mole, $p_i = 0.48$). Consequently, the contribution of the small amount of form X to the total absorption in this region can be neglected.

The hydrogen bond method also allows one to determine the "basicity" of a compound with respect to the standard organic acid, phenol. We considered the "basicity" of this class of compounds for the example of 1-acetyl-2-phenyl-5-methoxypyrazolidine(XI), which does not have a proper center of proton donation and appears as a base to be close in strength to hydroxypyrazolines I-IX.



The shift of the absorption band of the phenolic hydroxyl group in the phenol-XI complex is 280 cm^{-1} ($-\Delta H$ = 5.4 kcal/mole, $\varepsilon_j = 0.96$). Such a shift negates the possibility of a hydrogen bond between phenol and the amide carbonyl group, because the reaction of phenol with DMFA [8] and 1-acetyl-2-phenylpyrazolidine (XII) leads to $\Delta\nu_{OH}$ = 350 cm^{-1}. The shifts in the absorption bands of the complexes with dialkylanilines ($\Delta\nu_{OH}$ = 260 cm^{-1}) [9] and saturated ethers ($\Delta\nu_{OH}$ = 290 cm^{-1}) [4] are similar. Obviously, the oxygen atom of the hydroxyl group is preferred in the role of proton acceptor here, as well as in the self-associates of I-IX, because the proximity of the second nitrogen atom in the hydrazines can lead to only a decrease in $\Delta\nu_{OH}$ compared to $\Delta\nu_{OH}$ for the amines [10].

EXPERIMENTAL

The IR spectra were measured on a Specord IR-75 (DDR) instrument. The scan rate was 100 cm^{-1}/2.6 min, and the recorder scale was 10 mm/10 cm^{-1} in the 1600-1700 cm^{-1} range and 5 mm/10 cm^{-1} in the 3200-3650 cm^{-1} range. The range of concentrations in CH_2Cl_2 was 150-1.5 mmole/liter. The cuvets used were CaF_2 with a constant thickness of 0.1-20 mm. In determining $\Delta\nu$ in the self-associates and in determining the basicity and acidity, we determined the centers of gravity of the absorption bands. In the determination of the complexes of compounds IV-IX with THF, the average values are given with a precision of ±10 cm^{-1}. This leads to an error of ±0.015 in the determination of p_i, the overall ordering remaining unchanged. We determined the enthalpy of the hydrogen bond from the formula $-\Delta H = 0.33\sqrt{\Delta\nu} - 40$ [4].

*Such tautomerism is known for compound IV [7].

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SYNTHESIS AND PMR SPECTRA OF 2-HETARYL-SUBSTITUTED IMIDAZO[4,5-b]-PYRIDINES AND IMIDAZO[4,5-c]PYRIDINES

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A simple method for the synthesis of 2-hetarylimidazopyridines based on the oxidation with sulfur of a mixture of p-diaminopyridine and heterocyclic compounds that contain an active methyl group is proposed. The reaction of diamines with N-oxides of of α- and γ-picolines and the intramolecular oxidative cyclization of 3-amino-4-(2-pyridylmethylamino)pyridine lead to the same result. The PMR spectra of the synthesized 2-pyridylimidazopyridines were studied.

Despite certain experimental difficulties, the reaction of o-diaminopyridines and carboxylic acids of the heterocyclic series or their nitriles in polyphosphoric acid (PPA) is most often used to obtain 2-hetarylimidazopyridines [1-5]. The use of frequently difficult-to-obtain derivatives and precursors of carboxylic acids such as thioamides [6], hydrazides [7], an imino ester [8], and trichloromethylbenzimidazole [9] has lesser significance in the synthesis of 2-hetarylimidazopyridines.

The principle of the oxidative cyclization of o-diaminopyridines with compounds that contain a methylidyne or methylene group that is activated by a heteroatom (N or O) and an aryl (hetaryl) group was placed at the foundation of the new method for the synthesis of 2-hetarylimidazopyridines [10]. In conformity with this o-diaminopyridines should also be capable of reacting with methylheterocycles of the α- and γ-picoline type. A similar possibility was previously established in the case of the synthesis of 2-pyridyl and 2-quinolyl derivatives of benzimidazole from 2-picoline or quinaldine and o-phenylenediamine in the presence of sulfur [11].

We demonstrated for the first time [12] that 2-hetarylimidazo[4,5-b]- and -[4,5-c]-pyridines Ia-f and IIa-t (Table 1) can be readily obtained by this method in high yields.

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