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RESEARCH ON 1-AZA TWO-RING SYSTEMS.

XVII.* SYNTHESIS OF 5-(γ -HYDROXYPROPYL)-1,2-DIHYDROPYRROLIZINES

AND PROPERTIES OF THEIR INTRAMOLECULAR π -HYDROGEN BONDS

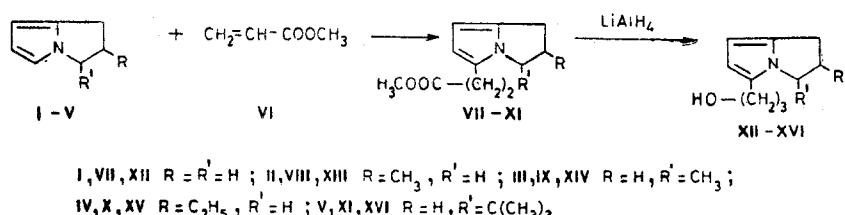
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Reduction of 5-[2-(methoxycarbonyl)ethyl]-1,3-dihydropyrrolizines with lithium aluminum hydride gave 5-(γ -hydroxypropyl)-1,2-dihydropyrrolizines (in 70-90% yields), which have intramolecular π -hydrogen bonds in dilute solutions. The parameters of the π -hydrogen bonds were determined in the IR spectra, and their enthalpies were found. The data obtained ($\Delta\nu_{OH}$ 95-99 cm^{-1} , $-\Delta H$ 3.05 $\text{kJ} \cdot \text{mole}^{-1}$) show that among compounds with an aliphatic hydroxyl group and a system of π electrons, 5-(γ -hydroxypropyl)-1,2-dihydropyrrolizines have some of the strongest intramolecular π -hydrogen bonds.

We have previously obtained and investigated 5-hydroxymethyl- [2] and 5-(β -hydroxyethyl)-1,2-dihydropyrrolizines [3, 4]. In the present communication we describe the synthesis of 5-(γ -hydroxypropyl)-1,2-dihydropyrrolizines and the results of a study of the properties of their intramolecular π -hydrogen bonds.

Instances of nonselective substitution reactions of 1,2-dihydropyrrolizines are known [3, 5]. In the present research we therefore monitored the isomeric purity of the products of the reaction of 1,2-dihydropyrrolizines I-V with methyl acrylate (VI) — 5-[2-(methoxycarbonyl)ethyl]-1,2-dihydropyrrolizines VII-XI (Table 1) — which are starting compounds for the synthesis of 5-(γ -hydroxypropyl)-1,2-dihydropyrrolizines XII-XVI.



Analysis of the PMR spectra of the products of the first reaction shows that, in contrast to the cases described in [3, 5], a substituent is incorporated virtually only in the 5 position of the dihydropyrrolizines.

In order to investigate the intramolecular π -hydrogen bonds in 1,2-dihydropyrrolizine systems with a hydroxyl group three methylene links away from the ring we subjected VII-XI to reduction with lithium aluminum hydride to alcohols XII-XVI (Table 2). A study of the

*See [1] for communication XVI.

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TABLE 1. Characteristics of 5-[2-(Methoxycarbonyl)ethyl]-1,2-dihydropyrrolizines VII-XI

Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Found, %			Empirical formula	Calc., %			PMR spectra, region of pyrrole protons		Yield, %
				found	calc.	C	H	N		6-11	7-11	$I_{6,7}$, Hz			
VII ^a	122 (1)	1.0975	1.5180	53.36	53.26	68.4	7.8	7.1	$C_{11}H_{15}NO_2$	68.4	7.8	5.74	5.52	3.4	47
VIII ^a	124-124.5 (3)	1.0668	1.5080	57.92	57.88	69.6	8.1	6.7	$C_{12}H_{17}NO_2$	69.5	8.3	5.68	5.46	3.4	58
IX ^b	121-122 (1)	1.0732	1.5110	57.86	57.88	69.1	8.3	6.5	$C_{12}H_{17}NO_2$	69.5	8.3	5.68	5.45	3.3	64
X	129-130 (1)	1.0514	1.5060	62.49	62.53	70.5	8.7	6.3	$C_{13}H_{19}NO_2$	70.6	8.7	6.3	5.63	3.4	50
XI	130-131 (1)	1.0383	1.5096	71.76	71.73	9.3	6.0	6.0	$C_{15}H_{23}NO_2$	72.3	9.3	5.78	5.57	3.3	61

^aAccording to the data in [6], this compound was obtained in 64.2% yield and had bp 118-119°C (1 mm), d_4^{20} 1.0975, and n_D^{20} 1.5180. ^bAccording to the data in [6], this compound was obtained in 72% yield and had bp 122-124°C (1 mm), d_4^{20} 1.0750, and n_D^{20} 1.5120.

TABLE 2. Characteristics of 5-(γ -Hydroxypropyl)-1,2-dihydropyrrolizines XII-XVI

Compound	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D		Found, %			Empirical formula	Calc., %			IR spectra ^a , region of the OH stretching vibrations cm ⁻¹ (ε ^a mole ⁻¹ liter cm ⁻¹)		Yield, %
				found	calc.	C	H	N		C	H	N	ν_{OH} (ε ^a)	ν'_{OH} (ε ^a)	
XII	136 (5)	1.0652	1.5364	48.40	48.51	72.7	9.1	8.3	$C_{10}H_{15}NO$	72.7	9.1	8.5	3644 (47)	3547 (15)	77
XIII	133-133.5 (2)	1.0368	1.5272	53.17	53.13	73.7	9.8	7.8	$C_{11}H_{17}NO$	73.7	9.6	7.8	3645 (48)	3549 (15)	93
XIV	140.5-141.5 (4)	1.0445	1.5300	53.01	53.13	74.0	9.7	7.9	$C_{11}H_{17}NO$	73.7	9.6	7.8	3645 (48)	3546 (13)	91
XV	148-149 (4)	1.0223	1.5230	57.76	57.75	74.6	9.9	7.3	$C_{12}H_{19}NO$	74.6	9.9	7.2	3645 (48)	3550 (15)	72
XVI	142-143 (1)	1.0154	1.5255	66.85	66.98	76.1	10.7	6.5	$C_{14}H_{23}NO$	76.0	10.5	6.3	3644 (50)	3549 (14)	79

^aThe data presented are for 3·10⁻³ mole/liter solutions of the compounds in CCl_4 (layer thickness 5 cm).

concentration dependence of the IR spectra of XII-XVI in the region of the stretching vibrations of the hydroxyl group [7] reveals their identical character and the existence of an intramolecular π -hydrogen bond in dilute CCl_4 solutions. The absorption of a free hydroxyl group appears in the spectra as a characteristic strong band with a maximum at $3644-3645 \text{ cm}^{-1}$ and a shoulder at $3630-3632 \text{ cm}^{-1}$, whereas the absorption of an associated hydroxyl group shows up as a band with a maximum at $3546-3550 \text{ cm}^{-1}$. The shoulder on the long-wave side of the ν_{OH} band is probably due to rotational isomerism about the C-O bond [8] in the XIIa-XVIa forms. This assumption is confirmed by the weakening of the intensity of the shoulder as the temperature is raised.



The relatively large $\Delta\nu_{\text{OH}}$ value ($95-99 \text{ cm}^{-1}$) of XII-XVI provides evidence for a relatively strong intramolecular π -hydrogen complex. A comparison of this value with the data presented in the literature for compounds with intramolecular hydrogen bonds between the π electrons of the aromatic system or the C=C bond and an aliphatic hydroxyl group [4, 7, 9] makes it possible to assume that among alcohols of this type the π -hydrogen bonds of XII-XVI are evidently some of the strongest. The factors that determined this quality of XII-XVI are the same as in the case of 5-(β -hydroxyethyl)-1,2-dihydropyrrolizine [4]. These factors should additionally include the greater possibilities (than in the example in [4]) for the realization of a favorable geometry for an intramolecular hydrogen bridge that are present in the case of γ location of the hydroxyl group relative to the ring (XIIb-XVIb). We will not touch upon the details of this geometry, since they require special study.

The material set forth above regarding the π -hydrogen bonds of alcohols XII-XVI compelled us to quantitatively determine their energy in the case of XII by a study of the temperature dependence of the absorption of associated and free hydroxyl groups. In the calculations we used both the optical densities and the integral intensities. Formula (1), which is similar to the previously described expression (2) [10], was used for the calculations:

$$\lg \frac{c}{d} = - \frac{\Delta H}{2.3RT} + \frac{\Delta S'}{2.3R}, \quad (1)$$

where c and d are the optical densities or integral intensities, respectively, of the associated and free hydroxyl groups, ΔH is the change in the enthalpy during the formation of a hydrogen bond, and $\Delta S'$ is a term associated with the entropy, and

$$\ln \frac{A_i}{A_f} = - \frac{\Delta H}{RT} + \left(\frac{\Delta S}{R} - \ln \alpha \right), \quad (2)$$

where A_i and A_f are, respectively, the integral intensities of the absorption of the associated and free hydroxyl groups, and $\alpha = a_f/a_i$ (a_f and a_i are the molar intensities of the free and associated hydroxyl groups).

From expressions (1) and (2) we find that $\Delta S' = \Delta S - R \ln \alpha$.

The results of the measurements were treated by the method of least squares. The confidence interval was calculated for a reliability of 95%. The enthalpies of the intramolecular π -hydrogen bond according to data on the temperature trend of the optical densities and integral intensities of the bands of the free and associated hydroxyl groups are, respectively, -2.05 ± 0.08 and $-3.05 \pm 0.13 \text{ kJ} \cdot \text{mole}^{-1}$ (-0.49 ± 0.02 and $-0.73 \pm 0.03 \text{ kcal/mole}$), and $\Delta S' = -17.61 \pm 0.29$ and $15.15 \pm 0.38 \text{ J} \cdot \text{K}^{-1} \cdot \text{mole}^{-1}$ (4.21 ± 0.07 and $-3.62 \pm 0.09 \text{ cal/mole.deg}$). The identical character of XII-XVI and the virtual equality of their $\Delta\nu_{\text{OH}}$ values make it possible to assume that the energy of intramolecular π -hydrogen bond in each of XII-XVI has a value close to the value found for alcohol XII.

EXPERIMENTAL

The PMR spectra of VII-XI in CCl_4 solutions (the ratio of the volume of the compound to the volume of the solvent was 1:3) were obtained with Hitachi-Perkin-Elmer R-20 (60 MHz) and BS-487C (80 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The

TABLE 3. Temperature Dependence of the Optical Density and Integral Intensity of the ν_{OH} and ν'_{OH} Bands of 5-(γ -Hydroxypropyl)-1,2-dihydropyrrolizine

Temp., °C	Optical density (D) and integral intensity (A) of the bands of the stretching vibrations of the hydroxyl group			
	free		associated	
	D	$A \cdot 10^{-3}$ mole ⁻¹ · liter·cm ⁻²	D	$A \cdot 10^{-3}$ mole ⁻¹ · liter·cm ⁻²
24	0,479	1,457	0,136	0,850
25	0,487	1,531	0,139	0,863
25	0,494	1,550	0,135	0,854
37	0,469	1,449	0,125	0,741
37	0,469	1,438	0,125	0,739
37	0,469	1,431	0,125	0,730
41	0,464	1,302	0,121	0,712
41	0,464	1,461	0,123	0,743
41	0,469	1,439	0,125	0,740
46	0,456	1,402	0,121	0,785
46	0,459	1,484	0,120	0,733
46	0,456	1,409	0,121	0,765
52	0,453	1,419	0,118	0,714
52	0,453	1,424	0,116	0,739
52	0,448	1,396	0,112	0,701
62	0,441	1,367	0,107	0,685
62	0,441	1,399	0,107	0,681
62	0,441	1,444	0,111	0,705
66	0,438	1,432	0,106	0,692
66	0,433	1,399	0,107	0,679
66	0,433	1,409	0,104	0,688
69	0,419	1,377	0,102	0,626
71	0,412	1,371	0,104	0,635
71	0,405	1,394	0,104	0,663
78	0,405	1,370	0,100	0,627
78	0,409	1,403	0,104	0,651
78	0,409	1,415	0,104	0,644

chemical shifts were converted to values relative to tetramethylsilane and are presented on the δ scale.

The IR spectra were recorded with a UR-20 spectrometer with an LiF prism. The concentration dependence of the optical densities of the ν_{OH} and ν'_{OH} bands were determined for solutions of XII-XVI in CCl_4 at concentrations of 10^{-2} , $5 \cdot 10^{-3}$ ($l = 2$ cm), $3 \cdot 10^{-3}$, and $2 \cdot 10^{-3}$ mole/liter ($l = 5$ cm). The temperature measurements were made for a $5 \cdot 10^{-3}$ mole/liter solution of XII in CCl_4 in a 2-cm long cuvette with NaCl windows. The temperature was monitored by means of a Chromel kapelevoi differential thermocouple and an EPV-2-10A potentiometer. The accuracy in the thermostatting was $\pm 0.5^\circ C$. The slight decrease in the concentration as the temperature rises because of the increase in the volume of the solvent was taken into account in the determination of the integral intensities. The coefficient of volume expansion of CCl_4 (0.00123 ml/deg) was found by the method in [11]. The following values were obtained without correction for the thermal expansion of the solvent: $\Delta H = -3 \cdot 10 \pm 0.13$ $kJ \cdot mole^{-1}$ (-0.74 ± 0.03 kcal/mole) and $\Delta S' = -15.23 \pm 0.42$ $J \cdot ^\circ K^{-1} \cdot mole^{-1}$ (-3.64 ± 0.10 cal/mole·deg)

The calculations from the data in Table 3 were made by the method of least squares from the standard program, modified relative to Eq. (1),* with an Odra-1013 computer.

1,2-Dihydropyrrolizines I-V were obtained by the method described in [2, 12].

5-[2-(Methoxycarbonyl)ethyl]-1,2-dihydropyrrolizines VII-XI were obtained by reaction of I-V with methyl acrylate (VI) by the method in [6]. A few crystals of hydroquinone were added to the reaction mixture. Esters VIII, X, and XI were obtained for the first time in this research.

*The authors thank V. I. Lavrushin for preparing the program.

5-(γ -Hydroxypropyl)-1,2-dihydropyrrolizine (XII). A solution of 1.7 g (45 mmole) of LiAlH₄ in 70 ml of absolute ether was placed in a three-necked 500-ml flask equipped with a mechanical stirrer, a dropping funnel, and a reflux condenser, and a solution of 11 g (57 mmole) of VII in 70 ml of absolute ether was added with vigorous stirring in the course of 30 min. The reaction mixture was then refluxed for 1 h, after which the excess LiAlH₄ was decomposed by the successive addition of 10 ml of moist ether and 10 ml of water. The ether layer was separated, and the solid material was extracted three times with ether. The ether extract was dried with magnesium sulfate, the ether was removed, and the residue was distilled at reduced pressure to give 7.2 g (77%) of XII in the form of a moderately viscous colorless liquid.

Compounds XIII-XVI were similarly obtained.

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REACTION OF PYRIDINE-2-THIONE WITH ACETYLENES

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In contrast to 2-pyridone, pyridine-2-thione reacts with acetylene with the participation of one reaction center — the sulfur atom. The reaction with phenylacetylene and diacetylene proceeds stereospecifically to give products with *cis* structures. The structures of the synthesized compounds were confirmed by chemical and spectroscopic methods.

The most stable tautomeric form of pyridine-2-thione, which is capable of prototropic transformations, is form I with a proton attached to the nitrogen atom [1]. In this connection, in the reaction with acetylenes one should have expected the formation of primarily N-vinyl derivatives; however, the possibility of the manifestation by thione I of dual reactivity with the formation of both N-substituted and S-substituted derivatives [2] is not excluded.

In the present research we studied the reaction of thione I with acetylene, phenylacetylene, and diacetylene under various catalytic conditions in order to search for methods for the synthesis of new N- and S-vinyl monomers of the pyridine series and to study their properties.

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