1-AROYL-2-BENZYL-5-HYDROXYPYRAZOLIDINES

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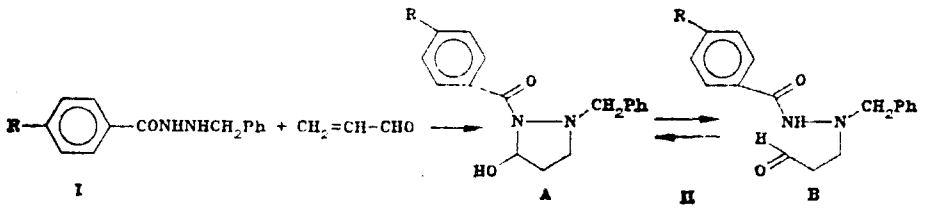
The PMR spectral data show that 1-aroyl-2-benzyl-5-hydroxypyrazolidines are preferentially present in cyclic form in solution, while the proportion of the linear form increases to ~50% in the gaseous phase, according to mass spectra.

It was shown previously that, unlike 1-alkanoyl derivatives [1], 1-benzoyl-2-benzyl-5-hydroxypyrazolidine IIa exists in polar solvents in equilibrium with its linear tautomer – β-hydrazidoaldehyde [2].

In the present work, we studied the behavior of the newly synthesized p-substituted 1-aroyl-2-benzyl-5-hydroxypyrazolidines IIb-e in solutions and in the gaseous phase*:



I, II a R=H, b R=Br, c R=NO_2, d R=CH_3, e R=CH_3O

The synthesis of hydroxypyrazolidines II was carried out by condensation of hydrazides I with acrolein, in analogy to [1]. The starting β-benzylhydrazides were obtained by acylation of benzylhydrazine with an acid chloride (Ic) or ester (Id) of the corresponding acids, or by alkylation of unsubstituted hydrazides (Ib, e).

We showed that ring-chain tautomerism is characteristic for all the 1-aroyl derivatives (see Table 1). We took as a criterion for the determination of a cyclic (A) or linear (B) structure of the compound the presence in the PMR spectra of a signal of a semiaminal proton in the 6.00-6.10 ppm region (for form A) or the signal of the aldehyde proton in the 9.6-9.7 ppm region and an NH group proton at 9.2-9.6 ppm (for form B), while the content of the tautomeric forms was determined from the ratio of the integral intensities of these signals. The data in Table 1 show that compounds Ia-d exist exclusively in a cyclic form in a nonpolar solvent (deuterochloroform), while for hydroxypyrazolidine Ie the presence of signals of the linear tautomer was detected, the amount of which in the equilibrium mixture was ~5%. The authors of [3] showed from IR spectroscopy that the presence of the B form (absorption band at 1710 cm^{-1}) is observed in CH_2Cl_2 solutions not only for compound Ie, but also for hydroxypyrazolidine Id. However, the ratio of the two tautomers cannot be evaluated quantitatively in this case.

When the PMR spectra are run in DMSO-D_6, signals of the two forms are observed for all the obtained compounds as well as for the unsubstituted 1-benzoyl-2-benzyl-5-hydroxypyrazolidine IIa. Their ratio depends on the character of the substituents at the para-position of the aroyl group, such that the greatest amount of the linear tautomer is observed for compounds with donor substituents (see Table 1). The position of the tautomeric equilibrium greatly determines stability of 1-aroyl-2-benzyl-5-hydroxypyrazolidines II. The considerable amount of the open form in compounds Id, e existing in solution increases the tendency of their molecules to be split with the formation of a polymer of acrolein and benzylhydrazide, and also of disproportionation products of the latter – hydrazide and β,β-dibenzylhydrazide.

*The IR spectra of these compounds were discussed in [3].

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TABLE 1. Characteristics of 1-Aroyl-2-benzyl-5-hydroxypyrazolidines IIa-e

Compound	mp, °C	R_f	PMR spectrum, δ, ppm (J, Hz)												Content of form B, % (±2%)	Yield %
			solvent	form A							form B					
				R, s	4-H, m	3-H, m	$PhCH_2$	OH	5-H, m	Ar	R, s	$PhCH_2$ s	NH br.s	HC=O, t		
IIa	116...117*	0,40	$CDCl_3$	—	2,38	3,08	3,80 s	4,61 br.s	6,03	6,84...7,82 m	—	—	—	—	—	56
			DMSO-D_6	—	2,27	2,91	3,92 s	6,32d (5,4)	5,83	7,04...7,40 m	—	4,07	9,27	9,71 (1,5)	10	—
IIb	130...132	0,41	$CDCl_3$	—	2,42	3,13	3,86 s	4,37 br.s	6,01	6,9...7,68 m	—	—	—	—	—	60
			DMSO-D_6	—	2,31	2,98	3,87 d 3,95d (AB, 17)	6,39 d (4,2)	5,83	6,90...7,70 m	—	4,09	9,41	9,69 (1,5)	8	—
IIc	150...151	0,49	$CDCl_3$	—	2,49	3,21	3,82 d 3,93d (AB, 18)	4,2 br.s	6,07 d.d (5,8)	6,7...7,47 m ($PhCH_2$); 7,56 d (*o*-H)**; 8,05 d (*m*-H)**	—	—	—	—	—	46
			DMSO-D_6	—	2,40	3,06	3,87 d, 3,34d (AB, 20)	6,54 d (4,3)	5,89	6,84...7,3 m ($PhCH_2$); 7,40 d, (*o*)**; 8,12 m (*m*)**	—	4,04	9,63	9,67 (1,4)	7	—
IId	111...113	0,34	$CDCl_3$	2,38	2,20	3,01	3,86	4,5 br.s	6,00	6,9...7,5 m ($PhCH_2$+*m*-H); 7,77 d (*o*) (7)	—	—	—	—	—	38
			DMSO-D_6	2,34	2,30	2,90	3,94	6,26 d (3,5)	5,83	7,00...7,60 m	2,52	4,00	9,20	9,63 (1,4)	14	—
IIe	92...93	0,37	$CDCl_3$	3,79	2,39	3,06	3,88	5,01 br.s	6,01	7,15 s (Ph); 6,84 d (*m*); 7,86 d (*o*) (7)	3,74	3,99	9,09	9,71 (1,4)	5	30
			DMSO-D_6	3,47	2,50	2,84	3,87	6,22 d (3)	5,83	7,17 s (Ph); 6,88 d (*m*)**; 7,64 d (O)***	3,81	3,79	9,20	9,65 (1,5)	20	—

*According to the data in [2], mp 115°C.

**J = 9 Hz.

***J = 8 Hz.

TABLE 2. Peak Intensities of Characteristic Ions in Mass Spectra of Compounds II

Compound	I, % of I_{max}					
	M^+	F_1	F_2	F_3	F_4	A, %
IIa	3,0	0,8	8	8	0,9	49
IIb	0,7	—	3	4	—	43
IIc	1,3	—	2	2	—	50
IId	1,7	0,3	4	4	0,8	47
IIe	2,0	0,5	9	6	1	57

TABLE 3. Mass Spectra of 5-Hydroxypyrazolidines II

Compound	m/z (I, %)*
IIa	282 M^+ (3), 265 (0,8), 239 (0,9), 226 (0,7), 191 (2), 178 (6), 177 (36), 162 (8), 161 (6), 160 (8), 159 (6), 133 (10), 132 (10), 106 (38), 105 (93), 91 (100)
IIb**	362 M^+ (0,7), 202 (5), 201 (6), 186 (2), 185 (24), 178 (3), 177 (22), 162 (4), 160 (3), 159 (4), 157 (10), 103 (5), 105 (25), 91 (100)
IIc	327 M^+ (1,3), 177 (25), 167 (6), 162 (2), 160 (2), 159 (2), 151 (3), 150 (21), 133 (7), 132 (6), 120 (6), 106 (12), 105 (5), 104 (17), 91 (100)
IId	296 M^+ (1,7), 279 (0,3), 253 (0,8), 177 (14), 162 (4), 160 (4), 136 (11), 133 (3), 120 (8), 119 (74), 117 (5), 106 (18), 105 (3), 104 (6), 91 (100)
IIe	312 M^+ (2), 295 (0,5), 269 (1), 177 (7), 162 (6), 160 (9), 159 (4), 152 (16), 151 (25), 136 (17), 135 (100), 133 (8), 107 (15), 91 (63)

*The peaks of M^+ and 15 of the most intense ions, starting from m/z 91, are given.

**The values are given for the ^{81}Br isotope.

We studied the behavior of hydroxypyrazolidines II in the gaseous phase under the action of electron impact. The $PhCH_2^+$ and $ArCO^+$ ions have the maximal intensity in the mass spectra, while the peaks of the characteristic ions (including those of molecular ions) have low intensity. The ratio of forms A and B in the gaseous phase was evaluated according to a previously determined sequence of paths of fragmentation of M^+ of the cyclic and linear forms of hydroxypyrazolidines [4]. A parallel decomposition of M^+ of the two forms is observed for all the compounds studied. The $[M - COAr]^+$ and $[M - PhCH_2]^+$ ions may be formed from the two structures and, therefore, to characterize the decomposition of the cyclic form A, in addition to the secondary (fragmentary) ions, we used ions F_1 (loss of radical OH) and F_2 (elimination of OH radical and the aroyl group), while for the M^+ of the linear form B, the dissociation of the hydrazine bond (formation of ion F_3) and the β-C–C bond were found to be characteristic.

Allowing for the above limitations, the approximate ratio of the cyclic and open forms of compounds II in the gaseous phase can be evaluated from the formula:

$$A = (F_1 + F_2)/(F_1 + F_2 + F_3 + F_4) \cdot 100, \ \%.$$

Analysis of the data obtained (Table 2) shows that for 1-aroyl-2-benzyl-5-hydroxypyrazolidines, unlike for the 1-acetyl derivatives (13%) [4], the amount of the open form B is greater in the gaseous phase. The nature of the substituent in the aroyl group does not substantially influence the content of the cyclic isomer, and it remains approximately the same (~50%).

The ratio between the two forms of M^+ observed in the gaseous phase may be related to the absence of solvational and intermolecular interactions.

EXPERIMENTAL

The PMR spectra were recorded on an FX-100 (JEOL) spectrometer using TMS as internal standard, the chemical shifts were measured with an accuracy of up to 0.01 ppm. The mass spectral investigations were carried out using an MKh-1303

and Varian MAT-111 spectrometers with introduction of the samples into the ionic source at temperatures close to the melting points of the compounds. The ionizing voltage was 70 eV. The course of the reactions and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in a benzene–ethyl acetate (1:1) system.

The data of the elemental analysis for C, H, N for compounds Ib-e, IIb-e correspond to the calculated values.

p-Bromobenzoic Acid β-Benzylhydrazide (Ib, $C_{14}H_{13}BrN_2O$). A mixture of 2.5 g (0.02 mole) of benzyl chloride, 4.4 g (20 mmoles) of p-bromobenzoic acid hydrazide and 1.6 ml (20 mmoles) of pyridine was boiled for 10 h in 50 ml of benzene, was then shaken with 15 ml of water, and filtered from the initial hydrazide (3 g). The benzene layer was separated, washed with water, dried over magnesium sulfate, and the benzene was evaporated. The residue was recrystallized from aqueous alcohol (1:1). Yield 0.9 g (46%, based on the hydrazide that entered the reaction) of compound Ib. R_f 0.69, mp 142-144°C. IR spectrum: 1670, 3245 cm^{-1}. PMR spectrum ($CDCl_3$): 4.06 (2H, s, CH_2); 5.1 (1H, s, NH); 7.2-7.8 (4H, m, arom.); 8.0 ppm (1H, s, NH).

Anisic Acid β-Benzylhydrazide (Ie, $C_{15}H_{16}N_2O_2$) was obtained in a similar way as above from 3.3 g (20 mmoles) of anisic acid hydrazide, 2.5 g (20 mmoles) of benzyl chloride and 1.6 ml (20 mmoles) of pyridine. After boiling for 40 min, 1.5 g of the initial hydrazide was recovered. Yield 1.8 g (64%, based on the hydrazide that entered the reaction) of compound Ie. R_f 0.48, mp 163-165°C. IR spectrum: 1665, 3230 cm^{-1}. PMR spectrum ($CDCl_3$): 3.7 (2H, s, CH_2); 3.8 (3H, s, CH_3O); 7.3 (1H, s, NH); 6.9 (2H, d, arom.); 7.6 ppm (2H, d, arom.).

p-Nitrobenzoic Acid β-Benzylhydrazide (Ic, $C_{14}H_{13}N_3O_3$). A suspension of 3.04 g (16 mmoles) of p-nitrobenzoyl chloride in 10 ml of benzene was added slowly with stirring to a solution of 2 ml (16 mmoles) of benzylhydrazine and 2.3 ml (16 mmoles) of triethylamine in 10 ml of benzene. After stirring for 1 h (when the warming up ceased), the reaction mixture was boiled for 30 min, the cooled mixture was filtered from triethylamine hydrochloride, and the precipitate was washed with benzene. The benzene solution was washed with water, dried over sodium sulfate, and evaporated. After recrystallization, 1.6 g (36%) of compound Ic was obtained, mp 140°C (decomp., from benzene). R_f 0.56. IR spectrum: 1660, 3255 cm^{-1}. PMR spectrum ($CDCl_3$): 5.3 (2H, s, CH_2); 5.5 (1H, s, NH); 7.3 (2H, d, arom.), 7.9 (2H, d, arom.); 7.8 ppm (1H, s, NH).

p-Toluic Acid β-Benzylhydrazide (Id, $C_{15}H_{16}N_2O$). A mixture of 5.2 g (30 mmoles) of ethyl ester of p-toluic acid and 3.2 g (26 mmoles) of benzylhydrazine was boiled with 1 drop of water in an argon current for 20 h. The precipitate that separated out from the reaction mixture was filtered off, washed with cold hexane, and 3.4 g (54%) of pure hydrazide was obtained, mp 125-127°C. R_f 0.45. IR spectrum: 1660, 3280 cm^{-1}. PMR spectrum ($CDCl_3$): 2.36 (3H, s, CH_3); 4.05 (2H, s, CH_2); 5.0 (1H, s, NH); 7.13 (2H, d, arom.); 7.6 (2H, d, arom.); 7.30 ppm (1H, s, NH).

1-p-Bromobenzoyl-2-benzyl-5-hydroxypyrazolidine (IIb, $C_{17}H_{17}BrN_2O_2$). 1-p-Bromobenzoyl-2-benzylhydrazine (3.6 g, 12.5 mmoles) was added in portions to a solution of 2.8 ml (50 mmoles) of acrolein in 20 ml of CH_2Cl_2, without allowing the mixture to warm up above 30°C. The mixture was allowed to stand for 2 h at room temperature, the solvent was evaporated and excess of aldehyde was distilled off under vacuum, and the residue was recrystallized from a mixture of benzene with ether.

1-p-Nitrobenzoyl-2-benzyl-5-hydroxypyrazolidine (IIc, $C_{17}H_{17}N_3O_4$) was obtained in a similar way from 2.8 ml of acrolein and 3.1 g of the corresponding hydrazide.

1-p-Toluyl-2-benzyl-5-hydroxypyrazolidine (IId, $C_{18}H_{20}N_2O_2$). A mixture of 0.24 g (1 mmole) of p-toluic acid β-benzylhydrazide was boiled with 1.2 ml (20 mmoles) of acrolein for 30 min. The excess of aldehyde was evaporated on an oil pump at 20°C. The residue was dissolved in absolute CH_2Cl_2 and passed through a two-layer filter (0.3 cm SiO_2 and 0.3 cm of activated charcoal) to remove the polymer of acrolein. The solvent was evaporated, and the oil that formed was triturated with ether.

1-p-Methoxybenzoyl-2-benzyl-5-hydroxypyrazolidine (IIe, $C_{18}H_{20}N_2O_3$) was obtained in a similar way as compound IId.

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