1-ACYL-5-HYDRAZINOPYRAZOLIDINES AND THEIR RING-CHAIN TAUTOMERISM

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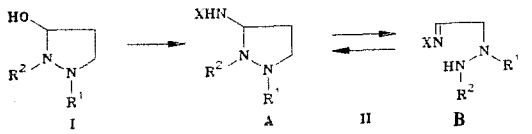
UDC 547.772:542.953:543.422.25'4:543.51

1-Acetyl-5-hydroxyl-2-isopropyl(phenyl)pyrazolidines, as well as 1-hydroxyperhydropyrazolo[1,2-a]-4H-pyridazine-5,8-dione, react readily with alkyl-, aryl-, and acylhydrazines and hydroxylamine to give the corresponding products of substitution of the OH group, which, depending on the nature of the hydrazine, exist in the linear β-hydrazidohydrazone (oxime) form or in the form of a cyclic tautomer, viz., the corresponding 1-acetyl-5-hydrazinopyrazolidine.

It is known that the reaction of alkenals with β-substituted hydrazides can, depending on the conditions and structural factors, lead to 1-acyl-5-hydroxypyrazolidines or 1-acyl-5-hydrazidopyrazolidines; the formation of the latter is most likely the result of reaction of the hydrazide with intermediate 5-hydroxypyrazolidine I [1]. We studied the action of aliphatic and aromatic hydrazines, acetyl- and benz- and thiobenzhydrazides, and hydroxylamine on various 5-hydroxyacylpyrazolidines Ia-c, since promising physiologically active substances have been found among hydroxy- and hydrazinopyrazolidines [1].

We found that the corresponding products of replacement of the OH group in the starting hydroxypyrazolidines, viz., IIa-i (see Tables 1 and 2), are formed in high yields in all cases.



I A II B

Ic, IIc R^1—R^2=COCH=CHCO, in the remaining compounds R^2=$COCH_3$; Ia R^1=*i*-Pr, b R^1=Ph, IIa, f, h, i R^1=*i*-Pr, d, e, g R^1=Ph, a—c X=NMe_2, d X=$NHC_6H_4NO_2$-*p*, e X=$NHCOCH_3$, f, g X=NHCOPh, h X=NHCSPh, i X=OH

As we have previously shown, starting hydroxypyrazolidines I exist primarily in the cyclic form (tautomerism was detected only in one case). The choice between the open and cyclic forms is decided unambiguously on the basis of data from the ^1H and ^{13}C NMR spectra, particularly on the basis of the differences in the chemical shifts of the methylidyne proton and the carbon atom of the linear and ring forms that is bonded to it [1, 2].

In contrast to the hydroxy compounds, hydrazino derivatives II exist primarily in the open form (see Tables 1 and 2). Tautomeric equilibrium A $\rightleftarrows$ B was detected in the case of benzoylhydrazine derivatives IIf, g; the fraction of the B form increases somewhat as the polarity of the solvent increases. The tautomeric equilibrium is established in a few days, which makes it possible, on the basis of the changes in the PMR spectra with time, to conclude that IIf has a cyclic structure in the crystalline state, in contrast to hydrazide IIg, the spectrum of which obtained immediately after the latter is dissolved does not contain signals of tautomer A. Compounds II are inferior to both the hydrazones of γ-hydroxy carbonyl compounds (including carbohydrate derivatives) [3] because of the nucleophilicity of the NHCO grouping as compared with the hydroxy group and to β-hydrazido aldehydes [1, 2] with respect to their tendency to undergo conversion to the cyclic form.

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0009-3122/85/2109-1031$09.50

TABLE 1. Characteristics of IIa-e

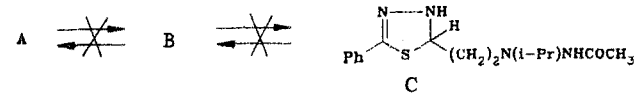
Compound	mp,[a] deg C	PMR spectrum, ppm (form)[b]						Amt. of form A, %	Yield, %
		CH_2—C	CH_2—N	CH	CH_3CO	X	NH		
IIa		2,25—2,0	3,0—2,85	6,60 (B_E); 6,70 (B_Z)	2,05 (B_E); 1,95 (B_Z)	2,70	6,89 (B_E); 6,78 (B_Z)	—	96
IIb	108	2,30—2,61	3,61	6,52 (B_E)[c]	1,95 (B_E); 1,85 (B_Z)	2,62	8,90 (B_Z); 9,73 (B_E)	—	83
IIc	141	2,54,t	4,06t	6,39	6,9 (AB)d	2,54, c	—	—	90
IId	170	2,38—2,59	3,50—3,69	—c	1,84 (B_Z); 1,90 (B_E)	6,9—8,1 (Ar); 10,88 (NH)	9,15 (B_Z); 9,84 (B_E)	—	90
IIe	162	2,29—2,61	3,58	7,35 } $B_{E,Z}$ 7,50 }	1,73; 1,82; 1,90; 1,94	1,83; 1,85; 2,05; 2,10	—e	—	69
						11,05; 10,85 (NH, B_E) 11,03; 10,91 (NH, B_Z)	9,85 9,78 (E); 9,10; 9,15 (Z)		
IIf	118	2,10—2,49	2,58—3,51	5,24 (A); 6,97 (B)	2,24 (A); 2,10 (B_E); 2,01 (B_Z)	7,4—8,1 (Ar); 9,88 (NH)	5,18 (A); 11,12 (B_Z); 11,21 (B_E)	— 90	60
IIg	176	2,60	3,70	5,48 (A); 6,65 (B)	1,89 (A); 1,85 (B_Z); 1,98 (B_E)	6,7—8,0 (Ar) 11,60 (NH)	5,62 (A); 9,94 (B_E); 9,0 (B_Z)	15	64
IIh	132	1,81—2,0	2,59—3,11	5,50 (A_E); 5,59 (A_Z)	1,83 (A_E); 1,85 (A_Z)	7,2—7,6 (Ar); 8.47 &8,41 (Z); 8,03 &7,78 (E)		100	70
IIi		2,22—2,65	2,66—3,10	7,45 (syn), 6,75 (anti)	2,02 } (B_E) 2,00 } 1.85 } (B_Z) 1,87 }	10,15 (syn); 9,85 (anti)	7,23 (B_E); 6,82 (B_Z)	—	60

[a]The compounds were crystallized: IIb from benzene—hexane (3:1), IIc from ethyl acetate—methanol (10:1), IId-g from acetonitrile, and IIh from methanol. Compounds IIa, i were oils (they were purified by chromatography with a column packed with silica gel). [b]The signals of substituents R^1 have the requisite chemical shifts and are not presented here; the solvents were $CDCl_3$ for IIa,f,i, d_6-DMF for IIb, CD_3OD for IIc, d_6-DMSO for IId,e, and d_7-DMF for IIg,h. [c]The signal is located in the region of the R^1 signals. [d]Signals of vinyl protons. [e]Signals of the stereoisomers due to retarded rotation of both CH_3CO groups (recorded with a Bruker WM-250 spectrometer).

TABLE 2. ^{13}C NMR Spectra of Hydrazinopyrazolidines II

Compound	Chemical shifts, δ, ppm
IIa	15,3; 17,4, 18,3; 18,6 (q, CH_3—C); 29,8 (t, CH_2—C); 41,55 (q, CH_3—N); 50,8; 51,4 (t CH_2—N); 54,1; 55,2 [d, **CH**—$(CH_3)_2$]; 134,1; 135,5 (d, C=N); 168,2; 174,8 (C=O)
IId	19,4; 20,8 (CH_3); 30,0 (CH_2—C); 49,0 (CH_2—N); 110—150 (s, 15C, Ar), 151,25; 151,8 (C=N); 169,2; 175,1 (C=O)
IIe	19,5; 20,4; 20,7; 21,3 (CH_3); 30,3 (CH_2—C); 49,3 (CH_2—N); 113,1—146 (s, 6C, Ar); 149,2 (C=N); 167,7; 170,2; 172,8; 175,9 (C=O)
IIf	24,2; 26,5; 27,6; 28,1; 29,0; 29,4; 29,7 (CH_3—C); 37,8; 38,9 (CH_2—C); 58,1; 59,3; 60,0 (CH_2—N); 62,4; 64,2; 64,8 [**CH**$(CH_3)_2$]; 82,9 (N—C—N); 135,0—141,2 (5C, Ar); 158,9—159,9 (C=N); 172,7; 173,0; 178,1; 174,3 (C=O)
IIg	18,5; 20,9; 21,3 (CH_3); 29,4; 30,1 (CH_2—C); 49,1; 51,2; 53,0 (CH_2—N); 110—149,5 (12C, Ar); 150,6; 160,0; 160,5 (C=N); 163,5; 166,5; 169,1; 175,1 (C=O)
IIh	17,2; 18,3; 19,4; 19,5; 20,9 (CH_3); 35,0 (CH_2—C); 50,0 (CH_2—N); 55,2; 56,0 [**CH**$(CH_3)_2$]; 71,25; 71,85 (N—C—N); 125,0—141,6 (9C, Ar); 168,7; 174,0 (C=O); 200,1 (C=S).
IIi	20,3; 22,0; 23,0; 24,3; 26,9 (CH_3); 26,7; 26,8; 31,4; 31,6 (CH_2—C); 53,6; 54,6; 54,8; 55,3 (CH_2—N); 59,2; 59,7 [**CH**$(CH_3)_2$]; 151,8; 152,7; 164,4; 167,4 (C=N); 172,6; 178,6; (C=O)

It is interesting that IIh, which, in principle, is capable of the ring-chain tautomeric equilibrium A ⇄ B ⇄ C, exists, according to the NMR spectra data, entirely in pyrazolidine form A, in contrast to the other alkylidene derivatives of thiobenzhydrazide [4], and does not display any tendency to undergo conversion to 1,3,4-thia-diazolidine tautomer C.



C

Compounds IIa-d,i with a linear structure and linear tautomers B in the case of IIf,g, which evidently have a syn configuration relative to the C=N bond [5], are represented by mixtures of Z and E isomers with preponderance of the latter due to retarded rotation of the N-acetyl group. The assignment of the signals of the individual forms in the ^1H and ^{13}C NMR spectra was based on the known regularities in the relative positions of the signals of the fragments or the individual atoms that are sensitive to a change in the configuration in the $NCOCH_3$ grouping [6] and also on the fact of the increase in the fraction of the Z isomer as the polarity of the medium increases or on passing to polar solvents (in the order $CDCl_3$, d_6-DMSO, CD_3OD) [7, 8]. The explanation of the observed phenomenon of doubling of the signals in the PMR spectra by retarded rotation is confirmed by the fact that merging of these signals was noted in the case of heating to no higher than 120°C. Oxime IIi is a mixture of four stereoisomers due to "amide" rotation and as a consequence of stereoisomerism in the azomethine fragment (see Tables 1 and 2). The percentages of all four stereoisomers are approximately identical.

Cyclic tautomers A of derivatives IIf,g are represented by a single form, the configuration of which is unclear, whereas thiobenzoyl derivative IIh exists in the form of a mixture of Z and E forms with significant (up to 85%) preponderance of the Z isomer.

Thus 5-hydroxypyrazolidines have a quite labile hydroxy group, the replacement of which under the influence of hydrazines or hydroxylamine serves as a convenient method for the synthesis of β-hydrazidohydrazones (and oximes) or the corresponding 5-hydrazinopyrazolidines, depending on the structural peculiarities.

EXPERIMENTAL

The PMR spectra of 10% solutions of the compounds in $CDCl_3$, d_6-DMSO, and CD_3OD were recorded with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The quantitative determinations were made from two measurements by fivefold integration of the signals of the methylidyne protons; the error in the determinations was ±5%. The ^{13}C NMR spectra of concentrated (3 M) solutions in $CDCl_3$ were obtained with a Brucker HX-90 spectrometer (22.63 MHz) under pulse conditions with Fourier transformations under conditions of noise decoupling of the protons and also under monoresonance conditions; the internal standard was $(CD_3)_2CO$ (δ 30.4 ppm). The purity of the compounds obtained was monitored by thin-layer chromatography (TLC) on activity Al_2O_3 in a chloroform–methanol system (40:1) and on Silufol plates in a benzene–ethyl acetate system (4:1).

Hydroxypyrazolidines Ia,b were obtained by the method in [1], and Ic was obtained by the method in [9].

1-Acetyl-5-hydrazinopyrazolidines II. Equimolar amounts of 5-hydroxypyrazolidine I and the corresponding hydrazine were mixed in benzene or ethanol, and the mixture was refluxed until the reaction was complete according to monitoring by TLC. In the case of IIa,h the reaction proceeded at room temperature. After evaporation of the solvent, the hydrazinopyrazolidines were purified by recrystallization or by chromatography with a column packed with silica gel (100/160 μ). The results of elementary analysis were in agreement with the calculated values. The characteristics of pyrazolidines II are presented in Tables 1 and 2.

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THREE-DIMENSIONAL STRUCTURES OF 1-ACYL-5-HYDROXYPYRAZOLIDINES

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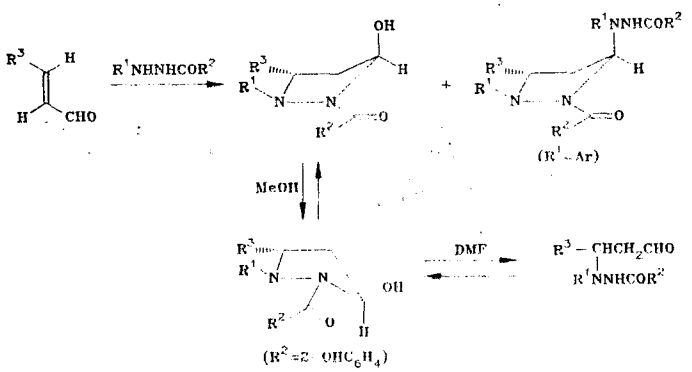
UDC 548.737+547.772: 542.953:543.51'422.25

It was shown by x-ray diffraction analysis and PMR spectroscopy that 1-acyl-5-hydroxy- and -5-hydrazinopyrazolidines have a conformation with an axial orientation of the functional group attached to the $C_{(5)}$ atom. The 1-salicylyl derivatives constitute an exception: in methanol solutions they exist in a conformation with an equatorial hydroxy group, whereas in dimethylformamide (DMF) the ring undergoes partial opening to give the corresponding β-hydrazido aldehydes.

We have previously observed that 1-acyl-2-alkyl(aryl)-5-hydroxyprazolidines and 1-acyl-2-aryl-5-(β-acyl-αaryl)hydrazinopyrazolidines are formed in the reactions of 1-acyl-2-alkyl (aryl)-hydrazines with unsaturated aldehydes [1, 2]. Two asymmetric centers develop in the molecules of the resulting pyrazolidines in the reaction of acid hydrazides with β-substituted unsaturated aldehydes (crotonaldehydes and cinnamaldehydes), and this leads to the possibility of the existence of two pairs of diastereomers. We found that the isolated 5-hydroxy- and 5-hydrazinopyrazolidines are represented by only one pair of diastereomers. The chromatographic and spectral characteristics of the compounds obtained constitute evidence in favor of this. It may therefore be asserted that the reaction of hydrazides with unsaturated aldehydes proceeds regio- and stereoselectively.

A combined analysis of the x-ray diffraction data for 1-acetyl-2-phenyl-3-methyl-5-hydroxypyrazolidine (I) and the PMR spectra of the remaining derivatives (see [1]) enabled us to establish a relationship between the spin-spin coupling constants (SSCC) of the protons in the pyrazolidine ring and the orientation of the functional substituents and to ascertain the three-dimensional structures of these compounds.



M. V. Lomonosov Moscow State University, Moscow 117234. S. M. Kirov Military Medical Academy, Leningrad 194175. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1242-1247, September, 1985. Original article submitted February 15, 1985.

 0009-3122/85/2109-1034$09.50