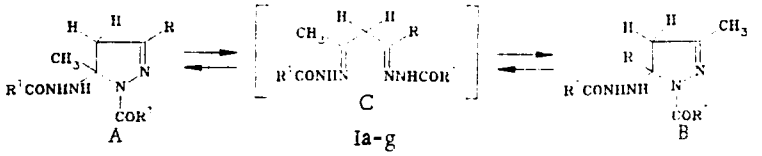
STRUCTURE OF ASYMMETRIC 5-HYDRAZINO-2-PYRAZOLINES

M. Yu. Malov, K. N. Zelenin, and S. I. Yakimovich

UDC 547.772.2:543.422.25:541.634

NMR (^1H and ^{13}C) spectroscopy was used to show the existence of ring-ring tautomers for 5-hydrazino-2-pyrazolines with asymmetric structure and the predominant formation of cis-isomers for 4-substituted compounds.

The existence of the condensation products of 1,3-dioxocompounds with hydrazides in a 1:2 stoichiometry as substituted 5-hydrazino-2-pyrazolines [1, 2] suggests the possibility of ring-ring tautomers (or isomers) for 5-hydrazino-2-pyrazoline rings for derivatives of asymmetric structure, examples of which exist [3]. This work studies the influence of structural factors on the position of the equilibrium A ⇄ B.



Ia-g

I a—c R=CH_3, d R=H, e R=C_2H_5, f R=C_3H_7, g R=i-C_4H_9; a R^1=i-C_3H_7, b R^1=i-C_4H_9, c R^1=t-C_4H_9, d-g R^1=C_6H_5

In particular, compounds Ia-c were synthesized with increasingly bulky acyl substituents in order to produce the linear tautomeric structure C, for which the probability of appearance increases with increasing steric strain in the cyclic isomer [4]. However, these compounds in various solvents (DMF-D_7, DMSO-D_6, acetone-D_6, pyridine-D_5, CD_3CN, $CDCl_3$) between -40-140°C exist only in the cyclic form, which follows immediately from their PMR spectra (Table 1).

The influence of the 3- and 5-substituents of the pyrazoline ring on the tautomeric equilibrium was studied through the reaction products of benzhydrazide with asymmetric aliphatic β-dicarbonyl compounds. In a series of these derivatives, Id-g (Table 1), the fraction of tautomer A quickly increases with increasing bulkiness of the 3-substituent, i.e., the cyclization occurs preferentially through the sterically more accessible C=N bond. The A and B forms exist simultaneously only in Ie, f, where the bulkiness of the 3- and 5-substituents differ little. The equilibrium A ⇄ B is established after a few hours, and is practically unaffected by the solvent or temperature.

Differentiation of the A and B forms was based on the splitting of the 4-H and 3-CH_3 signals due to spin-spin coupling (∿1.0 Hz) and also by comparison of the chemical shift of the protons of the 3- and 5-substituents: the signals of a particular substituent usually are found at a weaker field near a C=N bond than in the 5-position [2]. The existence of Id as the B isomer follows directly from the ^{13}C and ^1H NMR spectra: the doublet for $C_{(5)}$ (73.4 ppm) and the spin-spin coupling of the 4-H and 5-H protons (∿7.0 Hz).

The occurrence of reverse cyclization is indirectly supported by data on the structure of the 5-hydrazino-2-pyrazolines IIa-c with substituents in the 4-position, since this was observed for 5-oxy-2-isoxazolines [5] and 5-oxy-2-pyrazolines [6].

The appearance of cis- and trans-isomers is possible for these compounds due to different positions of the 4- and 5-alkyl groups. Thus, IIa exists in solution as a mixture of stereoisomers (trans:cis, 1:2). However, for IIb and c only the cis-isomer is seen; its content rises sharply with increasing steric bulkiness of the 4-substituent.

S. M. Kirov Academy of Military Medicine, Leningrad 194175. Leningrad State University, Leningrad 199034. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1358-1361, October, 1988. Original article submitted March 30, 1987; revision submitted October 8, 1987.

 0009-3122/88/2410-1126$12.50

TABLE 1. PMR Spectra of 5-Hydrazino-2-pyrazolines *[1]

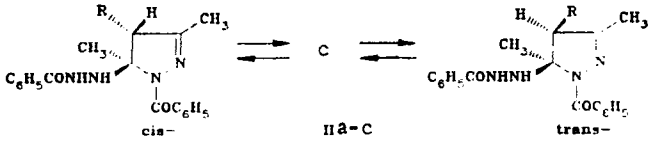
Compound*[2]	A, %	Chemical shift, ppm (Coupling const., Hz)
Ia	—	1,0...1,1 [12H, m, 2 $(CH_3)_2CH$]; 1,58 (3H, s, 5-CH_3); 1,88 (3H, t, *1,0*, 3-CH_3); 2,27 and 3,27 [1H+1H, sept., *7,0*, 2 $CH(CH_3)_2$]; 2,62 and 3,06 (2H, AB-system, q, 19,0, *1,0*, 4-H); 4,30 and 7,25 (1H+1H, br.s 2 NH)
Ib*[3]	—	0,6...1,0 [12H, m, 2 $(CH_3)_2CH$]; 1,61 (3H, s, 5-CH_3); 1,86 (3H, s 3-CH_3); 1,3...1,7 and 1,9...2,5 (6H, m 2 CH_2CH); 2,72 and 3,12 (2H, AB-system *19,0*, 4-H); 5,73 and 8,45 (1H+1H, d 5,0, 2 NH)
Ic	—	1,09 and 1,28 [9H+9H, s, 2 $(CH_3)_3C$]; 1,64 (3H, s 5-CH_3); 1,90 (3H, t, *1,0*, 3-CH_3); 2,60 and 2,96 (2H, AB-system, q, *19,0*, 1,0, 4-H); 5,98 and 6,95 (1H+1H, d, 2,0, 2 NH)
Id	0	1,98 (3H, s 3-CH_3); 3,03 (2H, d *7,0*, 4-H); 5,73 (1H, t, *7,0*, 5-H); 6,60 and 9,40 (1H+1H, br. s, 2 NH); 7,2...7,9 (10H, m, Ar)
Ie*[4]	60	A: 1,01 (3H, t, *7,5*, CH_3CH_2); 1,85 (3H, s, 5-CH_3); 2,31 (2H, q, *7,5*, 3-CH_2); 2,81 and 3,19 (2H, AB-system, *19,0*, 4-H); 6,26 and 9,20 (1H+1H, d, *5,5*, 2 NH); 7,1...8,0 (m, Ar); B: 0,91 (3H, t, 7,5, CH_3CH_2); 1,88 (3H, t, *1,0*, 3-CH_3); 2,98 and 3,08 (2H, AB-system, q, *19,0*, *10,0*, 4-H); 9,69 (1H, d, *5,5*, NHCO)
If*[4]	85	A: 0,78 (3H, t, *6,5*, $CH_3C_2H_4$); 1,43 (2H, sext, *6,5*, $CH_2CH_2CH_2$); 1,77 (3H, s, 5-CH_3); 2,16 (2H, t, *6,5*, 3-CH_2); 2,74 and 3,16 (2H, AB-system *19,0*, 4-H); 5,30 and 8,56 (1H+1H, d, *2,0*, 2 NH); 7,1...7,8 (m, Ar); B: 1,94 (3H, s, 3-CH_3); 2,90 and 3,12 (2H, AB-system, *18,0*, 4-H)
Ig*[4]	100	1,05 and 1,09 [3H+3H, d, *6,5*, $(CH_3)_2CH$]; 2,10 (3H, s, 5-CH_3); 2,36 (2H, d, *7,0*, 3-CH_2); 3,15 and 3,67 (2H, AB-system *19,0*, 4-H); 6,69 and 11,7 (1H+1H, d, *6,5*, 2 NH); 7,6...8,0 (10H, m Ar)
IIb	—	1,03 (3H, t, *6,5*, CH_3CH_2); 1,57 (3H, s, 5-CH_3); 1,87 (3H, d, *1,0*, 3-CH_3); 1,5...1,9 (2H, m, 4-CH_2); 2,94 (1H, t, q, *6,0*, *1,0*, 4-H); 5,15 and 8,87 (1H+1H, br. s, 2 NH); 7,2...7,8 (10H, m, Ar)
IIc	—	1,01 and 1,06 [3H+3H, d, *6,5*, $(CH_3)_2CH$]; 1,63 (3H, s 5-CH_3); 1,95 (3H, s, 3-CH_3); 1,3...2,0 (3H, m CH, 4-CH_2); 3,17 (1H, t, *6,0*, 4-H); 5,15 and 8,93 (1H+1H, br. s, 2 NH); 7,2...7,9 (10H, m, Ar)

*[1] See 2 for the NMR of IIa.

*[2] Solvents for Ia, c, f, IIb, c: $CDCl_3$; for Ib, e: acetone-D_6; for Id: pyridine-D_5; for Ig: DMSO-D_6; HMDS internal standard.

*[3] Restricted rotation about the amide bond in the exocyclic hydrazine fragment gives rise to E- and Z-isomers (E-isomer ∿5%).

*[4] Signals not included are hidden or unobserved.



II a R=CH_3; b R=C_2H_5; c R=*i*-C_4H_9

The difference in behavior of the 4-substituted 5-hydrazino-2-pyrazolines and 5-oxy-2-pyrazolines [6], in which the content of the predominant trans-isomer increases with increasing bulkiness of the 4-substituent, apparently is connected with the larger steric requirements of the hydrazino substituent compared to the hydroxyl group.

Differentiation of isomers for IIa was based on the fact that for the cis-isomer the signal of the 4-H proton should lie at a weaker field because of the influence of the 5-hydrazido group, while the 4-CH_3 should be at a stronger field [5, 6].

The possibility of the recyclization A $\rightleftarrows$ B for 5-hydrazino-2-pyrazolines should be considered in questions of regioisomers during reactions of monosubstituted hydrazines with asym-1,3-dioxo compounds, since the possibility of formation of pyrazoles at an intermediate stage of 5-hydrazino-2-pyrazoline formation is possible.

EXPERIMENTAL

PMR spectra were recorded on a Tesla BS-497 (100 MHz) spectrometer for 3-5% solutions with HMDS internal standard. NMR ^{13}C spectra were recorded on a Tesla BS-497 (20.41 MHz) instrument for 25% solutions with and without proton decoupling. Quantitative measurement of tautomeric forms used PMR spectra with duplicate integrations of suitable indicator signals.

TABLE 2. 5-Hydrazino-2-pyrazolines

Compound	mp.* °C	Found, N, %	Empirical formula	Calculated N, %	Yield, %
Ia	66...68	20.8	$C_{13}H_{24}N_4O_2$	20.9	60
Ib	97	18.9	$C_{15}H_{28}N_4O_2$	18.9	45
Ic	134...135	18.8	$C_{15}H_{28}N_4O_2$	18.9	25
Id	60...63	17.2	$C_{18}H_{18}N_4O_2$	17.4	90
If	156...158	15.5	$C_{21}H_{24}N_4O_2$	15.4	38
Ig	164...166	14.6	$C_{22}H_{26}N_4O_2$	14.8	50
IIb	63...65	15.1	$C_{21}H_{24}N_4O_2$	15.4	16
IIc	99...100	14.4	$C_{23}H_{28}N_4O_2$	14.3	20

*Crystallizations: Ia, c, hexane-benzene, 1:1; Ib, hexane-benzene, 10:1; If, g, hexane-benzene, 1:2; IIb, c, benzene.

Characteristics of the synthesized compounds are given in Tables 1 and 2.

1-Acyl-5-hydrazino-2-pyrazolines (Ia-c, f, g). In a suitable solvent (for Ia-c, ethanol; for If, g, benzene), were boiled for 8 h 20 mmole of hydrazide (isobutyric, isovaleric, pivalic, or benzoic) and 10 mmole of the corresponding 1,3-dioxo compound (2,4-pentanedione, 2,4-heptanedione, or 6-methyl-2,4-heptanedione). The residue after evaporation was recrystallized.

1-Benzoyl-5-benzoylhydrazino-3-methyl-2-pyrazoline (Id). In 50 ml chloroform for 5 h were boiled 1.6 g (10 mmole) 1,1-diethoxy-3-butanone and 2.72 g (20 mmole) benzhydrazide with addition of a few drops CF_3COOH. NMR ^{13}C spectra ($CDCl_3$): 15.7 (q, 3-CH_3); 40.2 (t, $C_{(4)}$); 73.4 (d, $C_{(5)}$); 157.6 (s, $C_{(3)}$); 167.3 and 168.1 (s, C=O); 127-134 ppm (C_{arom}).

The NMR spectrum of Ie is given in [3].

1-Benzoyl-5-benzoylhydrazino-4-alkyl-2-pyrazolines (IIb, c). To a solution of 8.16 g (60 mmole) of benzhydrazide in 40 ml ethanol was added dropwise with stirring a solution of 30 mmole 3-ethyl(isobutyl)-2,4-pentanedione in 20 ml ether. The mixture stood for a day. The residue after evaporation of solvent in a vacuum was extracted with ether, the ether solution was evaporated to dryness and dissolved in 50 ml benzene; the product crystallized after a few days at 0°C.

LITERATURE CITED

1. K. N. Zelenin, M. Yu. Malov, I. P. Bezhan, V. A. Khrustalev, and S. I. Yakimovich, Khim. Geterotsikl. Soedin., No. 6, 854 (1985).
2. K. N. Zelenin, M. Yu. Malov, I. V. Zerova, P. B. Terent'ev, and A. G. Kalandarishvili, Khim. Geterotsikl. Soedin., No. 9, 1210 (1987).
3. K. N. Zelenin, M. Yu. Malov, I. P. Bezhan, V. A. Khrustalev, and S. I. Yakimovich, Khim. Geterotsikl. Soedin., No. 7, 1000 (1985).
4. R. E. Walter, Ring-Chain Isomerism in Organic Chemistry [Russian translation], Zinatne, Riga (1978).
5. R. Jacquier, F. Petrus, J. Verducci, and Y. Vidal, Tetrahedron, Lett., No. 5, 387 (1974).
6. S. I. Yakimovich and I. V. Zerova, Zh. Org. Khim., in press.