ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 10, pp. 1720–1723. © Pleiades Publishing, Ltd., 2012.
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Synthesis, Structure, and Properties of Pyrazole-4-carbaldehyde Oximes

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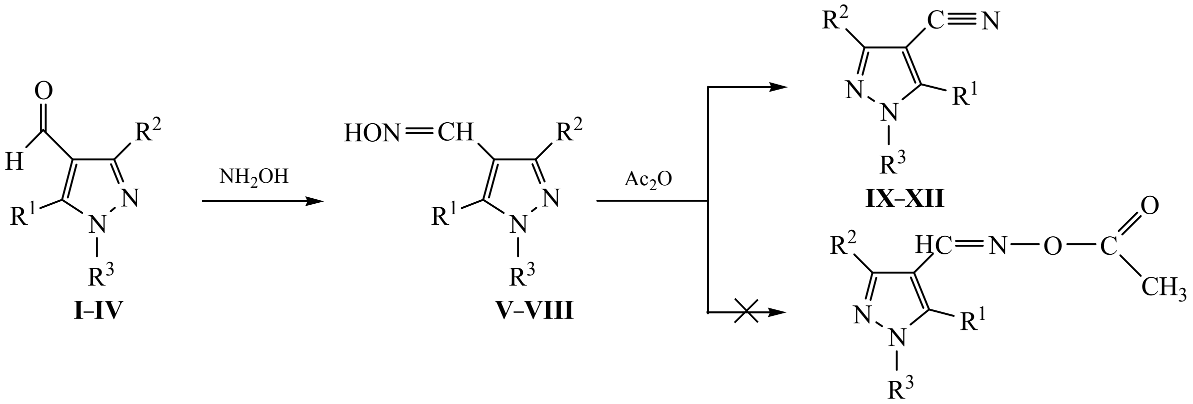
Received July 28, 2011

Abstract—1-Alkyl-1*H*-pyrazole-4-carbaldehyde oximes reacted with acetic anhydride to give the corresponding nitriles, which is typical for *anti* isomers of aldoximes. The *anti* configuration of 5-methyl-1-propyl-1*H*-pyrazole-4-carbaldehyde oxime in crystal was unambiguously determined by X-ray analysis.

DOI: 10.1134/S1070363212100131

Heterocyclic oximes are widely used as intermediates in organic synthesis [1]. However, oximes of the pyrazole range remain relatively poorly studied. The goal of the present research was synthesis of 1-alkyl-1*H*-pyrazole-4-carbaldehyde oximes and study of their structure and chemical transformations.

As was expected [2–4], 1-alkyl-1*H*-pyrazole-4-carbaldehydes **I**–**IV** were easily converted into the corresponding oximes **V**–**VIII** by treatment with hydroxylamine (Table 1). In the ^{1}H NMR spectra (Table 2) of all oximes **V**–**VIII** only spiting signal of OH group proton was absent, indicating formation of only one isomer [5].



I, **V**, **IX**, $R^1 = R^2 = H$, R^3 = Me (**a**), Pr (**c**); **II**, **VI**, **X**, $R^1 = H$, R^2 = Me, R^3 = Et (**b**), Pr (**c**); **III**, **VII**, **XI**: R^1 = Me, R^2 = H, R^3 = Et (**b**), Pr (**c**), **IV**, **VIII**, **XII**, $R^1 = R^2$ = Me, R^3 = Me (**a**), Et (**b**), Pr (**c**).

NMR spectroscopy is one of the most reliable methods for structure determination of isomeric oximes [6–14]. According to [8], the difference between chemical shifts of protons in the aldoxime group ($\delta_{OH} - \delta_{CH}$) is specific for *syn* and *anti* isomers. This difference is equal to ~3.0 ppm for *syn* isomers and ~4.0 ppm for *anti* isomer. In the ^{1}H NMR spectra of **V**–**VIII**, the difference $\delta_{OH} - \delta_{CH}$ was from 2.3 to 2.8 ppm, which is typical of *syn* oximes. Compounds **V**–**VIII** were thermally stable, and according to ^{1}H NMR spectra they neither changed on heating in DMSO to 150°C nor underwent *syn*–*anti* isomerization on heating in the presence of HCl.

Table 1. Yields, physical constants, and elemental analyses of substituted pyrazoles **V**–**XII**

Comp. no.	Yield, %	mp, °C or bp, °C (mm)	n_D^{20}	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
Va	89	113–114	–	48.24	5.72	33.29	$C_5H_7N_3O$	48.00	5.60	33.60
Vc	80	85–87	–	54.73	7.00	27.65	$C_7H_{11}N_3O$	54.90	7.18	27.45
VIb	89	103–105	–	54.73	7.00	27.65	$C_7H_{11}N_3O$	54.85	7.22	27.51
VIc	91	85–87	–	57.48	7.78	25.14	$C_8H_{15}N_3O$	57.32	7.69	25.00
VIIb	90	105–107	–	54.73	7.00	27.65	$C_7H_{11}N_3O$	54.63	7.20	27.52
VIIc	97	109–111	–	57.48	7.78	25.14	$C_8H_{15}N_3O$	57.54	7.39	25.38
VIIIa	91	183–185	–	54.99	7.18	27.45	$C_7H_{11}N_3O$	54.65	7.00	27.68
VIIIb	87	173–175	–	57.48	7.78	25.14	$C_8H_{13}N_3O$	57.23	7.39	25.38
VIIIc	88	125–127	–	59.66	8.28	23.20	$C_9H_{15}N_3O$	59.78	8.44	23.48
IXa	85	95(1)	1.4932	56.07	4.67	39.25	$C_5H_5N_3$	56.25	4.81	39.93
IXc	88	104(2)	1.4964	62.22	6.66	31.11	$C_7H_9N_3$	62.48	6.86	31.32
Xb	85	102(1)	1.4960	62.22	6.66	31.11	$C_7H_9N_3$	62.48	6.36	31.39
Xc	90	38–40	–	64.42	7.38	28.18	$C_8H_{11}N_3$	64.71	7.09	28.34
XIb	88	105(1)	1.4975	62.22	6.66	31.11	$C_7H_9N_3$	62.31	6.82	30.99
XIc	80	44–46	–	64.42	7.38	28.11	$C_8H_{11}N_3$	64.25	7.42	28.36
XIIa	75	118(2)	1.4996	62.22	6.66	31.11	$C_7H_9N_3$	62.38	6.93	31.29
XIIb	80	112(1)	1.4960	64.42	7.38	28.11	$C_8H_{11}N_3$	64.02	7.21	27.95
XIIc	78	120(1)	1.5076	66.66	7.40	25.92	$C_9H_{12}N_3$	66.38	7.63	25.40

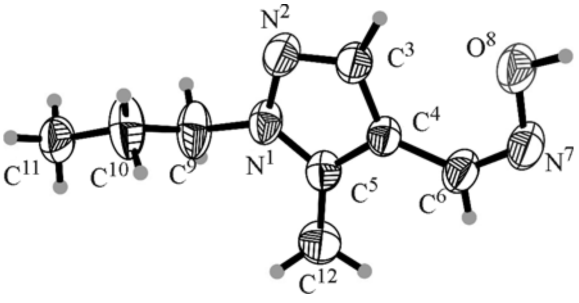
It is also known [15] that *syn*-aldoximes react with acetic anhydride forming acetyl derivatives and that *anti* isomers under similar conditions are converted into nitriles via elimination of water. We found that treatment of oximes with acetic anhydride gave exclusively pyrazole-4-carbonitriles **IX**–**XII**, i.e. compounds **V**–**VIII** behaved like *anti*-aldoximes.

We believe that assignment of oximes **V**–**VIII** to the *syn* or *anti* isomers on the basis of ^{1}H NMR data is not absolutely reliable. Therefore, the structure of 5-methyl-1-propyl-1*H*-pyrazole-4-carbaldehyde oxime (**VIIc**) was determined by X-ray analysis. According to the X-ray diffraction data, the oxime group in **VIIc** has *anti* configuration (see figure).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury spectrometer at 300 MHz from solutions in DMSO-d_6–CCl_4 (1 : 3). The IR spectra were measured on a Specord 75-IR instrument from thin films.

X-Ray analysis of compound VIIc. The unit cell parameters were determined on an Enraf–Nonius CAD-4 automatic diffractometer at room temperature and were refined from diffraction angles of 22 reflections in the range $12 < \theta < 14°$; triclinic crystal system, space group P-1; a = 7.607(3), b = 8.971(2), c = 9.161(3) Å; α = 117.15(3), β = 108.35(3), γ = 96.16(3)°; V = 504.2(5) Å^3; Z = 2. Total of 3349 reflection intensities were measured in the range $0 \le h \le 10$, $-12 \le k \le 12$, $-12 \le l \le 12$, θ_{max} = 30° (MoK_α irradiation, graphite monochromator). All calculations were performed using SHELXTL software package [16]. After averaging symmetrically equivalent reflections array contains 2927 non-equivalent reflections (R_{int} = 0.012) of which 1891 observed with $I > 2\sigma(I)$.



Structure of the molecule of 5-methyl-1-propyl-1*H*-pyrazole-4-carbaldehyde oxime (**VIIc**) according to the X-ray diffraction data.

Table 2. Parameters of IR and ^{1}H NMR spectra of substituted pyrazoles **V**–**XII**

Comp. no.	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz)
	ring	C=N or C=N	
Va	1510	1620	2.90 s (3H, NCH_3), 7.19 s (1H, 5-H), 7.61 s (1H, 3-H), 8.18 s (1H, N=CH), 10.99 s (1H, OH)
Vc	1510	1640	0.91 t (3H, CH_2CH_3, J = 7.0), 1.95 q (2H, CH_2CH_3, J = 7.0, 7.4), 4.12 t (2H, NCH_2, J = 7.4), 7.18 s (1H, 5-H), 7.61 s (1H, 3-H), 8.18 s (1H, N=CH), 10.98 s (1H, OH)
VIb	1510	1630	1.39 t (3H, CH_2CH_3, J = 7.2), 2.21 s (3H, CH_3), 4.0 q (2H, CH_2CH_3, J = 7.2), 7.10 s (1H, 5-H), 8.20 s (1H, N=CH), 10.92 s (1H, OH)
VIc	1510	1640	0.91 t (3H, CH_2CH_3, J = 7.9), 1.85 q (2H, NCH_2, J = 7.4), 7.10 s (1H, 5-H), 8.08 s (1H, N=CH), 10.78 s (1H, OH)
VIIb	1520	1630	1.40 t (3H, CH_2CH_3, J = 7.2), 2.38 s (3H, 5-CH_3), 4.12 q (2H, CH_2CH_3, J = 7.2), 7.11 s (1H, 3-H_{Ar}), 8.12 s (1H, N=CH), 10.72 s (1H, OH)
VIIc	1520	1630	0.90 t (3H, CH_2CH_3, J = 7.9), 1.80 q (2H, CH_2CH_3, J = 7.4, 7.9), 2.37 s (3H, 5-CH_3), 4.12 q (2H, NCH_2, J = 7.4), 7.11 s (1H, 3-H_{Ar}), 8.01 s (1H, N=CH), 10.78 s (1H, OH)
VIIIa	1550	1640	2.10 s (3H, 3-CH_3), 2.35 s (3H, 5-CH_3), 3.61 s (2H, NCH_3), 7.89 s (1H, N=CH), 10.21 s (1H, OH)
VIIIb	1550	1610	1.38 t (3H, CH_2CH_3, J = 7.2), 2.2 s (3H, 3-CH_3), 2.32 s (5H, 5-CH_3), 4.0 q (2H, CH_2CH_3, J = 7.2), 7.90 s (1H, N=CH), 10.29 s (1H, OH)
VIIIc	1530	1670	0.90 t (3H, CH_2CH_3, J = 7.9), 1.80 q (2H, CH_2CH_3, J = 7.4, 7.9), 2.1 s (3H, 3-CH_3), 2.35 s (3H, 5-CH_3), 7.90 s (1H, N=CH), 10.21 s (1H, OH)
IXa	1520	2210	2.90 s (3H, NCH_3), 7.18 s (1H, 5-H), 7.60 s (1H, 3-H)
Xb	1530	2230	1.41 t (3H, CH_2CH_3, J = 7.2), 2.30 s (3H, 3-H_{Ar}), 4.10 q (2H, NCH_2, J = 7.2), 8.20 s (1H, 5-H)
IXc	1520	2200	0.91 t (3H, CH_2CH_3, J = 7.0), 1.95 q (2H, CH_2CH_3, J = 7.0, 7.4), 4.12 t (2H, NCH_2, J = 7.4), 7.18 s (1H, 5-H), 7.73 s (1H, 3-H)
XIb	1530	2230	1.40 t (3H, CH_2CH_3, J = 7.2), 2.42 s (3H, 5-CH_3), 4.10 q (2H, CH_2CH_3, J = 7.2), 7.61 s (3H, 3-H)
Xc	1530	2230	0.92 t (3H, CH_2CH_3, J = 7.9), 1.85 q (2H, CH_2CH_3, J = 7.4, 7.9), 2.31 s (3H, 3-CH_3), 8.20 s (1H, 5-H)
XIc	1530	2230	0.95 t (3H, CH_2CH_3, J = 7.9), 1.87 q (2H, CH_2CH_3, J = 7.4, 7.9), 2.41 s (3H, 5-CH_3), 4.22 q (2H, NCH_2, J = 7.4), 8.45 s (1H, 3-H)
XIIa	1550	2240	2.10 s (3H, 3-CH_3), 2.38 s (3H, 5-CH_3), 2.61 s (3H, NCH_3)
XIIb	1540	2230	0.95 t (3H, CH_2CH_3, J = 7.9), 4.95 q (2H, CH_2CH_3, J = 7.4, 7.9), 2.10 s (3H, 3-CH_3), 2.37 s (3H, 5-CH_3), 4.0 t (2H, NCH_2, J = 7.4)
XIIc	1530	2230	1.41 t (3H, CH_2CH_3, J = 7.2), 2.10 s (3H, 3-CH_3), 2.40 s (3H, 5-CH_3), 4.20 q (2H, CH_2CH_3, J = 7.2)

The structure was solved by the direct method, and the coordinates of hydrogen atoms were determined from the Fourier difference series. The structure was refined by the full-matrix least-squares procedure in anisotropic approximation for non-hydrogen atom and in isotropic approximation for hydrogen atoms; final discrepancy factor $R = 0.057$, goodness of fit $S = 1.037$.

General procedure for the synthesis of 1-alkyl-1*H*-pyrazole-4-carbaldehyde oximes V–VIII. A solution of 0.1 mol of potassium hydroxide in 25 ml of ethanol was added under stirring to a solution of 0.1 mol of hydroxylamine hydrochloride in 10 ml of water. The precipitate of potassium chloride was filtered off, a solution of 0.05 mol of aldehyde **I**–**IV** in 25 ml of ethanol was added to the filtrate, and the white crystals were filtered off and recrystallized from water containing a few drops of ethanol. The yields, physical constants, elemental analyses, and spectral parameters of compounds **V**–**VIII** are given in Tables 1 and 2.

General procedure for the synthesis of 1-alkyl-1*H*-pyrazole-4-carbonitriles IX–XII. A mixture of 0.05 mol of oxime **V**–**VIII** and 100 ml of acetic anhydride was heated for 1 h under reflux. Excess acetic anhydride was removed, the residue was neutralized with potassium carbonate and extracted with chloroform (3 × 50 ml), the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was distilled under reduced pressure. The yields, physical constants, elemental analyses, and spectral parameters of compounds **IX**–**XII** are given in Tables 1 and 2.

REFERENCES

1. Abele, E., Abele, R., and Lukevits, E., *Khim. Geterotsikl. Soedin*., 2004, no. 1, p. 3.
2. Ocskay, G. and Vazgha, L., *Tetrahedron*, 1958, vol. 2, nos. 1–2, p. 140.
3. Shapranova, N.I., Somin, I.N., and Kuznetsov, S.G., *Khim. Geterotsikl. Soedin*., 1973, no. 8, p. 1093.
4. Martirosyan, S.S., *Khim. Zh. Arm*., 2004, vol. 57, no. 3, p. 90.
5. Attaryan, O.S., Antanosyan, S.K., Kinoyan, F.S., Tamazyan, R.A., Panosyan, G.A., and Matsoyan, S.G., *Russ. J. Org. Chem*., 2006, vol. 42, no. 12, p. 1868.
6. Karabatsos, G.J. and Taller, R.A., *Tetrahedron*, 1968, vol. 24, no. 8, p. 3347.
7. Crepaux, D. and Lehn, J.M., *Mol. Phys*., 1968, vol. 14, no. 2, p. 547.
8. Kleinspehn, G.G., Jung, J.A., and Studniarz, S.A., *J. Org. Chem*., 1967, vol. 32, no. 2, p. 460.
9. Guette, J.P., Armand, J., and Lacombe, L., *C.R. Acad. Sci., Ser. C*, 1967, vol. 264, no. 17, p. 1509.
10. Burakevich, J.V., Lore, A.M., and Volp, G.P., *J. Org. Chem*., 1971, vol. 36, no. 1, p. 1.
11. Afonin, A.F., Ushakov, I.A., Tarasova, O.A., Shmidt, E.Yu., Mikhaleva, A.I., and Voronov, V.K., *Russ. J. Org. Chem*., 2000, vol. 36, no. 12, p. 1837.
12. Moiseev, I.K., Kalinina, M.I., Strelenko, Yu.A., and Khmel'nitskii, L.I., *Zh. Obshch. Khim*., 1988, vol. 58, no. 1, p. 203.
13. Hawkes, E., Herwing, K., and Roberts, D., *J. Org. Chem*., 1974, vol. 39, no. 8, p. 1017.
14. Del' Pina, M., Budilin, V.A., Radriges, M., and Bundel', Yu.G., *Khim. Geterotsikl. Soedin*., 1989, no. 2, p. 185.
15. *Osnovy stereokhimii* (Principles of Stereochemistry), Terent'ev, A.P. and Potapov, M.V., Eds., Moscow: Khimiya, 1964, p. 182.
16. Sheldrick, G.M., *SHELXS97 and SHELXL97. Program for the Refinement of Crystal Structure*, Göttingen (Germany): University of Göttingen, 1997.