Brief Communications

3-(1,1-Dialkyl-2-hydroxyethyl)-5-hydroxyamino-5-trifluoromethyl-Δ^2-isoxazolines: the first representatives of β-dioximes existing in the cyclic form

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It was demonstrated by X-ray diffraction analysis that the reaction of 3,3-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone with hydroxylamine afforded 5-hydroxyamino-3-(2-hydroxy-1,1-dimethylethyl)-5-trifluoromethyl-Δ^2-isoxazoline.

Key words: 3-(1,1-dialkyl-2-hydroxyethyl)-5-hydroxyamino-5-trifluoromethyl-Δ^2-isoxazolines, X-ray diffraction analysis.

The data on the syntheses of 5-amino- and 5-hydrazino-Δ^2-isoxazolines, unlike those concerning 5-hydroxy-Δ^2-isoxazolines,[1,2] are scarce. In the series of nonfluorinated compounds, 5-amino(hydrazino)-Δ^2-isoxazolines are prepared by reactions of amines or hydrazines with 5-hydroxy-3,5-dimethyl- or 3,4,4-trimethyl-5-methylene-Δ^2-isoxazolines[3,4] and by reactions of hydroxylamine with β-diimines.[5,6] The presence of the polyfluoroalkyl substituent along with the amino group at the C(5) atom of the Δ^2-isoxazoline system enhances the stability of these compounds due to the stabilizing effect of the fluorinated radical on ketals, aminoketals, and geminal aminoalcohols.[7] 5-Amino(methylamino)-5-polyfluoroalkyl-Δ^2-isoxazolines were prepared by the reactions of hydroxylamine with 3-amino-4,4,5,5-tetrafluoro-1-phenyl-2-penten-1-one[8] or 2-amino(methylamino)-5,5-dimethyl-2-trifluoromethyltetrahydro-4-pyrones.[9]

Up to now, it has been believed[10,11] that 5-hydroxyamino-Δ^2-isoxazolines, which can be considered as a cyclic form of dioximes of β-dicarbonyl compounds, can exist only in solutions. Moreover, it was noted[11] that β-dioximes, which do not contain the fluoroalkyl group, are characterized by a high tendency to retain the dioxime structure and the conversion into the cyclic 5-hydroxyamino-Δ^2-isoxazoline form can occur only if the sizes of

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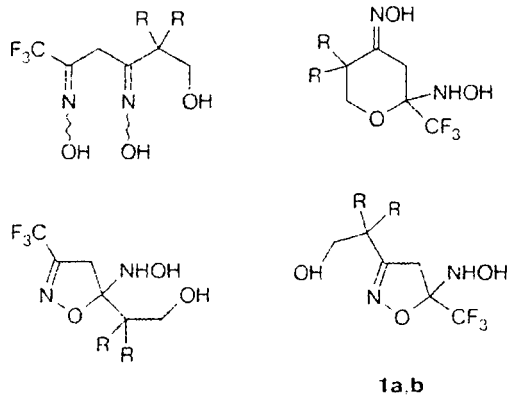
the terminal substituents are substantially different. Thus, the ring-chain tautomeric equilibrium is observed in solutions of dioximes of aroylacetones and aroylacetic anhydrides. This equilibrium is sensitive to the nature of the solvent. To the contrary, dioximes of symmetrical and unsymmetrical aliphatic and aromatic β-diketones containing terminal groups of similar sizes exist only in the dioxime form represented by a series of configurational isomers.[11,12]

Recently,[13] we have demonstrated that 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones react with two hydroxylamine molecules with elimination of one water molecule yielding products to which one of the four theoretically possible structures may be assigned:



1a,b

R = Me (**a**), R + R = $(CH_2)_5$ (**b**)

Based on the ^{1}H NMR spectra, it was established[13] that these compounds in deuterochloroform solutions exist as 5-hydroxyamino-5-trifluoromethyl-Δ^2-isoxazolines **1a,b**. In this solvent, no other structures corresponding to the ring-chain or ring-ring tautomerism were observed, unlike solutions of dioximes of β-dicarbonyl compounds[11] and 5-hydroxyamino-Δ^2-pyrazolines,[14] which do not contain a fluoroalkyl substituent. Taking into account the tendency of β-dioximes to retain the acyclic form in the crystalline state and the fact that functionalized Δ^2-isoxazolines **1a,b** (containing the NHOH at position 5 of the ring) were synthesized in such a manner for the first time, we studied the crystal structures of isoxazoline **1a** by X-ray diffraction analysis.

X-ray diffraction study demonstrated that there are two symmetrically independent molecules A and B in the crystal of compound **1a** (Fig. 1). Compound **1a** has an asymmetric center. The crystal consists of a racemic mixture of both enantiomers. Except for the CMe_2CH_2OH fragments, the conformations of the molecules A and B are identical and the positions of the atoms coincide to within 0.05 Å. The heterocycles are planar (the average deviations from the mean planes are smaller than 0.02(2) Å). The C(5) and C(13) atoms lie in the planes of the corresponding heterocycles.

The molecule A is disordered over two positions (A_1 and A_2) with the occupancies of 0.6 and 0.4, respectively. The molecules A_1 and A_2 differ in the orientation of the 2-hydroxy-1,1-dimethylethyl group, *i.e.*, the molecule A can be considered as a superposition of two conformers (A_1 and A_2) in an approximate ratio of 1 : 1. The molecule B represents the third conformational type in which the orientation of the CMe_2CH_2OH group with respect to the heterocycle differs from those observed in the molecules A_1 and A_2.

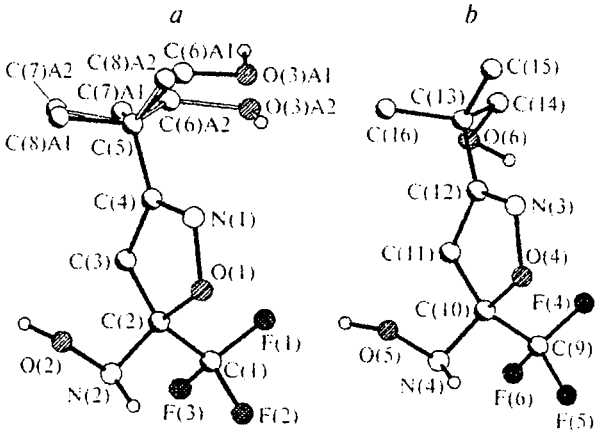


Fig. 1. Overall view of the symmetrically independent molecules A and B of compound **1a** in the crystal: *a*, A_1 and A_2; *b*, B. The hydrogen atoms of the CH_2 and Me groups are omitted. For simplicity of comparison of the conformations, the *S* enantiomers of both the B and A molecules are shown.

The orientations of the 2-hydroxy-1,1-dimethylethyl groups in the molecules A_1, A_2, and B are shown in Fig. 2. In the molecules A_1 and A_2, these groups differ in the rotation about the C(4)—C(5) bond (by approximately 76°) and in the rotation of the OH groups (by 37(1)°). The positions of the C(5), C(6(A_2)), C(7(A_2)), and C(8(A_2)) atoms in the molecule A_2 and the C(13), C(14), C(16), and C(15) atoms in the molecule B are virtually identical, whereas the C(6(A_2))—O(3(A_2)) and C(14)—O(6) bonds are rotated by 114(2)° with respect to each other. In the molecule A_1, the fragment containing

Table 1. Selected bond lengths (*d*) in compound **1a**

Bond	*d*/Å	Bond	*d*/Å
C(1)—F(2)	1.312(11)	C(5)—C(8(A_2))	1.569(9)
C(1)—F(3)	1.316(12)	C(5)—C(7(A_1))	1.571(9)
C(1)—F(1)	1.365(11)	C(6(A_1))—O(3(A_1))	1.35(2)
C(1)—C(2)	1.487(13)	C(6(A_2))—O(3(A_2))	1.51(3)
C(2)—N(2)	1.440(9)	N(1)—O(1)	1.407(8)
C(2)—O(1)	1.470(9)	N(2)—O(2)	1.410(8)
C(2)—C(3)	1.526(11)	C(12)—C(13)	1.482(10)
C(3)—C(4)	1.515(11)	C(13)—C(14)	1.503(11)
C(4)—N(1)	1.270(10)	C(13)—C(16)	1.546(10)
C(4)—C(5)	1.500(11)	C(13)—C(15)	1.559(10)
C(5)—C(6(A_1))	1.44(2)	C(14)—O(6)	1.439(10)
C(5)—C(6(A_2))	1.50(3)	N(3)—O(4)	1.422(8)
C(5)—C(7(A_2))	1.530(10)	N(4)—O(5)	1.442(8)
C(5)—C(8(A_1))	1.546(9)		

Table 2. Selected bond angles (ω) and torsion angles (φ) in compound **1a**

Bond angle	ω/deg	Bond angle	ω/deg	Bond angle	ω/deg
F(2)—C(1)—F(1)	104.9(8)	N(1)—C(4)—C(5)	122.1(7)	C(7(A$_1$))—C(5)—C(8(A$_1$))	101.3(9)
F(1)—C(1)—C(2)	111.3(8)	N(1)—C(4)—C(3)	113.0(7)	C(5)—C(6(A$_1$))—O(3(A$_1$))	114.9(12)
N(2)—C(2)—O(1)	111.6(6)	C(5)—C(4)—C(3)	124.8(7)	C(5)—C(6(A$_2$))—O(3(A$_2$))	114(2)
N(2)—C(2)—C(1)	105.3(6)	C(4)—C(5)—C(6(A$_1$))	115.5(8)	C(4)—N(1)—O(1)	111.4(7)
O(1)—C(2)—C(1)	105.8(7)	C(4)—C(5)—C(6(A$_2$))	107.3(12)	O(2)—N(2)—C(2)	110.3(6)
N(2)—C(2)—C(3)	115.1(6)	C(4)—C(5)—C(7(A$_1$))	108.8(8)	N(1)—O(1)—C(2)	108.9(5)
O(1)—C(2)—C(3)	105.1(6)	C(4)—C(5)—C(7(A$_2$))	115.8(12)	C(12)—C(13)—C(14)	110.9(6)
C(1)—C(2)—C(3)	113.7(7)	C(6(A$_1$))—C(5)—C(7(A$_1$))	107.7(10)	C(14)—C(13)—C(15)	106.3(6)
C(4)—C(3)—C(2)	101.5(6)	C(6(A$_2$))—C(5)—C(7(A$_2$))	110(2)	O(6)—C(14)—C(13)	112.4(6)

Torsion angle	φ/deg	Torsion angle	φ/deg	Torsion angle	φ/deg
F(3)—C(1)—C(2)—O(1)	−175.3(7)	N(1)—C(4)—C(5)—C(6(A$_1$))	26(1)	C(4)—C(5)—C(6(A$_1$))—O(3(A$_1$))	65(1)
F(6)—C(9)—C(10)—O(4)	173.2(6)	N(1)—C(4)—C(5)—C(6(A$_2$))	108(1)	C(4)—C(5)—C(6(A$_2$))—O(3(A$_2$))	−57(2)
O(1)—C(2)—N(2)—O(2)	66.3(7)	N(3)—C(12)—C(13)—C(14)	−110.4(7)	C(12)—C(13)—C(14)—O(6)	−67.5(8)
O(4)—C(10)—N(4)—O(5)	−63.4(7)				

the C(5), C(6(A$_1$)), C(7(A$_1$)), and C(8(A$_1$)) atoms is rotated with respect to the analogous fragments in the molecules A$_2$ and B, on the average, by 31°. Therefore, the crystal structure of **1a** contains three conformers, *viz.*, A$_1$, A$_2$, and B, in a ratio of approximately 1 : 1 : 2. These conformers differ only by the orientation of the CMe_2CH_2OH groups. The selected bond lengths, bond angles, and torsion angles characterizing the conformations of the molecules A$_1$, A$_2$, and B are given in Tables 1 and 2.

The molecular packing of compound **1a** in the crystal can be described as consisting of bulky molecular layers parallel to the crystallographic plane (001). All potential acceptor and donor groups (except for the cyclic oxygen atoms) are involved in a branched system of intermolecular hydrogen bonds[15] (Table 3).

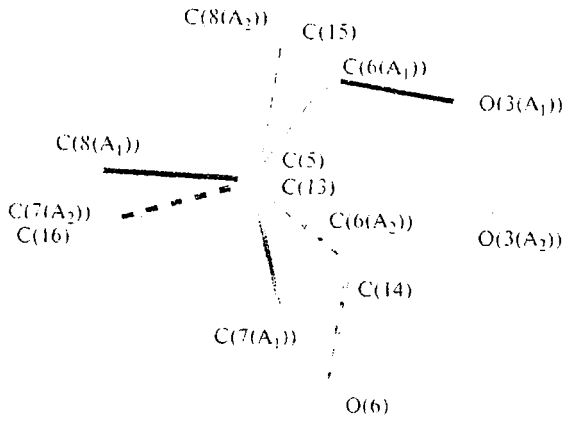


Fig. 2. Mutual orientation of the CMe_2CH_2OH groups in the symmetrically independent molecules: the projections along the C(4)—C(5) (for the molecules A$_1$ and A$_2$) and C(12)—C(13) bonds (for the molecule B). The positions of the C(7(A$_2$)) and C(16) atoms and the positions of the C(5) and C(13) atoms coincide. The hydrogen atoms are omitted.

Table 3. Parameters of the hydrogen bonds (*d*/Å and ω/deg) in the crystal of compound **1a**

D—H...A	*d*(D—H)	*d*(H...A)	*d*(D...A)	ω(DHA)
O(2)—H(2O)...N(3)#1	0.97	2.01	2.836(7)	141(11)
O(5)—H(5O)...N(1)	0.97	1.92	2.801(8)	149(8)
O(6)—H(6O)...O(3(A$_1$))#2	0.97	2.01(6)	2.92(1)	157(13)
O(6)—H(6O)...O(3(A$_2$))#2	0.97	1.92(7)	2.82(1)	154(13)
N(2)—H(2N)...O(5)#3	0.90	2.26(8)	3.05(1)	148(11)
N(4)—H(4N)...O(2)#4	0.87	2.21(4)	3.07(1)	170(5)

Note. Symmetry transformations used for generation of the equivalent atoms: #1 1+*x*, *y*, *z*; #2 −*x*, −*y*, 1−*z*; #3 0.5−*x*, 0.5+*y*, 1.5−*z*; #4 0.5−*x*, −0.5+*y*, 1.5−*z*.

To summarize, X-ray diffraction study demonstrated that the structure of compound **1a** in the crystalline state is identical to that in solutions. Apparently, the presence of the CF_3 group at one of the oxime carbon atoms in β-dioximes affects considerably the structures of these compounds and, as a result, they can exist only in the cyclic isoxazoline form.

Experimental

Isoxazolines **1a,b** have been described previously.[13]

The crystals of compound **1a** ($C_8H_{13}F_3N_2O_3$) are monoclinic. At 300 K, a = 10.792(4), b = 9.654(2), c = 20.743(3) Å, β = 95.85(2)°, V = 2149.9(10) Å^3, d_{calc} = 1.497 g cm^{-3}, the absorption coefficient μ = 0.15 mm^{-1}, space group $P2_1/n$, Z = 8. The intensities of 2632 independent reflections (R_{int} = 0.05) were measured on an automated four-circle CAD-4 diffractometer (Mo-Kα radiation, λ 0.71093 Å, graphite monochromator, $\theta/(^5/_3\theta)$ scanning technique, $2\theta_{max}$ = 44°).

The structure was solved by the direct method with the use of the SHELXTL PLUS 4.2 and SHELXTL PLUS 5.0 program packages.[16,17] The nonhydrogen atoms were refined anisotropically by the full-matrix least-squares method (based on F_o^2) to R_1 = 0.098, wR_2 = 0.22, GOOF = 1.119. The atoms of the 2-hydroxy-1,1-dimethylethyl fragments are disordered over two positions with the occupancies of 0.6 (the C(6(A$_1$)),

C(7(A$_1$)), C(8(A$_1$)), and O(3(A$_1$)) atoms) and 0.4 (the C(6(A$_2$)), C(7(A$_2$)), C(8(A$_2$)), and O(3(A$_2$)) atoms). In the course of the refinement, the bonds between the C(5) atom and the carbon atoms of the methyl groups (C(7(A$_1$)), C(8(A$_1$)), C(7(A$_2$)), and C(8(A$_2$))) were fixed (1.54(1) Å). The positions of the hydrogen atoms bound to the carbon atoms were calculated geometrically and included in the refinement using the riding model with fixed C—H distances (0.97 Å) and with the isotropic displacement parameters $U_{iso} = 1.5U_{eq}$ for the methyl groups and $U_{iso} = 1.2U_{eq}$ for the remaining atoms (U_{eq} are equivalent isotropic displacement parameters of the corresponding C atoms). The positions of the H(N(2)), H(N(4)), H(O(2)), H(O(3)), and H(O(6)) atoms were revealed from the difference Fourier synthesis and refined using restrictions imposed on the N—H and O—H bonds (0.90(5) Å and 0.97(1) Å, respectively).

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References

1. R. Escale, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.*, 1974, 725.
2. C. Massyn and A. Cambon, *J. Fluor. Chem.*, 1975, **5**, 67.
3. K. N. Zelenin and A. Yu. Ershov, *Khim. Geterotsikl. Soedin.*, 1990, 1385 [*Chem. Heterocycl. Compd.*, 1990 (Engl. Transl.)].
4. K. N. Zelenin, A. Yu. Ershov, I. P. Bezhan, V. A. Khrustalev, and S. I. Yakimovich, *Khim. Geterotsikl. Soedin.*, 1985, 855 [*Chem. Heterocycl. Compd.*, 1985 (Engl. Transl.)].
5. J. Barluenga, J. Jardon, V. Rubio, and V. Gotor, *J. Org. Chem.*, 1983, **48**, 1379.
6. J. Barluenga, J. Jardón, and V. Gotor, *J. Chem. Res. (S)*, 1986, **6**, 5218.
7. A. V. Fokin, A. F. Kolomiets, and N. V. Vasil'ev, *Usp. Khim.*, 1984, **53**, 398 [*Russ. Chem. Rev.*, 1984, **53** (Engl. Transl.)].
8. O. A. Kuznetsova, V. I. Filyakova, and K. I. Pashkevich, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1306 [*Russ. Chem. Bull.*, 1996, **45**, 1245 (Engl. Transl.)].
9. V. Ya. Sosnovskikh, M. Yu. Mel'nikov, and A. V. Zaitsev, *Mendeleev Commun.*, 1999, 40.
10. V. Szabó, J. Borrély, E. Theisz, J. Borda, and G. Janzsó, *Tetrahedron*, 1984, **40**, 413.
11. A. Yu. Ershov, S. I. Yakimovich, K. N. Zelenin, and I. V. Zerova, *Zh. Org. Khim.*, 1988, **24**, 2287 [*J. Org. Chem. USSR*, 1988, **24** (Engl. Transl.)].
12. L. G. Grishko, V. P. Khilya, M. F. Sedyuko, and D. Litkei, *Ukr. Khim. Zh.* [*Ukr. Chem. J.*], 1985, **51**, 211 (in Russian).
13. V. Ya. Sosnovskikh, M. Yu. Mel'nikov, and S. A. Pogozhikh, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1334 [*Russ. Chem. Bull.*, 1999, **48**, 1323 (Engl. Transl.)].
14. K. N. Zelenin, A. Yu. Ershov, M. Yu. Malov, and S. I. Yakimovich, *Dokl. Akad. Nauk SSSR*, 1986, **289**, 1132 [*Dokl. Chem.*, 1986 (Engl. Transl.)].
15. Yu. V. Zefirov and P. M. Zorkii, *Usp. Khim.*, 1995, **64**, 446 [*Russ. Chem. Rev.*, 1995, **64** (Engl. Transl.)].
16. G. M. Sheldrick, *SHELXTL Plus*, Release 4.2, Siemens Analytical Instruments Inc., Madison, Wisconsin, USA, 1991.
17. G. M. Sheldrick, *SHELXTL Plus*, Release 5.0, Siemens Analytical Instruments Inc., Madison, Wisconsin, USA, 1994.

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