Synthesis of annelated derivatives of tetrafluoro-10*H*-imidazo[1,2-*b*][1,2]benzooxazin-10-one and 2-pentafluorophenylpyrazine 1,4-dioxide by condensation of alicyclic 2-hydroxyamino oximes with pentafluorophenylglyoxal

S. A. Amitina, I. V. El´tsov, T. V. Rybalova, Yu. V. Gatilov, and I. A. Grigor´ev*

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9 prosp. Akad. Lavrent´eva, 630090 Novosibirsk, Russian Federation. Fax: +7 (383 2) 34 4752. E-mail: eiv@nioch.nsc.ru

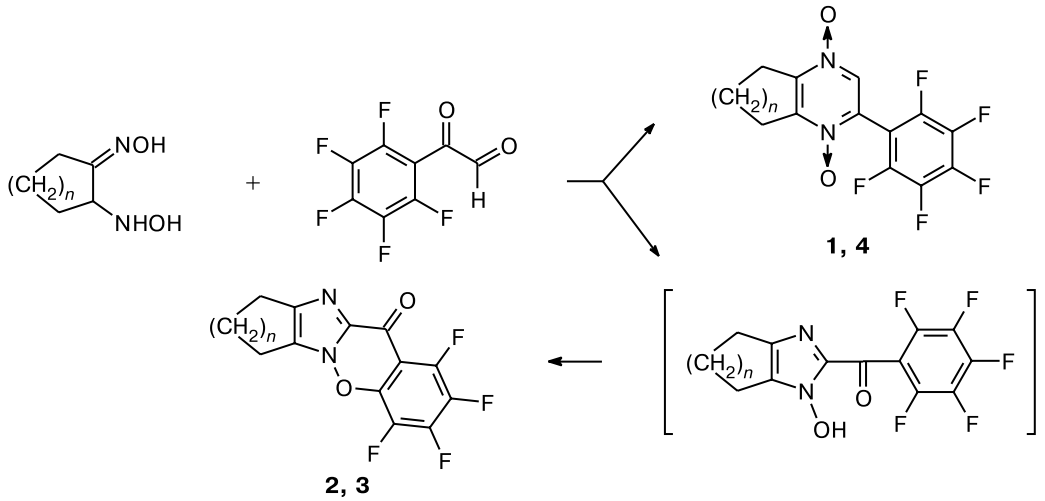
Reactions of alicyclic 2-hydroxyamino oximes with pentafluorophenylglyoxal afford mixtures of annelated derivatives of 2-pentafluorophenylpyrazine 1,4-dioxide and tetrafluoro-10*H*-imidazo[1,2-*b*][1,2]benzooxazin-10-one. The structures of the latter were established by X-ray diffraction analysis.

Key words: tetrafluoro-10*H*-imidazo[1,2-*b*][1,2]benzooxazin-10-one, 2-hydroxyamino oximes, pentafluorophenylpyrazine 1,4-dioxides, X-ray diffraction analysis.

Earlier, it has been found that alicyclic 2-hydroxyamino oximes react with arylglyoxals to form mixtures of annelated derivatives of 1-hydroxyimidazole and pyrazine 1,4-dioxide.[1] In the present study, we demonstrated that heating of 2-hydroxyaminocyclohexanone oxime hydroacetate with pentafluorophenylglyoxal hydrate[2] afforded a mixture of 2-pentafluorophenyl-5,6,7,8-tetrahydroquinoxaline 1,4-dioxide (**1**) and 6,7,8,9-tetrafluoro-1,2,3,4-tetrahydro-5-oxa-4b,11-diazabenzo[*b*]fluoren-10-one (**2**) in 18 and 26% yields, respectively (Scheme 1).

The IR spectrum of compound **2** shows a band at 1685 cm^{-1} belonging to the carbonyl group conjugated with the tetrafluorophenylene ring. In the ^1H NMR spectrum, a signal of the hydroxy group at δ 10—12 is absent. The ^{19}F NMR spectrum has four signals for the F atoms characteristic of the *o*-disubstituted tetrafluorophenylene ring. Presumably, tetrafluorotetrahydrooxadiazabenzofluorenone **2** results from cyclization of intermediate 1-hydroxy-2-pentafluorobenzoyl-4,5,6,7-tetrahydrobenzoimidazole with elimination of HF.

Scheme 1



n = 2 (**1**, **2**), 3 (**3**, **4**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1636—1639, August, 2004.

Table 1. ^{1}H and ^{19}F NMR spectra of compounds **1—4**

Compound	δ	
	^{1}H	^{19}F (m)
1	1.90 (m, 4 H, C(6)H_2, C(7)H_2); 2.92 (m, 4 H, C(5)H_2, C(8)H_2); 8.12 (s, 1 H, C(3)H)	1.7 (2 F, F(3′), F(5′)); 13.4 (1 F, F(4′)); 25.6 (2 F, F(2′), F(6′))
2	1.91 (m, 4 H, C(2)H_2, C(3)H_2); 2.75 (m, 2 H, C(1)H_2); 2.85 (m, 2 H, C(4)H_2)	2.1 (1 F, F(8)); 3.8 (1 F, F(6)); 16.8 (1 F, F(7)); 22.5 (1 F, F(9))
3	1.80 (m, 6 H, C(7)H_2, C(8)H_2, C(9)H_2); 2.93 (m, 4 H, C(6)H_2, C(10)H_2)	2.1 (1 F, F(2)); 3.7 (1 F, F(4)); 16.7 (1 F, F(3)); 22.5 (1 F, F(1))
4	1.84 (m, 6 H, C(6)H_2, C(7)H_2, C(8)H_2); 3.30 (m, 4 H, C(5)H_2, C(9)H_2); 8.07 (s, 1 H, C(3)H)	1.7 (2 F, F(3′), F(5′)); 13.2 (1 F, F(4′)); 25.6 (2 F, F(2′), F(6′))

The reaction of 2-hydroxyaminocycloheptanone oxime hydroacetate with pentafluorophenylglyoxal hydrate on heating in MeOH produced 1,2,3,4-tetrafluoro-7,8,9,10-tetrahydro-6*H*-5-oxa-5a,11-diazanaphtho[2,3-*a*]azulen-12-one (**3**) in 30% yield. The yield of 2-pentafluorophenyl-6,7,8,9-tetrahydro-5*H*-cycloheptapyrazine 1,4-dioxide (**4**) was ~1%.

Therefore, the reactions of alicyclic 2-hydroxyamino oximes with pentafluorophenylglyoxal, unlike those with phenylglyoxal, afforded mixtures of annelated derivatives of oxazinone and pyrazine 1,4-dioxide. This difference in the behavior is attributable to the ability of polyfluoroaromatic compounds to undergo nucleophilic substitution in acidic and weakly acidic media. Earlier, ethyl (hydroxyimino)pentafluorobenzoylacetate and 1-phenyl-2-pentafluorophenylglyoxal 2-*syn*-oxime have been demonstrated to undergo intramolecular cyclization giving rise to the corresponding substituted tetrafluoro-1,2-benzooxazin-4-ones.[3,4]

The ^{1}H and ^{19}F NMR spectra of the compounds synthesized are given in Table 1. The assignment of the signals in the ^{19}F NMR spectra is based on the known analogy.[5]

The structures of compounds **2** and **3** established by X-ray diffraction study are shown in Figs 1, *a* and *b*, respectively. The bond lengths (Table 2) and bond angles

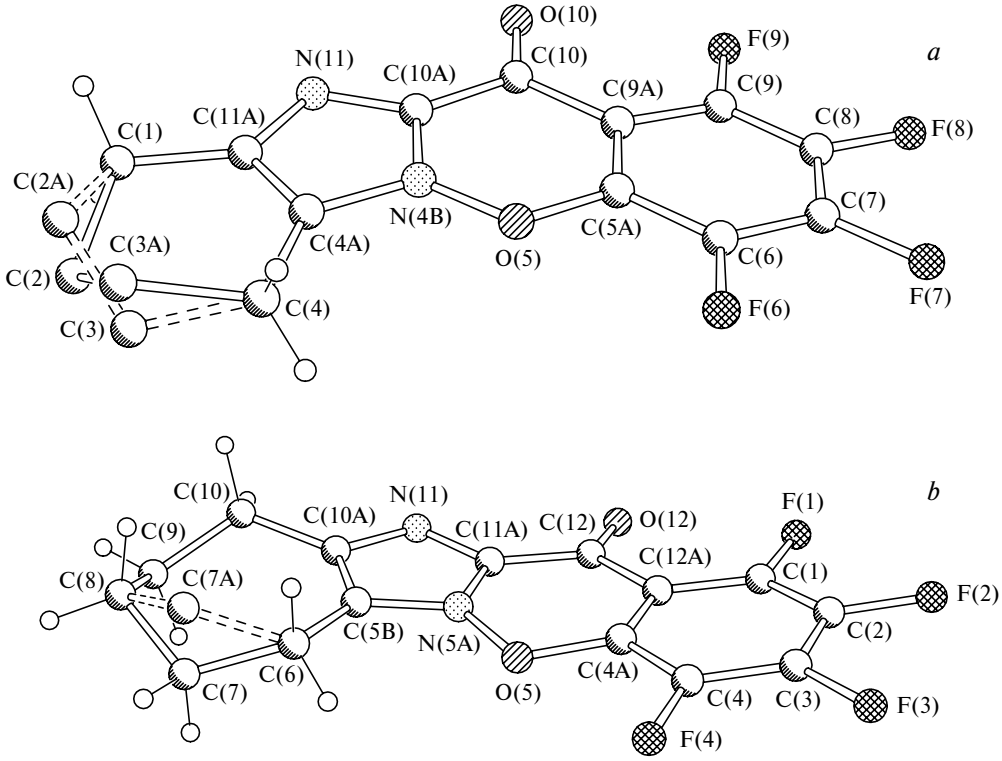


Fig. 1. Structures of molecules **2** (*a*) and **3** (*b*) established by X-ray diffraction analysis. The H atoms in the disordered fragments of the molecules are omitted.

Table 2. Selected bond lengths (*d*) in molecules **2** and **3** based on X-ray diffraction data

Bond	*d*/Å	Bond	*d*/Å
Molecule **2**		Molecule **3**	
N(4B)—C(10A)	1.359(4)	N(5A)—C(11A)	1.360(3)
N(4B)—C(4A)	1.371(4)	N(5A)—C(5B)	1.366(3)
N(4B)—O(5)	1.382(3)	O(5)—N(5A)	1.386(2)
C(4A)—C(11A)	1.383(5)	C(5B)—C(10A)	1.380(4)
O(5)—C(5A)	1.381(4)	C(4A)—O(5)	1.379(3)
C(5A)—C(9A)	1.380(5)	C(4A)—C(12A)	1.387(4)
C(5A)—C(6)	1.392(5)	C(4)—C(4A)	1.385(4)
C(6)—C(7)	1.381(5)	C(3)—C(4)	1.372(4)
C(7)—C(8)	1.366(5)	C(2)—C(3)	1.370(4)
F(8)—C(8)	1.357(4)	F(2)—C(2)	1.349(3)
C(8)—C(9)	1.361(5)	C(1)—C(2)	1.364(4)
C(9A)—C(9)	1.412(5)	C(1)—C(12A)	1.396(4)
C(9A)—C(10)	1.487(5)	C(12A)—C(12)	1.480(4)
O(10)—C(10)	1.220(4)	O(12)—C(12)	1.219(3)
C(10)—C(10A)	1.451(5)	C(11A)—C(12)	1.450(4)
C(10A)—N(11)	1.328(4)	C(11A)—N(11)	1.319(3)
N(11)—C(11A)	1.363(5)	C(10A)—N(11)	1.366(4)

in the oxadiazabenzoindene fragment in molecule **2** are identical to the corresponding values in molecule **3** within the experimental error (3σ).

This fragment in compounds **2** and **3** is planar within ±0.097 and ±0.167 Å, respectively. However, more detailed analysis demonstrated that the oxadiazabenzoindene fragment is folded along the O(5)—C(10) line by 6.0(1)° in **2** and along the O(5)—C(12) line by 10.2(1)° in **3**. For comparison, the analogous folding angle in 1,2,8-trimethoxy-9*H*-xanthen-9-one[6] is 9.3°. We found no data on the oxadiazabenzoindene fragment in the Cambridge Structural Database.[7] 9-Oxa-1,2,9a-triazacyclopenta[*b*]naphthalen-4-one can be considered as the closest analog of the compounds under study.[8] In this compound, the bond lengths are similar to those in the identical fragments in molecules **2** and **3** (taking into account the F atoms). It should be noted that the saturated carbocycles are partially disordered in a ratio of 0.65(3) : 0.35(3) in **2** and 0.94(1) : 0.06(1) in **3** (see Fig. 1). This fact can be interpreted as the presence of two conformations in the crystals, *viz.*, mirror forms of a half-chair in **2** and chair—distorted boat conformations in **3**.

Experimental

The IR spectra were recorded on a Bruker Vector 22 instrument in KBr pellets. The ^{1}H and ^{19}F NMR spectra for 5% solutions in $CDCl_3$ were measured on a Bruker WP-200SY spectrometer (200.13 MHz for ^{1}H and 188.28 MHz for ^{19}F). The signals for the residual proton of the solvent (δ_H 7.24) and hexafluorobenzene (δ_F 0.00) were used as the internal standard. The high-resolution mass spectrum of compound **4** was obtained on a Bruker Finnigan MAT 8200 instrument. The molecular weights of compounds **2** and **3** were determined by vapor-phase osmometry on a Knauer instrument. The UV spectra were recorded on an HP 8453 instrument.

Pentafluorophenylglyoxal hydrate was prepared by oxidation of pentafluoroacetophenone with SeO_2.[2] The starting 2-hydroxyaminocyclohexanone and -cycloheptanone oximes were synthesized according to a known procedure.[9]

2-Pentafluorophenyl-5,6,7,8-tetrahydroquinoxaline 1,4-dioxide (1) and 6,7,8,9-tetrafluoro-1,2,3,4-tetrahydro-5-oxa-4b,11-diazabenzo[*b*]fluoren-10-one (2). A mixture of 2-hydroxyaminocyclohexanone oxime hydroacetate (1.62 g, 8 mmol) and pentafluorophenylglyoxal hydrate (1.9 g, 8 mmol) in MeOH (20 mL) was heated until complete dissolution and then kept at 20 °C for one day. The precipitate of compound **2** that formed was filtered off, washed with MeOH, and crystallized from MeOH. The yield was 0.7 g (26%), m.p. 165 °C (decomp.). Found (%): C, 54.0; H, 2.5; F, 24.4; N, 9.1. $C_{14}H_8F_4N_2O_2$. Calculated (%): C, 53.7; H, 2.6; F, 24.3; N, 9.1. Molecular weight, found: 311. Calculated: M = 312. UV (EtOH), λ_{max}/nm (logε): 212 (4.30); 241 (4.01); 330 (4.12). IR, ν/cm^{-1}: 1685 (C=O); 1652 (C=O).

After separation of compound **2**, the solution was concentrated. The dark residue was dissolved in $CHCl_3$, washed with 3% HCl to remove 2-hydroxyaminocyclohexanone oxime and then with water, and dried with Na_2SO_4. The solution was concentrated and silica gel column chromatography (*tert*-butyl methyl ether as the eluent) of the residue afforded compound **1** in a yield of 0.4 g (18%), m.p. 162 °C (decomp.). Found (%): C, 50.3; H, 2.9; F, 28.6; N, 8.2. $C_{14}H_9F_5N_2O_2$. Calculated (%): C, 50.5; H, 2.7; F, 28.4; N, 8.4. IR, ν/cm^{-1}: 1500 (C_6F_5).

1,2,3,4-Tetrafluoro-7,8,9,10-tetrahydro-6*H*-5-oxa-5a,11-diazanaphtho[2,3-*a*]azulen-12-one (3) and 2-pentafluorophenyl-5,6,7,8-tetrahydro-5*H*-cycloheptapyrazine 1,4-dioxide (4). A mixture of 2-hydroxyaminocycloheptanone oxime hydroacetate (1.53 g, 7 mmol) and pentafluorophenylglyoxal hydrate (1.7 g, 7 mmol) in MeOH (20 mL) was heated until complete dissolution and then kept at 20 °C for one day. The solvent was evaporated and the residue was dissolved in $CHCl_3$. The solution was washed with 3% HCl to remove 2-hydroxyaminocycloheptanone oxime and then with water and dried with Na_2SO_4. The solution was concentrated and silica gel column chromatography ($CHCl_3$ as the eluent) of the residue afforded azulenone **3** in a yield of 0.6 g (30%). Elution with *tert*-butyl methyl ether gave pyrazine dioxide **4** in a yield of 0.03 g (~1%). Compound **3**: m.p. 190 °C (decomp.). Found (%): C, 55.4; H, 3.5; F, 23.1; N, 8.3. $C_{15}H_{10}F_4N_2O_2$. Calculated (%): C, 55.2; H, 3.7; F, 23.3; N, 8.6. Molecular weight, found: 325. Calculated: M = 326. UV (EtOH), λ_{max}/nm (logε): 212 (4.32), 245 (4.16), 329 (4.06). IR, ν/cm^{-1}: 1682 (C=O), 1653 (C=O). Compound **4**: m.p. 139 °C (decomp.). IR, ν/cm^{-1}: 1500 (C_6F_5). High-resolution mass spectrum, found: *m*/*z* 346.0741 [M]$^+$. Calculated: M = 346.0741.

X-ray diffraction study. The unit cell parameters and intensities of reflections were measured on a Bruker P4 diffractometer at 23 °C (Mo-Kα radiation, graphite monochromator, θ/2θ scanning technique at 2θ < 50°). The structures were solved by direct methods using the SIR2002 program[10] and refined by the least-

squares method with anisotropic and isotropic thermal parameters for nonhydrogen and H atoms, respectively, using the SHELXL-97 program package.[11] The positions of the H atoms were revealed from difference electron density maps. The positions of the atoms in the disordered fragments of the molecules were calculated geometrically.

Single crystals of **2** suitable for X-ray diffraction study were grown from a 2 : 1 benzene—$CHCl_3$ mixture by slow evaporation of the solvent. The crystals of compound **2** are monoclinic: $a = 25.274(4)$ Å, $b = 6.318(1)$ Å, $c = 15.480(4)$ Å, $\beta = 91.43(1)°$, $V = 2471.3(9)$ Å^3, space group $C2/c$, $C_{14}H_8F_4N_2O_2$, M = 312.22, $Z = 8$, $d_{calc} = 1.678$ g cm^{-3}, $\mu = 0.154$ mm^{-1}, a needle crystal with dimensions 0.06×0.09×1.5 mm. The intensities of 2149 independent reflections were measured. Absorption was ignored. The final parameters of the refinement were as follows: $wR_2 = 0.2019$, $S = 1.018$ for all reflections ($R = 0.0547$ for 1272 reflections with $I > 2\sigma$).

Single crystals of **3** suitable for X-ray diffraction analysis were grown from a 2 : 1 AcOEt—$CHCl_3$ mixture by slow evaporation of the solvent. The crystals of compound **3** are monoclinic: $a = 15.566(9)$ Å, $b = 6.186(4)$ Å, $c = 15.622(10)$ Å, $\beta = 117.54(2)°$, $V = 1333.7(14)$ Å^3, space group $P2_1/n$, $C_{15}H_{10}F_4N_2O_2$, M = 326.25, $Z = 4$, $d_{calc} = 1.625$ g cm^{-3}, $\mu = 0.147$ mm^{-1}, a platelet crystal with dimensions 0.06×0.14×1.2 mm. The intensities of 2334 independent reflections were measured. The absorption correction was applied by integration based on the crystal shape. The final parameters of the refinement were as follows: $wR_2 = 0.1395$, $S = 1.035$ for all reflections ($R = 0.0435$ for 1440 reflections with $I > 2\sigma$).

We thank the Russian Foundation for Basic Research for paying for the license for the Cambridge Structural Database (Project No. 02-07-90322). This study was financially supported by the STN Center at the N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry of the Siberian Branch of the Russian Academy of Sciences (Grant No. 00-03-40142).

References

1. L. N. Grigor´eva, S. A. Amitina, and L. B. Volodarskii, *Khim. Geterotsikl. Soedin.*, 1983, 1387 [*Chem. Heterocycl. Compd.*, 1983, **19** (Engl. Transl.)].
2. K. C. Joshi, V. N. Patar, and M. K. Goyal, *J. Heterocycl. Chem. (India)*, 1981, **18**, 1651; *Chem. Abstr.*, 1982, **96**, 181199.
3. G. S. Shchegoleva, I. S. Isaev, T. F. Ardyukova, and V. A. Barkhash, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.* [*Bull. Sib. Branch Acad. Sci. USSR, Div. Chem. Sci.*], 1971, Issue 2, 90 (in Russian).
4. G. S. Shchegoleva, E. D. Krivousova, and V. A. Barkhash, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.* [*Bull. Sib. Branch Acad. Sci. USSR, Div. Chem. Sci.*], 1971, Issue 2, 95 (in Russian).
5. L. N. Pushkina, A. P. Stepanov, V. S. Zhukov, and A. D. Naumov, *Zh. Org. Khim.*, 1972, **8**, 586 [*J. Org. Chem. USSR*, 1972, **8** (Engl. Transl.)].
6. L. Gales, M. E. de Sousa, M. M. M. Pinto, A. Kijjoa, and A. M. Damas, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2001, **57**, 1319.
7. F. H. Allen, *Acta Crystallogr., Sect. B*, 2002, **58**, 380 (Version 5.24).
8. J. L. Kristensen, P. Vedso, and M. Begtrup, *Tetrahedron*, 2002, **58**, 2397.
9. L. N. Grigor´eva, L. B. Volodarskii, and A. Ya. Tikhonov, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim.* [*Bull. Sib. Branch Acad. Sci. USSR, Div. Chem. Sci.*], 1989, Issue 3, 125 (in Russian).
10. M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, and R. Spagna, *J. Appl. Crystallogr.*, 2003, **36**, 1103.
11. G. M. Sheldrick, *SHELXL-97*, University of Göttingen, Göttingen (Germany), 1997.

Received March 31, 2004;
in revised form June 24, 2004