Unexpected isomerization in the series of fluorine-containing 2,3-dihydro-1*H*-1,4-diazepines with a 2-aminoethyl group at one of the nitrogen atoms

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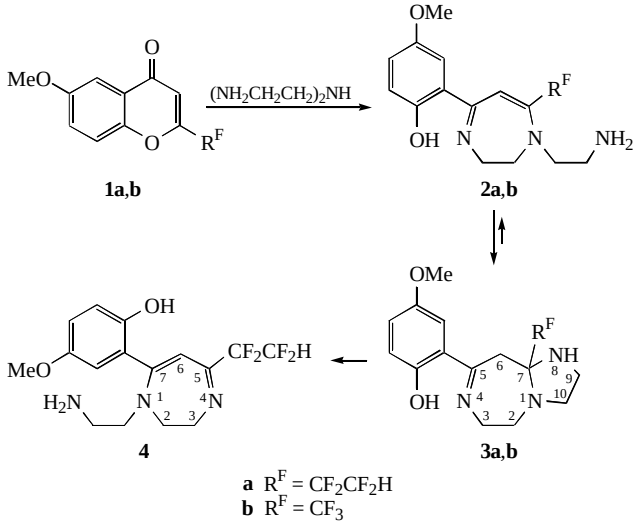
Under kinetic control conditions, 6-methoxy-2-(1,1,2,2-tetrafluoroethyl)chromone reacts with diethylenetriamine to form 5-(2-hydroxy-5-methoxyphenyl)-7-(1,1,2,2-tetrafluoroethyl)-1,4,8-triazabicyclo[5.3.0]dec-4-ene, and the latter undergoes isomerization to the title compound, which is more thermodynamically stable.

Previously,[1] we described the reaction between 2-polyfluoroalkylchromones and diethylenetriamine with the formation of a 1,4,8-triazabicyclo[5.3.0]dec-4-ene system, which can be considered as the cyclic form of 2,3-dihydro-1*H*-1,4-diazepines with a 2-aminoethyl group at the nitrogen atom nearest to the polyfluoroalkyl substituent. This work was devoted to an unusual behaviour of 6-methoxy-2-(1,1,2,2-tetrafluoroethyl)chromone **1a** in a reaction with diethylenetriamine. We found that if chromone **1a** reacts with diethylenetriamine in an alcoholic solution for a day, expected dihydrodiazepine **2a** which exists in the cyclic form 1,4,8-triazabicyclo[5.3.0]dec-4-ene **3a** (a kinetic control product) is formed.† However, a high-melting isomer (a thermodynamic control product) was isolated in place of **3a** when the reaction was performed for a week. Based on the spectral characteristics, the structure of dihydrodiazepine **4** with a 2-aminoethyl group at the nitrogen atom remote from the tetrafluoroethyl substituent was ascribed to this isomer.‡

We found in special experiments that compound **3a** undergoes isomerization to **4** on keeping its alcoholic solution at room temperature for a week. Note that in the case of trifluoromethylated chromone **1b** the reaction stopped at a step of the formation of bicyclic compound **3b**§ and did not result in the isomerization product under similar conditions. This is likely due to a higher capability of the CF_3 group to stabilise an imidazoline ring, as compared with the CF_2CF_2H group.[2]

The signals of aliphatic protons in the ^{1}H NMR spectrum of the high-melting isomer are complicated, and alternative structures cannot be eliminated on this basis. For this reason, we examined the crystals of compound **4** using X-ray diffraction analysis.¶ Figure 1 demonstrates the general view of a molecule of **4** and the numbering of atoms. The central seven-membered heterocyclic ring is nonplanar: the N(2), C(8), C(9) and C(10) atoms are arranged in a plane [the average deviation from a root-mean-square plane is 0.025(5) Å], and the N(1), C(11) and C(12) atoms are out of the plane by –0.356(7), –0.738(9) and



Scheme 1

† *5-(2-Hydroxy-5-methoxyphenyl)-7-(1,1,2,2-tetrafluoroethyl)-1,4,8-triazabicyclo[5.3.0]dec-4-ene* **3a**: yield 56%, mp 127–128 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.11 (br. s, 1H, NH), 2.89–3.25 [m, 5H, CH_2(9), CH_2(10), C*H*H(2)], 3.34 [AB system, $\Delta\delta$ 0.16 ppm, 2H, CH_2(6), J_{AB} 15.5 Hz], 3.40–3.54 [m, 1H, CH*H*(2)], 3.78 (s, 3H, MeO), 3.92 [ddd, 1H, C*H*H(3), ^2J 14.8 Hz, ^3J 6.8 and 4.8 Hz], 4.14 [dt, 1H, CH*H*(3), ^2J 14.8 Hz, ^3J 6.0 Hz], 6.11 (tdd, 1H, CF_2CF_2H, $^2J_{H,F}$ 53.5 Hz, $^3J_{H,F}$ 8.1 and 4.5 Hz), 6.89 [d, 1H, H(3′), ^oJ 9.0 Hz], 6.96 [dd, 1H, H(4′), ^mJ 2.7 Hz], 7.07 [d, 1H, H(6′)], 15.19 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3300 (NH), 1620 (C=N), 1585, 1505 (C=N, arom.). Found (%): C, 53.26; H, 5.21; N, 11.77. Calc. for $C_{16}H_{19}F_4N_3O_2$ (%): C, 53.18; H, 5.30; N, 11.63.

‡ *1-(2-Aminoethyl)-5-(1,1,2,2-tetrafluoroethyl)-7-(2-hydroxy-5-methoxyphenyl)-2,3-dihydro-1*H*-1,4-diazepine* **4**: yield 42%, mp 182–183 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.7–4.0 (m, 8H, $3CH_2$, NH_2), 3.77 (s, 3H, MeO), 4.0–4.3 (m, 2H, CH_2–N=), 5.18 (s, 1H, CH=), 6.26 (tt, 1H, CF_2CF_2H, $^2J_{H,F}$ 53.4 Hz, $^3J_{H,F}$ 5.6 Hz), 6.69 [d, 1H, H(6′), ^mJ 2.3 Hz], 6.82–6.90 [m, 2H, H(4′), H(3′)]. IR (Vaseline oil, ν/cm^{-1}): 3380, 3345 (NH_2), 1610 (C=N), 1540, 1510 (C=C, arom.). Found (%): C, 53.21; H, 5.49; N, 11.75. Calc. for $C_{16}H_{19}F_4N_3O_2$ (%): C, 53.18; H, 5.30; N, 11.63.

§ *5-(2-Hydroxy-5-methoxyphenyl)-7-trifluoromethyl-1,4,8-triazabicyclo-[5.3.0]dec-4-ene* **3b**: yield 37%, mp 100–101 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.14 (br. s, 1H, NH), 2.93–3.23 [m, 5H, CH_2(9), CH_2(10), C*H*H(2)], 3.33 [AB system, $\Delta\delta$ 0.06 ppm, 2H, CH_2(6), J_{AB} 15.7 Hz], 3.42–3.51 [m, 1H, CH*H*(2)], 3.77 (s, 3H, MeO), 3.96 [ddd, 1H, C*H*H(3), ^2J 15.1 Hz, ^3J 6.8 and 4.8 Hz], 4.16 [dt, 1H, CH*H*(3), ^2J 15.1 Hz, ^3J 6.0 Hz], 6.89 [d, 1H, H(3′), ^oJ 8.8 Hz], 6.95 [dd, 1H, H(4′), ^mJ 2.8 Hz], 7.02 [d, 1H, H(6′)], 15.21 (br. s, 1H, OH). IR (Vaseline oil, ν/cm^{-1}): 3345 (NH), 1625 (C=N), 1580, 1510 (arom.). Found (%): C, 54.62; H, 5.38; N, 12.94. Calc. for $C_{15}H_{18}F_3N_3O_2$ (%): C, 54.71; H, 5.51; N, 12.76.

¶ *Crystallographic data for* **4**: $C_{16}H_{19}F_4N_3O_2$, monoclinic crystals. At 300 K, a = 7.821(6), b = 9.394(6), c = 23.785(16) Å, β = 80.64(6)°, V = = 1724(2) Å^3, d_{calc} = 1.392 g cm^{-3}, absorption coefficient μ = 0.12 mm^{-1}, space group $P2_1/n$, Z = 4. The intensities of 3720 independent reflections (R_{int} = 0.06) were measured on a Siemens P3/PC automatic four-circle diffractometer (MoKα radiation, λ = 0.71093 Å, graphite monochromator, $\theta/2\theta$ scan, $2\theta_{max}$ = 55°). The structure was solved by the direct method with the use of the SHELXTL PLUS 5.0 program package.[3] Non-hydrogen atoms were refined by the full-matrix least-squares procedures (with F^2) in an anisotropic approximation. Atoms of MeO and CF_2CF_2H groups are disordered between two positions with equiprobable occupation; in the course of refining, the scatter of O(1)–C(7A), O(1)–C(7B) and C–F bond lengths was restricted by 0.02 Å. The positions of hydrogen atoms bonded to carbon atoms were calculated and included in the refinement by the rider model with fixed C–H distances (0.97 Å) and isotropic shift parameters U_{iso} = 1.5U_{eq} for methyl groups and 1.2U_{eq} for the other (U_{eq} are equivalent isotropic shift parameters of corresponding C atoms). The positions of hydrogen atoms of amino and hydroxyl groups were found by a difference Fourier synthesis and refined in an isotropic approximation. The final discrepancy factors R_1 = 0.074, wR_2 = 0.19, GOOF = 1.172 for 2486 reflections with $I > 2\sigma(I)$. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2000. Any request to the CCDC for data should quote the full literature citation and the reference number 1135/61.

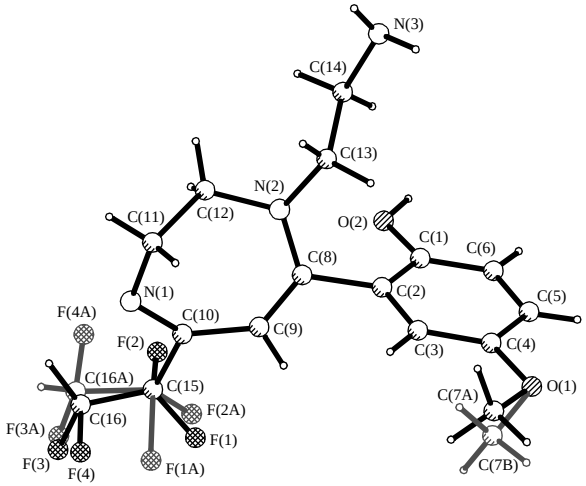
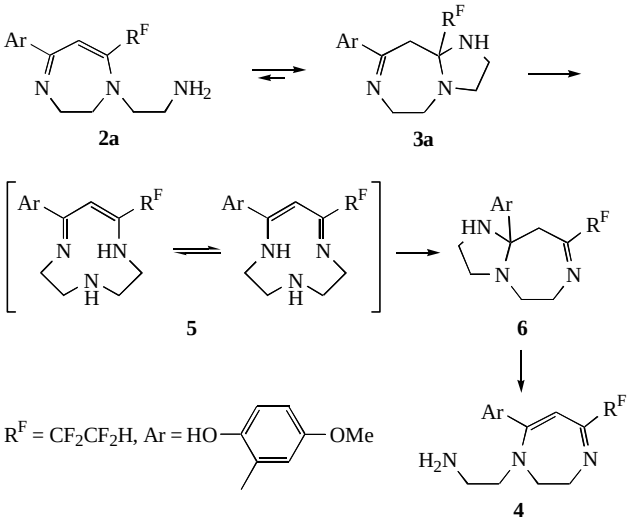


Figure 1 Molecular structure of **4**. Selected bond lengths (Å): N(1)–C(10) 1.293(4), N(1)–C(11) 1.447(5), N(2)–C(8) 1.358(4), N(2)–C(12) 1.450(5), N(2)–C(13) 1.453(5), N(3)–C(14) 1.435(5), C(2)–C(8) 1.493(4), C(8)–C(9) 1.363(5), C(9)–C(10) 1.431(5), C(10)–C(15) 1.511(5), C(11)–C(12) 1.509(6), C(13)–C(14) 1.528(5); selected bond angles (°): C(10)–N(1)–C(11) 115.9(3), C(8)–N(2)–C(12) 119.6(3), C(8)–N(2)–C(13) 123.4(3), N(2)–C(8)–C(9) 125.2(3), N(2)–C(8)–C(2) 116.9(3), C(9)–C(8)–C(2) 117.7(3), C(8)–C(9)–C(10) 131.1(3), N(1)–C(10)–C(9) 132.8(3), N(1)–C(10)–C(15) 110.7(3), C(9)–C(10)–C(15) 116.6(3), N(1)–C(11)–C(12) 113.3(4), N(2)–C(12)–C(11) 113.0(4), N(2)–C(13)–C(14) 111.6(3); selected torsional angles (°): N(1)–C(11)–C(12)–N(2) –89.7(5), C(10)–N(1)–C(11)–C(12) 50.7(5), C(11)–N(1)–C(10)–C(9) 1.9(7), C(1)–C(2)–C(8)–N(2) –79.1(4), C(12)–N(2)–C(13)–C(14) –74.5(4), N(2)–C(8)–C(9)–C(10) –9.7(6), N(2)–C(13)–C(14)–N(3) 170.6(3), C(8)–C(9)–C(10)–C(15) 166.9(4).

+0.268(8) Å, respectively. The planar fragment of the heterocycle and the plane of the benzene ring form an angle of 79.4(3)°. Disordered methoxy groups are turned about the C(4)–O(1) bond by 21° relative to each other. The positions of disordered CF_2CF_2H groups are characterised by a turn of 18° about the C(10)–C(15) bond. The terminal CF_2H groups have different orientations with respect to the C(10)–C(15) bond: the torsion angles C(10)–C(15)–C(16)–H(16) and C(10)–C(15)–C(16A)–H(16A) are equal to 38.9(8) and –44.9(8)°, respectively.

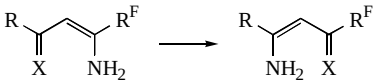
The formation of dihydrodiazepine **4** from bicyclic compound **3a**, which is a cyclic form of dihydrodiazepine **2a**, can be schematically represented as follows:



Scheme 2

It is likely that the isomerization begins with C(7)–N(1) bond rupture in kinetic control product **3a** to form triazacyclodecadiene **5**, which is shown in Scheme 2 as the most probable two tautomers. The subsequent intramolecular transamination at the carbon atom bonded to the aryl substituent proceeds *via* bicyclic nucleophilic-addition product **6**, which then undergoes ring opening to form dihydrodiazepine **4**. The latter compound is not prone to ring–chain tautomerism and, unlike dihydrodiazepine **2a**, exists only in the open form because of the impossibility of the aryl group to stabilise the imidazolidine ring.[4]

It is well known[5,6] that β-aminovinyl ketones (X = O) and thiones (X = S) with the geminate arrangement of an amino group and a polyfluoroalkyl substituent undergo irreversible isomerization to compounds with the γ-arrangement of the above groups.



X = O, S, NH

Scheme 3

Analogous isomerization in the series of β-aminovinyl imines (X = NH) was not reported in the literature, and the reaction under consideration is the first example of isomerization of β-aminovinyl imines with the geminate arrangement of amino and R^F groups to form β-aminovinyl imines with the γ-arrangement of the above groups.

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