# Mono- and diadducts and bicyclic adducts in reactions of 2,3-dicyano-1-ethylpyrazinium cation with C- and O-nucleophiles ✽

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Products of diaddition of O- and C-nucleophiles to the 2,3-dicyano-1-ethylpyrazinium cation were isolated for the first time. The tandem $A_N$—$A_N$ reactions of 2,3-dicyano-1-ethylpyrazinium tetrafluoroborate with 1,3-diketone enolates or keto esters afforded tetrahydrofuro[2,3-*b*]pyrazine derivatives, whereas cyclization with ethylene glycol gave tetrahydro-1,4-dioxino[2,3-*b*]pyrazine. Crystallographic data on the three-dimensional structures of these compounds were reported.

**Key words:** 2,3-dicyano-1-ethylpyrazinium tetrafluoroborate, σ-adducts with O- and C-nucleophiles (alcohols, nitroalkanes, β-diketone enolates, diols, *etc.*), cyclic adducts, tandem $A_N$—$A_N$ reactions.

It is known[1—5] that the 1-alkyl-1,4-diazinium cations tend to add carbo- and heteroatomic nucleophiles at unsubstituted carbon atoms to form successively mono- and diadducts. In most cases, $\sigma^H$-adducts with heteroatomic nucleophiles are unstable and detectable only in solutions, whereas cyclic adducts can be isolated in the crystalline state. Investigation of the formation processes and properties of $\sigma^H$-adducts are of considerable importance for an understanding of cyclization of azines with bifunctional nucleophiles. Detailed data on equilibrium mixtures of 1,4-diazinium salts with methoxide anions and water were published in the literature.[1,2,4] However, isolation of $\sigma^H$-adducts in the crystalline state and the determination of their three-dimensional structures still present problems.

Earlier,[7] we have prepared 1-alkyl-2,3-dichloropyrazinium salts and studied their reactions with N- and C-nucleophiles. These reactions involve competitive *ipso*- and *tele*-substitution of halogen. However, we failed to isolate $\sigma^H$-adducts at the unsubstituted carbon atoms of the pyrazine ring, which were detected by $^1H$ NMR spectroscopy. In the present study, we examined the reactivity of the 2,3-dicyano-1-ethylpyrazinium salts with respect to O-nucleophiles (alcohols, ethylene glycol) and C-nucleophiles (nitroalkanes) as well as to C,O-dinucleophiles (enolates of dicarbonyl compounds). We expected that electron-withdrawing groups would impart high stability to $\sigma^H$-adducts. At the same time, the nitrile groups present in pyrazines and pyrazinium salts are readily replaced with nucleophilic residues.[6—8] It is also known that the nitrile groups in cyanopyrazines can be subjected to the nucleophilic attack resulting in their transformation[9] or giving rise to cyclic products due to the attack of a dinucleophile on both nitrile groups.[9,10]

Alkylation of 2,3-dicyanopyrazine (**1**) with triethyloxonium tetrafluoroborate in $CH_2Cl_2$ at room temperature afforded 2,3-dicyano-1-ethylpyrazinium tetrafluoroborate (**2**). It was found that this salt readily reacts with alcohols in the presence of $NEt_3$ to give 2,3-dialkoxy-5,6-dicyano-1-ethyl-1,2,3,4-tetrahydropyrazines (**3a—c**) as a result of the nucleophilic attack on the unsubstituted C(5) and C(6) atoms of the pyrazinium ring (Scheme 1). The high reactivity of the cation of salt **2** allows one to prepare diadducts not only with primary alcohols but also with $Pr^iOH$. It should be noted that only monoadducts have been synthesized earlier by the reactions of *N*-alkylazinium salts with secondary alcohols,[4] which was accounted for by steric hindrance. The structures of the dialkoxy adducts were established by NMR spectroscopy as well as by X-ray diffraction study of compound **3b**. In molecule **3b**, the alkoxy groups are in the *trans*-diaxial arrangement (Fig. 1).

The reaction of **2** with ethylene glycol proceeded as the successive addition of the alcoholic $HOCH_2$ fragments to the C(5) and C(6) atoms of the heterocycle to form the cyclic product, *viz.*, 5-ethyl-2,3,4a,5,8,8a-hexahydro-1,4-dioxino[2,3-*b*]pyrazine-6,7-dicarbonitrile (**4**). The structure of cycloadduct **4** was confirmed by

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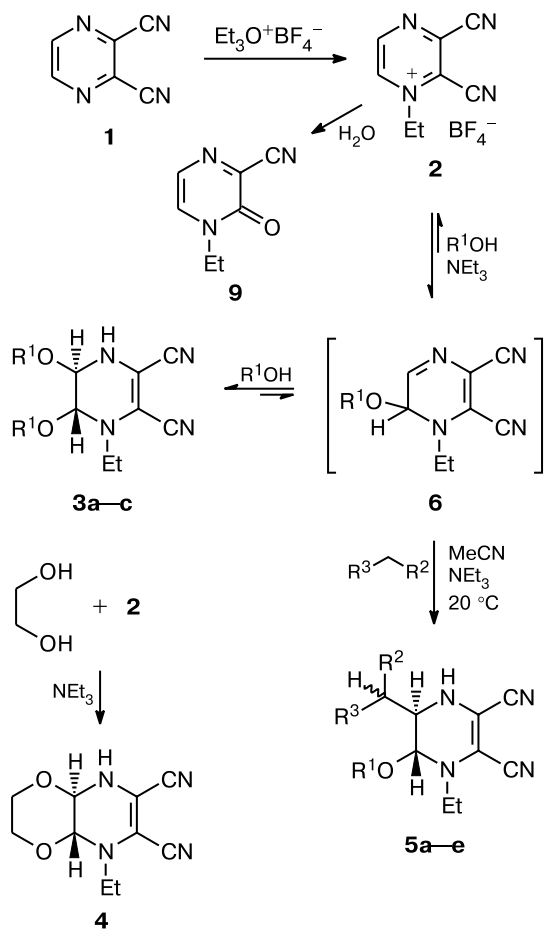
**Scheme 1**




| 3 | $R^1$ | 5 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|---|---|
| **a** | Me | **a** | Me | H | $NO_2$ |
| **b** | Et | **b** | Et | H | $NO_2$ |
| **c** | $Pr^i$ | **c** | Me | Me | $NO_2$ |
| | | **d** | Me | COMe | COMe |
| | | **e** | Me | COMe | COOEt |

$^1$H NMR spectroscopy. The chemical shifts of the protons at the bridgehead carbon atoms (Table 1) correspond to the tetrahydropyrazine structure, and the vicinal spin-spin coupling constant $^3J_{H(2),H(3)}$ is indicative of *cis*-fusion of the six-membered ring.[4]

**Table 1.** Spectroscopic characteristics (δ, *J*/Hz) of products **3a—c** and **4**

| Compound | R | Solvent | H(2) | | H(3) | | |
|---|---|---|---|---|---|---|---|
| | | | δ | $^3J_{H(2),H(3)}$ | δ | $^3J_{H(2),H(3)}$ | $J_{NH}$ |
| **3a** | Me | $(CD_3)_2SO$ | 4.65 | 2.2 | 4.54 | 2.2 | 4.6 |
| **3b** | Et | $(CD_3)_2SO$ | 4.71 | 2.2 | 4.65 | 2.2 | 4.7 |
| **3c** | $Pr^i$ | $CDCl_3$ | 4.59 | 2.1 | 4.67 | 2.1 | 4.8 |
| **4** | $CH_2CH_2$ | $(CD_3)_2SO$ | 4.75 | 2.4 | 4.76 | 2.4 | — |

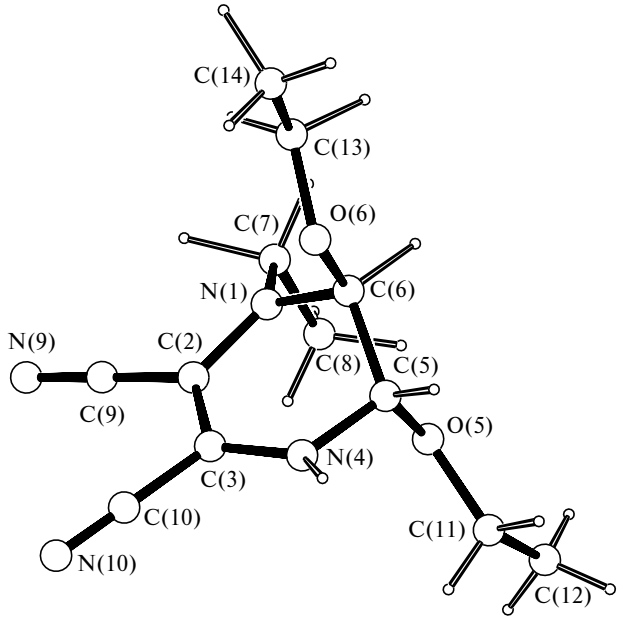



**Fig. 1.** Geometry of molecule **3b** in the crystal.

One of the alkoxy groups in adducts **3a—c** was found to be labile and is replaced with a C-nucleophilic fragment to form mixed *C*,*O*-diadducts **5a—e** under mild conditions (MeCN, $NEt_3$, 20 °C, 1—3 days). The absence of the spin-spin coupling constant between the N(4)H and CH(OR) protons indicates that the alkoxy group at the C(3) atom is involved in exchange. Apparently, the substitution reaction involves elimination of the alkoxy group at the C(3) atom followed by the addition of the C-nucleophile (Scheme 1). The reaction gives a product with the *trans* orientation of the substituents at the C(2) and C(3) atoms, which is confirmed by the X-ray diffraction data for adducts **5a**,**d** (Figs. 2 and 3). Hence, it can be concluded that the attack at the C=N double bond in monoalkoxy adduct **6** occurs from the side opposite to the alkoxy group. The $^1$H NMR spectra of compounds **5c**,**e** have signals of two products, which are, apparently, diastereomers. Their formation is associated with the appearance of a new asymmetric center, *viz.*, the carbon atom of the CH-active compound, after the formation of the C—C bond with the pyrazine moiety.

Interestingly, the formation of mixed adducts of type **5d**,**e** has been previously postulated in the discussion of the mechanisms of cyclization of the quinoxalinium cations with 1,3-diketone enolates. However, attempts to detect and all the more isolate such intermediates failed because of a high rate of formation of the final furo[2,3-*b*]qunoxalines.[11] It was demonstrated that adducts **5d**,**e**, which are stable in neutral and weakly basic media (compound **5d** remains unchanged upon refluxing in $CHCl_3$ for 3 h), rather readily undergo cyclization in AcOH to give tetrahydrofuro[2,3-*b*]pyrazines **7a**,**b**. In this case, protonation, evidently, facilitates elimination of the

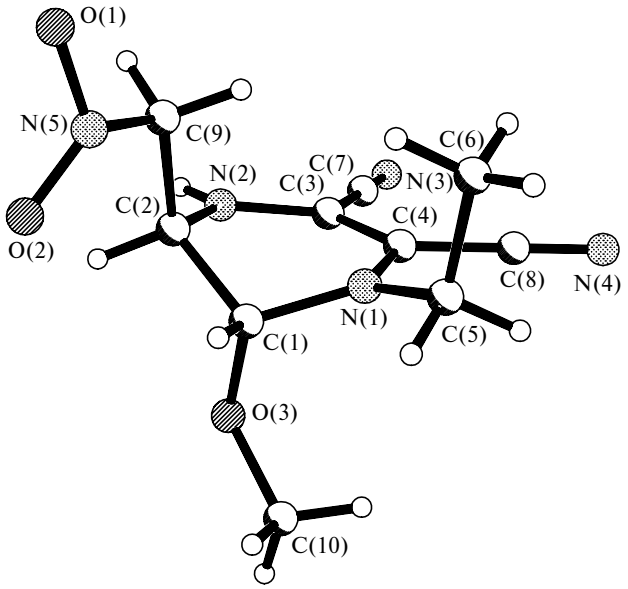



**Fig. 2.** Geometry of molecule **5a** in the crystal.

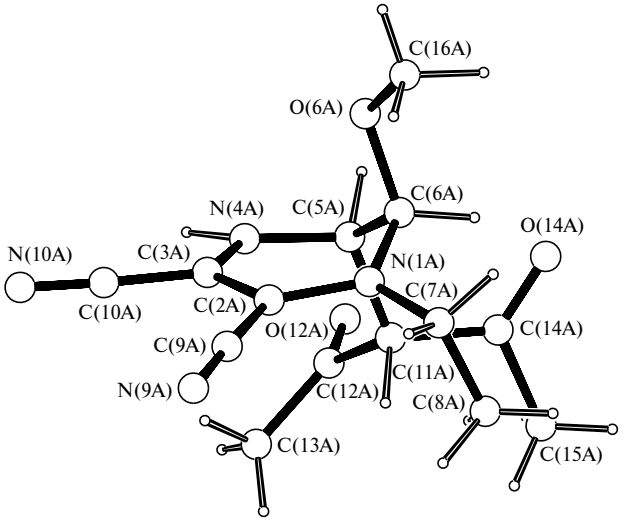
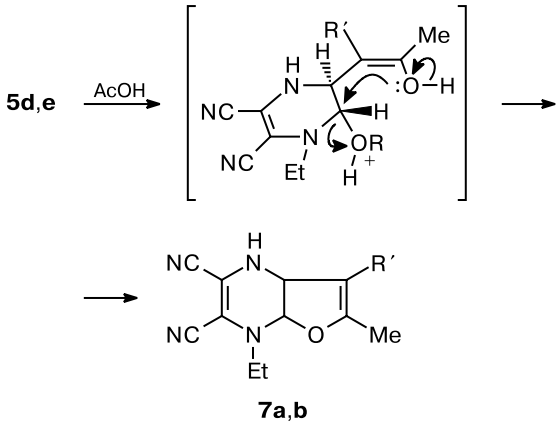



**Fig. 3.** Geometry of molecule **5d** in the crystal.

alkoxy group at the C(2) atom, which is a prerequisite for the intramolecular attack on the C(2) atom from the opposite side to give furo[2,3-*b*]pyrazine with the *cis* orientation of the bridgehead hydrogen atom (Scheme 2). The question as to whether the C—OR bond is cleaved simultaneously with the furan-ring closure or this is a dissociative process calls for a more detailed investigation.

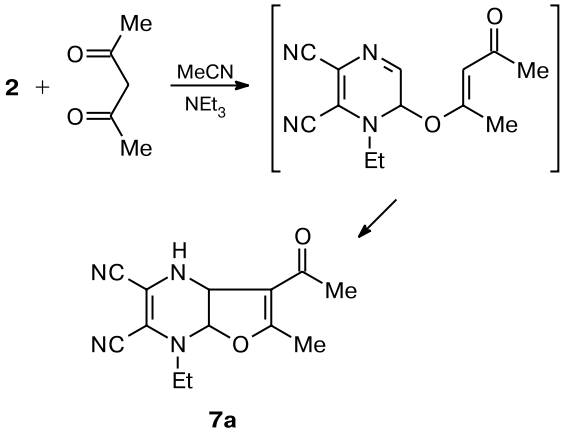
Another scheme of the construction of furo[2,3-*b*]pyrazines **7** involving the successive formation of the C—O and C—C bonds (Scheme 3) cannot also be ruled out. This scheme can take place in the reaction of salt **2** with 1,3-diketones in MeCN under conditions of basic catalysis. It is assumed that the reaction proceeds as the tandem $A_N$—$A_N$ addition of the enolate at the C(2) and C(3) atoms to give furo[2,3-*b*]pyrazines **7** (Schemes 3 and 4).

**Scheme 2**

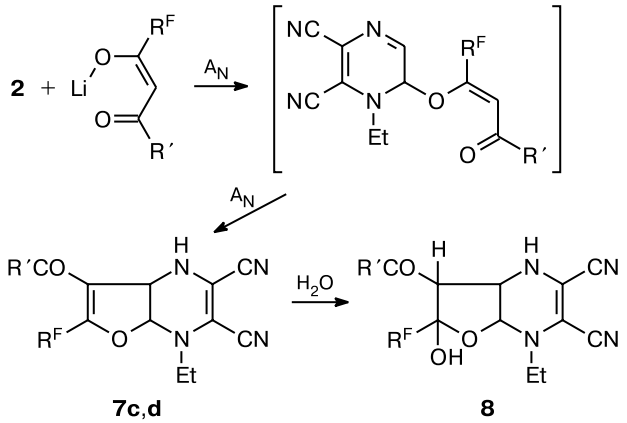



R′ = Ac (**7a**), COOEt (**7b**)

**Scheme 3**




**Scheme 4**




R′ = Me (**7c**), Ph (**7d**, **8**)
$R^F$ = $C_4F_9$ (**7c**), $HCF_2$ (**7d**, **8**)

In this case, the first step of the reaction gives rise to the *O*-adduct of 1,3-diketone at the C(6) atom of the pyrazine ring followed by the furan-ring closure.

This scheme is consistent with the fact that lithium 1,3-diketonates containing fluoroalkyl substituents,[12] in which the oxygen atom at the fluoroalkyl substituent serves as the O-nucleophilic fragment, are involved in cyclization. The mass spectra of compounds **7c**,**d** have peaks of the fluoroalkyl rather than fluorocarbonyl fragments. The mass spectrum of **7d** shows a peak of the $PhCO^+$ fragment. Compound **7d** adds a water molecule at the double bond of the furan ring to form compound **8**. The structure of the latter was established by $^1H$ NMR spectroscopy. Attempts to prepare cyclization products **7c**,**d** with the use of the corresponding fluorine-containing 1,3-dicarbonyl compounds (instead of lithium salts) and $NEt_3$ as a base failed. By contrast, the reaction of salt **2** with pentane-2,4-dione proceeds smoothly under the same conditions to give the target product in satisfactory yield.

Refluxing of salt **2** in water for 30 min or the reaction at room temperature over 24 h led to the replacement of the cyano group with the hydroxy group to give 3-cyano-1-ethylpyrazin-2(1*H*)-one (**9**) (see Scheme 1). The structure of compound **9** was confirmed by IR and $^1H$ NMR spectroscopy and elemental analysis.

## Experimental

The $^1H$ and $^{19}F$ NMR spectra were recorded on a Bruker DRX-400 instrument (400 MHz for $^1H$ and 376 MHz for $^{19}F$). The IR spectra were measured on a Specord-75IR instrument in a thin layer or as Nujol mulls. The melting points were measured on a Boetius hot-stage apparatus. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct inlet of the sample into the ion source; the accelerating voltage was 3 kV; the energy of ionizing electrons was 70 eV.

X-ray diffraction analysis of compounds **3b** and **5d** was carried out at the Department of X-ray Diffraction Studies of the Spectral and Analytical Center of the Collaborative Use of the Russian Foundation for Basic Research based on the A. E. Arbuzov Institute of Organic and Physical Chemistry of the Kazan Research Center of the Russian Academy of Sciences.

Crystals of compound **3b**, $C_{12}H_{16}N_4O_2$, are triclinic, space group $P\bar{1}$. The unit cell parameters at 20 °C: $a = 8.079(9)$ Å, $b = 8.789(6)$ Å, $c = 10.324(5)$ Å, $\alpha = 92.31(5)°$, $\beta = 103.36(6)°$, $\gamma = 92.02(7)°$, $V = 712(1)$ Å$^3$, $Z = 2$, $d_{calc} = 1.13$ g cm$^{-3}$. The intensities of 1570 reflections, of which 958 reflections were with $I \geq 3\sigma$, were measured on an automated four-circle Enraf-Nonius CAD-4 diffractometer ($\lambda$CuK$\alpha$, graphite monochromator, $\omega/2\theta$ scanning technique, $\theta \leq 76°$). The intensities of three check reflections showed no decrease in the course of X-ray data collection. Absorption was ignored ($\mu$(Cu) = 6.37 cm$^{-1}$). The structure was solved by direct methods using the SIR program[13] and refined first isotropically and then anisotropically. All hydrogen atoms were revealed from difference electron density syntheses and included in the refinement with fixed positional and isotropic thermal parameter in the final stage. The final reliability factors were as follows: $R = 0.063$, $R_w = 0.074$ for 821 reflections with $F^2 \geq 3\sigma$. All calculations were carried out using the MOLEN program package[14] on an AlphaStation 200. The hydrogen bonds and the conformation of the molecule were analyzed using the PLATON program.[15] Selected bond lengths and bond angles are given in Table 2.

**Table 2.** Selected bond lengths ($d$) and bond angles ($\omega$) in molecule **3b**

| Bond | $d$/Å | Angle | $\omega$/deg |
|---|---|---|---|
| O(5)—C(5) | 1.390(9) | C(5)—O(5)—C(11) | 115.2(7) |
| O(5)—C(11) | 1.44(1) | C(6)—O(6)—C(13) | 112.5(6) |
| O(6)—C(6) | 1.408(9) | C(2)—N(1)—C(6) | 117.7(6) |
| O(6)—C(13) | 1.421(9) | C(2)—N(1)—C(7) | 120.2(6) |
| N(1)—C(2) | 1.379(8) | C(6)—N(1)—C(7) | 120.5(5) |
| N(1)—C(6) | 1.43(1) | C(3)—N(4)—C(5) | 116.5(6) |
| N(1)—C(7) | 1.48(1) | N(1)—C(2)—C(3) | 119.2(7) |
| N(4)—C(3) | 1.37(1) | N(1)—C(2)—C(9) | 119.1(6) |
| N(4)—C(5) | 1.428(8) | C(3)—C(2)—C(9) | 121.7(6) |
| N(9)—C(9) | 1.15(1) | N(4)—C(3)—C(2) | 123.4(6) |
| N(10)—C(10) | 1.136(9) | N(4)—C(3)—C(10) | 119.3(6) |
| C(2)—C(3) | 1.37(1) | C(2)—C(3)—C(10) | 117.2(7) |
| C(2)—C(9) | 1.39(1) | O(5)—C(5)—N(4) | 112.2(6) |
| C(3)—C(10) | 1.441(9) | O(5)—C(5)—C(6) | 103.1(6) |
| C(5)—C(6) | 1.527(9) | N(4)—C(5)—C(6) | 111.1(5) |
| C(7)—C(8) | 1.51(1) | O(6)—C(6)—N(1) | 111.9(5) |
| C(11)—C(12) | 1.38(2) | O(6)—C(6)—C(5) | 105.0(6) |
| C(13)—C(14) | 1.50(1) | N(1)—C(6)—C(5) | 109.6(5) |
| | | N(1)—C(7)—C(8) | 112.5(6) |
| | | N(9)—C(9)—C(2) | 179.4(8) |
| | | N(10)—C(10)—C(3) | 180(1) |
| | | O(5)—C(11)—C(12) | 113(1) |
| | | O(6)—C(13)—C(14) | 108.4(7) |

X-ray diffraction study of compound **5a** was carried out on a Bruker AXS SMART 1000 diffractometer at 293 K. The crystal of **5a** of dimensions 0.42×0.22×0.13 mm is triclinic, space group $P\bar{1}$. The unit cell parameters: $a = 8.327(2)$ Å, $b = 8.418(2)$ Å, $c = 10.410(2)$ Å, $\alpha = 89.91(3)°$, $\beta = 88.94(3)°$, $\gamma = 61.27(3)°$. The structure was solved by direct method using the SHELXS97 program package. The bond lengths and selected bond angles are given in Table 3.

The crystals of compound **5d**, $C_{14}H_{18}N_4O_3$ are monoclinic, at 20 °C $a = 7.480(1)$ Å, $b = 13.428(4)$ Å, $c = 31.207(5)$ Å, $\beta = 92.24(1)°$, $V = 3132(1)$ Å$^3$, $d_{calc} = 1.23$ g cm$^{-3}$, $Z = 8$, space group $P2_1/c$ (two independent molecules *A* and *B*). The intensities of 8618 reflections, of which 3033 reflections were with $I \geq 3\sigma$, were measured on an automated four-circle Enraf-Nonius CAD-4 diffractometer ($\lambda$CuK$\alpha$, graphite monochromator, $\omega$ scanning technique, $\theta \leq 76°$). The intensities of three check reflections showed no decrease in the course of X-ray data collection. Absorption was ignored ($\mu$(Cu) = 6.98 cm$^{-1}$).

The structure was solved by direct methods using the SIR program[13] and refined first isotropically and then anisotropically. All hydrogen atoms were revealed from difference electron density syntheses and included in the refinement with fixed positional and isotropic thermal parameter in the final stage. The final reliability factors were as follows: $R = 0.062$, $R_w = 0.067$ for 2347 reflections with $F^2 \geq 3\sigma$. All calculations were carried out

**Table 3.** Bond lengths (*d*) and bond angles (ω) in molecule **5a**

| Bond | *d*/Å | Angle | ω/deg |
|---|---|---|---|
| O(1)—N(5) | 1.204(5) | O(2)—N(5)—O(1) | 120.9(4) |
| C(3)—C(7) | 1.424(2) | O(2)—N(5)—C(9) | 118.6(4) |
| C(4)—C(8) | 1.433(2) | O(1)—N(5)—C(9) | 111.2(3) |
| C(5)—C(6) | 1.493(3) | O(3)—C(1)—N(1) | 112.98(13) |
| O(2)—N(5) | 1.177(6) | O(3)—C(1)—C(2) | 104.30(12) |
| C(2)—C(9) | 1.520(3) | N(1)—C(1)—C(2) | 110.36(12) |
| C(3)—C(4) | 1.362(2) | N(2)—C(2)—C(9) | 109.39(13) |
| O(3)—C(1) | 1.416(2) | N(2)—C(2)—C(1) | 109.38(13) |
| O(3)—C(10) | 1.428(2) | C(1)—O(3)—C(10) | 114.11(13) |
| N(1)—C(4) | 1.379(2) | C(4)—N(1)—C(1) | 115.62(12) |
| N(1)—C(1) | 1.4345(18) | C(4)—N(1)—C(5) | 122.11(13) |
| N(1)—C(5) | 1.467(2) | C(1)—N(1)—C(5) | 122.26(13) |
| N(2)—C(3) | 1.376(2) | C(3)—N(2)—C(2) | 119.03(12) |
| N(2)—C(2) | 1.443(2) | C(9)—C(2)—C(1) | 112.18(14) |
| N(3)—C(7) | 1.142(3) | C(4)—C(3)—N(2) | 121.85(14) |
| N(4)—C(8) | 1.137(2) | C(4)—C(3)—C(7) | 120.44(15) |
| N(5)—C(9) | 1.470(3) | N(2)—C(3)—C(7) | 117.70(14) |
| C(1)—C(2) | 1.538(2) | C(3)—C(4)—N(1) | 120.66(13) |
| | | C(3)—C(4)—C(8) | 120.92(14) |
| | | N(1)—C(4)—C(8) | 118.35(13) |
| | | N(1)—C(5)—C(6) | 113.10(18) |
| | | N(3)—C(7)—C(3) | 178.9(2) |
| | | N(4)—C(8)—C(4) | 178.6(2) |
| | | N(5)—C(9)—C(2) | 112.06(15) |

using the MOLEN program package[14] on an AlphaStation 200. The hydrogen bonds and the conformation of the molecule were analyzed using the PLATON program.[15] Selected bond lengths and bond angles in molecule **5d** are given in Table 4.

**2,3-Dicyano-1-ethylpyrazinium tetrafluoroborate (2).** Triethyloxonium tetrafluoroborate (474 mg, 2.5 mmol) was added to a solution of 2,3-dicyanopyrazine (300 mg, 2.3 mmol) in $CH_2Cl_2$ (8 mL). The reaction mixture was kept for 7 days with protection from air. After one week, the crystalline precipitate of salt **2** that formed was filtered off, reprecipitated with benzene from MeCN, filtered, and dried. Tetrafluoroborate **2** was obtained in a yield of 479 mg (84%) as a colorless precipitate, m.p. 127 °C (decomp.). Found (%): C, 39.27; H, 2.86; N, 22.86. $C_8H_7BF_4N_4$. Calculated (%): C, 39.06; H, 2.87; N, 22.78. $^1$H NMR ($CD_3CN$), δ: 1.75 (t, 3 H, $C\underline{H}_3$, $J$ = 7.2 Hz); 5.00 (q, 2 H, $NC\underline{H}_2$, $J$ = 7.2 Hz); 9.34 (d, 1 H, H(3), $J$ = 3.2 Hz); 9.77 (d, 1 H, H(2), $J$ = 3.2 Hz). MS, *m/z*: 159 $[M]^+$, 130 $[M - Et]^+$.

**1-Ethyl-5,6-dimethoxy-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (3a).** Triethylamine (0.2 mL) was added to a solution of salt **2** (82 mg, 0.33 mmol) in MeOH (2 mL). After 24 h, volatile components were removed from the reaction mixture and the residue was treated with water. The colorless precipitate of tetrahydropyrazine **3a** that formed was filtered off and dried. The yield was 21 mg (28%), m.p. 132 °C (decomp.). Found (%): C, 53.83; H, 6.34; N, 25.03. $C_{10}H_{14}N_4O_2$. Calculated (%): C, 54.04; H, 6.35; N, 25.21. $^1$H NMR ($(CD_3)_2SO$), δ: 1.11 (t, 3 H, Me, $J$ = 7.2 Hz); 3.17 (s, 3 H, $OC\underline{H}_3$); 3.19 (s, 3 H, $OC\underline{H}_3$); 3.32 and 3.47 (both m, 1 H each, $NC\underline{H}_2$); 4.57 and 4.65 (both d, 1 H each, H(2) and H(3), $J$ = 2.1 Hz); 7.80 (d, 1 H, NH, $J$ = 4.6 Hz).

**5,6-Diethoxy-1-ethyl-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (3b).** Triethylamine (200 μL) was added to a solution of salt **2** (85 mg, 0.345 mmol) in EtOH (5 mL). After 2 h, volatile components were removed from the reaction mixture

**Table 4.** Bond lengths (*d*) and bond angles (ω) in independent molecules *A* and *B* of compound **5d**

| Parameter | Molecule *A* | Molecule *B* |
|---|---|---|
| Bond: | *d*/Å | |
| O(6)—C(6) | 1.429(8) | 1.409(8) |
| O(6)—C(16) | 1.450(8) | 1.440(8) |
| O(12)—C(12) | 1.204(8) | 1.200(8) |
| O(14)—C(14) | 1.219(8) | 1.206(9) |
| N(1)—C(2) | 1.370(8) | 1.365(8) |
| N(1)—C(6) | 1.437(8) | 1.471(8) |
| N(1)—C(7) | 1.457(9) | 1.418(9) |
| N(4)—C(3) | 1.380(8) | 1.390(8) |
| N(4)—C(5) | 1.434(8) | 1.463(8) |
| N(9)—C(9) | 1.136(9) | 1.149(9) |
| N(10)—C(10) | 1.145(9) | 1.182(9) |
| C(2)—C(3) | 1.382(9) | 1.360(8) |
| C(2)—C(9) | 1.415(9) | 1.426(9) |
| C(3)—C(10) | 1.413(9) | 1.365(9) |
| C(5)—C(6) | 1.558(9) | 1.543(9) |
| C(5)—C(11) | 1.552(9) | 1.526(9) |
| C(7)—C(8) | 1.41(1) | 1.32(2) |
| C(11)—C(12) | 1.565(9) | 1.526(9) |
| C(11)—C(14) | 1.502(9) | 1.50(1) |
| C(12)—C(13) | 1.49(1) | 1.49(1) |
| C(14)—C(15) | 1.51(1) | 1.48(1) |
| Angle: | ω/deg | |
| C(6)—O(6)—C(16) | 112.9(5) | 113.3(5) |
| C(2)—N(1)—C(6) | 116.4(5) | 113.3(5) |
| C(2)—N(1)—C(7) | 122.1(5) | 123.9(6) |
| C(6)—N(1)—C(7) | 121.3(5) | 122.6(6) |
| C(3)—N(4)—C(5) | 117.9(5) | 118.7(5) |
| N(1)—C(2)—C(3) | 119.9(5) | 123.7(5) |
| N(1)—C(2)—C(9) | 120.9(6) | 119.0(5) |
| C(3)—C(2)—C(9) | 119.2(6) | 117.3(6) |
| N(4)—C(3)—C(2) | 122.5(6) | 120.5(6) |
| N(4)—C(3)—C(10) | 118.2(6) | 118.3(6) |
| C(2)—C(3)—C(10) | 119.3(6) | 121.2(6) |
| N(4)—C(5)—C(6) | 109.0(5) | 107.9(5) |
| N(4)—C(5)—C(11) | 112.6(5) | 111.6(5) |
| C(6)—C(5)—C(11) | 109.8(5) | 111.5(5) |
| O(6)—C(6)—N(1) | 112.1(5) | 111.7(5) |
| O(6)—C(6)—C(5) | 103.4(5) | 104.9(5) |
| N(1)—C(6)—C(5) | 109.7(5) | 110.7(5) |
| N(1)—C(7)—C(8) | 112.9(7) | 118.1(9) |
| N(9)—C(9)—C(2) | 176.5(8) | 178.1(8) |
| N(10)—C(10)—C(3) | 177.9(7) | 176.9(7) |
| C(5)—C(11)—C(12) | 107.7(5) | 108.5(5) |
| C(5)—C(11)—C(14) | 113.7(5) | 112.4(5) |
| C(12)—C(11)—C(14) | 106.4(5) | 107.6(5) |
| O(12)—C(12)—C(11) | 119.0(6) | 121.1(6) |
| O(12)—C(12)—C(13) | 123.7(6) | 121.3(6) |
| C(11)—C(12)—C(13) | 117.3(5) | 117.6(6) |
| O(14)—C(14)—C(11) | 122.1(6) | 123.1(6) |
| O(14)—C(14)—C(15) | 121.2(6) | 119.2(7) |
| C(11)—C(14)—C(15) | 116.7(6) | 117.7(6) |

and the residue was treated with water. The precipitate of tetrahydropyrazine **3b** was filtered off and dried. The yield was 70 mg (81%), m.p. 142 °C. Found (%): C, 57.24; H, 7.23; N, 22.33. $C_{12}H_{18}N_4O_2$. Calculated (%): C, 57.58; H, 7.25; N, 22.38. $^1$H NMR ($(CD_3)_2SO$), δ: 1.05—1.15 (m, 9 H, Me); 3.25—3.50 (m, 6 H, OC<u>H</u>$_2$, NC<u>H</u>$_2$); 4.65 (dd, 1 H, H(3), *J* = 4.7 Hz, *J* = 2.4 Hz); 4.71 (d, 1 H, H(2), *J* = 2.1 Hz); 7.77 (d, 1 H, NH, *J* = 4.7 Hz). IR, ν/cm$^{-1}$: 2215 (C≡N).

**1-Ethyl-5,6-diisopropyl-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (3c).** Triethylamine (200 μL) was added to a solution of salt **2** (100 mg, 0.406 mmol) in Pr$^i$OH (5 mL). After 6 h, the solvent was removed and the residue was triturated with water. The precipitate of tetrahydropyrazine **3c** was filtered off and dried. The yield was 61 mg (54%), m.p. 132 °C (decomp.). Found (%): C, 60.63; H, 7.53; N, 20.47. $C_{14}H_{22}N_4O_2$. Calculated (%): C, 60.85; H, 7.30; N, 20.27. $^1$H NMR ($CDCl_3$), δ: 1.10 (m, 12 H, OCH(C<u>H</u>$_3$)$_2$); 1.21 (t, 3 H, Me, *J* = 7.2 Hz); 3.20 and 3.67 (both m, 1 H each, OC<u>H</u>); 3.77 and 3.87 (both m, 1 H each, NC<u>H</u>$_2$); 4.33 (d, 1 H, NH, *J* = 4.2 Hz); 4.59 (d, 1 H, H(2), *J* = 2.1 Hz); 4.66 (dd, 1 H, H(3), *J* = 4.2 Hz, *J* = 2.1 Hz). IR, ν/cm$^{-1}$: 2215 (C≡N).

**5-Ethyl-2,3,4a,5,8,8a-hexahydro-1,4-dioxino[2,3-*b*]pyrazine-6,7-dicarbonitrile (4).** Ethylene glycol (23 μL, 0.41 mmol) and $NEt_3$ (62 μL, 0.45 mmol) were added to a solution of salt **2** (100 mg, 0.41 mmol) in MeCN (3 mL). After 24 h, the solvent was removed and the residue was triturated with water. The pale-yellow precipitate of dinitrile **4** was filtered off and dried. The yield was 52 mg (58%), m.p. 137 °C. Found (%): C, 54.64; H, 5.49; N, 25.10. $C_{10}H_{12}N_4O_2$ Calculated (%): C, 54.54; H, 5.49; N, 25.44. $^1$H NMR ($(CD_3)_2SO$), δ: 1.11 (t, 3 H, Me, *J* = 7.2 Hz); 3.26 (q, 2 H, $NCH_2$, *J* = 7.2 Hz); 3.59 (m, 2 H, OC<u>H</u>$_2$C<u>H</u>$_2$O); 3.70 (m, 1 H, OC<u>H</u>$_2$C<u>H</u>$_2$O); 3.77 (m, 1 H); 4.75 and 4.76 (both d, 1 H each, H(2) and H(3), *J* = 2.4 Hz); 7.56 (s, 1 H, NH).

**1-Ethyl-6-methoxy-5-nitromethyl-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (5a).** A solution of tetrahydropyridine **3a** (115 mg, 0.52 mmol) in $MeNO_2$ (3 mL) in the presence of $NEt_3$ (72 (μL, 0.72 mmol) was stirred at ~20 °C for three days. The solution was concentrated. The residue was treated with a small amount of water, filtered, dried, and fractionated on silica gel using $CH_2Cl_2$ as the eluent. Compound **5a** was obtained as a dark-yellow substance. The yield was 54 mg (41%), m.p. 128—130 °C. Found (%): C, 47.60; H, 5.38; N, 28.06. $C_{10}H_{13}N_5O_3$. Calculated (%): C, 47.81; H, 5.22; N, 27.87. $^1$H NMR ($CDCl_3$), δ: 1.29 (t, 3 H, $CH_2C$<u>H</u>$_3$, *J* = 7.2 Hz); 3.36 (s, 3 H, OMe); 3.41 and 3.62 (both m, 1 H each, NC<u>H</u>$_2$); 4.09 (br.s, 1 H, NH); 4.15 (dd, 2 H, $O_2NC$<u>H</u>$_2$, *J* = 6.85 Hz, *J* = 3.0 Hz); 4.30 (m, 1 H, <u>H</u>C(3)C); 4.50 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.1 Hz).

**6-Ethoxy-1-ethyl-5-nitromethyl-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (5b)** was prepared analogously to **5a** starting from **3b**. The yield was 41%, m.p. 98—100 °C (yellow crystals). Found (%): C, 49.93; H, 5.77; N, 26.30. $C_{11}H_{12}N_5O_3$. Calculated (%): C, 49.81; H, 5.70; N, 26.40. $^1$H NMR ($CDCl_3$), δ: 1.15—1.30 (m, 6 H, $CH_2C$<u>H</u>$_3$); 3.37 and 3.51 (both m, 1 H each, $NCH_2$); 3.60 (m, 2 H, $OCH_2$); 4.10 (d, 1 H, NH, *J* = 7.2 Hz); 4.15 (dd, 2 H, $O_2NC$<u>H</u>$_2$, *J* = 7.2 Hz, *J* = 2.5 Hz); 4.27 (m, 1 H, <u>H</u>C(3)C); 4.57 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.0 Hz).

**1-Ethyl-6-methoxy-5-(1-nitroethyl)-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (5c)** was prepared analogously to **5a**. The yield was 44%, m.p. 116—117 °C. Found (%): C, 49.63; H, 5.50; N, 26.38. $C_{11}H_{12}N_5O_3$. Calculated (%): C, 49.81; H, 5.70; N, 26.40. $^1$H NMR ($CD_3CN$), δ: isomer A: 1.22 (t, 3 H, $CH_2C$<u>H</u>$_3$, *J* = 7.2 Hz); 1.50 (d, 3 H, $O_2NCHC$<u>H</u>$_3$, *J* = 7.0 Hz); 3.27 (s, 3 H, OMe); 3.30—3.60 (m, 2 H, $NCH_2$); 3.94 (ddd, 1 H, <u>H</u>C(3)C, *J* = 9.0 Hz, *J* = 7.0 Hz, *J* = 2.1 Hz); 4.33 (m, 1 H, <u>H</u>C($NO_2$)Me); 4.48 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.1 Hz); 5.33 (br.d, 1 H, NH, *J* = 9.0 Hz); isomer B: 1.22 (t, 3 H, $CH_2C$<u>H</u>$_3$, *J* = 7.2 Hz); 1.50 (d, 3 H, $O_2NCHC$<u>H</u>$_3$, *J* = 7.0 Hz); 3.31 (s, 3 H, OMe); 3.30—3.60 (m, 2 H, $NCH_2$); 3.87 (ddd, 1 H, <u>H</u>C(3)C, *J* = 9.0 Hz, *J* = 7.0 Hz, *J* = 2.1 Hz); 4.20 (m, 1 H, <u>H</u>C($NO_2$)Me); 4.48 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.1 Hz); 5.15 (br.d, 1 H, NH, *J* = 9.0 Hz). The ratio A : B = 2 : 1, the signals of the NEt groups of the isomers overlap with each other.

**5-(1-Acetyl-2-oxopropyl)-1-ethyl-6-methoxy-1,4,5,6-tetrahydropyrazine-2,3-dicarbonitrile (5d).** A solution of **3a** (111 mg, 0.5 mmol), pentane-2,4-dione (50 μL), and $NEt_3$ (139 μL) in MeCN (3 mL) was kept for 24 h. The solution was concentrated. The residue was treated with water, filtered off, dried, and fractionated on silica gel using $CH_2Cl_2$ as the eluent. Compound **5d** was obtained as a beige precipitate in 44% yield, m.p. 105—106 °C. Found (%): C, 57.55; H, 6.01; N,19.38. $C_{14}H_{18}N_4O_3$. Calculated (%): C, 57.92; H, 6.25; N, 19.30. $^1$H NMR ($CDCl_3$), δ: 1.23 (t, 3 H, $CH_2C$<u>H</u>$_3$, *J* = 7.2 Hz); 2.18 and 2.31 (both s, 3 H each, C(O)Me); 3.30—3.50 (m, 2 H, $NCH_2$); 3.35 (s, 3 H, OMe); 3.58 (d, 1 H, C<u>H</u>$(COMe)_2$, *J* = 11.0 Hz); 4.01 (d, 1 H, NH, *J* = 6.9 Hz); 4.19 (ddd, 1 H, <u>H</u>C(3)C, *J* = 2.0 Hz, *J* = 6.9 Hz, *J* = 11.0 Hz); 4.33 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.0 Hz).

**Ethyl 2-(5,6-dicyano-4-ethyl-3-methoxy-1,2,3,4-tetrahydropyrazin-2-yl)-3-oxobutanoate (5e)** was prepared analogously to **5d**. The yield was 42%, m.p. 87—88 °C. Found (%): C, 56.42; H, 6.30; N,17.50. $C_{15}H_{20}N_4O_4$. Calculated (%): C, 56.24; H, 6.29; N, 17.49. $^1$H NMR ($CDCl_3$), δ: isomer A, 1.15—1.35 (m, 6 H, $CH_2C$<u>H</u>$_3$); 2.29 (s, 3 H, C(O)Me); 3.35 (s, 3 H, OMe); 3.30—3.50 (m, 2 H, $NCH_2$); 4.10—4.30 (m, 4 H, $OCH_2$, <u>H</u>C(3)C, <u>H</u>C(COOEt)(COMe)); 4.49 (d, 1 H, <u>H</u>C(2)OMe, *J* = 2.0 Hz); isomer B, 1.15—1.35 (m, 6 H, $CH_2C$<u>H</u>$_3$); 2.25 (s, 3 H, C(O)Me); 3.37 (s, 3 H, OMe); 3.30—3.50 (m, 2 H, $NCH_2$); 4.10—4.30 (m, 4 H, $OCH_2$, <u>H</u>C(3)C, <u>H</u>C(COOEt)(COMe)); 4.42 (d, 1 H, <u>H</u>C(2)OMe, *J* = 1.2 Hz). The ratio A : B = 2 : 1.

**7-Acetyl-2,3-dicyano-4-ethyl-6-methyl-1,4,4a,7a-tetrahydrofuro[2,3-*b*]pyrazine (7a).** ***A.*** Compound **5d** (145 mg, 0.5 mmol) was dissolved in AcOH (5 mL). The reaction mixture was stirred for 30 min. The precipitate that formed was filtered off, washed with a small amount of AcOH, and dried. Compound **7b** was obtained in a yield of 34 mg (26%). The filtrate was concentrated. The residue was dissolved in $CHCl_3$ and fractionated on silica gel using $CHCl_3$ as the eluent. Compound **7a** was additionally obtained in a yield of 29 mg (22%). The total yield was 48%.

***B.*** Salt **2** (100 mg, 0.41 mmol) was added with stirring to a solution of pentane-2,4-dione (1 mL) in MeCN (3 mL) in the presence of $NEt_3$ (200 μL). After 1 h, volatile components were removed from the reaction mixture and the residue was treated successively with water and hexane. The precipitate was separated, dissolved in $CH_2Cl_2$, and fractionated on silica gel using a 5 : 1 $CH_2Cl_2$—acetone mixture as the precipitate. The product was reprecipitated with hexane from acetone. Compound **7a** was obtained as a colorless precipitate in a yield of 70 mg (82.7%), m.p. 174—175 °C. Found (%): C, 60.17; H, 5.46; N, 21.52. $C_{13}H_{14}N_4O_2$. Calculated (%): C, 60.45; H, 5.46; N, 21.69.

$^1$H NMR ($CDCl_3$), δ: 1.31 (t, 3 H, Me, $J$ = 7.2 Hz); 2.33 (d, 3 H, =CMe, $J$ = 0.7 Hz); 2.33 (s, 3 H, COMe); 3.47 (q, 2 H, NC$\underline{H}_2$, $J$ = 7.2 Hz); 4.68 (d, 1 H, NC$\underline{H}$C, $J$ = 7.1 Hz); 4.72 (s, 1 H, N$\underline{H}$); 5.54 (d, 1 H, NC$\underline{H}$O, $J$ = 7.1 Hz).

**Ethyl 2,3-dicyano-4-ethyl-6-methyl-1,4,4a,7a-tetrahydrofuro[2,3-*b*]pyrazine-7-carboxylate (7b).** Compound **5e** (140 mg, 0.437 mmol) was dissolved in AcOH (4 mL). After one day, the solution was concentrated. The residue was tritutated with water and fractionated on silica gel using $CH_2Cl_2$ as the eluent. Compound **7b** was obtained as a yellowish precipitate in a yield of 65 mg (52%), m.p. 110—112 °C. Found (%): C, 58.40; H, 5.61; N, 19.59. $C_{14}H_{16}N_4O_3$. Calculated (%): C, 58.32; H, 5.59; N, 19.43. $^1$H NMR ($(CD_3)_2SO$), δ: 1.15—1.25 (m, 6 H, Me); 2.16 (s, 3 H, COMe); 3.39 (m, 2 H, OC$\underline{H}_2$); 4.07 (m, 2 H, NC$\underline{H}_2$); 4.33 (d, 1 H, NC$\underline{H}$C, $J$ = 5.7 Hz); 5.87 (d, 1 H, NC$\underline{H}$(O), $J$ = 5.7 Hz); 7.09 (s, 1 H, N$\underline{H}$).

**7-Acetyl-2,3-dicyano-4-ethyl-6-nonafluorobutyl-1,4,4a,7a-tetrahydrofuro[2,3-b]pyrazine (7c).** A mixture of salt **2** (100 mg, 0.41 mmol) and lithium perfluorobutylmethyl-1,3-diketonate (127 mg, 0.41 mmol) was dissolved with stirring in MeCN (4 mL) at ~20 °C. After 4 h, the reaction mixture was concentrated and the residue was fractionated on silica gel using a 5 : 1 benzene—MeCN mixture as the eluent. Product **7c** was obtained as a pale-yellow precipitate in a yield of 58 mg (31%), m.p. 118 °C. Found (%): C, 41.40; H, 2.57; N, 11.81. $C_{16}H_{11}F_9N_4O_2$. Calculated (%): C, 41.48; H, 2.61; N, 12.09. $^1$H NMR ($(CD_3)_2SO$), δ: 1.21 (t, 3 H, Me, $J$ = 7.2 Hz); 2.36 (s, 3 H, COMe); 3.43 (m, 2 H, NC$\underline{H}_2$); 4.35 (s, 1 H, N$\underline{H}$); 4.65 (dd, 1 H, N(4)C$\underline{H}$C, $J$ = 4.3 Hz); 6.21 (d, 1 H, NC$\underline{H}$O, $J$ = 4.3 Hz). IR, ν/cm$^{-1}$: 2220 (C≡N); 2215 (C≡N); 1671 (CO). MS (EI, 70 eV), $m/z$ ($I_{rel}$ (%)): 462 $[M]^+$ (100), 433 $[M - Et]^+$ (18), 419 $[M - COMe]^+$ (12), 391 $[M - COMe - Et]^+$ (8), 243 $[M - C_4F_9]^+$ (7), 215 $[M - C_4F_9 - Et]^+$ (5).

**7-Benzoyl-2,3-dicyano-6-difluoromethyl-4-ethyl-6-hydroxy-1,4,4,6,7,7a-hexahydrofuro[2,3-*b*]pyrazine (8).** A solution of lithium 4,4-difluoromethyl-1-phenylbutadionate[12] (0.2 g, 0.00081 mol) and salt **2** (0.17 g, 0.85 mmol) in MeCN was stirred until the starting reagents were consumed (TLC control). After completion of the reaction, MeCN was evaporated. The residue was chromatographed ($CHCl_3$ as the eluent) and recrystallized from a $CHCl_3$—*n*-hexane mixture. Colorless compound **8** was obtained in a yield of 0.3 g (87%), m.p. 129—130 °C. Found (%): C, 57.76; H, 4.41; N, 15.00. $C_{18}H_{16}F_2O_3N_4$. Calculated (%): C, 57.75; H, 4.31; N, 14.97. $^1$H NMR ($CD_3CN$), δ: 1.27 (t, 3 H, Me, $J$ = 7.2 Hz); 3.52 (m, 2 H, NC$\underline{H}_2$); 3.61 (s, 1 H, N$\underline{H}$); 4.26 (d, 1 H, O=C(Ph)C$\underline{H}$, $J$ = 7.0 Hz); 4.56 (m, 1 H, N(4)C$\underline{H}$C); 5.17 (d, 1 H, OC(2)$\underline{H}$, $J$ = 4.5 Hz); 5.49 (s, 1 H, OC($CHF_2$)O$\underline{H}$); 5.64 (t, 1 H, C$\underline{H}F_2$, $J$ = 55.83 Hz); 7.56 (m, 2 H, Ar); 7.71 (m, 1 H, Ar); 7.98 (m, 2 H, Ar). $^{19}$F NMR ($(CD_3)_2SO$), δ: 30.86 (dd, HC$\underline{F}^A$, $J_{F,F}$ = 237.7 Hz, $J_{F,H}$ = 54.9 Hz); 33.23 (dd, HC$\underline{F}^B$, $J_{F,F}$ = 237.7 Hz, $J_{F,H}$ = 55.0 Hz). IR, ν/cm$^{-1}$: 3360 (NH, OH), 2210 and 2208 (C≡N), 2215 (C≡N), 1669 (CO).

**3-Cyano-1-ethylpyrazin-2(1*H*)-one-2 (9).** ***A.*** A solution of salt **2** (118 mg, 0.479 mmol) in $H_2O$ (3 mL) was refluxed for 0.5 h. The solvent was distilled off and the residue was extracted with $CHCl_3$. The extract was concentrated and pyrazinone **9** was obtained as a yellow oil in a yield of 38 mg (53%). Found (%): C, 56.44; H, 4.89; N, 28.33. $C_7H_7N_3O$. Calculated (%): C, 56.37; H, 4.73; N, 28.17. $^1$H NMR ($CDCl_3$), δ: 1.45 (t, 3 H, Me, $J$ = 7.2 Hz); 4.06 (q, 2 H, $NCH_2$, $J$ = 7.2 Hz); 7.49 and 7.53 (both d, 1 H each, H(5) and H(6), $J$ = 4.07 Hz). IR, ν/cm$^{-1}$: 2232 (C≡N), 1667 (C = O).

***B.*** A mixture of salt **2** (50 mg, 0.203 mmol), $H_2O$ (500 μL), and $NEt_3$ (100 μL) in MeCN (2 mL) was stirred at ~20 °C for 0.5 h. The course of the reaction was monitored by TLC (Silufol, a 1 : 1 : 2 acetone—AcOEt—hexane system as the eluent). Compound **9** was accumulated in the reaction mixture. This compound was identified by TLC by comparing with a sample prepared according to the method ***A***.

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