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Generation of oxodiazonium ions

3.* Synthesis of [1,2,5]oxadiazolo[3,4-*c*]cinnoline-1,5-dioxides

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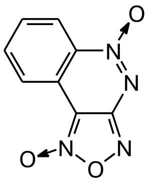
A reaction of 4-(*N*-nitramino)-3-phenylfuroxane with the Ac_2O/H_2SO_4 system leads to the formation of [1,2,5]oxadiazolo[3,4-*c*]cinnoline-1,5-dioxide, the first representative of furoxanocinnolines. The reaction presumably proceeds through the transformation of the nitramine fragment $NHNO_2$ to the oxodiazonium ion $[N=N=O]^+$ with subsequent intramolecular attack by this cation on the phenyl ring. Furoxanocinnoline is also formed in the reaction of the 4-(*N*-nitramino)-3-phenylfuroxane *O*-methyl derivative with H_2SO_4. It is assumed that this reaction also proceeds with involvement of the intermediate cation $[N=N=O]^+$ formed by the protonation of the N=N(O)OMe group and subsequent elimination of MeOH. 7-Nitro derivative is formed when furoxanocinnoline is nitrated with the concentrated HNO_3/H_2SO_4 mixture. The compounds obtained were characterized by ^1H, ^{13}C, and ^{14}N NMR spectroscopy.

Key words: *N*-nitramines, furoxanes, cinnolines, oxodiazonium ion, nitration, ^1H, ^{13}C, ^{14}N NMR spectroscopy.

Nitric oxide (NO) is an important physiological regulator of cardiovascular, immune, and nervous systems (see, for example, review 2). Several classes of organic compounds capable of forming NO in living organisms are known. Benzofuroxane derivatives[3,4] belong to one of these classes. Immunodepressants,[5] substances displaying antileukemia activity,[5] and vasodilators[6—8] are found among them. The purpose of the present work is to synthesize new annulated furoxanes, potential NO-donors.

Earlier, we have reported on the development of approaches to the preparation of furazanocinnoline-5-oxide **1** by the reaction of 3-(*N*-nitramino)-4-phenylfurazane with the Ac_2O/H_2SO_4 system,[1] as well as by the reaction of 3-[methoxy(oxido)diazenyl]-4-phenylfurazane with acids[9] (Scheme 1). The reaction presumably proceeds *via* the intermediate oxodiazonium ion $[N=N=O]^+$.

In the present work, these approaches were used for the synthesis of furoxanocinnoline-5-oxide (FCO) **2**.



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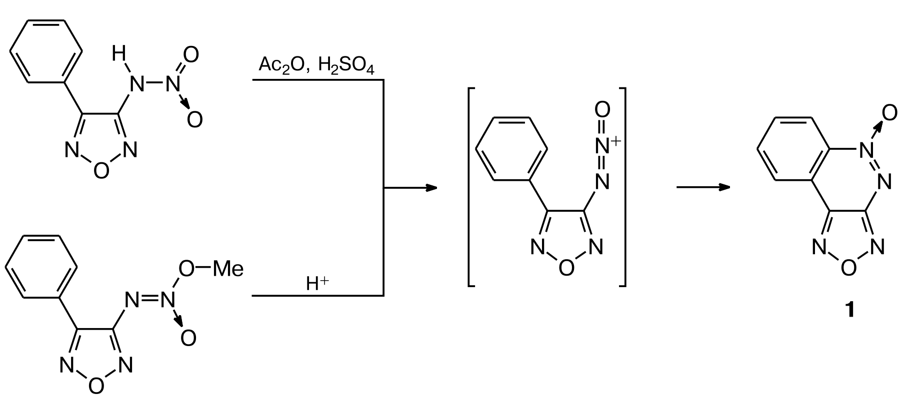
Synthesis of the starting compounds. Nitramine **3** and its *O*-methyl derivative **4** are the starting compounds for the synthesis of FCO **2** (Scheme 2). Note that before our work,

Scheme 1



For Part 2, see Ref. 1.

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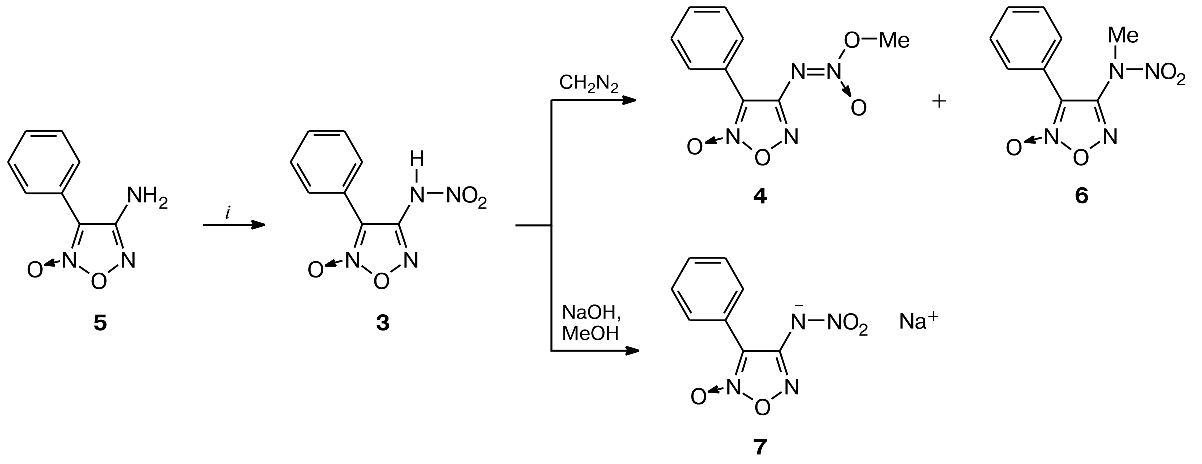
Scheme 2



i. HNO_3 (70%), NH_4NO_3 (20%), H_2O (10%), 10 °C, 1 h.

no furoxanes containing a primary nitramine group were known.

Nitration of 4-amino-3-phenylfuroxane (**5**) with 70% HNO_3 according to the method developed for the synthesis of nitramines of the furazane series[10] led to nitramine **3**, which contained a large amount of impurities. Considerably better results were obtained for the nitration with the $HNO_3/NH_4NO_3/H_2O$ system. The nitrating mixtures containing 68, 17, and 15% or 70, 20, and 10% of HNO_3, NH_4NO_3, and H_2O, respectively, were used for the nitration. In the first case, the nitration was carried out at 25 °C for 2 h, in the second case, at 10 °C for 1 h. In both cases, the yields of nitramine **3** (64—76%, calculated on the Na-salt) were approximately the same. The reaction product was dissolved in diethyl ether and dried with $MgSO_4$. According to the TLC data (AcOEt—light petroleum, 1 : 3), this solution contains nitramine **3**, some unreacted starting compound **5**, and unidentified impurities. A solution of nitramine **3** in Et_2O can be stored in refrigerator for several hours.

Nitramine **3** in the solid state is unstable: at room temperature it rapidly decomposes with the formation of several unidentified products. The reaction of nitramine **3** solutions and diazomethane in diethyl ether leads to a mixture of *O*- and *N*-methyl derivatives **4** and **6** in the ratio 59 : 41, respectively (^{1}H NMR spectroscopic data). The reaction of the ethereal solution of **3** with the solution of NaOH in MeOH gives Na-salt **7** (see Scheme 2).

Compounds **4**, **6**, and **7** were characterized by ^{1}H, ^{13}C, and ^{14}N NMR spectra. ^{14}N NMR spectra are especially informative, which exhibit sharp signals for the nitro groups of the salt **7** (acetone-d$_6$, δ_N −13, $\Delta\nu_{1/2}$ = 55 Hz) and nitramine **6** ($CDCl_3$, δ_N −36) and somewhat broad signal for the diazenoxide group N→O in the compound **4** ($CDCl_3$, δ_N −52), resonating in the regions characteristic of these classes. The signals for the N→O group of the furoxane ring in these compounds are very broad ($\Delta\nu_{1/2}$ > 500 Hz).

Synthesis of [1,2,5]oxadiazolo[3,4-*c*]cinnoline-1,5-dioxides. The reaction of the Na-salt **7** with the Ac_2O/H_2SO_4 system leads to the formation of FCO **2** in 89% yield (Scheme 3).

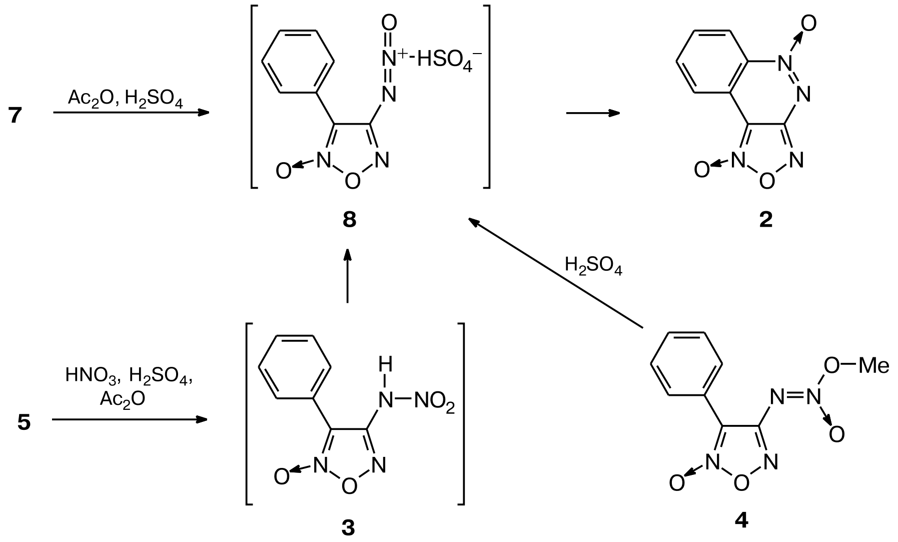
Apparently, the process proceeded through the intermediate **8** with the subsequent reaction of the oxodiazonium ion with the benzene ring.

Compound **2** can be obtained directly from aminofuroxane **5** (see Scheme 3). An equimolar amount of HNO_3 was added to a solution of aminofuroxane **5** in Ac_2O, followed by immediate addition of a solution of H_2SO_4 (1 equiv.) in Ac_2O. Initially, formation of nitramine **3** was observed, followed by a gradual accumulation of cinnoline **2** (TLC monitoring, AcOEt—light petroleum, 1 : 3). The reaction reached completion within 10 min at 5—10 °C, the yield of FCO **2** was 72%.

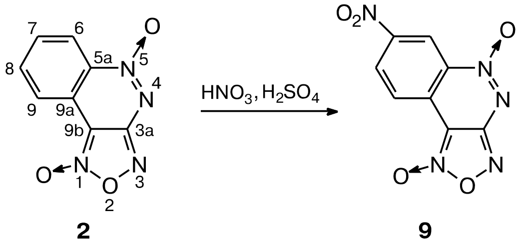
The reaction of the *O*-methylated nitramine **4** with 93% H_2SO_4 also leads to FCO **2** (25 °C, 10 min, the yield was 75%). This reaction presumably also proceeds through the intermediate oxodiazonium ion, which is formed as a result of protonation of the N=N(O)—OMe group and subsequent elimination of methanol (see Scheme 3). The detailed mechanism of this reaction, including quantum chemical calculations, has been considered by us earlier[9] for the synthesis of furazanocinnoline-5-oxide **1** as an example (see Scheme 1).

Nitration of FCO **2** with the conc. HNO_3/H_2SO_4 mixture resulted in the 7-nitro-substituted compound **9** in 75% yield, which, like compound **2**, is a potential NO-donor (Scheme 4).

Scheme 3



Scheme 4



The structures of FCO **2** and **9** were confirmed by ^{1}H, ^{13}C, and ^{14}N NMR spectroscopic data. The ^{14}N NMR spectra of these compounds exhibit sharp signals for the N(5) atoms of the azoxy group and broad signals for the N(1) atoms of the furoxane ring,[4a] whereas the spectrum of compound **9** additionally contains a signal for the NO_2 group (Table 1).

Peaks of the molecular ions and the fragment ions $[M - NO]^+$ and $[M - 2\,NO]^+$ characteristic of furoxanes[4b] are observed in the mass spectra of FCO **2** and **9**.

The ^{13}C—^{1}H correlations (HMBC and HSQC) were used to assign signals in the ^{13}C NMR spectra, which unambiguously indicate that the N-oxide oxygen atom of the furoxane ring is in the neighborhood of the phenyl ring. The ^{13}C NMR spectra of compounds **2** and **9** are specifically characterized by broadening of the signals for the C(5a) atoms bound to the fragment N→O of the azoxy group. In compound **9**, the signal for the C(7) atom bound to the NO_2 group is also broadened. An upfield shift of the signal for the C(9b) atom bound to the fragment N→O of the furoxanes ring is also typical of both compounds.[4c]

Compounds **2** and **9** exist as one isomer. Cinnolinofuroxane **2** does not isomerize giving compound **2′** on heating at 150—160 °C for 4 h in benzonitrile or without solvent (Scheme 5).

Scheme 5

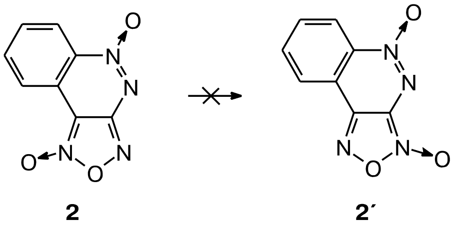


Table 1. The ^{1}H and ^{14}N NMR spectra of cinnolinofuroxanes **2** and **9**

Compound	^{1}H NMR (DMSO-d$_6$, δ, J/Hz)	^{14}N NMR (acetone-d$_6$, δ, $\Delta\nu_{1/2}$/Hz)
2	8.01 (ddd, 1 H, H(7), J = 8.7, J = 7.9, J = 1.4); 8.15 (td, 1 H, H(8), J = 7.9, J = 1.0); 8.34 (dd, 1 H, H(9), J = 7.9, J = 1.4); 8.54 (dd, 1 H, H(6), J = 8.7, J = 1.0)	−22 (N(1) furoxane, $\Delta\nu_{1/2}$ = 500); −50 (N(O)=N, $\Delta\nu_{1/2}$ = 15)
9	8.58 (d, 1 H, H(9), J = 8.6); 8.88 (dd, 1 H, H(8)); 9.09 (d, 1 H, H(6), J = 2.0)	−54 (N(O)=N, $\Delta\nu_{1/2}$ = 20); −19 (NO_2, $\Delta\nu_{1/2}$ = 110)*

* The signal for the N-oxide nitrogen atom of the furoxane ring is overlapped with the signal for the nitro group.

Table 2. The ^{13}C NMR spectra[a,b] of cinnolinofuroxanes **2** and **9**

Compound	δ							
	C(3a)	C(5a)	C(6)	C(7)	C(8)	C(9)	C(9a)	C(9b)
2	156.5	139.7 (br.s)	122.9	132.9	135.6	123.0	116.5	100.6 (br.s)
9	156.5	139.8 (br.s)	118.2 (br.s)	149.0	129.6	124.8	121.6	100.5

[a] In DMSO-d$_6$.

[b] The signals were assigned using the 2 D ^{13}C—^{1}H NMR spectra (HMBC and HSQC).

Experimental

^{1}H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13, 125.76, and 36.14 MHz, respectively). Chemical shifts are given relative to Me_4Si (^{1}H, ^{13}C) or $MeNO_2$ (^{14}N, external standard, the high-field chemical shifts are negative). IR spectra were recorded on a Specord M-80 spectrometer. Mass spectra were recorded on a Kratos MS-300 instrument (EI, 70 eV). Reaction progress was monitored using thin-layer chromatography (Merck 60 F$_{254}$). Silica gel was used for column chromatography. A solution of diazomethane in diethyl ether[11] and 4-amino-3-phenylfuroxane (**5**) (see Ref. 12) were obtained according to the known procedures.

4-Nitramino-3-phenylfuroxane (3). ***A.*** 4-Amino-3-phenylfuroxane (**5**) (0.18 g, 1 mmol) was added to a nitrating mixture (2.68 g, containing HNO_3 (1.88 g, 29.9 mmol), NH_4NO_3 (0.52 g, 6.5 mmol), and H_2O (0.28 g)) with stirring at 8 °C. The reaction mixture was stirred for 1 h at 10 °C, then poured on finely crushed ice (20 g). The aqueous solution was rapidly extracted with Et_2O (3×10 mL). The organic layers were washed with cold water (2×3 mL) and dried with $MgSO_4$ in refrigerator for 1 h periodically shaking the mixture, then the drying agent was filtered off. According to the TLC data (AcOEt—light petroleum, 1 : 3), the solution contained nitramine **3**, some amount of unreacted starting compound **5** and unidentified impurities.

B. 4-Amino-3-phenylfuroxane (**5**) (0.18 g, 1 mmol) was added to a nitrating mixture (3.58 g, containing HNO_3 (2.42 g, 38.4 mmol), NH_4NO_3 (0.62 g, 7.7 mmol), and H_2O (0.54 g)) with stirring at 25 °C (water bath). The reaction mixture was stirred for 2 h at 25 °C. The subsequent treatment was similar to that in method ***A***.

4-Nitramino-3-phenylfuroxane Na-salt (7). A solution of NaOH (80 mg, 2 mmol) in anhydrous MeOH (2 mL) was added dropwise to the solution of nitramine **3** in diethyl ether obtained by method ***A*** with stirring; temperature was maintained from −10 to −12 °C, pH was control using indicator paper. The addition of the NaOH solution was stopped when the pH reached 7 (the solution turned its color from yellow to orange), a precipitate was filtered off, washed with Et_2O (2×5 mL), and dried in air. A solid residue was obtained (270 mg), which was the Na-salt of nitramine **7** with impurities of other salts. To remove $NaNO_3$, the salt **7** was dissolved on a filter in the AcOEt : MeOH = 5 : 1 mixture (4×5 mL). After the solvents were evaporated *in vacuo*, Na-salt **7** (184 mg, 76%) was obtained. This substance begins to decompose without melting at 160 °C. It was used for the synthesis of FCO **2** without additional purification.

An analytical sample of Na-salt **7** was obtained as follows. A solution of H_2SO_4 (30 mg, 0.3 mmol) in AcOEt (3 mL) was added dropwise to a solution of crude Na-salt **7** (74 mg) in AcOEt (20 mL) at −40 °C, inorganic salts were rapidly separated by filtration. A solution of NaOH (80 mg) in anhydrous MeOH (2 mL) was added dropwise to a solution of nitramine **3** at −30 °C (to pH 7). After the solvents were evaporated *in vacuo*, the residue (67 mg) was crystallized (AcOEt (6 mL) and Et_2O (12 mL)) to obtain Na-salt **7** (51 mg) as white crystals, which start to decompose about 230 °C. Found (%): C, 39.57; H, 1.98; N, 22.67. $C_8H_5N_4NaO_4$. Calculated (%): C, 39.36; H, 2.06; N, 22.95. IR (KBr), ν/cm^{-1}: 1636 s, 1612 s, 1601 s, 1484 w, 1436 s, 1388 s, 1340 s, 1312 s. ^{1}H NMR (acetone-d$_6$), δ: 7.44—7.51 (m, 3 H, H(3´), H(4´), H(5´)); 8.17 (d, 2 H, H(2´), H(6´), *J* = 8.1 Hz). ^{13}C NMR (acetone-d$_6$), δ: 111.9 (C(3)); 125.6 (C(1´)); 128.0 (C(2´), C(6´)); 129.4 (C(3´), C(5´)); 130.7 (C(4´)); 159.8 (C(4)). ^{14}N NMR (acetone-d$_6$), δ: −13 (NO_2, $\Delta\nu_{1/2}$ = 55 Hz).

4-[Methoxy(oxido)diazenyl]-3-phenyl-1,2,5-oxadiazole-2-oxide (4) and 4-[*N*-methyl-(*N*-nitro)amino]-3-phenyl-1,2,5-oxadiazole-2-oxide (6). A solution of diazomethane in diethyl ether obtained from *N*-methylnitrosourea (380 mg, 3.7 mmol) was added to a stirred solution of nitramine **3** in diethyl ether obtained by method ***A*** and after the drying agent was removed at 5 °C. After 5 min, Et_2O was evaporated *in vacuo* to obtain a mixture of isomers (201 mg), which was separated by preparative TLC (benzene) to give *O*-methyl compound **4** (67 mg, 28%) and *N*-methyl compound **6** (51 mg, 22%).

Compound **4**. M.p. 68—71 °C. Found (%): C, 45.89; H, 3.29; N, 23.50. $C_9H_8N_4O_4$. Calculated (%): C, 45.77; H, 3.41; N, 23.72. ^{1}H NMR ($CDCl_3$), δ: 4.18 (s, 3 H, CH_3); 7.48—7.53 (m, 3 H, H(3´), H(4´), H(5´)); 8.02 (d, 2 H, H(2´), H(6´), *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$), δ: 58.7 (CH_3); 110.1 (C(3)); 121.8 (C(1´)); 127.3 (C(2´), C(6´)); 128.9 (C(3´), C(5´)); 130.8 (C(4´)); 153.7 (C(4)). ^{14}N NMR ($CDCl_3$), δ: −52 (=N(O), $\Delta\nu_{1/2}$ = 140 Hz).

Compound **6**. M.p. 76—79 °C. Found (%): C, 45.82; H, 3.33; N, 23.45. $C_9H_8N_4O_4$. Calculated (%): C, 45.77; H, 3.41; N, 23.72. ^{1}H NMR ($CDCl_3$), δ: 3.86 (s, 3 H, CH_3); 7.50—7.53 (m, 3 H, H(3´), H(4´), H(5´)); 7.71—7.74 (m, 2 H, H(2´), H(6´)). ^{13}C NMR ($CDCl_3$), δ: 39.7 (CH_3); 111.3 (C(3)); 121.5 (C(1´)); 126.2 (C(2´), C(6´)); 129.4 (C(3´), C(5´)); 131.3 (C(4´)); 152.1 (C(4)). ^{14}N NMR ($CDCl_3$), δ: −36 (NO_2, $\Delta\nu_{1/2}$ = 35 Hz).

[1,2,5]Oxadiazolo[3,4-*c*]cinnoline-1,5-dioxide (2). ***A.*** A freshly prepared and cooled (to 0 °C) solution of HNO_3 (38 mg, 0.6 mmol) (*d* = 1.5 g cm^{-3}) in Ac_2O (1 mL) was added to a suspension of compound **5** (107 mg, 0.6 mmol) in Ac_2O (1 mL) at 5 °C with stirring, followed by addition of a solution of H_2SO_4 (60 mg, 0.6 mmol) (*d* = 1.83 g cm^{-3}) in Ac_2O (1.5 mL). After 10 min, the reaction mixture was poured into the water—ice mixture (25 mL), stirred for 30 min to complete the hydrolysis of Ac_2O, a precipitate was filtered and dissolved in benzene (20 mL).

The filtrate was extracted with benzene (10 mL). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated *in vacuo* to obtain crude product (126 mg). Column chromatography ($CHCl_3$) yielded compound **2** (89 mg, 72%) as yellow crystals, m.p. 203—204 °C (from $CHCl_3$). After crystallization from DMSO m.p. 206—207 °C. Found (%): C, 47.23; H, 1.78; N, 27.24. $C_8H_4N_4O_3$. Calculated (%): C, 47.07; H, 1.97; N, 27.44. IR (KBr), ν/cm^{-1}: 1603 s, 1592 s, 1560 s, 1480 s, 1450 s, 1440 s, 1412 s, 1348 s, 1204 s, 1164 s. MS, *m/z* (I_{rel} (%)): 204 $[M]^+$ (82), 174 $[M - NO]^+$ (62), 144 $[M - 2\,NO]^+$ (100).

B. Sulfuric acid (1 mL) was added in one portion to the *O*-methylated nitramine **4** (10 mg, 0.045 mmol) at 25 °C with vigorous stirring. The reaction mixture was kept at 25 °C for 10 min, poured into water with ice (3 mL), and extracted with CH_2Cl_2 (5×3 mL). The organic extracts were combined, washed with water (2 mL), dried with $MgSO_4$, the solvent was evaporated *in vacuo*. The yield of FCO **2** was 7 mg (75%). The compound was identical to that obtained earlier.

C. A solution of H_2SO_4 (28 mg, 0.29 mmol) ($d = 1.83$ g cm^{-3}) in Ac_2O (1 mL) was added to a solution of Na-salt **7** (34 mg, 0.14 mmol) in Ac_2O (1 mL) at 5 °C with stirring. During addition of H_2SO_4, the yellow reaction solution initially turned colorless, but then acquired yellow color again. The reaction mixture was stirred at 15±3 °C for 1.5 h, then poured in the water—ice mixture (30 mL) and stirred for 30 min. A precipitate was filtered off and dissolved in benzene (10 mL). The filtrate was extracted with benzene (3×10 mL), the combined organic extracts were dried with $MgSO_4$, benzene was removed *in vacuo* to give FCO **2** (25 mg, 89%), m.p. 199—203 °C, which was identical to that obtained earlier.

7-Nitro-[1,2,5]oxadiazolo[3,4-*c*]cinnoline-1,5-dioxide (9). Furoxanocinnoline-5-oxide **2** (80 mg, 0.39 mmol) was added to a mixture of HNO_3 (3 mL) ($d = 1.5$ g cm^{-3}) and H_2SO_4 (2 mL) ($d = 1.83$ g cm^{-3}) at 5 °C. The reaction mixture was stirred at 22—23 °C for 1 h, poured into ice (50 g), and extracted with AcOEt (4×10 mL). The combined organic extracts were washed with H_2O (3×5 mL), dried with $MgSO_4$, and the solvent was evaporated *in vacuo* to obtain FCO **9** (73 mg, 75%) as bright yellow crystals, m.p. 181—187 °C. After crystallization from AcOEt, pure FCO **9** (57 mg, 58%) was obtained, m.p. 186—188.5 °C. Found (%): C, 38.65; H, 1.20; N, 28.05. $C_8H_3N_5O_5$. Calculated (%): C, 38.57; H, 1.21; N, 28.11. IR (KBr), ν/cm^{-1}: 1652 s, 1620 m, 1608 s, 1532 s, 1488 s, 1428 s, 1392 w, 1348 s, 1276 m, 1248 m. MS, *m/z*: 249 $[M]^+$, 219 $[M - NO]^+$, 189 $[M - 2\,NO]^+$.

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