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Replacement of Imine Fragment in the Ring of 2,6-Disubstituted 1,4,3,5-Octathiadiazine-4,4-dioxides in Reaction with Cyano-containing Compounds

E. N. Utkina, A. A. Michurin, and A. V. Shishulina

Nizhegorodskii State Technical University, Nizhni Novgorod, 603600 Russia

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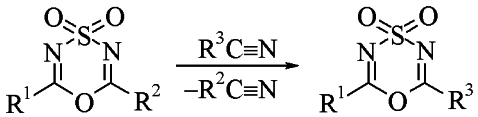
Abstract–Reactions of 2,6-disubstituted 1,4,3,5-octathiadiazine-4,4-dioxides with cyano-containing compounds (nitriles, thiocyanates, *N*,*N*-disubstituted cyanamides) proceeding with replacement of imine fragment in dioxide by corresponding fragment of cyanide were investigated. The limits of the reaction were revealed determined by electronic effects of substituents R^1 and R^2 in dioxide and R^3 in cyanide. Transimination occurred in dioxides with strong electron-withdrawing substituents R^1 (CCl_3, CBr_3, C_6F_5) and weak acceptor or donor substituents R^2 (4-$NO_2C_6H_4$, 4-ClC_6H_4, CH_3) under the action of compounds $R^3C{\equiv}N$ with cyano groups of relatively high nucleophilicity (R^3 = 4-ClC_6H_4, C_6H_5, $(CH_3)_2CHS$, piperidino, morpholino, diethylamino), on the one hand, and with strong electron-withdrawing substituents R^3 (CCl_3) on the other hand.

2,6-Disubstituted 1,4,3,5-octathiadiazine-4,4-dioxides (**I**) are known to be suitable for application as building blocks in the synthesis of hard-to-obtain cyclic and acyclic sulfonyl- and nitrogen-containing compounds, a number of which are biologically active [1–3]. It was recently shown that dioxides **I** reacted with disubstituted cyanamides furnishing various compounds [4]. Among the dioxides **I** conversions was found a reaction proceeding as recyclization–cyclization with replacement of the imine fragment $R^2C{=}N$ in dioxide **I** by the corresponding fragment $R^3C{\equiv}N$ from the cyanamide molecule, i.e. transimination [4].

In extension of this research and taking into consideration the synthetic importance of transimination reaction we have studied some rules governing this reaction that are reported here. The role of the character of substituents R^1 and R^2 in dioxide **I** was investigated in more detail, and also the possibility to use in this reaction of the other classes of cyano-containing compounds (nitriles, thiocyanates).

As was shown recently [4] the direction of cyano group reaction with dioxides **I** was governed first of all by electronic effects of substituents R^1 and R^2 in the ring of 1,4,3,5-octathiadiazine-4,4-dioxide (**I**). Therefore to reveal the general trends of transimination we used a large set of dioxides **I** with substituents R^1 and R^2 differing in electronic effects within a wide range from strong acceptors to strong donors.



Ia–e **IIa–i**

I, R^1 = CCl_3, R^2 = 4-$NO_2C_6H_4$ (**a**); R^1 = CCl_3, R^2 = 4-ClC_6H_4 (**b**); R^1 = CCl_3, R^2 = CH_2= C_CH_3 (**c**); R^1 = CBr_3, R^2 = CH_3 (**d**); R^1 = C_6F_5, R^2 = CH_3 (**e**); **II**, R^1 = CCl_3, R^3 = 4-ClC_6H_4 (**a**); R^1 = CCl_3, R^3 = C_6H_5 (**b**); R^1 = CCl_3, R^3 = $(CH_3)_2CHS$ (**c**); R^1 = CCl_3, R^3 = piperidino (**d**); R^1 = CBr_3, R^3 = piperidino (**e**); R^1 = CBr_3, R^3 = morpholino (**f**); R^1 = CBr_3, R^3 = $(C_2H_5)_2N$ (**g**); R^1 = C_6F_5, R^3 = piperidino (**h**); R^1 = R^3 = CCl_3 (**i**).

As cyano-containing we used a wide range of compounds, from cyanamides and thiocyanates with strongly nucleophilic cyano groups to trichloroacetonitrile with an electron-deficient cyano group [5].

It was established that transimination occurred in reactions of dioxides **I** with strong electron-withdrawing substituents R^1 (CCl_3, CBr_3, C_6F_5) and weak electron-acceptor or donor substituents R^2 (4-$NO_2C_6H_4$, 4-ClC_6H_4, CH_3). The substitution of imine fragment in dioxide **I** proceeded as a rule at the use of compounds with more nucleophilic cyano groups than in the nitrile eliminated from the ring of dioxide **I** in the course of reaction. Thus at heating 6-(4-nitrophenyl)-2-trichloromethyl-1,4,3,5-octathia-

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Table 1. Reaction time, yields, melting points, and IR spectra of dioxides **IIa**–**i**

Compd. no.	Time, h (60°C, C_6H_5)	Yield, %	mp (decomp.), °C	IR spectrum, ν, cm^{-1}	
				SO_2	C=N
IIa	7	96	125–126[a]	1190, 1350	1635, 1730
IIb	4	97	152–154[b]	1200, 1400	1640, 1725
IIc	4	95	127	1180, 1350	1635, 1725
IId	5	85	144[c]	1170, 1395	1680, 1750
IIe	5	94	152	1180, 1375	1650, 1725
IIf	5	89	178	1185, 1360	1650, 1720
IIg	5	93	139	1180, 1360	1655, 1720
IIh	9	93	138	1185, 1360	1670, 1730
IIi	9	94	146–147[d]	1185, 1385	1720

[a] Publ. mp 125–126°C [2]. [b] Publ. mp 153–155°C [2]. [c] Publ. mp 144°C [2]. [d] Publ. mp 146–147°C [2].

Table 2. ^{1}H NMR spectra and elemental analyses of 2,6-disubstituted 1,4,3,5-octathiadiazine-4,4-dioxides **IIc**–**h**

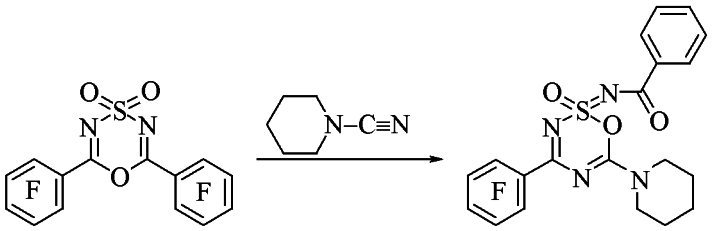
Compd. no.	^{1}H NMR spectrum, δ, ppm	Found, %					Formula	Calculated, %				
		C	H	Hlg	N	S		C	H	Hlg	N	S
IIc	1.24 d (6H, CH_3), 3.12–3.84 m (1H, CH)[a]	23.07	2.19	34.21	4.50	20.50	$C_6H_7Cl_3NO_3S_2$	23.11	2.25	34.19	4.49	20.55
IId	1.48–1.84 m (6H, CH_2), 3.44–3.82 t [4H, $(CH_2)_2N$][b]	–	–	–	–	–	–	–	–	–	–	–
IIe	1.75–1.99 m (6H, CH_2), 3.50–3.81 t [4H, $(CH_2)_2N$][b]	20.75	2.13	51.11	8.81	6.83	$C_8H_{10}Br_3N_3O_3S$	20.53	2.15	51.22	8.98	6.85
IIf	–	17.95	1.70	51.10	8.98	6.80	$C_7H_8Br_3N_3O_4S$	17.90	1.72	51.04	8.94	6.83
IIg	–	18.48	1.10	52.62	5.25	7.00	$C_7H_5Br_3N_2O_3S$	18.45	1.11	52.60	5.27	7.04
IIh	1.55–1.70 m (6H, CH_2), 3.50–3.65 t [4H, $(CH_2)_2N$][b]	40.81	2.60	24.72	10.75	8.32	$C_{13}H_{10}F_5N_3O_3S$	40.74	2.63	24.78	10.96	8.36

[a] ^{1}H NMR spectrum taken in $CDCl_3$. [b] Spectra taken in acetone-d_6.

diazine-4,4-dioxide (**Ia**) with 4-chlorobenzonitrile and benzonitrile the corresponding dioxides **IIa** and **IIb** were obtained in close to quantitative yields. In reaction of 6-(4-chlorophenyl)-2-trichloromethyl-1,4,3,5-octathiadiazine-4,4-dioxide (**Ib**) with isopropyl thiocyanate formed dioxide **IIc**. From 6-methyl-2-pentafluorophenyl-1,4,3,5-octathiadiazine-4,4-dioxide (**Ie**) and *N*-cyanopiperidine dioxide **IIh** was obtained in a virtually quantitative yield.

As was shown before [5–8] nitriles were capable to demonstrate dual reactivity in reaction with SO_3. The same pattern of behavior they show also in transimination. The trichloroacetonitrile with a strong electron-withdrawing group (R^3 = CCl_3) easily replaced imine fragment in dioxide **Ib** containing less acceptor group 4-ClC_6H_4 to afford dioxide **IIi** in virtually quantitative yield.

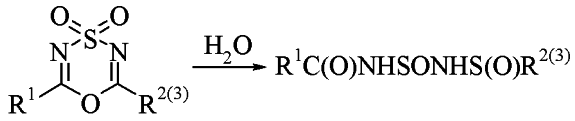
It should be noted that at sharply increased electron-withdrawing effect of substituent R^2 in dioxide **I** (R^2 = CCl_3) and high nucleophilicity of cyano group in the cyanide R^3CN (at the use cyanamides instead if nitriles) the direction of reaction changes. Here instead of transimination form 2,4,6-trisubstituted 1,2,3,5-oxathiadiazin-2-oxides (**III**) in conformity to



If **III**

data of [4]. For instance, the reaction of 2,6-bis(pentafluorophenyl)-1,4,3,5-oxathiadiazine-4,4-dioxide (**If**) with *N*-cyanopiperidine gave rise to a single product, 6-piperidino-2-pentafluorobenzoylimino-4-pentafluorophenyl-1,2,3,5-oxathiadiazin-2-oxide (**III**).

The composition and structure of dioxides **IIa–i** were determined from elemental analyses, IR and ^{1}H NMR spectra. Besides the hydrolysis of newly prepared by us initial dioxides **Ie, f**, and of dioxides



Ie, f, IIe–h **IVa–f**

IV, R^1 = C_6F_5, R^2 = CH_3 (**a**); R^1 = R^2 = C_6F_5 (**b**); R^1 = CBr_3, R^3 = piperidino (**c**); R^1 = CBr_3, R^3 = morpholino (**d**); R^1 = CBr_3, R^3 = $(C_2H_5)_2N$ (**e**); R^1 = C_6F_5, R^3 = piperidino (**f**).

IIe–h into the corresponding *N*,*N*'-diacylsulfamides **IVa, b** and *N*-amidosulfonylureas **IVc–f** confirmed the structures of oxides **I, IId–h**.

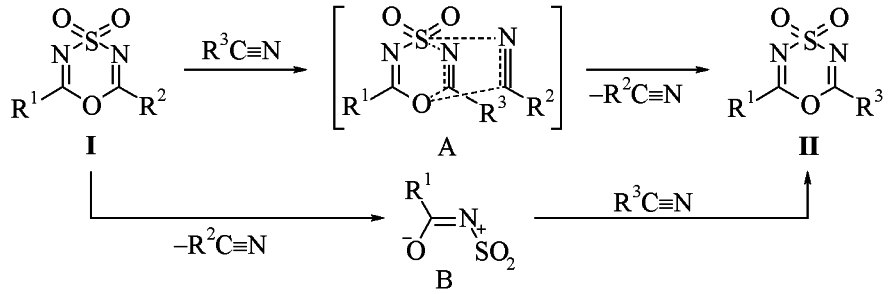
The results obtained permit some assumptions on the pathroutes of the reaction. The transimination occurs with participation in the reaction with cyano group of electrophilic sulfur and nucleophilic oxygen of the dioxide **I** ring. It is presumable that the difference in behavior of cyanides with strong donor group on the one hand, and strong acceptor groups on the other hand is due to formation in the reaction of dissimilar intermediates. Dioxides **I** with strong acceptor (R^1 = CCl_3, CBr_3, C_6F_5) and less acceptor groups [R^2 = 4-$NO_2C_6H_4$, C_6H_5, CH_2= $C(CH_3)$, CH_3] react with nitriles possessing donor or weak acceptor groups (C_6H_5, 4-ClC_6H_4) apparently by the type of [4+2]-cycloaddition via transition state A, or in the limiting case, through formation of reactive species, N-sulfonylamides B.

Table 3. Yields, melting points, and IR spectra of *N*-amidosulfonylureas **IVc–f**

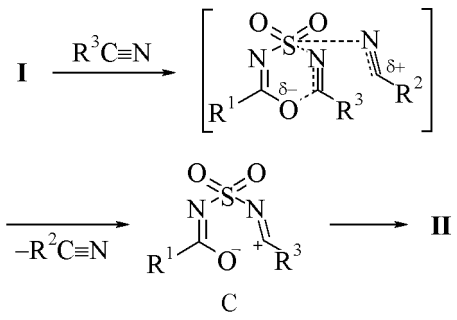
Compd. no.	Yield, %	mp (decomp.), °C	IR spectrum, ν, cm^{-1}		
			C=O	SO_2	N–H
IVc	96	124	1695, 1745	1165, 1370	3095, 3220
IVd	97	129	1700, 1755	1190, 1370	3100, 3300
IVe	98	112	1695, 1750	1175, 1375	3120, 3310
IVf	99	126	1700, 1600	1175, 1375	3070, 3290

Table 4. Elemental analyses and neutralization equivalents of *N*-amidosulfonylureas **IVc–f**

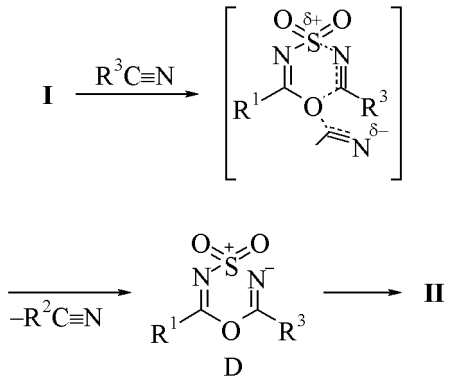
Compd. no.	Found, %						Formula	Calculated, %					
	C	H	Hlg	N	S	neutralization equiv.		C	H	Hlg	N	S	neutralization equiv.
IVc	19.73	2.45	49.39	8.62	6.63	487.50	$C_8H_{12}Br_3N_3O_4S$	19.78	2.49	49.35	8.65	6.60	485.70
IVd	17.29	2.12	49.20	8.53	6.59	488.75	$C_7H_{10}Br_3N_3O_5S$	17.24	2.07	49.15	8.62	6.57	487.70
IVe	17.71	2.59	50.68	8.75	6.75	474.85	$C_7H_7Br_3N_2O_4S$	17.75	2.55	50.60	8.87	6.57	473.70
IVf	38.97	3.04	23.64	10.43	7.98	403.00	$C_{13}H_{12}F_5N_3O_4S$	38.93	3.02	23.69	10.48	8.00	402.00



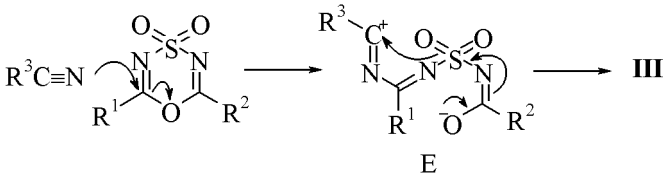
In reactions of the same dioxides with cyanamides and thiocyanates possessing cyano groups with higher nucleophilicity due the presence of strong *n*-donor groups [9] a stronger contribution makes the coordination of sulfur atoms in dioxide **I** and nitrogen of the cyano group. In this case the reaction proceeds through an intermediate C.



In reaction of the above dioxides **I** with trichloroacetonitrile characterized by strong deficit of electron density on the cyano group an important contribution makes coordination of the oxygen in heterocycle **I** and carbon atom of the cyano group. A probable reaction scheme may be represented via formation of intermediate D.



In reactions between dioxides with two strong electron-withdrawing substituents R^1 and R^2 and sufficiently nucleophilic cyano groups (cyanamide) the reaction centers change. Instead of sulfur a carbon atom C^2 operates as an electron-deficient center, and the role of nucleophilic center plays the oxygen of SO_2 group. The reaction involves formation of intermediate E [4] and results in compound **III**.



EXPERIMENTAL

IR spectra of compounds **I–IV** were recorded on spectrophotometers UR-20 and Specord M-80 from solutions in dichloromethane. ^{1}H NMR spectra were registered on spectrometers Gemini (300 MHz) and Tesla BS-487B (80 MHz) at 20°C with the use as internal reference TMS and HMDS respectively. Chemical shifts were measured in the δ scale with an accuracy within 0.02 ppm.

The reaction progress was monitored and homogeneity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent acetone–hexane, 1 : 1.

Initial unsymmetrical dioxides **Ia–e** were obtained from the corresponding nitriles R^1CN, R^2CN, and SO_3 [7].

Symmetrical dioxide **If** was prepared from pentafluorobenzonitrile and SO_3 by procedure [10].

Syntheses of dioxides **I** were carried out under atmosphere of dry nitrogen.

6-Methyl-2-pentafluorophenyl-1,4,3,5-oxathiadiazine-4,4-dioxide (Ie). A mixture of 0.42 g (2.17 mmol) of pentafluorobenzonitrile and 0.35 g (4.34 mmol) of SO_3 was kept for 24 h at 20°C. We obtained 0.75 g (99%) of 6-pentafluorophenyl-

1,3,2,4,5-dioxadithiazine-2,2,4,4-tetroxide (**V**). Found, %: C 23.67; F 27.01; N 3.94; S 18.21. $C_7F_5NO_6S_2$. Calculated, %: C 23.80; F 26.9; N 3.97; S 18.15. By hydrolysis of 0.1 g of tetroxide **V** with water at 50°C we obtained 0.06 g (97%) of pentafluorobenzamide, mp 150°C (publ. 150°C [11]).

To a solution of 0.75 g (2.12 mmol) of tetroxide (**V**) in 10 ml of CH_2Cl_2 at –80°C was added at vigorous stirring a mixture of 0.16 g (4.24 mmol) of acetonitrile and 0.15 g (2,12 mmol) of pyridine in 10 ml of CH_2Cl_2, The mixture was kept for 1 h at –80°C and 2 h at 16°C. The precipitate of $PySO_3$ was filtered off. After evaporation of solvent from the filtrate we obtained 0.66 g (99%) of dioxide **Ie**, mp 105°C. IR spectrum (CH_2Cl_2, ν, cm^{-1}): 1730, 166z0 (C=N), 1380, 1200 (SO_2). Found, %: C 34.51; H 1.01; F 30.15; N 8.99; S 10.25. $C_9H_3F_5N_2O_3S$. Calculated, %: C 34.41; H 0.96; F 30.23; N 8.92; S 10.20.

The hydrolysis of 0.15 g of dioxide **Ie** at 20°C afforded 0.15 g (97%) of *N*-acetyl-*N*'-pentafluorobenzoylsulfamide (**IVa**), mp 89°C. IR spectrum (oily compound, ν, cm^{-1}): 3300, 3240 (N–H); 1735, 1670 (C=O); 1370, 1160 (SO_2). Found, %: C 32.49; H 1.48; F 28.50; N 8.47; S 9.61. Neutralization equiv 165.60. $C_9H_5F_5N_2O_4S$. Calculated, %: C 32.54; H 1.52; F 28.59; N 8.43; S 9.65. Neutralization equiv 166.10.

2,6-Bis(pentafluorophenyl)-1,4,3,5-oxathiadiazine-4,4-dioxide (If). A mixture of 1.26 g (6.53 mmol) of pentafluorobenzonitrile and 0.25 g (3.27 mmol) of SO_3 was heated for 12 h to 65°C. Then the product was washed with hexane. We obtained 1.44 g (99%) of dioxide **If**, mp (decomp.) 149°C (from dichloromethane–hexane). IR spectrum (CH_2Cl_2, ν, cm^{-1}): 1650 (C=N), 1345, 1205 (SO_2). By hydrolysis of dioxide **If** with 30% solution of NaOH followed by treating with H_2SO_4 at 0°C we obtained 98% of *N*,*N*'-bis(pentafluorobenzoyl)sulfamide (**IVb**), mp (decomp.) 127°C (from ethanol). IR spectrum (oily substance, ν, cm^{-1}): 3340 (N–H), 1705 (C=O), 1345, 1165 (SO_2). Found, %: C 34.69; H 0.45; F 39.19; N 5.83; S 6.57. Neutralization equiv 240.12. $C_{14}H_2F_{10}N_2O_4S$. Calculated, %: C 34.73; H 0.42; F 39.23; N 5.79; S 6.62. Neutralization equiv 242.11.

Transimination of dioxides Ia–e into dioxides IIa–i. To a solution of 0.6 mmol of dioxide **Ia** in 10 ml of benzene was added 0.7 mmol of an appropriate cyanide R^3CN in 4 ml of benzene at 80°C under atmosphere of dry nitrogen. The mixture was kept at this temperature for the time specified in Table 1. Then the solvent was removed, the residue was treated with hexane to obtain dioxides **IIa–i**. The reaction time, yields, melting points, IR spectra of dioxides **IIa–i** are given in Table 1, ^1H NMR spectra of dioxides **IIc–e, h** and elemental composition of dioxides **IIc, e–h** are presented in Table 2.

2-Trichloromethyl-6-(4-chlorophenyl)-1,4,3,5-oxathiadiazine-4,4-dioxide (IIa) was obtained by reaction of dioxide (**Ia**) and 4-chlorobenzonitrile; **2-trichloromethyl-6-phenyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IIb)** from dioxide **Ia** and benzonitrile; **2-isopropyl-6-trichloromethyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IIc)** from dioxide **Ib** and isopropyl thiocyanate; **2-piperidino-6-trichloromethyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IId)** from dioxide **Ib** and *N*-cyanopiperidine; **2-piperidino-6-tribromomethyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IIe)** from dioxides **Ic** and **Id** and *N*-cyanopiperidine; **2-morpholino-6-tribromomethyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IIf)** from dioxide **Id** and *N*-cyanomorpholine; **2-diethylamino-6-tribromomethyl-1,4,3,5-oxathiadiazine-4,4-dioxide (IIg)** from dioxide (**Id**) and *N*,*N*-diethylcyanamide; **2-pentafluorophenyl-6-piperidino-1,4,3,5-oxathiadiazine-4,4-dioxide (IIh)** from dioxide (**Ie**) and *N*-cyanopiperidine; **2,6-bis(trichloromethyl)-1,4,3,5-oxathiadiazine-4,4-dioxide (IIi)** from dioxide **Ib** and trichloroacetonitrile.

General procedure for hydrolysis of dioxides IIe–h. With 30% solution of NaOH was treated 0.25 mmol of dioxide **IIe–h** for 5 min, and the mixture was cooled to 0°C. To the mixture was added 0.2 ml of H_2SO_4. The separated precipitate was washed with water and dried. We obtained the corresponding *N*-amidosulfonylureas (**IVc–f**) (97–99%): ***N*-tribromoacetamido-*N*',*N*'-pentamethylenesulfonylurea (IVc), *N*-tribromoacetamido-*N*',*N*'-bis(dimethylene)oxysulfonylurea (IVd), *N*-tribromoacetamido-*N*',*N*'-diethylsulfonylurea (IVe), *N*,*N*-pentamethylene-*N*'-pentafluorobenzamidosulfonylurea (IVf).** The precipitates were crystallized from a mixture dichloromethane–hexane (2:1). Yields, melting points, and IR spectra of sulfonylureas **IVc–f** are given in Table 3, elemental composition and neutralization equivalents in Table 4.

Pentafluorobenzamido-4-pentafluorophenyl-6-piperidino-1,2,3,5-oxathiadiazine-2-oxide (III). A solution of 0.21 g (1.93 mmol) of *N*-cyanopiperidine and 0.3 g (0.64 mmol) of dioxide **If** in 20 ml of benzene was heated to 70°C for 15 h. The solvent was distilled off, the residue was treated in succession with hexane and ether. We obtained 0.33 g

(89%) of oxide **III**, mp 160°C (from dichloromethane–hexane). IR spectrum (CH_2Cl_2, ν, cm^{-1}): 1720 (C=O), 1670, 1550 (C=N), 1355, 1165 (SO_2). ^1H NMR spectrum [$(CD_3)_2CO$, δ, ppm]: 1.55–1.82 m (6H, CH_2), 3.55–3.82 t [4H, $(CH_2)_2N$]. Found, %: C 41.64; H 1.79; F 32.87; N 9.57; S 5.52. $C_{20}H_{10}F_{10}N_4O_3S$. Calculated, %: C 41.68; H 1.75; F 32.96; N 9.73; S 5.57.

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