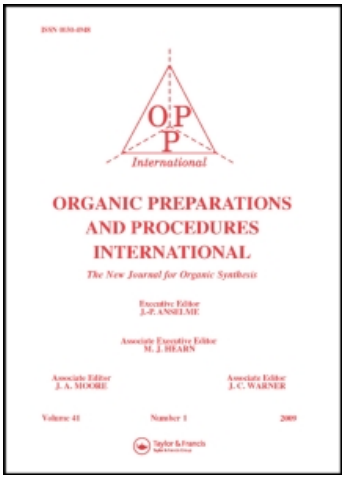

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5-NITRO-2-FURYL DIIMIDOYL DISULFIDES BY IODINE OXIDATION OF *N*-ARYL-5-NITRO-2-THIOFURAMIDES

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5-NITRO-2-FURYL DIIMIDOYL DISULFIDES BY IODINE OXIDATION OF *N*-ARYL-5-NITRO-2-THIOFURAMIDES†

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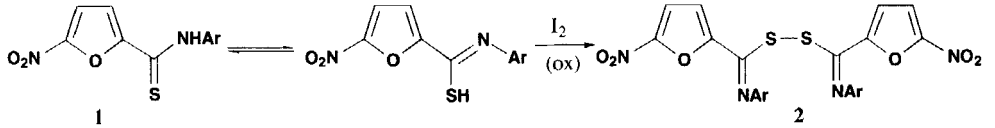
One of the most striking differences between of thioamides and amides is their behavior on oxidation. While amides are oxidized at the carbon atom of the side-chain under forcing conditions, their thio analogues are readily attacked at the sulfur atom yielding a variety of products. The type of product is highly dependent on the oxidizing agent used; desulfurization and the formation of disulfides, sulfides, thioamide *S*-oxides, heterocycles have been observed.[1] The most favorable method for conversion to diimidoyl disulfides seems to be the oxidation by iodine.[2]



a) Ar = C_6H_5; b) Ar = *o*-MeC_6H_4; c) Ar = *m*-MeC_6H_4; d) Ar = *p*-MeC_6H_4;
e) Ar = *p*-$MeOC_6H_4$; f) Ar = *p*-ClC_6H_4; g) Ar = *p*-$NO_2C_6H_4$.

The potential biological activity of nitrofurans[3] has prompted us to prepare several substituted 5-nitro-2-thiofuramides and to study their oxidation. Reports on the oxidation of nitro-substituted thiofuramides are scarce[4] and the formation of the title compounds has not been reported. Thus, *N*-aryl-5-nitro-2-thiofuramides (**1**) were oxidized with iodine in the presence of tertiary amine to yield the corresponding 5-nitro-2-furyl-substituted diimidoyl disulfides (**2**) exclusively. The starting thioamides (**1**) were obtained by a standard method[5,6] and their structure was confirmed by elemental analyses, MS, UV, IR and ^{1}H NMR spectra (Tables 1-3).

TABLE 1. Yields, mps. and Analyses for New 5-Nitro-2-thiofuramides[a]

Cmpd	Yield (%)	mp. (C°)	Anal. Calcd (Found) C		H		N	
1b	91	137-138	54.95	(54.68)	3.84	(3.97)	10.68	(10.75)
1c	40[b]	110-111	54.95	(55.05)	3.84	(4.09)	10.68	(10.28)
1f	94	186-187	46.74	(46.76)	2.50	(2.66)	9.91	(9.74)
1g	90	192-194	45.05	(45.36)	2.41	(2.64)	14.33	(13.73)
3	97	145-146	51.95	(51.94)	5.55	(5.48)	11.02	(10.91)
4	93	139-140	62.95	(63.07)	3.73	(3.83)	8.64	(8.90)

a) Compounds **1a**, **1d** and **1e** were prepared earlier.[6] b) Eluted from a silica gel column with cyclohexane-benzene 10:1.

TABLE 2. Mass Spectra of *N*-Aryl-5-nitro-2-thiofuramides (**1a-g**)

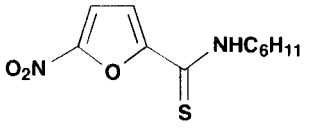
Cmpd	m/z (Relative intensity, %)
1a	249(15), 248($M^{+\cdot}$, 100), 247(92), 215(25), 173(20), 156(14), 110(52), 77(37), 65(12), 57(14), 51(15), 43(15).
1b	263(11), 262($M^{+\cdot}$, 55), 247(41), 242(41), 201(54), 163(56), 91(71), 83(41), 78(46), 77(45), 71(62), 69(49), 65(44), 57(90), 51(25), 43(60), 41(46).
1c	263(11), 262($M^{+\cdot}$, 58), 261(53), 247(12), 229(15), 187(13), 124(26), 91(41), 82(17), 65(20), 58(78), 43(100).
1d	263(18), 262($M^{+\cdot}$, 100), 261(51), 229(43), 187(13), 173(10), 156(11), 124(81), 91(63), 82(40), 79(16), 77(20), 65(26).
1e	279(11), 278($M^{+\cdot}$, 62), 245(28), 141(11), 140(100), 125(20), 122(35), 95(15), 82(51), 77(16), 65(10), 64(18), 58(22), 43(50).
1f	284($M^{+\cdot}$, 26), 283(21), 282($M^{+\cdot}$, 65), 281(30), 249(32), 163(41), 156(30), 146(40), 144(100), 111(27), 98(46), 82(60), 69(30), 57(59), 55(37) 42(42).
1g	294(19), 293($M^{+\cdot}$, 100), 292(74), 260(25), 246(15), 173(20), 172(18), 156(72), 155(27), 139(23), 110(14), 82(78), 76(22), 72(21), 63(15), 50(17), 43(17).

TABLE 3. Spectroscopic Data for 5-Nitro-2-thiofuramides **(1a-g, 3 and 4)**

Cmpd	UV[a] λ_{max}(log ε)	IR[b] (cm^{-1})	^{1}H NMR[d] (δ_{ppm})
1a[g]	201 (4.43) 227 (4.33) 253 (4.14) 336 (4.46)	3220(m) 1540(s) 1360(s) 1006(s)	9.55(bs, 1H), NH[e]; 7.90-7.20(m, 5H), phenyl; 7.49 (d, 1H, J = 4) and 7.32(d, 1H, J = 4), furan (3-H and 4-H).[f]
1b	201 (4.29) 228 (4.15) 328 (4.16)	3250(m)[c] 1520(s) 1360(s) 1015(vs)	9.40 (bs, 1H), NH[e]; 7.70-7.15 (m, 5H), unresolved *o*-substituted phenyl and furan (3-H or 4-H); 7.50 (d, 1H, J = 4), furan (3-H or 4-H); 2.34 (s, 3H), CH_3.
1c	201 (4.29) 224 (4.15) 257 (3.89) 338 (4.22)	3250(m) 1530(m) 1360(s) 1015(m)	9.50 (bs, 1H), NH[e]; 7.72-7.00 (m, 4H), *m*-substituted phenyl; 7.48 (d, 1H, J = 4), and 7.32 (d, 1H, J = 4), furan (3-H and 4-H)[f]; 2.42 (s, 3H), CH_3.
1d[g]	200 (4.18) 225 (4.17) 260 (3.95) 339 (4.27)	3220(m) 1525(m) 1365(vs) 1005(s)	9.56 (bs, 1H), NH[e]; 7.64 (d, 2H, J = 9) and 7.20 (d, 2H, J = 9), *p*-substituted phenyl; 7.48 (d, 1H, J = 4) and 7.36 (d, 1H, J = 4), furan (3-H and 4-H)[f]; 2.38 (s, 3H), CH_3.
1e[g]	200 (4.18) 226 (4.00) 270 (3.76) 343 (4.13)	3300(m) 1540(vs) 1365(vs) 1010(m)	9.50 (bs, 1H), NH[e]; 7.60 (d, 2H, J = 9) and 9.96 (d, 2H, J = 9), *p*-substituted phenyl; 7.48(d, 1H, J = 4) and 7.35 (d, 1H, J = 4), furan (3-H and 4-H)[f]; 3.85 (s, 3H), OCH_3.
1f	200 (4.55) 233 (4.48) 335 (4.55)	3220(w)[c] 1505(s) 1360(vs) 1010(vs)	9.45 (bs, 1H), NH[e]; 7.94-7.27 (m, 6H), unresolved *p*-substituted phenyl and furan (3-H and 4-H).
1g	236 (3.79) 270 (3.57) 344 (4.15)	3200(m)[c] 1500(s) 1370(m) 1010(m)	12.70 (bs, 1H), NH[e]; 8.37 (d, 2H, J = 9) and 8.10 (d, 2H, J = 9), *p*-substituted phenyl; 7.83 (d, 1H, J = 4) and 7.63 (d, 1H, J = 4), furan (3-H and 4-H)[f].
3	232 (3.96) 326 (4.01)	3320(m) 1540(s) 1005(s)	8.00(bs, 1H), NH[e]; 7.43 (d, 1H, J = 4) and 7.30 (d, 1H, J = 4), furan (3-H and 4-H)[f]; 2.40-1.50 (m, 11H), cyclohexyl.
4	202 (4.44) 250 (4.06) 341 (4.14)	1500(vs) 1360(s) 1030(s)	7.50-7.00 (m, 12H), unresolved phenyl and furan (3-H and 4-H).

a) In ethanol. b)Peak intensity is represented as very strong (vs), strong (s), medium (m) or weak (w).
c) In KBr pellet; d) In $CDCl_3$ except for **1g** when NMR spectra were taken in DMSO-d_6. Peak multiplicities are represented by s (singlet), bs (broad singlet), d (doublet), and m (multiplet). Chemical shift (δ) in ppm, J in Hz. e) D_2O exchangeable. f) Assignments uncertain. g) Prepared earlier.[6]

The oxidation was carried out in ether or in dioxane at 0-5°. Higher temperatures led to profound decomposition and/or polymerization. The reaction is highly dependent on the purity of the starting *N*-aryl-5-nitro-2-thiofuramide. Attempts to oxidize the *N*-cyclohexyl derivative (**3**) were unsuccessful, yielding mostly unchanged starting material; evidently compound (**4**) is structurally



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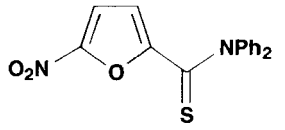

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incapable being oxidized in this fashion. The products were stable on prolonged standing at room temperature or upon heating for 6 hrs in boiling benzene. Similar heating of analogous compounds without the nitro group in the furan ring led to partial desulfurization to the corresponding sulfides.[2a] This stabilization by nitro group seems to be similar to the known stabilization of *N*-aryl-diimidoyl disulfides by electron-acceptors in aryl group.[2a,7] When a nitro group was present both on the 2-furyl and the *N*-phenyl substituent (**2g**), the stabilization is even more pronounced. The disulfides were characterized by elemental analyses, UV, IR, ^{1}H NMR and mass spectra.

There are certain similarities in the UV spectra of prepared diimidoyl disulfides (Table 6) and the corresponding starting 5-nitrofurylthioamides (Table 3); however, the 250-270 nm absorption was absent and, as expected, there was a moderate hypsochromic shift of the 330 nm maximum. The intensities of all maxima were increased in comparison with those of the starting thioamides. The disulfide and thioamide IR spectra had distinct similarities. However, beside the absence of NH stretch at 3210-3300 cm^{-1} found in the starting thioamides[8] and appearance of one or two additional bands at the 855-898 cm^{-1} region, the most significant difference in the IR spectra was the band in the 1600 cm^{-1} region due to the C=N stretch[2a,7] found in diimidoyl disulfides. The ^{1}H NMR spectra of all the 5-nitrofuryl-substituted diimidoyl disulfides show a more or less resolved multiplet at δ 8.47-6.63 ppm due to the substituted furan and the substituted benzene ring protons. Distinction between these signals was possible and was most obvious for compound **2g** where the furan protons 3-H and 4-H appeared as two separate doublets at δ 7.80 ppm (J = 4 Hz) and 7.43 ppm (J = 4 Hz) but not necessarily respectively, while the benzene ring protons *(o, o' and m, m')* exhibited two doublets at δ 8.30 ppm (J = 8 Hz) and 7.17 ppm (J = 8 Hz). In the mass spectra of the diimidoyl disulfides prepared, the molecular ion was absent or very weak, except for **11** in which case $M^{+\cdot}$ was found to be the most abundant peak. Except for **11**, the characteristic fragments with highest mass number were $M^{+\cdot}$-78. For all of the compounds prepared, the most characteristic fragments were $M^{+\cdot}/2$ and $M^{+\cdot}/2$ +1 caused by cleavage of the disulfide bond. In other respects, the fragmentation patterns were similar to those of the corresponding thioamides (Table 2) and to the usual fragmentations of other disulfides and nitrofurans.[9]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler micro hot-stage (Reichert, Wien) and are not corrected. The IR spectra were obtained for samples in nujol mull or, when stated, in potassium bromide pellets on a Perkin-Elmer Infracord 137 instrument. The UV spectra were recorded on a Hitachi-Perkin-Elmer Model 124 spectro-photometer using ethanolic solutions. The ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer with TMS as internal standard. Chemical shifts are given in ppm (δ). Mass spectra were run by a Varian MAT CH-7 or a Varian MAT 112S spectrometer at 70 eV by direct insertion probe at elevated temperature (150-200°). The starting 5-nitro-2-furamides[10] were prepared from 5-nitro-2-furoyl chloride and an excess of the appropriate amine in dry dioxane according to the reported procedure.[10b]

Preparation of bis-[*N*-Aryl-(5-nitro-2-furyl)formimidoyl] Disulfides (2a-g). General Procedure.- To the solution of an *N*-aryl-5-nitro-2-thiofuramide (**1**) (0.005 mole) and a tertiary amine (0.006 mole) in 40 mL of anhydrous dioxane, iodine (0.006 gatom) in 25 mL of dry ether at 5° under nitrogen was added. After standing for 0.5-2 hrs the solution was filtered and evaporated under reduced pressure. To an acetone solution (10 mL) of the residue, water was added dropwise until precipitation occurred. Recrystallization from acetone-water gave crystals of pure **2a-g** (Tables 4-6).

TABLE 4. Reactions Conditions for the Preparation, Yields, mps and Analysis of **2a-g**

Product[a,b]	Starting Compd	Time (hrs)	Yield[d] (%)	mp. (°C)	*Anal.* Calcd (Found) C	H	N	S
2a	**1a**	2	32	163-164	53.44 (53.52)	2.85 (2.88)	11.34 (11.11)	12.97 (12.95)
2b	**1b**	1	57	147-148	55.16 (55.19)	3.47 (3.24)	10.72 (10.51)	12.27 (11.70)
2c	**1c**	0.5	90	115-116	55.16 (55.14)	3.47 (3.79)	10.72 (10.49)	12.27 (12.35)
2d	**1d**	0.75	85	161-162	55.16 (54.90)	3.47 (3.31)	10.72 (11.01)	12.27 (12.75)
2e	**1e**	2	43	149-150	51.98 (52.15)	3.27 (3.17)	10.10 (10.19)	11.56 (11.60)
2f	**1f**	1	77	146-148	46.90 (47.13)	2.15 (2.26)	9.94 (10.15)	11.38 (11.05)
2g	**1g**	1	60	213[e]	—	—	14.38[f] (14.39)	—

a)All compunds are pale yellow except for **2e** and **2g** which are orange yellow and yellow respectively. b) Tributylamine was used except for **2b** and **2e** where N-ethylpiperidine was used; triethylamine was used for **2a**. All products were recrystallized from acetone-water. c) Freshly crystallized from methanol. d) Yield of pure product. e) Recrystallization was preceded by chromatography on silical gel (hexane-acetone as eluent). f) Other elemental analyses are unreliable because of the explosive combustion of the sample.

TABLE 5. Spectroscopic Data for Diimidoyl Disulfides **2a-g**

Compd	UV[a] λ_{max}(logε)	IR[b] (cm^{-1})		^{1}H NMR[c] (δ_{ppm})
2a	201(4.65)	1600(w)	1570(m)	7.70-6.63 (m, 12H), phenyl and furan 3-H
	222(4.47)	1550(m)	1525(vs)	or 4-H; 7.53 (d, 2H, J = 4 Hz), furan 4-H or
	321(4.47)	1475(vs)	1350(vs)	3-H.
		990(m)	1015(s)	
		885(m)	875(m)	
2b	201(4.71)	1600(w)	1570(m)	7.57-6.47 (m, 10H), benzene protons and
	222(4.49)	1520(s)	1500(m)	furan (3-H or 4-H); 7.50 (d, 2H, J = 4 Hz),
	316(4.41)	1370(s)	1345(s)	furan (4-H or 3-H); 2.03 (s, 6H), methyl
		1015(s)	995(m)	groups.
		880(m)	875(m)	
2c	201(4.84)	1595(w)	1570(m)	7.60-6.48 (m, 8H), *m*-substituted phenyl;
	224(4.64)	1520(s)	1475(m)	7.48 (d, 2H, J = 4 Hz) and 7.32 (d, 2H, J =
	322(4.58)	1450(s)	1345(s)	4Hz), furan (3-H and 4-H)[d]; 2.05 (s, 6H),
		1020(s)	990(m)	methyl groups.
		865(m)	855(m)	
2d	200(4.58)	1600(m)	1570(m)	7.65 (d, 2H, J = 4 Hz) and 7.22 (d, 2H, J =
	225(4.38)	1550(m)	1525(vs)	4 Hz), furan (3-H and 4-H)[d]; 7.10 (d, 4H, J
=				
	327(4.32)	1495(s)	1470(m)	8 Hz) and 6.72 (d, 4H, J = 8 Hz), *p*-substi-
		1350(s)	1015(s)	tuted phenyl; 2.03 (s, 6H) methyl groups.
		995(m)	890(s),	
		880(s)		
2e	200(4.41	1600(s)	1570(m)	7.63 (d, 2H, J = 3.5 Hz) and 7.21(d, 2H, J =
	227(4.30)	1550(m)	1520(s)	3.5 Hz), furan (3-H and 4-H)[d]; 6.91 (s, 8H),
	326(4.19)	1490(s)	1470(s)	*p*-substituted phenyl; 3.74 (s, 6H), methoxy
		1350(s)	1015(s)	groups.
		990(m)	885(m)	
		878(s)		
2f	202(4.70)	1600(w)	1575(w)	7.58 (d, 2H, J = 3.5 Hz), furan (3-H or
	233(4.55)	1550(m)	1500(s)	4-H)[e]; 7.30 (d, 4H, J = 8.5 Hz) and 6.82 (d,
	323(4.57)	1495(s)	1390(s)	4H, J = 8.5 Hz), *p*-substituted phenyl.
		1310(m)	1010(s)	
		995(m)	885(s)	
		880(s)		
2g	223(4.05)	1600(m)	1575(m)	8.30 (d, 4H, J = 8.5 Hz) and 7.17 (d, 4H, J
	317(4.35)	1510(m)	1500(m)	= 8 Hz), *p*-substituted phenyl; 7.80 (d, 2H, J
		1480(m)	1450(vs)	= 4 Hz) and 7.43 (d, 2H, J = 4 Hz), furan
		1340(s)	1020(m)	(3-H and 4-H)[d].
		990(m)	885(m)	
		865(m)		

a) In ethanol, except **2g** in which case dioxane was used. b) Peak intensity is represented as very strong (vs), strong (s), medium (m) or weak (w). c) In DMSO-d_6. Peak multiplicities are represented by s (singlet), d (doublet) and m (multiplet). d) Assignments uncertain. e) The signals of the other two protons were overlapped by those of the benzene hydrogens.

TABLE 6. Mass Spectra of Disulfides **2a-g**

Compd	m/z (Relative intensity, %)
2a	416(16, $M^{+\cdot}$ -78), 265(19), 264(100), 248(40, $M^{+\cdot}/2$ +1), 247(39, $M^{+\cdot}/2$), 246(35), 235(16), 220(22), 219(61), 218(50), 215(37), 192(20), 191(64), 190(40), 189(75), 178(23), 172(16), 165(34), 163(16), 152(24), 143(17), 128(12), 110(23), 82(22), 77(45), 64(22), 32(96), 30(35), 28(60).
2b	524(25, $M^{+\cdot}$ +2), 523(15, $M^{+\cdot}$ +1), 522(100, $M^{+\cdot}$), 449(15), 265(10), 264(13), 263(15), 261(22, $M^{+\cdot}/2$), 229(12), 133(16), 59(12), 43(13).
2c	445(8), 444(20, $M^{+\cdot}$ -78), 262(25, $M^{+\cdot}/2$ +1), 261(22, $M^{+\cdot}/2$), 229(55), 187(16), 132(12), 91(48), 58(64), 43(100).
2d	552(less than 2%, $M^{+\cdot}$), 445(11), 444(33, $M^{+\cdot}$ -78), 262(40, $M^{+\cdot}/2$ +1), 261(23, $M^{+\cdot}/2$), 260(16), 230(14), 229(80), 186(12), 157(12), 149(33), 133(17), 124(33), 116(13), 91(75), 82(33), 77(18), 65(27), 64(16), 44(30), 43(17), 39(17), 32(100), 30(48), 28(65).
2e	554(trace, $M^{+\cdot}$), 279(11), 278(58, $M^{+\cdot}/2$ +1), 277(11, $M^{+\cdot}/2$), 272(25), 262(100), 256(21), 245(29), 140(72), 128(18), 124(11), 122(42), 111(15), 97(24), 85(28), 82(12), 81(20), 71(42), 69(34), 67(13), 57(68), 55(40), 43(58), 41(31).
2f	562(less than 1%, $M^{+\cdot}$), 486(23), 484(30, $M^{+\cdot}$ -78), 284(14, $M^{+\cdot}/2$ +1), 283(10, $M^{+\cdot}/2$), 282(48, $M^{+\cdot}/2$ +1), 281(32, $M^{+\cdot}/2$), 280(15), 264(11), 251(24), 250(14), 249(100), 177(21), 159(10), 155(40), 145(67), 143(68), 139(10), 138(11), 113(12), 111(27), 96(10), 82(65), 75(27), 64(50), 43(26), 28(98).
2g	506(18, $M^{+\cdot}$ -78), 293(19, $M^{+\cdot}/2$ +1), 292(15, $M^{+\cdot}/2$), 291(23), 277(74), 261(13), 260(73), 214(14), 180(15), 171(10), 164(10), 156(23), 140(100), 134(11), 96(14), 90(23), 82(73), 77(11), 76(22), 66(15), 64(14), 63(20), 54(15), 50(14), 44(69), 38(16), 30(29), 28(38).

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RESOLUTION OF 5-VINYL-2-PYRROLIDINONE. A PRACTICAL SYNTHESIS OF (S)- AND (R)-VIGABATRIN

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Vigabatrin (γ-vinyl GABA, 4-amino-5-hexenoic acid) is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain,[1] which crosses the blood-brain-barrier (BBB), and is used clinically primarily to control seizures refractory to other anticonvulsant drugs.[2] (S)-Vigabatrin is the pharmacological active enantiomer, whereas the (R)-antipode is inactive. The two enantiomers of vigabatrin have been prepared by asymmetric syntheses,[3-7] or by enzyme-catalyzed resolution[8] of