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THIOAMIDES OF 5-NITROFURAN-2-CARBOXYLIC AND 3-(5'-NITROFURYL-2') ACRYLIC ACIDS

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Phosphorus pentasulfide reacts with the amides and substituted amides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2') acrylic acids in ethyl acetate to give the corresponding thioamides. Some amides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2') acrylic acids are synthesized for the first time. Iodine oxidation of 5-nitrofuran-2-thiocarboxamide gives 3,5-bis(5'-nitrofuryl-2')-1,2,4-thiazole.

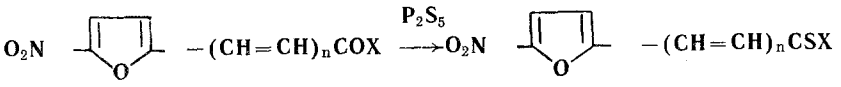
Thioamides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2')- acrylic acid have hitherto been unknown. Regarding furan-2-thiocarboxamides, papers by a number of authors [1-7] deal with their preparation. The unsubstituted furan-2-thiocarboxamide is obtained by treating the nitrile of the acid with hydrogen sulfide in the presence of bases [1-2].

N-substituted furan-2-thiocarboxamides are obtained by treating the corresponding N-substituted amides with phosphorus pentasulfide in the presence of inert solvents (xylene, toluene [1], pyridine [3, 4]). Here the yields are better. To prepare N, N-disubstituted furan-2-thiocarboxamides, use is made of the reaction between furfural, sulfur, and a secondary amine [1], or between ammonium dithiofuroate and a secondary amine [5]. N-cyclohexyl furan-2-thiocarboxamide is obtained from cyclohexylamine and sodium dithiofuroate [6, 7].

We have now effected preparation of the thioamides of 5-nitrofuran-2-carboxylic (III) and 3-(5'-nitrofuryl-2') acrylic (IV) acids by treating the corresponding amides of types I and II with phosphorus pentasulfide.

We synthesized the starting amides (Table 1) partly for the first time, and partly using methods differing from those previously used to prepare them. The methylamides, ethylamides, and dimethylamides of the acids were prepared from the chlorides of the corresponding acids and the amine hydrochlorides, the free amine being liberated by the action of sodium carbonate. In the treatment of the chlorides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2') acrylic acids with diethylamine, morpholine, piperidine, and pyrrolidine, pyridine was used to combine with the liberated hydrogen chloride, and, in some cases, this led to better yields of the corresponding amides than those given in the literature.

The reaction for synthesis of the thioamides (Table 2) was run in ethyl acetate. Use of toluene instead led to considerable resinification. We also prepared the unsubstituted thioamides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2') acrylic acids by reacting the corresponding unsubstituted amides with phosphorus pentasulfide in ethyl acetate.

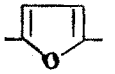


I, II a—g
I, III $n=0$
II, IV $n=1$

III, IV a—g
X=a NH_2; b $NHCH_3$; c $N(CH_3)_2$;
d NHC_2H_5; e $N(C_2H_5)_2$; f  ;
g  ; h 

The thioamides III obtained are a bright yellow to orange color, while IV are orange to red. The melting points of the thioamides III and IV are generally 10° -60° C lower than those of the corresponding starting amides. III and IV compounds are somewhat soluble in water, more soluble in ether and benzene, readily soluble in ethanol, chloroform, and acetone. The thioamides were purified by recrystallization from hexane, heptane, mixed benzene-hexane, or dichloroethane-hexane. Iodine oxidation of 5-nitrofuran-2-thiocarboxamide in ethanol gave 3,5-bis(5'-nitrofuryl-2')-1,2,4-thiadiazole, analogous to the corresponding reaction in the furan series [1].

Table 1

Amides of the Acids O_2N–  –$(CH=CH)_nCOX$

Compound number	X	n	Method of preparation	Mp °C	Found, %			Formula	Calculated, %			Reference	Yield, %
					C	H	N		C	H	N		
Ia	NH_2	0		161—162[a]	—	—	—	$C_5H_4N_2O_4$	—	—	—	8,9	83
Ib	$NHCH_3$	0	A	202—204[b]	—	—	—	$C_6H_6N_2O_4$	—	—	—	9	68
Ic	$N(CH_3)_2$	0	A	130—131[b]	45.68	4.41	15.35	$C_7H_8N_2O_4$	45.64	4.35	15.21	10*	49
Id	NHC_2H_5	0	A	128—129[b]	—	—	—	$C_7H_8N_2O_4$	—	—	—	—	71
Ie	$N(C_2H_5)_2$	0	B	60— 61[c]	50.70	5.64	13.09	$C_9H_{12}N_2O_4$	50.93	5.69	13.20	—	62
If	$N(CH_2)_5$	0	B	92— 94[b]	53.60	5.29	12.47	$C_{10}H_{12}N_2O_4$	53.57	5.36	12.20	10*	82
Ig	$N(CH_2CH_2)_2O$	0	B	115—116[b]	—	—	—	$C_9H_{10}N_2O_5$	—	—	—	—	55
Ih	$N(CH_2)_4$	0	B	159—161[b]	51.42	5.29	13.51	$C_9H_{10}N_2O_4$	51.43	4.75	13.33	—	76
IIa	NH_2	1		225—226[c]	—	—	—	$C_7H_6N_2O_4$	—	—	—	12	93
IIb	$NHCH_3$	1	A	198—199[d]	—	—	—	$C_8H_8N_2O_4$	—	—	—	12	93
IIc	$N(CH_3)_2$	1	A	194—195[d]	—	—	—	$C_9H_{10}N_2O_4$	—	—	—	12	84
IId	NHC_2H_5	1	A	178—180[d]	—	—	—	$C_9H_{10}N_2O_4$	—	—	—	12	86
IIe	$N(C_2H_5)_2$	1	B	89— 90[d]	—	—	—	$C_{11}H_{14}N_2O_4$	—	—	—	12	78
IIf	$N(CH_2)_5$	1	B	134—135[d]	57.44	5.78	11.18	$C_{12}H_{14}N_2O_4$	57.59	5.64	11.19	13*	73
IIg	$N(CH_2CH_2)_2O$	1	B	168—169[e]	52.67	5.08	11.04	$C_{11}H_{12}N_2O_5$	52.38	4.80	11.11	—	76
IIh	$N(CH_2)_4$	1	B	231—232[f]	56.11	4.99	11.67	$C_{11}H_{12}N_2O_4$	55.93	5.12	11.18	—	80

* The reference came to our notice only after completion of the experimental.

[a] Ex n-BuOH, [b] Ex benzene-hexane, [c] Ex iso-PrOH, [d] Ex dilute EtOH, [e] Ex EtOH, [f] Ex BuOAc.

Table 2

Thioamides of the Acids O_2N  $(CH=CH)_nCSX$

Compound number	X	n	Mp, °C	Found, %				Formula	Calculated, %				Yield,* %
				C	H	N	S		C	H	N	S	
III a	NH_2	0	164—165[a]	34.90	2.63	16.03	18.58	$C_5H_4N_2O_3S$	34.88	2.34	16.27	18.62	67
III b	$NHCH_3$	0	145—147[b]	38.66	3.26	15.10	16.89	$C_6H_6N_2O_3S$	38.71	3.22	15.05	17.20	38
III c	$N(CH_3)_2$	0	43— 45[c]	42.22	4.18	13.74	15.70	$C_7H_8N_2O_3S$	41.99	4.03	13.99	16.02	32
III d	NHC_2H_5	0	109—110[b]	42.00	4.13	13.74	16.24	$C_7H_8N_2O_3S$	41.99	4.03	13.99	16.02	53
III e	$N(C_2H_5)_2$	0	74— 76[b]	47.64	5.28	12.18	13.90	$C_9H_{12}N_2O_3S$	47.32	5.26	12.27	14.03	25
III f	$N(CH_2)_5$	0	97— 99[d]	50.19	5.31	11.44	13.41	$C_{10}H_{12}N_2O_3S$	49.99	5.03	11.66	13.34	65
III g	$N(CH_2CH_2)_2O$	0	132—134[e]	47.72	4.30	11.76	13.23	$C_9H_{10}N_2O_4S$	44.62	4.13	11.57	13.22	63
III h	$N(CH_2)_4$	0	123—125[d]	47.52	4.55	12.18	14.18	$C_9H_{10}N_2O_3S$	47.77	4.45	12.38	14.17	94
IV a	NH_2	1	178—179[d]	42.56	3.34	14.09	15.69	$C_7H_6N_2O_3S$	42.42	3.05	14.13	16.18	22
IV b	$NHCH_3$	1	162—163[d]	45.25	3.91	13.31	15.23	$C_8H_8N_2O_3S$	45.32	3.80	13.21	15.15	50
IV c	$N(CH_3)_2$	1	144—145[d]	45.53	4.65	12.20	14.06	$C_9H_{10}N_2O_3S$	47.78	4.46	12.33	14.17	66
IV d	NHC_2H_5	1	165—166[d]	47.59	4.82	12.37	14.18	$C_9H_{10}N_2O_3S$	47.78	4.46	12.32	14.17	37
IV e	$N(C_2H_5)_2$	1	79— 81[d]	52.18	5.80	10.69	12.30	$C_{11}H_{14}N_2O_3S$	51.95	5.55	12.02	12.61	33
IV f	$N(CH_2)_5$	1	122—123[d]	54.29	5.60	10.46	11.79	$C_{12}H_{14}N_2O_3S$	54.08	5.30	10.52	12.04	49
IV g	$N(CH_2CH_2)_2O$	1	152—153[d]	48.98	4.49	10.28	11.60	$C_{11}H_{12}N_2O_4S$	49.24	4.51	10.44	11.95	56
IV h	$N(CH_2)_4$	1	171—172[d]	52.52	4.96	10.90	12.42	$C_{11}H_{12}N_2O_3S$	52.37	4.79	11.10	12.71	63

* The yields stated are those of purified products.

[a] Ex dichloroethane, [b] Ex hexane, [c] Ex Et_2O-hexane, [d] Ex dichloroethane-hexane, [e] Ex heptane.

Experimental

5-Nitrofuran-2-carboxamide. 0.05 mole 5-nitrofuran-2-carbonylchloride was dissolved in 150 ml ether, and dry ammonia passed in with ice cooling. The products were filtered, the precipitate triturated with water, the solid filtered off, washed with water, and dried in air. 3-(5'-Nitrofuryl-2') acrylamide was prepared similarly, except that the acid chloride was dissolved in benzene instead of ether.

Substituted amides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2')-acrylic acids. a) 0.03 mole amine hydrochloride was dissolved in 15 ml water, and a solution of 0.02 mole 5-nitrofuran-2-carbonylchloride or 3-(5'-nitrofuryl-2') acrylyl chloride in 150 ml AcOEt added, and a solution of 0.03 mole Na_2CO_3 crystals in 20 ml water added dropwise, with stirring. The organic layer was separated off and evaporated to dryness. The residue was triturated with water, the solid filtered off, and dried in air.

b) 0.02 mole 5-nitrofuran-2-carbonylchloride or 3-(5'-nitrofuran-2')-acrylyl chloride was dissolved in 50 ml benzene, and a solution of 0.025 mole amine plus 0.02 mole pyridine in 20 ml benzene added dropwise at 20°–25° C, after which stirring was continued for 1 hr more, the solvent distilled off, the residue triturated with water, the solid filtered off, and dried in air.

Thioamides of 5-nitrofuran-2-carboxylic and 3-(5'-nitrofuryl-2')-acrylic acids. 0.02 mole amide or N-substituted amide, 3 g P_2S_5, and 50 ml EtOAc were carefully refluxed together on a water bath for 5 hr, the mixture cooled, the insoluble material twice extracted with 30 ml EtOAc, and the extracts bulked with the main solution. The solvent was distilled off under reduced pressure, and the residue recrystallized.

3,5-Bis(5'-nitrofuryl-2')-1,2,4-thiadiazole. 0.86 g 5-nitrofuran-2-thiocarboxamide was dissolved in 100 ml dry EtOH, and a solution of 7 g I_2 in 100 ml dry EtOH added. Minute glistening plates began to separate. The flask was closed with a stopper, and left for 10 hr, after which the precipitate was filtered off and washed with a small amount of cold dry EtOH. Yield 0.44 g (56%), mp 230°–231° C (ex toluene+petrol ether). Found: C 39.67; H 1.48; N 18.21; S 10.30%. Calculated for $C_{10}H_4N_4O_6S$: C 39.97; H 1.31; N 18.18; S 10.40%.

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