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SYNTHESIS OF TETRAFLUOROBENZOTHIAZOLES AND TETRAFLUORO-4H-1,3,4-BENZOTHIADIAZINES

F. E. HERKES

Contribution 2518 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Inc., Experimental Station Laboratory, Wilmington, Delaware 19898

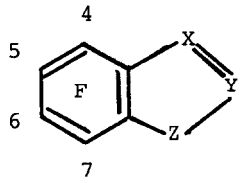
ABSTRACT

2-Substituted, 4,5,6,7-tetrafluorobenzothiazoles (4) and 2-substituted 5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazines (5) can be prepared by intramolecular cyclization of N-pentafluorophenylthioamides (6) and pentafluorophenylthiohydrazides (14), respectively. The thioanilides (6) are prepared either by addition of nucleophiles to pentafluorophenylisothiocyanate or by thioacylation of pentafluoroaniline. The thiohydrazides, (14) are isolated from the reaction of their respective hydrazides with P_2S_5.

When pentafluorophenylanilides are reacted with P_2S_5, the intermediate pentafluorothioamides cannot be isolated and instead are cyclized directly to (4). The ^{19}F chemical shifts and coupling constants for (4) and (5) are tabulated. The latter show a long-range coupling between F7 and NH.

The intramolecular thermal cyclization of nucleophilic centers in substituted side chains of pentafluorophenyl aromatics has proven to be an excellent route to fused five-membered heterocyclic perfluorobenzo and dibenzo derivatives [1],[2]. For example, reaction of sodium hydride with methyl 2,3,4,5,6-pentafluorophenyl ketone yielded 2-methyl-4,5,6,7-tetrafluorobenzofuran via intramolecular displacement of the ortho

fluorine by the oxygen atom [3]. Analogous displacement of fluorine by carbon, nitrogen and sulfur leading to a variety of tetrafluorophenylbenzoaromatics (1) has also been documented.

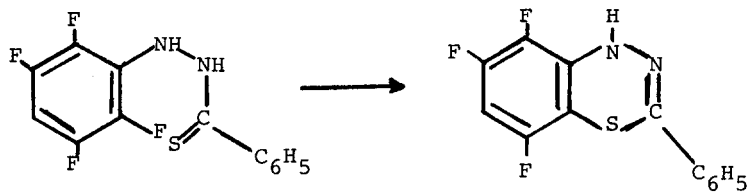


(1)

(1)

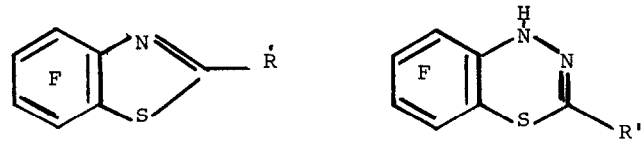
X	Y	Z	
C	C	O	[3-7]
C	C	S	[8-10]
C	C	N	[11-13]
C	N	O	[14]
N	N	N	[15-16]
N	C	N	[17]
O	C	N	[18]

No combination of both sulfur and nitrogen in a five-membered ring, however, has been reported. A recent report by Elliott and Gibson [19] on the intramolecular cyclization of N-(2,3,5,6-tetrafluorophenyl)-N-thiobenzoylhydrazine (2) to phenyl-5,6,8-trifluoro-4H-1,3,4-benzothiadiazine (3) has prompted us to report our results on the synthesis of



(2) (3)

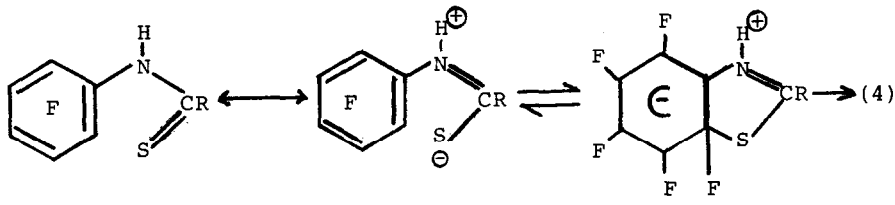
2-substituted-4,5,6,7-tetrafluorobenzothiazoles (4) and 2-substituted-5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazines(5).



(4) (5)

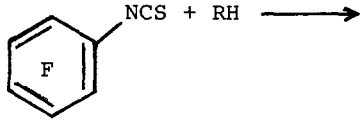
RESULTS AND DISCUSSION

The use of pentafluorophenylthioanilides (6) as a route to (4) was suggested by their polar resonance structures (7) and (8) both of which provide a suitable path for nucleophilic displacement of fluoride by the sulfur enolate atom. Loss of HF



(6) (7) (8)

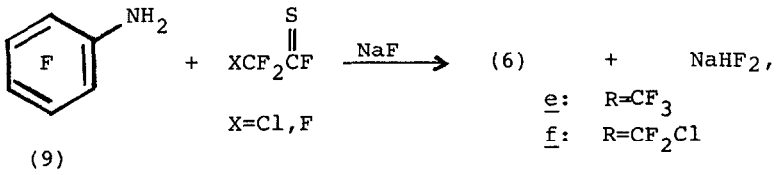
with the formation of the benzothiazole nucleus provides the final driving force for the reaction sequence. Few derivatives of (6) have been reported so we devised a suitable synthesis. Pentafluoroaniline [20] (9) and pentafluorophenylisothiocyanate (10) are convenient starting materials for preparing derivatives of (6). 1,2-Addition of ammonia, 2-propylthiol, diethylamine and ethanol to (10) afforded the respective adducts, (6a-d), in good yields.



(10)

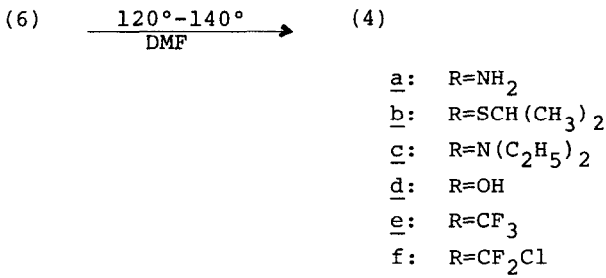
a: R=NH_2
b: R=$SCH(CH_3)_2$
c: R=$N(C_2H_5)_2$
d: R=OC_2H_5

Acylation of (9) provided a second route to derivatives of (6). Trifluoromethyl- and chlorodifluoromethyl-N-pentafluorophenyl-thioacetamides, (6e) and (6f), were prepared in 70% and 83% yield, respectively by addition of trifluoro- and chlorofluorothioacetyl fluoride [21] to (9) in methylene chloride containing NaF.

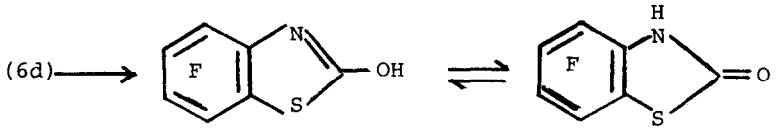


(9)

The intramolecular cyclization of compounds (6a-f) to their respective 2-substituted tetrafluorobenzothiazoles readily occurred by heating a DMF solution of (6) at 120°-140° for 3-4 hr. Addition of KF as a catalytic base and HF scavenger had little effect on the product yield. DMF-KF combinations have been employed in similar situations involving the intramolecular displacement of fluorine by an amino moiety [11,22]. The DMF in the present case apparently acts as its own basic catalyst and/or HF scavenger. DMF also provides dipolar stabilization of the intermediates (7) and (8) on route to (4).



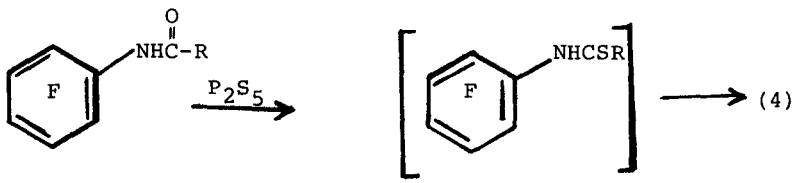
With (6d), 2-hydroxy-4,5,6,7-tetrafluorobenzothiazole (4d) was isolated in only 27% yield instead of the 2-ethoxy product. Heating at 6 wt % solution of (6d) in DMF at 130° for 3 hr followed by cooling and addition to ice water resulted in precipitation of (4d). Sublimation of (4d) yielded an analytically pure sample.



(4d)

If a more concentrated solution of (6d) in DMF was used (i.e., 12 wt %) and the time extended to 6 hr at 130°, only a yellow mobile liquid was obtained after reaction work-up. ^{1}H nmr analysis of the liquid showed four different ethyl groups indicative of four major by-products. GC/MS analysis of the liquid indicated products from rearrangement of the ethyl group from either oxygen to sulfur or oxygen to nitrogen. Only a small amount of the desired 2-ethoxytetrafluorobenzothiazole was detected (via mass spec).

A second route to (4) uses acylated derivatives of (9). In this reaction sequence, which was designed initially for the preparation of the corresponding thioacylated product, N-pentafluorophenylacetamide (11a) was stirred with P_2S_5 in dioxane at 90° until solution of the P_2S_5 occurred (usually 18 hr). The product, after final work-up was 2-methyltetrafluorobenzothiazole (4g) formed by an in situ thermal cyclization of the intermediate thioamide. Similarly, (11b-c) yielded (4 g,h). With N-pentafluorophenyl-2,2,2-trifluoroacetamide (11d) conversion to (4e) required heating at 85° for 13 days. Conversion to (4e) was 27% and 43%, respectively after 9 and 13 days.



(11) a: R = CH_3
b: R = H
c: R = C_6H_5
d: R = CF_3

e: R = CF_3
g: R = CH_3
h: R = H
i: R = C_6H_5

The yields of (4) from both routes were good with few exceptions. Their physical and spectral properties as well as their elemental analyses are summarized in Tables I and II, respectively.

TABLE I

Properties of 2-Substituted-4,5,6,7-Tetrafluorobenzothiazoles (4)[a]

(4)	R	% Yield	mp(bp), °C	$\mu\nu(\varepsilon)$[b]., nm
a	NH_2	78	202-203	217(31,700), 264(11,700)
b	$SCH(CH_3)_2$	31	16(228)[c]	220(15,800), 282(14,100)
c	$N(C_2H_5)_2$	86	53-54	222(27,000), 277(17,600)
d	OH	27	188-189	245(4,900), 278(9,100)
e	CF_3	89	10(185)[c]	231(8,960), 260(5,360) 298(2,390)
f	CF_2Cl	59	-5(217)[c]	233(9,450), 262(6,400) 299(2,330)
g	CH_3	77	26(232)[c]	247(5,800), 283(1,710)
h	H	27	68-71	250(1,935), 285(4,470)
i	C_6H_5	57	121-122	292(23,900)
j	$NHCOCH_3$[d]	37	244-246	216(30,700), 265(11,600)
k	$NHCOCF_3$[e]	56	140	271(14,700)

[a]Satisfactory analytical data were obtained for all new compounds, [b]Ethanol, [c]DTA measurement at atmospheric pressure, [d]Prepared by acylation of (4a) with acetic anhydride in refluxing toluene (24 hr) and recrystallization from benzene, [e]Prepared by acylation of (4a) with trifluoroacetic anhydride in toluene at 50° (2 hr) and recrystallization from benzene.

TABLE II

Elemental Analyses for (4a-i)

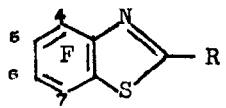
(4)	R	Calcd			Obs		
		C	N	F	C	N	F
a	NH_2	37.63	12.42	34.61	37.87	12.62	34.23
b	$SCH(CH_3)_2$	43.38	5.00	27.29	42.74	4.99	27.05
c	$N(C_2H_5)_2$	47.79	3.96	27.09	47.48	3.62	27.31
d	OH	37.73	6.17	34.68	37.30	6.28	34.08
e	CF_3	35.10	5.35	48.10	34.94	5.09	48.36
f	CF_2Cl	33.10	4.96	39.04	32.95	4.80	39.09
g	CH_3	43.52	6.21	34.14	43.48	6.34	34.89
h	H	39.99	6.83	37.42	40.61	6.77	36.71
i	C_6H_5	55.20	5.02	1.78[a]	55.13	4.95	1.78[a]
j	$NHCOCH_3$	40.80	10.24	-	40.92	10.60	-
k	$NHCOCF_3$	33.32	8.75	0.58[a]	33.22	8.80	0.32[a]

[a] Hydrogen

The ^{19}F spectra of (4) are tabulated in Table III. The assignments of F_4 and F_7 were based on the fluorine chemical shifts reported for 4,5,6,7-tetrafluorobenzo- and dibenzothiophenes [10, 23-26] as well as those for 2-(o-aminotetrafluorophenyl)-2H-tetrafluorobenzotriazole [15] and 4,5,6,7-tetrafluoro-1-pentafluoroanilinobenzotriazole [16]. The ^{19}F chemical shifts of F_4 and F_7 for the reported tetrafluorobenzo- and dibenzothiophenes appear at 156-159 ppm and 140-142 ppm, respectively, upfield from fluorotrichloromethane. In (4a-k), F_4 and F_7 are observed at 144-154 ppm, respectively. Variations within these ranges depend on the 2-substituent. The chemical shift of F_7 was relatively

TABLE III

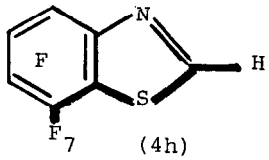
^{19}F Chemical Shifts[a] and Coupling Constants[b] in 2-Substituted-4,5,6,7-Tetrafluorobenzothiazoles (4)



4	R	Solvent	F_4	F_5	F_6	F_7	J_{45}	J_{46}	J_{47}	J_{67}	J_{57}	J_{56}	Other
a	NH_2	DMSO-d_6	154.2	161.8	168.1	141.8	20.5	4.1	13.0	23.5	1.7	21.5	8.07,s,NH_2
b	$SCH(CH_3)_2$	$CDCl_3$	149.0	159.1	161.3	139.2	19.2	c	14.8	20.8	1.0	19.2	1.55,d,CH_3; 3.85,septet,H
c	$N(C_2H_5)_2$	$CDCl_3$	154.0	161.9	175.0	142.1	19.6	3.6	13.0	21.2	1.3	19.8	1.33,t,CH_3; 3.59,q,CH_2
d	OH	DMSO-d_6	153.9	165.9	159.7	142.2	21.0	3.2	12.0	22.5	d	22.5	-
e	CF_3	CCl_4	144.3	155.4	154.1	138.1	18.0	2.5	15.0	19.5	d	18.0	57.2,s,CF_3
f	CF_2Cl	Neat	145.6	157.6	157.0	140.3	17.5	2.5	16.0	19.0	d	18.0	51.9,s,CF_2Cl
g	CH_3	CCl_4	148.4	160.9	159.7	139.2	18.0	c	15.0	19.2	1.0	19.2	2.86,s,CH_3
h	H	$CDCl_3$	147.5	157.9	158.6	138.0	17.5			d			9.07,d,H,J=2.0
i	C_6H_5	$CDCl_3$	148.5	158.4	159.3	138.9	19.0	c	15.0	19.0	c	19.0	Ph,m
j	$NHCOCH_3$	DMSO-d_6	152.3	160.2	163.1	140.9	20.2	1.5	15.0	22.5	1.0	21.0	1.1,s,CH_3;6.39,s,NH_2
k	$NHCOCF_3$	DMSO-d_6	154.5	161.5	168.2	140.9	20.5	4.0	12.7	22.5	1.5	20.5	75.2,d,CF_3

[a] Expressed in ppm upfield from internal $CFCl_3$, [b] Hz, [c] <1Hz, [d] Complex and not resolved.

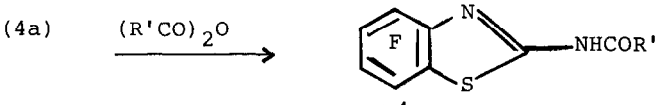
insensitive to substitution at the 2-position whereas F_4 and F_6 did show a slight correlation with the inductive effect of the substituent. The ortho, meta and para F-F coupling constants were typical of those reported earlier [26]. With (4h) (R=H), the multiplicity of F_7 was complex because of an added long-range, through-bond coupling with the 2-hydrogen substituent. The ^1H nmr spectrum of (4h) consisted only of a doublet with J_{H-F}=2Hz. A similar long-range coupling over five bonds involving H_2 and F_7



(4h)

has been observed for 4,5,6,7-tetrafluorobenzothiophene [27]. These authors attribute the coupling to an "electronic interaction of F_7 with H along the trans C_7-C-S-C_2 path." The mass spectra (70eV) of (4f-h) (Table IV) were similar to that of benzothiazole [28]. Loss of carbon monosulfide was observed in (4) in contrast to benzothiazole. Other common fragments with m/e of 87, 111 and 117 were also observed for (4f-h) whose identify and composition were not determined.

The amino group of (4a) was still basic enough to be acetylated by acetic or trifluoroacetic anhydride to yield the corresponding amides (4j) and (4k) in 37% and 56% yield, respectively.



(4)

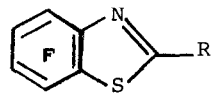
j: $R'=CH_3$

k: $R'=CF_3$

The 2-substituted 5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazines (5) were prepared like (4) using the respective thiohydrazides (14a-c). The thiohydrazides were prepared in good yield by reacting the hydrazides (13a-c) with P_2S_5 in dioxane. In contrast to the intermediate thioamides which were not isolated from the reaction of (11) with P_2S_5, the thiohydrazides (14a-c) were easily isolatable stable solids.

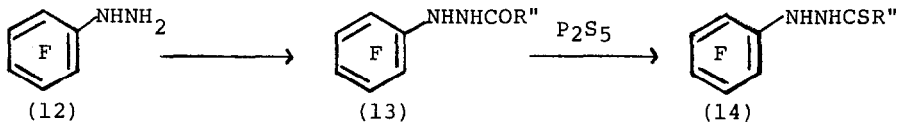
TABLE IV

Mass Spectral Fragmentation[a] of 2-Substituted-4,5,6,7-Tetrafluorobenzothiazoles(4)



Compound	R								
(4f)	CF_2Cl	M/e	293	291	258	257	256	206	1
		I%	12	32	5	10	100	29	
		m/e	124	117	111	93	87	85	
		I%	5	8	10	5	10	8	
		m/e	31						
		I%	12						
(4g)	CH_3	m/e	222	221	193	189	181	180	1
		I%	10	100	8	5	7	38	
		m/e	117	111	93	87	63	45	
		I%	12	21	5	12	5	6	
(4h)	H	m/e	208	207	183	180	163	136	1
		I%	9	100	9	32	7	5	
		m/e	117	111	104	93	90	87	
		I%	14	23	5	6	8	14	
		m/e	44	31					
		I%	14	15					

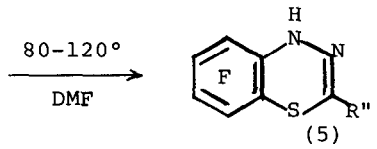
[a] All peaks having an intensity >5% are reported.



a: R" = CH_3
b: R" = C_2H_5
c: R" = C_6H_5

a: R" = CH_3
b: R" = C_2H_5
c: R" = C_6H_5

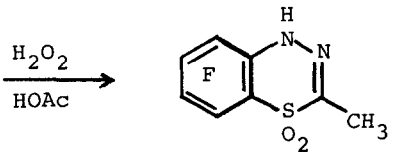
Cyclization of (14) in DMF at 80-120° for 3-20 hr yielded the corresponding benzothiadiazines (5).

(14) 

(5)

a: R" = CH_3
b: R" = C_2H_5
c: R" = C_6H_5

The ^{19}F nmr spectra (Table V) of (5) were similar to those of (4) with the exception of a noticeable long-range coupling between N-H and F_5 [11]. Exchange with D_2O eliminated this coupling as well as the N-H absorption in the ^1H nmr spectrum (see Table V). The magnitude of the ortho, F-F coupling was comparable to that observed in (4), whereas the para F-F coupling was lower (8.5-9.25 Hz) than that for (4) (12-15 Hz). Oxidation of (5a) with H_2O_2 in glacial acetic acid at 60° yielded the 1,1-dioxide derivative (15) in 70% yield.

(5a) 

(15)

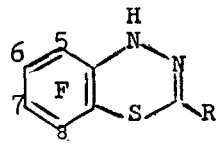
EXPERIMENTAL

All melting and boiling points are uncorrected. Proton and fluorine nmr spectra were recorded on Varian Associates A56/60, A60 and HA 100 nmr spectrophotometers. Proton and fluorine chemical shifts are expressed in ppm upfield from internal TMS and fluorotrichloromethane, respectively. Infrared spectra were recorded on a Perkin Elmer 21 and the ultraviolet spectra obtained on a Cary 17 spectrometer. The mass spectra of (4) were run on a CEC-21-103C mass spectrometer at 70eV.

Pentafluoroaniline (9) and pentafluorophenylhydrazine (12) were prepared using hexafluorobenzene and ammonia and hydrazine hydrate, respectively [20]. Pentafluorophenylacetamide (11a) [29] and pentafluorophenyltrifluoroacetamide (11d) [30] were prepared by known procedures in 76% and 69% yield, respectively.

TABLE V

^{19}F Chemical Shifts[a] and Coupling Constants[b] in 2-Substituted 5,6,7,8-Tetrafluoro-4H-1,3,4-Benzothiadizines (5)



5	R	Solvent	F_5	F6	F7	F8	J_{56}	J_{57}	J_{58}	J_{67}	J_{68}	J_{78}	J_{H8}
a	CH_3	$CDCl_3$	143.4	166.2	159.2	158.2	23.5	.55	9.39	21.7	5.0	22.0	1.4
b	C_2H_5	DMSO-d_6	143.3	166.2	159.4	158.3	24.8	1.25	8.50	20.5	5.0	22.5	1.5
c	C_6H_5	DMSO-d_6	142.8	165.3	158.5	158.6	23.9	1.00	9.25	22.5	5.0	22.5	1.5
15	CH_3	DMSO-d_6	142.0	162.8	149.6	152.6	20.5	1.5	10.8	22.5	6.2	23.0	1.5
c	CH_3	DMSO-d_6	143.8	166.6	159.8	158.9	23.2	<1	9.00	20.5	5.0	20.5	-

[a] Expressed in ppm upfield from internal $CFCl_3$, [b] Hz, [c] N-Deuterio derivative

Cyclization of Pentafluorophenyl Derivatives to 2-Substituted-4,5,6,7-Tetrafluorobenzothiazoles(4)

Method A

A solution of 16-18 mmoles of the appropriate pentafluorophenyl thiocarbamates (6b, 6d), thioureas (6a, 6c) or thioacetanilides (6e, 6f) in 25-35 ml dry DMF was heated at 120-140° for 3-4 hr. The cooled solution was added to 200 ml ice-water followed by ether extraction. Purification of the residue after ether removal of the respective derivatives is summarized below:

Compd.	Method of Purification
(4a) (nc)	Sublimation at 160°/0.5 Torr
(4b) (nc)	Chrom. on neutral silica gel with hexane
(4c) (nc)	Sublimation at 50°/0.5 Torr
(4d) (nc)	Sublimation at 105°/0.7 Torr
(4e) (nc)	Fractionation at 133°/100 Torr
(4f) (nc)	Fractionation at 86°/12 Torr

Method B

A mixture of 15 mmoles of (11a-c) and 5 mmoles P_2S_5 in 50 ml dioxane was stirred and heated at 90° for 18 hr. The solvent was removed under vacuum from the yellow homogeneous solution. The residue was added to 200 ml of cold 2% sodium bicarbonate solution, and the mixture either filtered or extracted with ether depending upon the physical nature of the product. Purification of the products is summarized below:

Compd.	
(4g) (nc)	Distillation 84-85°/8.5 Torr
(4h) (nc)	Sublimation at 65°/0.4 Torr
(4i) (nc)	Recry. benzene

Pentafluorophenylisothiocyanate (10) - A solution of 50 g (0.272 mole) pentafluoroaniline (9) and 4 ml DMF in 500 ml chlorobenzene was treated dropwise with a solution of 42 g (0.635 mole) thiophosgene in 100 ml chlorobenzene at 25° over 2.25 hr. The

viscous red mixture was heated to 90° for 1.5 hr and then 2 hr at 80°. The mixture was cooled, filtered and the solvent removed under vacuum. The residue was fractionated on a 36 cm Teflon® fluorocarbon resin spinning band column to yield 39.3 g (65%), bp 71°/10 Torr; ir (Nujol): 2020 (N=C=S) and 1634 (C=C) cm^{-1}; ^{19}F ($CDCl_3$): 163.5 (t, m-F), 145.0 (t, p-F IF, J=21Hz), 153.0 (dd, o-F, J=22Hz). The ir and ^{19}F nmr were identical to that of an authentic sample obtained from Pierce Chemical (Prod. No. 26931

Pentafluorophenylthiourea (6a) - A mixture of 20 g (0.089 mole of (10) and 13 ml ammonia (d = 0.88) was stirred at 25°. After one hour, the mixture became exothermic ($\Delta T \sim 15-25°$) and a white solid precipitated. After an additional hour of stirring at 25°, the product was filtered and dried to yield 18.7 g (87%) of (6a). Recrystallization from benzene gave mp 154.8 - 155.2°; ir (Nujol): 3448, 3185, 1563, 1516, 1072, 1004 and 732 cm^{-1}.
Anal. Calcd. for $C_7H_3F_5N_2S$: C, 34.71; H, 1.24; N, 11.47.
Found: C, 34.90; H, 1.30; N, 11.45.

S-Isopropyl-N-pentafluorophenyldithiocarbamate (nc)(6b) - A solution of 15 ml 2-propylthiol and 5.0 g (0.022 mole)(10) was refluxed for 4 days. The excess thiol was removed by atmospheric distillation under N_2. Increasing the bath temperature to 130° with vacuum (0.4 Torr) yielded a small amount of unreacted (10). Molecular Still distillation of the residue oil at 100°/100 Torr produced 4.2 g (62% yield) of a light yellow liquid which solidified upon cooling, mp 50°; ir ($CHCl_3$): 3311, 2933, 1497, 1272, 1026, and 987 cm^{-1}; UV (EtOH): 255 nm (ε = 10,300), 278 nm (10,100) and 357 nm (66); ^1H nmr ($CDCl_3$): δ7.52 (s,NH), δ3.18 (septet,1H) and δ0.59 (d,6H); ^{19}F nmr ($CDCl_3$): 143.4 (m,o-F, J_F-F = 21 Hz, 1F) and 162.1 (m,m-F,2F).
Anal. Calcd. for $C_{10}H_8NH_2F_5S_2$: C, 39.90; H, 2.68; N, 4.65, F, 31.5
Found: C, 39.79; H, 2.64; N, 4.70; F, 31.90

N,N-Diethylpentafluorophenylthiourea (nc)(6c) - A solution of 5 g (0.0222 mole) of (10) in 25 ml carbon tetrachloride was treated dropwise at 5° with a solution of 14 g (0.019 mole) diethylamine in 10 ml carbon tetrachloride. The solution was

stirred 0.5 hr at 5°, and then warmed to 25°. The solvent was removed, and the resulting oil crystallized. Recrystallization from benzene-petroleum ether gave 4.0 g (61%) of 6c, mp 98°; ir (Nujol): 3125, 1529, 1374, 1326, 1267, 999 and 743 cm^{-1}.

Ethyl Pentafluorophenylthiocarbamate (nc)(6d) - A solution of 10 g (0.044 mole) of (10) and 1 drop triethylamine in 50 ml ethanol was heated at 50° for 20 hr. The solvent was removed, and the residue recrystallized from benzene to yield 9.6 g (80%) of (6d), mp 57-58°; ir (Nujol): 3226, 1323, 1233, 1103, 1053, 990 and 719 cm^{-1}; ^{19}F nmr ($CDCl_3$): 145.0 (broad d, o-F, 2F), 155.8 (t, p-F, 1F) and 162.8 (m, m-F, 2F). Anal. Calcd. for $C_9H_6NHOF_5$: C, 39.89; H, 2.21; N, 5.17 Found: C, 40.42; H, 2.65; N, 5.14.

Pentafluorophenyl-2,2,2-trifluorothioacetamide (nc)(6e) - Trifluorothioacetyl fluoride [21] (22.5 g, 0.170 mole) was slowly distilled into a mixture of 30.8 g (0.168 mole)(9) and 8 g NaF in 175 ml methylene chloride at -10°. The mixture was stirred at -10° for 2 hr, then 0° for 1 hr and finally at 25° for 1 hr. The mixture was filtered, and solvent removed to yield 45.2 g of a light yellow oil of product and unreacted pentafluoroaniline. The yield of thioacetanilide (6e) was 70% as determined from the ^1H nmr spectrum. Pure (6e)(oil) was obtained by chromatography on neutral SilicAR CC7 with chloroform; ir (Neat): 3413, 3257, 1531, 1370, 1049 and 1000 cm^{-1}; UV (EtOH): 27 nm (ε = 9,180) and 398 [23]. Anal. Calcd. for $C_8H\ NSF_8$: C, 32.56; N, 4.75; F, 51.49 Found C, 33.49; N, 4.85; F, 50.99.

Pentafluorophenyl-2,2,2-chlorodifluorothioacetamide (nc)(6f) - A mixture of 14.3 g (0.096 mole) chlorodifluorothioacetyl fluoride [21] and 6 g sodium fluoride in 80 ml methylene chloride was treated with a solution of 17.2 g (0.094 mole) of (9) in 40 ml methylene chloride at 20°. After 15 hr at 25°, the mixture was filtered and the solvent removed to yield 24.1 g (83%)(6f). An analytically pure sample was obtained by bulb-to-bulb vacuum distillation. Ir (Neat): 1527, 1361, 1045, 995 and 894 cm^{-1}; UV (EtOH): 217 nm (ε = 8000), 283 nm (8160) and 400 nm (48); ^1H nmr (Neat): δ8.75 (s, NH); ^{19}F nmr. ($CDCl_3$): δ56.3 (d, J = 1.5 Hz,

2F), δ143.0 (m, o-F, 2F), δ162.0 (m, m-F, 2F). Anal. Calcd. for $C_8HNSClF_7$: C, 30.90; N, 4.49; F, 42.77. Found: C, 31.60; N, 4.69; F, 43.22.

Pentafluorophenylformanilide (11b) - A solution of 10 g (0.054 mole)(9) and 35 ml of formic acid in 40 ml toluene was refluxed in a Dean-Stark apparatus for 12 hr. The solvent was removed and the residue recrystallized from benzene-petroleum ether (40-60°) to yield 1.8 g (17%)(11b) mp 95-96°C; ir (Nujol): 3226, 1672, 1522, 1493, 999, 971 and cm^{-1}; ^1H nmr ($CDCl_3$): 8.40 (s, CHO); ^{19}F nmr ($CDCl_3$): δ145.1 (broad, o-F, 2F), δ158.1 (t, J_{f-F} = 21 Hz, p-F, 1F); δ163.9 (m, m-F, 2F).
Anal. Calcd. for $C_7H_2F_5NO$: C, 39.83; N, 6.65; F, 45.00
Found: C, 40.44; N, 6.77; F, 45.20

N-Pentafluorophenylbenzamide (nc)(11c) - A solution of 5.0 g (29.2 mmole)(9) and 2.6 g (29.2 mmole) pyridine in 25 ml carbon tetrachloride was treated with a solution of 4.0 g (29.2 mmole) benzoyl chloride in 15 ml carbon tetrachloride at 10°. The mixture was stirred 0.5 hr at 10° then overnight at 25°. The solids were filtered and washed with water. Recrystallization of the insoluble material from toluene gave 6.2 g (77%)(11c), and mp 179-180°; ir (Nujol): 3226, 1664, 1481, 1105, 985, 909, 799 and 714 cm^{-1}; ^1H nmr (DMSO-d_6): δ10.5 (s, NH, 1H) and δ7.78 (m, Ph, 5H); ^{19}F nmr (DMSO-d_6): 144.9 (m, o-F 2F), 162.1 (t, J_{F-F} = 22 Hz, p-F, 1F) and 164.1 (m, m-F, 2F).

N-(2,3,4,5,6-Pentafluorophenyl)-N'-acetylhydrazine (nc)(13a) - A solution of 22.5 g (0.114 mole)(12) in 300 ml toluene was treated dropwise at 25° with a solution of 11.7 g (0.114 mole) glacial acetic anhydride in 30 ml toluene. The temperature rose to 40° during the addition forming an insoluble solid. After stirring at 40° for 1 hr, the mixture was cooled to 10° and filtered. The solvent was removed from the filtrate to yield additional product. The yield was 26.7 g (98%), mp 188.5°-189.5° (Toluene); ir (Nujol): 3215 (NH), 1647 (C=O), 1504 cm^{-1} (2° amide); ^1H nmr (DMSO-d_6): δ1.85 (singlet, CH_3, 3H), δ7.80 (broad singlet, NH, 1H)

and δ10.00 (broad singlet, NH, 1H); ^{19}F nmr (DMSO-d): 170.5 (p-F, 1F), 165 (m-F, 2F), and 157.2 (o-F, 2F).

Anal. Calcd. for $C_8H_5N_2OF_5$: C, 40.01; H, 2.10; N, 11.67
Found: C, 39.93; H, 1.89; N, 11.63

N-(2,3,4,5,6-Pentafluorophenyl)-N'-propanoylhydrazine (nc)(13b)

A solution of 10 g (0.051 mole)(12) in 200 ml toluene was treated dropwise at 25° with a solution of 6.7 g (0.051 mole) propionic anhydride in 25 ml toluene. The mixture was stirred and heated at 40° for 1 hr followed by cooling to 10°. The insoluble product was filtered and dried to yield 11.5 g (81%). Recrystallization from toluene gave pure (13b) mp 156.5°; ir (Nujol): 3279 (NH), 1658 (C=O), and 1515 cm^{-1} (2° amide).

Anal. Calcd for $C_9H_7N_2OF_5$: C, 42.53; H, 2.78; N, 11.02
Found: C, 42.31, H, 2.37, N, 10.71

N-(2,3,4,5,6-Pentafluorophenyl)-N'-benzoylhydrazine(nc)(13c)

A solution of 10 g (0.051 mole)(12) in 200 ml toluene containing 5.2 g (0.051 mole) triethylamine was treated dropwise at 25° with a solution of 7.2 g (0.051 mole) benzoyl chloride in 20 ml toluene. The heterogeneous mixture was stirred 2 hr at 40°, cooled to 10° and filtered. The insoluble product was stirred in 700 ml water, filtered and dried to yield 13.9 g (91%) of a white powder. Recrystallization from toluene gave pure (13c), mp 193.5°-194.5°; ir (Nujol): 3236 (NH), 1634 (C=O), 1575, 1515 cm^{-1} (2° amide).

Anal. Calcd. for $C_{13}H_7N_2OF_5$: C, 52.03; H, 2.38; N, 9.39
Found: C, 51.67; H, 2.33; N, 9.27

N-(2,3,4,5,6-Pentafluorophenyl)-N'-thioacetylhydrazine (nc)(14a)

A solution of 9.5 g (0.040 mole)(13a) and 2.2 g (9.4 mmole) P_2S_5 in 200 ml dioxane was heated and stirred at 90° for 20 hr. The clear orange solution was decanted from a small amount of tan solid and the solvent removed under vacuum. The residual orange oil was treated with 20 g crushed ice to yield an ivory solid. The product was filtered, dried and recrystallized from toluene

to yield 6.6 g (65%) of (14a), mp 130.5°-131.5°; uv (EtOH): sh 350 nm (ε = 44) and 269 nm (9040); ^{1}H nmr (DMSO-d_6); δ2.43 (singlet, CH_3, 3H), 7.68 (broad singlet, NH, 1H) and δ11.86 (singlet, NH, 1H); ^{19}F nmr (DMSO-d_6): 168.2 (p-F, 1F), 164.9 (m-F, 2F), and 154.2 (o-F, 2F).

Anal. Calcd. for $C_8H_5N_2SF_5$: C, 37.51; H, 1.97; N, 10.93
Found: C, 37.24; H, 1.89; N, 10.77

N-(2,3,4,5,6-Pentafluorophenyl)-N'-thiopropanoylhydrazine (nc)(14b) - A solution of 9.0 g (0.34 mole)(13b), 1.8 g (0.0076 mole) P_2S_5 in 225 ml dioxane was heated at 90°-95° for 20 hr to produce a light-yellow dioxane was heated at 90°-95° for 20 hr to produce a light-yellow solution. The solvent was removed under vacuum to yield an oil. The oil was filtered and dried to yield 7.7 g (84%). Recrystallization from toluene gave pure (14b), mp 108.5°-110.5°; uv(Cyclohexane): sh 350 nm (ε = 45) and 268 nm (ε = 9640), Beer's Law not obeyed in ethanol. IR (Nujol): 3247 (NH), 1534, 1468, 1379, 1105, 1020, 976 and 819 cm^{-1}.

Anal. Calcd. for $C_9H_7N_2SF_5$: C, 40.00; H, 2.61; N, 10.37
Found: C, 40.13; H, 2.43; N, 10.32

N-(2,3,4,5,6-Pentafluorophenyl)-N'-thiobenzoylhydrazine (nc)(14c) - A mixture of 11.0 g (36.5 mmole)(13c) 1.9 g (8.2 mmole) P_2S_5 in 225 ml was heated and stirred at 90°-95° for 20 hr. The solvent was removed under vacuum and the yellow residual oil added to crushed ice. The mixture was extracted with ether and dried. Removal of solvent and recrystallization from cyclohexane yielded 6.5 g (58%) of (14c), mp 86°-87°; uv (Cyclohexane): sh 382 nm (ε = 229) and a continuous peak from 300 nm to 200 nm with inflection at 290 nm (6320).

Anal. Calcd. for $C_{13}H_7N_2SF_5$: C, 49.06; H, 2.22; N, 8.80
Found: C, 49.01; H, 2.15; N, 8.74

2-Methyl-5,6,7,8-tetrafluoro-4H-1,3,4,-benzothiadiazine (nc)(5a) - A solution of 35 g (0.134 mole)(14a) in 300 ml DMF containing 0.5 g KF was stirred and heated at 110° for 1.5 hr. The cooled dark mixture

was added to 1200 ml ice water. The solid was filtered and sublimed at 80°/0.25 Torr to yield 20 g (63%) of (5a), mp 104°-106°; ir (Nujol): 3333 (NH) and 1650 cm^{-1} (C=N); uv (EtOH): 299 nm (ε = 1400) and 239 nm (14,800); ^1H nmr (DMSO-d_6): δ2.15 (singlet, CH_3) and δ9.91 (broad singlet, NH); m/e (%I): 236 (100), 203 (14.3), 195 (57.0), 194 (20.0), 176 (12.2), 175 (10.1), 150 (21.9), 149 (29.3), 12.5 (14.2), 124 (66.5), 118 (52.9), 117 (15.5), 111 (14.1), 106 (10.7), 100 (29.7), 99 (16.7), 94 (13.5), 93 (33.8), 87 (38.3), 75 (12.7), 74 (13.4).

Anal. Calcd. for $C_8H_4N_2SF$: C, 40.68; H, 1.71; N, 11.86
Found: C, 40.21; H, 1.56; N, 11.61

2-Ethyl-5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazine (nc) (5b) - A mixture of 3.3 g (0.0122 mole) (14b) and 0.1 g KF in 35 ml dry DMF was stirred and heated at 110° for 2 hr. The mixture was cooled and added to 300 ml ice water. The precipitate was filtered, dried and sublimed at 70°/0.25 Torr to yield 1.8 g (5b) (59%), mp 67°-69°; ir (Nujol): 3257 (NH) and 1637 cm^{-1} (C=N); uv (EtOH): 296 nm (ε = 1650) and 240 nm (14,200).

Anal. Calcd for $C_9H_6N_2SF_4$: C, 43.20; H, 2.42; N, 11.20
Found: C, 42.87; H, 2.26; N, 11.2

2-Phenyl-5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazine (nc) (5c) - A solution of 7.0 g (0.022 mole) of (14c) in 100 ml dry DMF was heated at 120° for 3 hr. The light yellow solution changed to a deep red-brown color. The cooled solution was added to 400 ml ice water, and a yellow precipitate filtered. The product was dried, and sublimed at 100°/25 Torr to yield 3.3 g (50%) pure (5c), mp 114°-117°; ir (Nujol): 3333 (NH) and 1645 cm^{-1} (C=N); uv (EtOH): 364 nm (ε = 1710) and 257 nm (14,300); ^1H nmr (DMSO-d_6): δ7.5 (m, phenyl) and δ10.5 (broad singlet, NH).

Anal. Calcd for $C_{13}H_6N_2SF_4$: C, 52.35; H, 2.03; N, 9.39
Found: C, 51.98; H, 1.95; N, 9.36

2-Methyl-5,6,7,8-tetrafluoro-4H-1,3,4-benzothiadiazine-1,1-dioxide (nc)(15) - A solution of 3.4 g (0.0144 mole) (5a) in 25 ml glacial acetic acid was treated in one portion at 25° with 10 ml 30% H_2O_2. A solid precipitated. The mixture was heated at 60° for 3 hr whereupon dissolution of the solid occurred. The cooled solution was poured onto crushed ice and a white solid filtered. The yield of (15) was 2.7 g (70%) mp 192°-193.5° (Benzene); ir (KBr): 3289 (NH), 1661, 1534, 1513 (aromatic C=C), 1610 (C-N), 1299 and 1131 cm^{-1} (SO_2); uv (EtOH): 289 nm (ε = 11,400); ^1H nmr (DMS-d_6): δ2.38 (singlet, CH_3-3H) and δ12.8 (singlet, NH, 1H); m/e (%I): 268 (55.2), 204 (64.7), 203 (100), 202 (10.9), 176 (32.2), 163 (83.8), 136 (79.9), 124 (26.4), 117 (52.2).

Anal. Calcd for $C_8H_4N_2O_2SF_4$: C, 35.83; H, 1.50; N, 10.45
Found: C, 36.04; H, 1.52; N, 10.16.

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