Potential Antithyroid Agents. 1. *N*-Alkylformamidino-*N*-arylthiocarbamide Hydrochlorides

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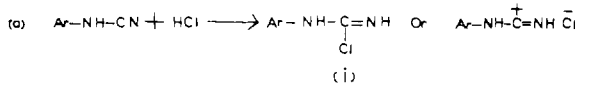
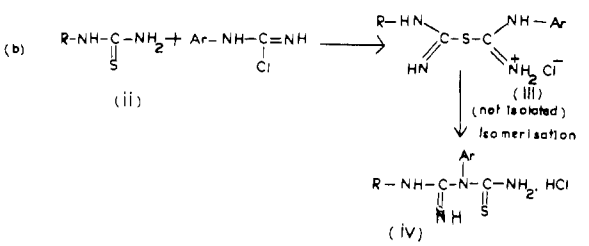
Various *N*-alkylformamidino-*N*-arylthiocarbamide hydrochlorides have been synthesized by the condensation of corresponding arylcyanamides with 1-substituted alkylthiocarbamides in the presence of HCl gas. The intermediates required in these syntheses were prepared according to the methods given in the literature.

Antithyroid compounds may be broadly defined as chemical compounds that depress thyroid function. They have potential use wherever control of thyroid function is desirable. The most highly active antithyroid compounds contain the thiourylene moiety (>NC(–S)N<), being capable of forming a –SH grouping by enolization or tautomerization. This thiourylene moiety is capable of being easily oxidized; therefore, it has been suggested that the interference with thyroxine synthesis is actually by a direct reaction between I_2 and –SH to form a disulfide (*1–4*).

The present communication deals with the syntheses and pharmacological screening of some typical formamidinothiocarbamide hydrochlorides, which were synthesized by the condensation of corresponding arylcyanamide (i) and alkylthiocarbamides (ii). Although we failed to isolate the monosulfide (iii), this intermediate stage has been confirmed by many workers in an analogous reaction (*6–9*). These salts could not be crystallized without decomposition and, hence, purification was achieved by repeated washings with several solvents. IR spectra and conversion of acetone-soluble ii to the highly acetone-insoluble salts iv reassure one as to the identify of iv. IR: 1510 cm^{-1} (NC═S), 1620 cm^{-1} (C═N), 770 cm^{-1} (substituted benzene ring). Further more, elemental analysis and chemical behavior of compound iv confirms the structure and its identity.



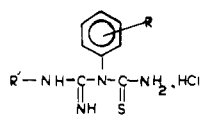


The compounds were found to be desulfurized with aqueous sodium plumbite. When boiled with dilute HCl for a few minutes followed by cooling, corresponding arylthiocarbamides were isolated. When the compounds were treated with aqueous sodium hydroxide, corresponding monoarylguanidines (isolated as picrates) were obtained. The filtrate also gave the test of thiocyanic acid with ferric chloride further confirming the structure.

Experimental Section

Melting points were determined with a Kofler hot stage apparatus and are uncorrected.

Table I. *N*-Alkylformamidino-*N*-arylthiocarbamide Hydrochlorides[a]



no.	R	R′	mp, °C	yield, %
1	H	Et	167–168	70
2	H	*i*-Pr	158–159	72
3	H	*n*-Bu	133–135	60
4	H	*t*-Bu	128–130	64
5	2-Me	*i*-Pr	142–143	68
6	2-Me	allyl	118–119	64
7	2-Me	*n*-Bu	126–127	60
8	2-Me	*t*-Bu	122–124	68
9	3-Me	Me	160–162	65
10	3-Me	*i*-Pr	145–146	60
11	3-Me	*t*-Bu	117–119	62
12	4-Me	*i*-Pr	142–144	70
13	4-Me	*n*-Bu	129–130	68
14	4-Me	*t*-Bu	126–128	72
15	2-Cl	Et	118–119	68
16	2-Cl	*i*-Pr	116–117	58
17	2-Cl	*t*-Bu	121–122	60
18	3-Cl	H	156–157	74
19	3-Cl	Me	133–134	61
20	3-Cl	*i*-Pr	142–143	80
21	4-Cl	H	165–166	80
22	4-Cl	Et	163–164	78
23	4-Cl	allyl	149–150	70
24	4-Cl	*i*-Pr	147–148	74
25	4-Cl	*n*-Bu	144–146	65
26	4-Cl	*t*-Bu	138–139	65
27	2-OMe	allyl	125–126	58
28	4-OMe	*i*-Pr	136–137	68
29	2-OEt	*i*-Pr	133–134	60
30	4-OEt	*i*-Pr	137–138	70

[a] The analytical values for C, H, N, and S were within ±0.4% of the calculated values.

Arylcyanamide hydrochlorides were prepared as reported in the literature (*10*).

1-Alkylthiocarbamides were prepared by the addition of ammonia to the corresponding alkylisothiocyanates (*11*).

***N*-Formamidino-*N*-phenylthiocarbamide Hydrochloride.** Thiocarbamide (0.76 g, 0.01 mol) dissolved in acetone (20.0 mL) and phenylcyanamide hydrochloride (1.54 g, 0.01 mol) dissolved in acetone (10.0 mL) were mixed slowly with constant shaking. After keeping the mixture overnight at room temperature (25 °C), a colorless, crystalline pure *N*-formamidino-*N*-phenylthiocarbamide hydrochloride was separated, filtered, and washed several times with anhydrous warm acetone and ether to remove unreacted constituents: yield 1.75 g, 75%; mp 160–162 °C.

Anal. Calcd for $C_8H_{10}N_4S$·HCl: C, 41.66; H, 4.77; N, 24.3; S, 13.89; equiv wt = 230.5. Found: C, 41.42; H, 4.85; N, 23.99; S, 14.50 equiv wt = 235.0.

This product also formed a picrate (mp 166 °C) and a *p*-toluenesulfonate (mp 178 °C).

IR: 1510 cm^{-1} (NC═S), 1620 cm^{-1} (C═N), ~770 cm^{-1} (substituted benzene ring).

By use of a similar procedure as above, several formamidinothiocarbamide hydrochlorides were prepared and pharmacologically screened for antithyroidal activity, and those compounds which show appreciable activity are tabulated in

0021-9568/79/1724-0381$01.00/0

Table II. Pharmacological Screening Results of *N*-Alkylformamidino-*N'*-arylthiocarbamide Hydrochlorides

compd no.	thyroid radioactivity[a] total ^{131}I uptake	thyroid radioactivity[a] PB^{131}I	inorganic ^{131}I[a]	approx estimated activity in rats[b]
control	112 345 ± 42	98 378 ± 36	7936 ± 12	
thiouracil	42 976 ± 18	35 421 ± 16	5448 ± 09	1.00
1	41 212 ± 21	33 886 ± 17	6549 ± 13	1.01
2	35 623 ± 35	26 429 ± 15	7215 ± 11	1.20
3	36 376 ± 18	29 648 ± 03	6542 ± 16	1.18
4	21 994 ± 31	15 348 ± 19	6301 ± 07	1.95
5	30 189 ± 27	24 575 ± 13	5641 ± 11	1.42
6	38 793 ± 24	31 647 ± 21	6728 ± 07	1.10
7	35 117 ± 22	29 176 ± 19	5112 ± 11	1.22
8	28 019 ± 23	19 429 ± 13	7755 ± 13	1.53
9	49 647 ± 32	43 305 ± 29	5991 ± 05	0.86
10	29 878 ± 17	25 429 ± 16	3908 ± 12	1.43
11	30 677 ± 18	22 695 ± 14	7404 ± 08	1.40
12	29 039 ± 28	23 115 ± 13	5885 ± 11	1.47
13	28 453 ± 21	22 524 ± 13	5809 ± 09	1.51
14	20 967 ± 14	14 789 ± 18	5910 ± 12	2.04
15	32 373 ± 21	25 721 ± 10	6209 ± 08	1.32
16	28 379 ± 25	21 429 ± 15	6912 ± 15	1.51
17	30 827 ± 18	24 331 ± 17	6221 ± 08	1.42
18	32 689 ± 19	26 458 ± 21	6015 ± 12	1.31
19	40 399 ± 23	34 217 ± 16	5910 ± 16	1.06
20	28 087 ± 14	22 315 ± 14	5749 ± 15	1.53
21	31 378 ± 13	24 243 ± 20	6989 ± 11	1.36
22	31 287 ± 22	24 223 ± 19	6832 ± 12	1.37
23	20 058 ± 21	13 739 ± 12	6221 ± 09	2.14
24	27 422 ± 24	20 351 ± 21	7017 ± 14	1.56
25	23 543 ± 17	16 198 ± 14	7119 ± 08	1.82
26	29 813 ± 27	22 325 ± 16	6301 ± 11	1.43
27	42 116 ± 19	35 983 ± 15	6432 ± 10	1.02
28	35 468 ± 25	28 213 ± 17	7012 ± 10	1.19
29	33 343 ± 27	26 462 ± 18	6677 ± 06	1.28
30	30 773 ± 15	23 056 ± 12	7288 ± 09	1.39

[a] Units are disintegrations/min. ± Standard error.
[b] Thiouracil = 1.00.

Table I and their pharmacological screening results are described in Table II.

Pharmacological Screening (12). Male Holtzman rats (100–125 g) were maintained on a low-iodide diet for 3 days and then divided into groups consisting of four rats in each group. The animal in each group received an intraperitoneal injection of 1 mL of either a blank (0.9% NaCl), thiouracil, or one of the test compounds. One hour later, 1 μCi of Na ^{131}I (Career free) was injected intraperitoneally. Three hours after the injection of ^{131}I, the animals were sacrificed and the thyroids were removed. The whole lobes were placed in ground-glass homogenizing tubes and counted in a Nuclear-Chicago well scintillation counter to determine total thyroid uptake. The whole lobes were then homogenized in 1 mL of 0.05 M barbital buffer (pH 8.6) containing 1.0×10^{-5} M thiouracil. One milliliter of cold 20% TCA was added and the homogenate was centrifuged. The precipitate was washed twice with 1.0 mL of cold 10% TCA. The original supernatant and the two washes were combined and the radioactivity was determined. The ^{131}I in this fraction indicated the concentration of inorganic ^{131}I or TCA-soluble ^{131}I. The washed precipitate was counted in the homogenizing tube. The radioactivity in this fraction indicated the PB ^{131}I or the TCA-precipitable ^{131}I. The counts were all corrected for counting efficiency and are expressed as disintegrations per minute.

All compounds were dissolved in saline for injection. Thiouracil was dissolved with heating to 55 °C. All compounds were assayed at concentrations equimolar to 0.5 mg of thiouracil (3.9 μmol) and the biological effect was noted. Table II summarizes the observations made with compounds **1–30**.

The pharmacological results show that the compounds having chlorine in aryl nucleus have enhanced activity. Furthermore the compounds with isopropyl and *tert*-butyl groups are having appreciable antithyroidal activity. It is also evident from the data that the ratio of PBI level has decreased and inorganic iodine level has proportionately increased.

Acknowledgment

The authors are thankful to Professor K. N. Udupa, Director, and Dr. J. P. N. Chansouria, J.R.O., I.M.S., B.H.U., Varanasi, for providing necessary facilities for work and for helping in the experiments related with biological testing, respectively.

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Received for review November 1, 1978. Accepted June 13, 1979. Financial assistance from UGC and CSIR is greatfully acknowledged.

Preparation and Properties of 2-Fluoro-2,2-dinitroethyl Pentafluorothioacetate

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The preparation and properties of 2,2,2-fluorodinitroethyl pentafluorothioacetate is reported.

There has been considerable work done on the synthesis of aliphatic sulfur pentafluoride compounds (*1–3*). These are an interesting class of compounds because of their high fluorine content, which imparts high density and good physical properties to the molecule. However, there has been no report of such compounds containing energetic nitro groups. Since aliphatic derivatives of sulfur pentafluoride are currently of interest as potential high-energy compounds, it was pertinent to determine the feasibility of preparing aliphatic compounds containing both the SF_5 and NO_2 moieties.

0021-9568/79/1724-0382$01.00/0