associated with reductions in pulse pressures and rises in portal venous pressures. These changes appeared to exhibit rapid and complete tachyphylaxis. The lack of apparent changes in the morphology of the lead II ECG indicates that the effects of the agent did not produce arrhythmias or ectopic foci of excitation. A determination of whether minor local changes in excitation occurred secondary to such effects as regional changes in myocardial circulation cannot be inferred from these limited data.

Experiments with lower dosages or apparently ineffective 1.0-mg/kg iv and 50-mg/kg intragastric dosages indicated that the individual components of the retch response (increased frequency of respiration, gastric mucus secretion, antral contractions, and corporal-fundal atonia) were invariably present but of such small intensity that the composite response was decidedly less than that constituting frank retching.

A similar set of sequelae is also present in humans who report feelings of nausea but who do not visibly retch. It is impossible to make this judgment with dogs, particularly anesthetized dogs. But these observations furnish an adequate physiological basis to suspect that the gastric or intravenous administration of dosages that are insufficient to produce frank retching might be accompanied by sensations of nausea.

It is concluded that the high molecular weight, branched polyethyleneimine, whether administered to dogs by gastric intubation or intravenously, produces an emetic response similar to ipecac in that it can act reflexly or by direct stimulation of the chemoreceptor trigger zone.

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ˣ To whom inquiries should be directed.

New Compounds: Potential Antituberculous Agents I: Alkylaryl 4-Arylformamidinothiosemicarbazones

P. K. SRIVASTAVA ˣ and J. S. UPADHYAYA

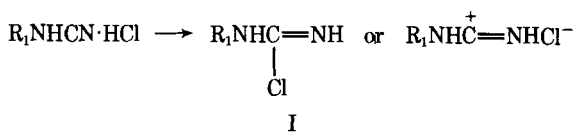
Abstract □ A series of alkylaryl 4-arylformamidinothiosemicarbazones was synthesized for evaluation as antituberculous agents. The synthesis was effected by the condensation of different arylcyanamides with various thiosemicarbazones. The required intermediates also are described.

Keyphrases □ Thiosemicarbazones, various—synthesized for evaluation as antituberculous agents □ Antituberculous agents, potential—various thiosemicarbazones synthesized

Interest in the synthesis and biological evaluation of thiosemicarbazone derivatives was renewed by the fact that tibione (*p*-acetylaminobenzaldehyde thiosemicarbazone) (1–3) possesses antituberculous activity. Many reports (4–13) discussed the change of activity due to variations in the structure of the parent compound.

DISCUSSION

The present report deals with the synthesis of acetophenone 4-arylformamidinothiosemicarbazones (V*a*–V*m*, Table I) and 1-acetonaphthone 4-arylformamidinothiosemicarbazones (VI*a*–VI*m*, Table II) by the condensation of corresponding arylcyanamide hydrochlorides (I, Scheme I) with the appropriate thiosemicarbazones (II or III, Scheme II). Although the monosulfides (IV) could not be isolated, this intermediate stage was confirmed previously in analogous reactions (14–17).



Scheme I

Precursors (I) were obtained by the desulfurization of related thioureas by lead hydroxide and conversion to related hydrochlorides (18). The synthesized thiosemicarbazones (Tables I and II) are white crystalline compounds soluble in polar solvents. Since these compounds could not be crystallized without decomposition, purification was achieved by repeated washings with several solvents. It was hoped that these potential antituberculous agents would have low toxicity to normal cells and have a good chemotherapeutic index[1].

EXPERIMENTAL[2]

Phenylcyanamide (18)—A mixture of phenylthiourea (15.2 g, 0.1 mole) dissolved in sodium hydroxide (3 g in 200 ml of water) and freshly prepared lead hydroxide (24.12 g, 0.1 mole) was heated on a water bath for 4 hr. It then was cooled and filtered, and the filtrate was acidified with acetic acid. The fluffy precipitate of phenylcyanamide was dissolved in ether and dried by adding anhydrous sodium sulfate. The hydrochloride of phenylcyanamide was prepared by passing dry hydrogen chloride gas through the ethereal solution.

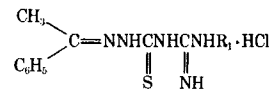
By adopting a similar procedure, the following cyanamides were prepared: 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 2,5-dimethylphenyl, and 1-naphthyl.

Acetophenone Thiosemicarbazone (II) (12, 13)—Acetophenone (12.0 g, 0.1 mole) was dissolved in ethanol (50%, 100 ml) and acetic acid (2.0 ml), and thiosemicarbazide (9.10 g, 0.1 mole) was added. The solution was warmed with occasional swirling until the thiosemicarbazide dissolved, and then the solution was refluxed for 1 hr. After cooling, crys-

[1] These compounds have been submitted for testing, and the results will be reported elsewhere.

[2] Melting points were determined with a Kofler hot-stage apparatus and are uncorrected.

Table I—Physical Constants of Acetophenone 4-Arylformamidinothiosemicarbazone Hydrochlorides

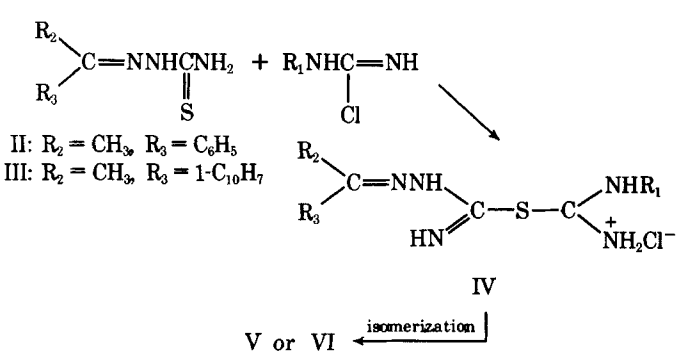


Compound	R_1	Yield, %	Melting Point	Molecular Formula	Analysis, %	
					Calc.	Found
V*a*	C_6H_5	75	208–209°	$C_{16}H_{18}ClN_5S$	C 55.25	55.08
					H 5.18	5.06
					N 20.14	20.06
					S 9.20	9.15
V*b*	2-$CH_3C_6H_4$	78	210–212°	$C_{17}H_{20}ClN_5S$	C 56.43	56.38
					H 5.53	5.51
					N 19.36	19.27
					S 8.85	8.81
V*c*	3-$CH_3C_6H_4$	65	157–158°	$C_{17}H_{20}ClN_5S$	C 56.43	56.37
					H 5.53	5.48
					N 19.36	19.27
					S 8.85	8.78
V*d*	4-$CH_3C_6H_4$	70	207–208°	$C_{17}H_{20}ClN_5S$	C 56.43	56.40
					H 5.53	5.50
					N 19.36	19.24
					S 8.85	8.77
V*e*	2-$CH_3OC_6H_4$	68	200–201°	$C_{17}H_{20}ClN_5OS$	C 54.04	53.88
					H 5.29	5.18
					N 18.54	18.46
					S 8.47	8.42
V*f*	4-$CH_3OC_6H_4$	60	160–162°	$C_{17}H_{20}ClN_5OS$	C 54.04	53.96
					H 5.29	5.24
					N 18.54	18.47
					S 8.47	8.39
V*g*	4-$C_2H_5OC_6H_4$	72	187–188°	$C_{18}H_{22}ClN_5OS$	C 55.17	55.10
					H 5.61	5.54
					N 17.88	17.81
					S 8.17	8.11
V*h*	2-ClC_6H_4	70	145–146°	$C_{16}H_{17}Cl_2N_5S$	C 50.26	50.18
					H 4.45	4.40
					N 18.32	18.28
					S 8.37	8.33
V*i*	3-ClC_6H_4	66	132–133°	$C_{16}H_{17}Cl_2N_5S$	C 50.26	50.20
					H 4.45	4.42
					N 18.32	18.25
					S 8.37	8.31
V*j*	4-ClC_6H_4	74	151–152°	$C_{16}H_{17}Cl_2N_5S$	C 50.26	50.22
					H 4.45	4.39
					N 18.32	18.27
					S 8.37	8.32
V*k*	4-BrC_6H_4	65	171–172°	$C_{16}H_{17}BrClN_5S$	C 45.01	44.78
					H 3.98	3.86
					N 16.41	16.34
					S 7.50	7.46
V*l*	2,5-$(CH_3)_2C_6H_3$	68	209–210°	$C_{18}H_{22}ClN_5S$	C 57.52	57.47
					H 5.85	5.78
					N 18.64	18.60
					S 8.52	8.49
V*m*	1-$C_{10}H_7$	72	203–204°	$C_{20}H_{20}ClN_5S$	C 60.37	60.22
					H 5.03	4.98
					N 17.61	17.29
					S 8.08	8.01

talline II was collected and recrystallized from 50% ethanol as white needles, 18.9 g (90%), mp 116–117° [lit. (19) mp 118–119°].

1-Acetonaphthone thiosemicarbazone (III) was prepared similarly.

Acetophenone 4-Phenylformamidinothiosemicarbazone Hydrochloride (V*a*)—Compound II (3.0 g, 0.015 mole) was dissolved in acetone (20.0 ml), and the solution was cooled in a freezing mixture. To this cooled solution, phenylcyanamide hydrochloride (2.4 g, 0.015 mole) dissolved in acetone (10.0 ml) was gradually added with constant shaking. After this solution was in the freezing mixture for 1 hr, crystalline pure V*a* was separated, filtered, and washed with acetone and petroleum ether to remove any unreacted material, 4.15 g (18%), mp 208–209°.



Scheme II

Anal.—Calc. for $C_{16}H_{18}ClN_5S$: C, 55.25; H, 5.18; N, 20.14; S, 9.20. Found: C, 55.08; H, 5.06; N, 20.06; S, 9.15.

Compounds V*b*–V*m* (Table I) were prepared by condensing II with the appropriate I.

With a similar procedure, VI*a*–VI*m* (Table II) were obtained.

These thiosemicarbazone hydrochlorides were characterized by elemental analyses and the presence of characteristic bands at 1520 (N=C=S), 1625 (C=N), and 3400 (NH) cm^{-1} and a substituted benzene ring (760 cm^{-1}) in their IR spectra.

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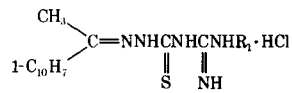
Table II—Physical Constants of 1-Acetonaphthone 4-Arylformamidinothiosemicarbazone Hydrochlorides



Compound	R_1	Yield, %	Melting Point	Molecular Formula	Analysis, %	
					Calc.	Found
VI*a*	C_6H_5	67	197–198°	$C_{20}H_{20}ClN_5S$	C 60.37	60.22
					H 5.03	4.98
					N 17.61	17.29
					S 8.05	8.00
VI*b*	2-$CH_3C_6H_4$	65	200–201°	$C_{21}H_{22}ClN_5S$	C 61.23	61.12
					H 5.34	5.28
					N 17.01	16.92
					S 7.77	7.68
VI*c*	3-$CH_3C_6H_4$	60	148–149°	$C_{21}H_{22}ClN_5S$	C 61.23	61.14
					H 5.34	5.30
					N 17.01	16.96
					S 7.77	7.70
VI*d*	4-$CH_3C_6H_4$	75	208–210°	$C_{21}H_{22}ClN_5S$	C 61.23	61.19
					H 5.34	5.27
					N 17.01	16.99
					S 7.77	7.66
VI*e*	2-$CH_3OC_6H_4$	65	195–196°	$C_{21}H_{22}ClN_5OS$	C 58.94	58.82
					H 5.14	5.08
					N 16.37	16.22
					S 7.48	7.42
VI*f*	4-$CH_3OC_6H_4$	70	203–204°	$C_{21}H_{22}ClN_5OS$	C 58.94	58.84
					H 5.14	5.12
					N 16.37	16.24
					S 7.48	7.40
VI*g*	4-$C_2H_5OC_6H_4$	60	155–156°	$C_{22}H_{24}ClN_5OS$	C 59.79	59.68
					H 5.43	5.39
					N 15.85	15.78
					S 7.24	7.16
VI*h*	2-ClC_6H_4	72	146–147°	$C_{20}H_{19}Cl_2N_5S$	C 55.55	55.48
					H 4.39	4.28
					N 16.20	16.12
					S 7.40	7.22
VI*i*	3-ClC_6H_4	64	141–142°	$C_{20}H_{19}Cl_2N_5S$	C 55.55	55.47
					H 4.39	4.32
					N 16.20	16.14
					S 7.40	7.32
VI*j*	4-ClC_6H_4	72	152–153°	$C_{20}H_{19}Cl_2N_5S$	C 55.55	55.50
					H 4.39	4.27
					N 16.20	16.18
					S 7.40	7.34
VI*k*	4-BrC_6H_4	62	167–168°	$C_{20}H_{19}BrClN_5S$	C 50.36	50.24
					H 3.98	3.82
					N 14.69	14.62
					S 6.71	6.65
VI*l*	2,5-$(CH_3)_2C_6H_3$	64	206–207°	$C_{22}H_{24}ClN_5S$	C 62.04	61.98
					H 5.64	5.59
					N 16.45	16.40
					S 7.52	7.48
VI*m*	1-$C_{10}H_7$	69	202–204°	$C_{24}H_{22}ClN_5S$	C 64.35	64.22
					H 4.91	4.80
					N 15.64	15.49
					S 7.15	7.02

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[x] To whom inquiries should be directed.