New Compounds: Potential Antituberculous Agents. 2. *N*-Arylformamidino-*N'*-(dialkyl and diaryl substituted)thiosemicarbazones

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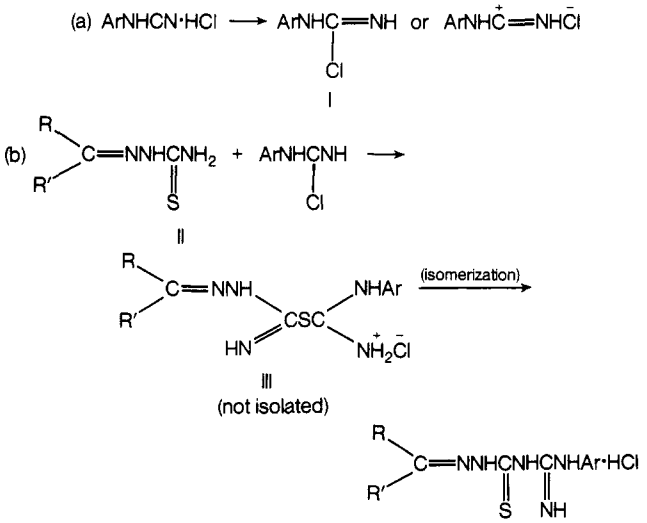
Various *N*-arylformamidino-*N'*-dimethylthiosemicarbazones and *N*-arylformamidino-*N'*-diphenylthiosemicarbazones have been synthesized by the condensation of corresponding arylcyanamides with 1-substituted thiosemicarbazones. The intermediates required in these syntheses were prepared according to the methods given in the literature.

The interest in the syntheses and biological evaluation of thiosemicarbazone derivatives has been renewed by the fact that tibione (*2, 3, 8*) (*p*-acetylaminobenzaldehydethiosemicarbazone) possesses antituberculous activity. Many workers (*1, 4–6, 9–12, 18, 19*) in this field studied the change of activity due to several variations in the structure of the parent compound.

The present communication deals with the syntheses of *N*-arylformamidino-*N'*-dimethylthiosemicarbazones and *N*-arylformamidino-*N'*-diphenylthiosemicarbazones by the condensation of corresponding arylcyanamides (I) with 1-substituted thiosemicarbazones (II). Although we failed to isolate the monosulfide (III), this intermediate stage has been confirmed by many workers in an analogous reaction (*13, 15–17*). Precursors



i, R = methyl; R′ = methyl
ii, R = phenyl; R′ = phenyl

arylcyanamides (I) were obtained by the desulfurization of related thioureas by lead hydroxide (*14*). Thiosemicarbazones (II) react with I to yield the corresponding *N*-arylformamidino-*N'*-dimethylthiosemicarbazones (Table I) and *N*-arylformamidino-*N'*-diphenylthiosemicarbazones (Table II) congeners. They are all white crystalline compounds and are soluble in polar solvents. These formamidinothiosemicarbazones (IV) could not be crystallized without decomposition and hence purification was achieved by repeated washings with several solvents. It was hoped that these potential antituberculous agents might afford compounds that would be relatively less toxic to normal cells and have a better chemotherapeutic index.

These compounds have been submitted for biological screening and the results will be reported elsewhere.

Experimental Section

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

Phenylcyanamide (14). A mixture of phenylthiourea (15.2 g, 0.1 mol) dissolved in sodium hydroxide (3 g in 200 ml of water) and freshly prepared lead hydroxide (24.12 g, 0.1 mol) was heated on a water bath for 4 h. It was cooled and filtered and the filtrate was acidified with acetic acid. The fluffy precipitate of phenylcyanamide was dissolved in ether and was dried by adding anhydrous sodium sulfate. Phenylcyanamide hydrochloride was prepared by passing dry hydrogen chloride gas in etherial solution.

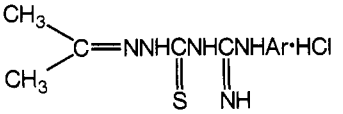
By adopting a similar procedure as above several, viz., 2-MePh, 3-MePh, 4-MePh, 2-MeOPh, 4-MeOPh, 2-EtOPh, 4-EtOPh, 2-ClPh, 3-ClPh, 4-ClPh, 4-BrPh, 2,5-Me_2Ph, and 1-naphthyl, cyanamides were prepared.

Dimethylthiosemicarbazone (1, 6). Acetone (5.80 g, 0.1 mol) was dissolved in ethanol (50%, 100 ml) and glacial acetic acid (2.0 ml) and thiosemicarbazide (9.10 g, 0.1 mol) added. The solution was warmed with occasional swirling until the thiosemicarbazide dissolved and then refluxed for 1 h. After cooling, the crystalline thiosemicarbazone was collected and recrystallized from 50% ethanol as white crystalline needles, yield 9.2 g, 90%, mp 178° (lit. (*7*) mp 179°).

Diphenylthiosemicarbazone was prepared by adopting a similar procedure.

N-Phenylformamidino-N'-dimethylthiosemicarbazone Hydrochloride. Dimethylthiosemicarbazone (1.78 g, 0.015 mol)

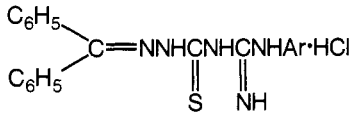
Table I. *N*-Arylformamidino-*N'*-dimethylthiosemicarbazone Hydrochloride[a]



No.	Ar	Mp, °C	Yield, %	Formula
1.	Phenyl	203–204	70	$C_{11}H_{16}ClN_5S$
2.	2-MePh	195–196	72	$C_{12}H_{18}ClN_5S$
3.	3-MePh	140–142	60	$C_{12}H_{18}ClN_5S$
4.	4-MePh	200–201	64	$C_{12}H_{18}ClN_5S$
5.	2-MeOPh	208–209	65	$C_{12}H_{18}ClN_5OS$
6.	4-MeOPh	170–172	60	$C_{12}H_{18}ClN_5OS$
7.	4-EtOPh	210–211	75	$C_{13}H_{20}ClN_5OS$
8.	2-ClPh	168–169	68	$C_{11}H_{15}Cl_2N_5S$
9.	3-ClPh	180–182	62	$C_{11}H_{15}Cl_2N_5S$
10.	4-ClPh	160–162	70	$C_{11}H_{15}Cl_2N_5S$
11.	4-BrPh	165–166	55	$C_{11}H_{15}BrClN_5S$
12.	2,5-Me_2Ph	201–202	62	$C_{13}H_{20}ClN_5S$
13.	1-Naphthyl	205–206	68	$C_{15}H_{18}ClN_5S$

[a] All of the compounds gave elemental analyses (C, H, N, S) within ±0.30 of the calculated values.

Table II. *N*-Arylformamidino-*N'*-diphenylthiosemicarbazone Hydrochlorides[a]



No.	Ar	Mp, °C	Yield, %	Formula
1.	Phenyl	202–203	68	$C_{21}H_{20}ClN_5S$
2.	2-MePh	198–199	70	$C_{22}H_{22}ClN_5S$
3.	3-MePh	150–152	62	$C_{22}H_{22}ClN_5S$
4.	4-MePh	200–201	71	$C_{22}H_{22}ClN_5S$
5.	2-MeOPh	195–196	67	$C_{22}H_{22}ClN_5OS$
6.	4-MeOPh	197–198	65	$C_{22}H_{22}ClN_5OS$
7.	4-EtOPh	160–162	72	$C_{23}H_{24}ClN_5OS$
8.	2-ClPh	175–176	64	$C_{21}H_{19}Cl_2N_5S$
9.	3-ClPh	155–156	69	$C_{21}H_{19}Cl_2N_5S$
10.	4-ClPh	182–183	73	$C_{21}H_{19}Cl_2N_5S$
11.	4-BrPh	205–206	60	$C_{21}H_{19}BrClN_5S$
12.	2,5-Me_2Ph	204–205	66	$C_{23}H_{24}ClN_5S$
13.	1-Naphthyl	207–208	67	$C_{25}H_{22}ClN_5S$

[a] All of the compounds gave elemental analyses (C, H, N, S) within ±0.30 of the calculated values.

was dissolved in acetone (20.0 ml) and the solution was cooled in freezing mixtures. To this cooled solution, phenylcyanamide hydrochloride (2.4 g, 0.015 mol) dissolved in acetone (10.0 ml) was added slowly with constant shaking. After keeping it in a freezing mixture for 1 h, crystalline pure *N*-phenylformamidino-*N'*-dimethylthiosemicarbazone hydrochloride was separated, filtered, and washed with acetone and petroleum ether to remove any unreacted constituents, yield 3.3 g, 80%, mp 203–204.

Other *N*-arylformamidino-*N'*-dimethlthiosemicarbazone hydrochlorides, prepared by condensing dimethylthiosemicarbazone with different arylcanamides hydrochloride are summarized in Table I.

Using similar procedure as above several *N*-arylformamidino-*N'*-diphenylthiosemicarbazone hydrochlorides, described in Table II, were obtained.

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Mass Spectral and Nuclear Magnetic Resonance Data of Some Bicyclo[3.2.1] Compounds

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The mass spectra and NMR spectra of some bicyclo[3.2.1]-octanes are reported. The main fragmentation process observed is the loss of a C_2H_5 or CHO unit. The abundance of $(P - H_2O)^+$ ions in the spectra of the alcohols was found to be related to their stereochemistry and based upon these observations a structure is suggested for one of the alcohols whose stereochemistry was initially undefined. High resolution mass measurement define the exact composition of some of the principal fragment peaks.

This mass spectrometric and NMR study of selected bicyclo[3.2.1]octanes was undertaken as an extension of the work previously reported (*5*) on the related bicyclo[3.3.1] system. Kwart and Blazer (*6*) have reported on the mass spectrum of 2-hydroxybicyclo[3.2.1]octane, and the present paper also extends their field of investigation.

The derivatives whose mass spectra are reported here (Tables I–III) are: I, bicyclo[3.2.1]octane (*5*); II, bicyclo[3.2.1]oct-2-ene (*1, 5*); III, *endo*-2-hydroxybicyclo[3.2.1]octane (*1, 5*); IV, *exo*-2-hydroxybicyclo[3.2.1]oct-3-ene (*2, 5*); V, 2-hydroxy-2-methylbicyclo[3.2.1]octane (*5*); VI, bicyclo[3.2.1]octan-2-one (*1, 5*); VII, *syn*-8-hydroxybicyclo[3.2.1]octane (*4, 5*); VIII, *syn*-8-hydroxybicyclo[3.2.1]oct-2-ene (*3, 5*).

These compounds were prepared by methods analogous to those used for the bicyclo[3.2.1]nonyl series previously reported.[5] From the preparative methods employed and analysis of the products, compounds III and IV were assigned the endo and exo configurations, respectively.

Compound VIII was prepared from a mixture of 2-*exo*-morpholino-8-ketobicyclo[3.2.1]octane and 2-*endo*-morpholino-8-ketobicyclo[3.2.1]octane by $LiAlH_4$ reduction followed by amine oxide pyrolysis. This procedure led to a mixture of the *syn*- and *anti*-8-hydroxybicyclo[3.2.1]oct-2-enes, the syn isomer accounting for 95% of the yield.