

STUDIES ON POTENTIAL ANTITUMOR AGENTS (I).

Thiosemicarbazones of p-Chlorophenyl- and
m-Chlorophenylpyridine-2-carboxaldehydes

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Thiosemicarbazones of eight p- and m-chlorophenylpyridine-2-carboxaldehydes have been synthesized. The biological activity of these compounds was evaluated by animal test. 4-(p-Chlorophenyl)pyridine-2-carboxaldehyde thiosemicarbazone was found to possess potential antitumor activity with low toxicity.

Thiosemicarbazones of α (N)-heterocyclic carboxaldehydes, typically of pyridine-2- and isoquinoline-1- groups, have been known to have antitumor activity.¹ 4-(m-Aminophenyl)pyridine-2-carboxaldehyde thiosemicarbazone has been reported to possess potential antitumor activity on mice bearing Sarcoma 180 ascites cells.² This study was undertaken to synthesize further thiosemicarbazones of arylpyridine-2-carboxaldehydes for biological evaluation. 4-(p-Chlorophenyl)-pyridine-2-carboxaldehyde thiosemicarbazone was found to possess potential antitumor activity with low toxicity.

p-Chlorophenyl-2-picolines were synthesized by a procedure similar to the arylation of picoline with diazotized m-nitroaniline² (Scheme I). p-Chloroaniline (75 g) was diazotized at 0° and the

resulting solution was added dropwise to 2-picoline (300 ml) at 30-40°. The reaction mixture was kept at 80° for 30 minutes and worked up as usual² to obtain 25 g of a semisolid, which was chromatographed on silica gel eluting with chloroform. Four isomeric p-chlorophenyl-2-picolines (1-4) were obtained. The isomers were differentiated by nmr studies. These structural assignments were consistent with the nmr data, which are shown in Table I. p-Chlorophenyl-2-picolines (1-4) were oxidized with selenium dioxide in refluxing dioxane to p-chlorophenylpyridine-2-carboxaldehydes (5-8), which were converted to thiosemicarbazones (9-12). Relevant data for these compounds are listed in Table II.

m-Chlorophenyl-2-picolines were similarly synthesized. Chromatography of the reaction mixture afforded 4- and 6-(m-chlorophenyl)-2-picoline but 3- and 5-isomers came out as a mixture, which as separated at aldehyde stage by chromatography on silica gel. The compounds of m-chloro series are listed in Table III.

Biological evaluation of these thiosemicarbazones was made on mice bearing Sarcoma 180 ascites cells. 4-(p-Chlorophenyl)pyridine-2-carboxaldehyde thiosemicarbazone was found to possess potential antitumor activity with low toxicity.

Scheme I

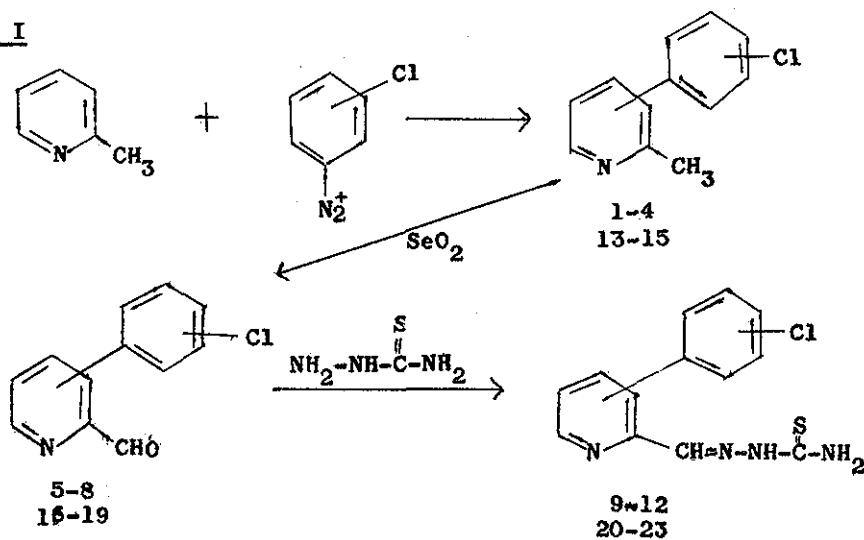
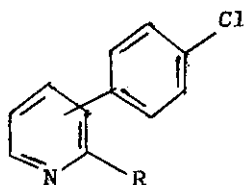


Table I. NMR Data*

Compd	Position of Chlorophenyl Substitution	2-Methyl Protons	Protons on Phenyl and Pyridine Rings	H-6 on Pyridine Ring	Proton of Aldehyde CHO	Solvent
1	3	2.53 (3H, s)	7.13-7.68 (6H, m)	8.65 (1H, dd) J=5.2 Hz		CCl ₄
2	4	2.53 (3H, s)	7.11-7.60 (6H, m)	8.47 (1H, dd) J=5.1 Hz		CDCl ₃
3	5	2.53 (3H, s)	7.05-7.73 (6H, m)	8.66 (1H, d) J=2 Hz		CCl ₄
4	6	2.53 (3H, s)	6.86-8.01 (7H, m)			CDCl ₃
16	3		7.16-7.90 (6H, m)	8.94 (1H, dd) J=5.2 Hz	10.28 (1H, s)	CDCl ₃
14	4	2.55 (3H, s)	7.23-7.68 (6H, m)	8.67 (1H, dd) J=5.1 Hz		CDCl ₃
18	5		7.40-8.06 (6H, m)	9.05 (1H, d) J=2 Hz	10.23 (1H, s)	CDCl ₃
15	6	2.53 (3H, s)	6.88-8.06 (7H, m)			CCl ₄

*NMR spectra were determined with a JEOL-C-60-HL High Resolution NMR Instrument. The Chemical shifts are reported in p.p.m. downfield from internal TMS.

Table II



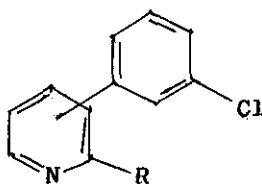
Compd*	R	Position of p-Chlorophenyl Substituent	Mp, °C	% Yield	Formula	Mass Spectra (M ⁺)
1	CH ₃	3	41.5-42	15.1 ^a	C ₁₂ H ₁₀ ClN	203
2	CH ₃	4	68-70	16.3 ^a	C ₁₂ H ₁₀ ClN	203
3	CH ₃	5	90-91	12.3 ^a	C ₁₂ H ₁₀ ClN	203
4	CH ₃	6	66-69	56.1 ^a	C ₁₂ H ₁₀ ClN	203
5	CHO	3	72.5-73	22.1(36 ^b)	C ₁₂ H ₈ ClNO	217
6	CHO	4	97-97.5	20.0(33 ^b)	C ₁₂ H ₈ ClNO	217
7	CHO	5	99-100	61.0(96 ^b)	C ₁₂ H ₈ ClNO	217
8	CHO	6	95-97	78.0(145 ^b)	C ₁₂ H ₈ ClNO	217
9	CH=NNHCSNH ₂	3	218-219 (dec)	80.0	C ₁₃ H ₁₁ ClN ₄ S	
10	CH=NNHCSNH ₂	4	228-230 (dec)	79.0	C ₁₃ H ₁₁ ClN ₄ S	
11	CH=NNHCSNH ₂	5	246-250 (dec)	80.0	C ₁₃ H ₁₁ ClN ₄ S	
12	CH=NNHCSNH ₂	6	217-218	60.0	C ₁₃ H ₁₁ ClN ₄ S	

*Compounds are all new except 2.

^aYield are based on the recovery of various isomers from a mixture obtained in 17.7% yield by the arylation of p-chloroaniline with 2-picoline.

^bReflux time in hours in selenium dioxide oxidation of the 2-picolines.

Table III



Compd*	R	Position of m-Chlorophenyl Substitution	Mp ₀ (Bp) C	% Yield	Formula	Mass Spectra (M ⁺)
13 ^a	CH ₃	3, 5	>300 (Bp)	2.70	C ₁₂ H ₁₀ ClN	203
14	CH ₃	4	39-42	1.40	C ₁₂ H ₁₀ ClN	203
15	CH ₃	6	>300 (Bp)	2.80	C ₁₂ H ₁₀ ClN	203
16	CHO	3	>300 (Bp)	79.0 (156 ^b)	C ₁₂ H ₈ ClNO	217
17	CHO	4	86-90	50.0 (96 ^b)	C ₁₂ H ₈ ClNO	217
18	CHO	5	92-96	79.0 (156 ^b)	C ₁₂ H ₈ ClNO	217
19	CHO	6	68-72	78.0 (126 ^b)	C ₁₂ H ₈ ClNO	217
20	CH=NNHCSNH ₂	3	212-215 (dec)	66.2	C ₁₃ H ₁₁ ClN ₄ S	
21	CH=NNHCSNH ₂	4	216-224 (dec)	80.0	C ₁₃ H ₁₁ ClN ₄ S	
22	CH=NNHCSNH ₂	5	220-221 (dec)	89.9	C ₁₃ H ₁₁ ClN ₄ S	
23	CH=NNHCSNH ₂	6	182-185	75.0	C ₁₃ H ₁₁ ClN ₄ S	

*New Compounds.

^aMixture of 3- and 5-isomers.^bReflux time in hours in selenium dioxide oxidation of the 2-picoline.

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