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-nitroaniline[2] (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 usual[2] 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 thiosemecarbazone was found to possess potential antitumor activity with low toxicity.

Scheme I

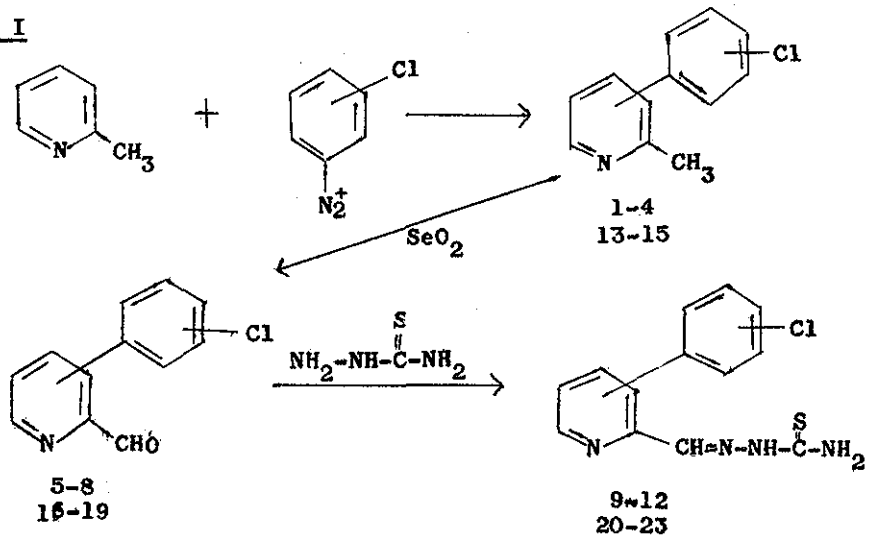
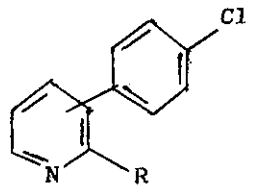


Table I. NMR Data*

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



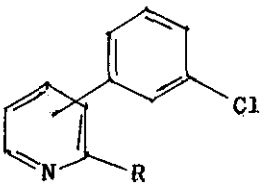
Compd*	R	Position of p-Chlorophenyl Substituent	Mp, °C	% Yield	Formula	Mass Spectra (M^+)
1	CH_3	3	41.5-42	15.1[a]	$C_{12}H_{10}ClN$	203
2	CH_3	4	68-70	16.3[a]	$C_{12}H_{10}ClN$	203
3	CH_3	5	90-91	12.3[a]	$C_{12}H_{10}ClN$	203
4	CH_3	6	66-69	56.1[a]	$C_{12}H_{10}ClN$	203
5	CHO	3	72.5-73	22.1(36[b])	$C_{12}H_8ClNO$	217
6	CHO	4	97-97.5	20.0(33[b])	$C_{12}H_8ClNO$	217
7	CHO	5	99-100	61.0(96[b])	$C_{12}H_8ClNO$	217
8	CHO	6	95-97	78.0(145[b])	$C_{12}H_8ClNO$	217
9	$CH=NNHCSNH_2$	3	218-219 (dec)	80.0	$C_{13}H_{11}ClN_4S$	
10	$CH=NNHCSNH_2$	4	228-230 (dec)	79.0	$C_{13}H_{11}ClN_4S$	
11	$CH=NNHCSNH_2$	5	246-250 (dec)	80.0	$C_{13}H_{11}ClN_4S$	
12	$CH=NNHCSNH_2$	6	217-218	60.0	$C_{13}H_{11}ClN_4S$	

*Compounds are all new except 2.

[a]Yield 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.

[b]Reflux time in hours in selenium dioxide oxidation of the 2-picolines.

Table III



Compd*	R	Position of m-Chlorophenyl Substitution	Mp, °C (Bp)	% 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])	$C_{12}H_8ClNO$	217
17	CHO	4	86-90	50.0(96[b])	$C_{12}H_8ClNO$	217
18	CHO	5	92-96	79.0(156[b])	$C_{12}H_8ClNO$	217
19	CHO	6	68-72	78.0(126[b])	$C_{12}H_8ClNO$	217
20	$CH{=}NNHCSNH_2$	3	212-215 (dec)	66.2	$C_{13}H_{11}ClN_4S$	
21	$CH{=}NNHCSNH_2$	4	216-224 (dec)	80.0	$C_{13}H_{11}ClN_4S$	
22	$CH{=}NNHCSNH_2$	5	220-221 (dec)	89.9	$C_{13}H_{11}ClN_4S$	
23	$CH{=}NNHCSNH_2$	6	182-185	75.0	$C_{13}H_{11}ClN_4S$	

*New Compounds.

[a]Mixture of 3- and 5-isomers.

[b]Reflux time in hours in selenium dioxide oxidation of the 2-picoline.

REFERENCES

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2. K. C. Agrawal, A. J. Lin, B. A. Booth, J. R. Wheaton, and A. C. Sartorelli., J. Med. Chem., 17, 631 (1974).

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