STUDIES ON POTENTIAL ANTITUMOR AGENTS (II). Thiosemicarbazones of p-Bromophenyl- and o-Chlorophenylpyridine-2-carboxaldehydes

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Thiosemicarbazones of eight p-bromophenyl- and o-chlorophenyl-pyridine-2-carboxaldehydes have been synthesized. Tumor-inhibitory potency and host toxicity of these compounds were assessed in mice bearing Sarcoma 180 ascites cells.

4-(m-Aminophenyl)pyridine-2-carboxaldehyde thiosemicarbazone was reported to have potential antitumor activity on mice bearing Sarcoma 180 ascites cells.[1] A previous communication from This Laboratory[2] described synthesis of thiosemicarbazones of p-chlorophenyl- and m-chlorophenylpyridine-2-carboxaldehydes. The present study was undertaken to prepare further thiosemicarbazones of p-bromophenyl- and o-chlorophenylpyridine-2-carboxaldehydes for biological evaluation.

p-Bromophenyl-2-picolines were synthesized by a procedure similar to the arylation of 2-picoline with diazotized p-chloroaniline[2] (scheme 1). p-Bromoaniline (103.2 g) was diazotized at 0° and the resulting solution was added dropwise to 2-picoline (300 ml) at 40°. The reaction mixture was kept at 80° for 30 minutes and worked up as usual[2] to obtain 38 g of a semisolid, which was chromatographed on silica gel and on neutral alumina. Four isomeric p-bromophenyl-2-picolines (1-4) were obtained pure. The isomers were differentiated by nmr studies

(Table I). These arylpicolines (1-4) were oxidized with selenium dioxide in refluxing dioxane to p-bromophenylpyridine-2-carboxaldehydes (5-8), which were converted to thiosemicarbazones (9-12). These compounds are listed in Table II.

o-Chlorophenyl-2-picolines resulted from the reaction of 2-picoline and diazotized o-chloroaniline in a similar fashion except that the reaction mixture was maintained at pH 4-5. This reaction gave, after chromatography, 3-, 4-, 6- and a mixture of 3- and 5-(o-chlorophenyl)-2-picolines (13-16). Selenium dioxide oxidation of these methyl compounds gave corresponding aldehydes (17-20), the mixture of 3- and 5- isomers being separated by chromatography. The aldehydes were converted to thiosemicarbazones (21-24), These results are listed in Table III.

Biological evaluation of these thiosemicarbazones on mice bearing Sarcoma 180 ascites cells showed 4-(o-chlorophenyl)-pyridine-2-carboxaldehyde thiosemicarbazone to be the best.

Scheme I.

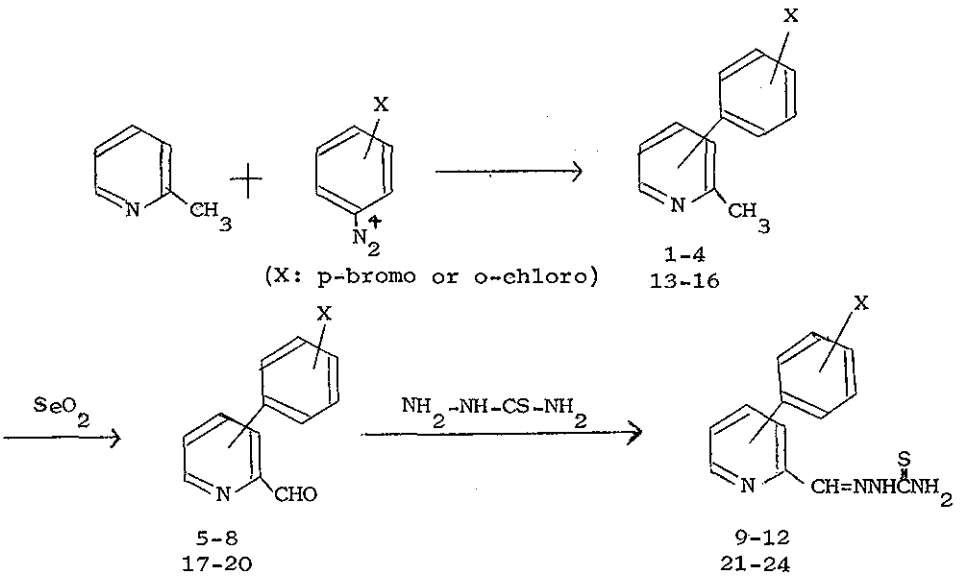
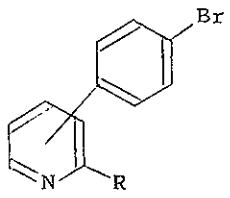


Table I. NMR Data*

Compd	Position of aryl group substitution	2-Methyl protons (3H, s)	Protons on phenyl and pyridine rings	H-6 on pyridine ring (1H, dd)	Proton of aldehyde CHO (1H, s)
1	3	2.45	7.03-7.73 (6H, m)	8.53 J=5,2 Hz	
2	4	2.53	7.13-7.70 (6H, m)	8.53 J=5, 1 Hz	
3	5	2.53	7.06-7.79 (6H, m)	8.76 J=2,1 Hz	
4	6	2.56	7.03-8.09 (7H, m)		
5	3		7.00-7.83 (6H, m)	8.82 J=5,2 Hz	10.05
6	4		7.20-8.13 (6H, m)	8.75 J=5,1 Hz	10.05
7	5		7.30-8.23 (6H, m)	9.00 J=2,1 Hz	10.10
8	6		7.13-8.03 (7H, m)		10.03
13	3	2.34	7.10-7.90 (6H, m)	8.65 J=5,2 Hz	
14	4	2.63	7.13-7.73 (6H, m)	8.71 J=5,1 Hz	
16	6	2.61	7.10-7.90 (7H, m)		
17	3		7.03-7.83 (6H, m)	8.78 J=5,2 Hz	9.91
18	4		7.06-8.06 (6H, m)	8.77 J=5,1 Hz	10.05
19	5		7.13-8.00 (6H, m)	8.73 J=2,1 Hz	9.98
20	6		7.10-8.00 (7H, m)		10.04

*NMR Spectra were recorded on a JEOL-C-60-HL High Resolution NMR Instrument. The chemical shifts are reported in ppm downfield from internal TMS. Compounds 1, 2, 3, 4, 19 were dissolved in CCl_4, all others in $CDCl_3$.

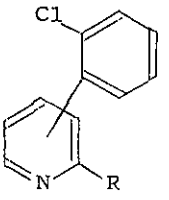
Table II. Compounds of p-Bromophenyl Series



Compd[a]	R	Position of p-Bromophenyl Substitution	Mp (Bp) °C	% Yield	Formula	Mass Spectra (M^+)
1	CH_3	3	50.5-51.5	13.7[b]	$C_{12}H_{10}BrN$	247
2	CH_3	4	75-76.2	20.7[b]	$C_{12}H_{10}BrN$	247
3	CH_3	5	100-101	6.2[b]	$C_{12}H_{10}BrN$	247
4	CH_3	6	75	59.4[b]	$C_{12}H_{10}BrN$	247
5	CHO	3	87-88	78(196)[c]	$C_{12}H_8BrNO$	261
6	CHO	4	101-102	47(286)[c]	$C_{12}H_8BrNO$	261
7	CHO	5	137-138.5	52.6(135)[c]	$C_{12}H_8BrNO$	261
8	CHO	6	84-85.5	72(297)[c]	$C_{12}H_8BrNO$	261
9	$CH=NNHCSNH_2$	3	218.5-220 (dec)	87.3	$C_{13}H_{11}BrN_4S$	
10	$CH=NNHCSNH_2$	4	217.5-220 (dec)	81	$C_{13}H_{11}BrN_4S$	
11	$CH=NNHCSNH_2$	5	235-237 (dec)	77	$C_{13}H_{11}BrN_4S$	
12	$CH=NNHCSNH_2$	6	217-219 (dec)	79	$C_{13}H_{11}BrN_4S$	

a. All compounds are new.
b. Yields are based on the recovery of various isomers from a mixture obtained in 7.0% yield from the arylation of 2-picoline with p-bromoaniline.
c. Reflux time (hours) in selenium dioxide oxidation of the 2-picolines.

Table III. Compounds of o-Chlorophenyl Series



Compd[a]	R	Position of o-Chlorophenyl Substitution	Mp (Bp) °C	% Yield	Formula	Mass Spectra (M^+)
13	CH_3	3	>300(Bp)	35.5[b]	$C_{12}H_{10}ClN$	203
14	CH_3	4	37-38.5	9.6[b]	$C_{12}H_{10}ClN$	203
15	CH_3	3,5[d]	>300(Bp)	6.1[b]	$C_{12}H_{10}ClN$	203
16	CH_3	6	>300(Bp)	48.8[b]	$C_{12}H_{10}ClN$	203
17	CHO	3	81-82	70.1(103)[c]	$C_{12}H_8ClNO$	217
18	CHO	4	68-70	43.4(110)[c]	$C_{12}H_8ClNO$	217
19	CHO	5	68-69.5	57.5(102)[c]	$C_{12}H_8ClNO$	217
20	CHO	6	86-86.5	78(147)[c]	$C_{12}H_8ClNO$	217
21	$CH{=}NNHCSNH_2$	3	204-205 (dec)	88	$C_{13}H_{11}ClN_4S$	
22	$CH{=}NNHCSNH_2$	4	207-208.5 (dec)	86	$C_{13}H_{11}ClN_4S$	
23	$CH{=}NNHCSNH_2$	5	204-205 (dec)	91	$C_{13}H_{11}ClN_4S$	
24	$CH{=}NNHCSNH_2$	6	187-188.5 (dec)	85	$C_{13}H_{11}ClN_4S$	

a. All compounds are new.
b. Yields are based on the recovery of various isomers from a mixture obtained in 13.5% yield from the arylation of 2-picoline with o-chloroaniline.
c. Reflux time (hours) in selenium dioxide oxidation of the 2-picolines.
d. Mixture of 3- and 5- isomers.

REFERENCES

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2. C. T. Chen, S. F. Chen, and S. J. Lee, Heterocycles, 5, 239 (1976); Bull. Inst. Chem. Academia Sinica, No. 24, p. 53, 1977.

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