3, CH_3), 2.69 (m, 2, CH_2), 3.89 (s, 1, OH), 7.1–7.9 (A-B, 4, ArH).

Anal. Calcd. for $C_{11}H_{10}Cl_2F_4O$: C, 43.30; H, 3.30; Cl, 23.24; mol wt 305.10. Found: C, 43.35; H, 3.82; Cl, 23.53; mol wt 301.

4-(1-Chloroethyl)phenyl-bis(trifluoromethyl)carbinol. A 115-gram portion of **I** in 500 ml of CCl_4 was chlorinated with 23.5 grams of chlorine over 0.75 hour at 60° to 76° using a 100-W Hanovia mercury vapor lamp. The mixture was separated by distillation to give 61 grams (47.4%) of 4-(1-chloroethyl)phenyl-bis(trifluoromethyl)carbinol, bp 65°–66°/1.0 mm, n_D^{20} 1.4520; ir (neat) 2.8 (hindered OH) 3.33, 3.39, 7.25 (CH_3 and CHCl), 8.20, 9.0 (CF and/or COH), 5.2, 5.53, 11.95 (1,4 disub. arom.) 12.57 (CCl); nmr ($CDCl_3$) δ1.77 (d, 3, CH_3), 5.08 (m, 1, CHCl), 3.50 (s, 1, OH), 7.47 (d, 2, ArH by CHCl), 7.86 [d, 2, ArH by $C(CF_3)_2OH$].

Anal. Calcd. for $C_{11}H_9ClF_6O$: C, 43.09; H, 2.96; Cl, 11.56. Found: C, 43.43; H, 3.04; Cl, 11.38.

4-(1-Chloroethyl)phenyl - bis(chlorodifluoromethyl)carbinol. In a manner similar to that described above, 60 grams of **II** was reacted with 12.6 grams of chlorine. The mixture was separated by distillation to give 17 grams of **II**, 10.5 grams (17.6%) of 4-vinylphenyl-bis(chlorodifluoromethyl)-carbinol, bp 76–80°/0.5–1.0 mm, n_D^{20} 1.4991, and 17.5 grams (29.7%) of 4-(1-chloroethyl)phenyl-bis(chlorodifluoromethyl)-carbinol, bp 112°/1.0 mm, n_D^{20} 1.4995; ir (neat) 2.80 (hindered OH), 3.32, 3.40, 7.26 (CH_3 and CHCl), 8.4, 8.7, 9.0 (CF and/or COH), 5.2, 5.5, 12.1 (1,4 disub. arom.), 13.2, 13.9 (CCl); nmr ($CDCl_3$) δ1.77 (d, 3, CH_3), 5.08 (m, 1, CHCl), 3.80 (s, 1, OH), 7.3–7.9 (A-B, 4, ArH).

Anal. Calcd. for $C_{11}H_9Cl_3F_4O$: Cl, 31.32. Found: Cl, 31.39.

4-Vinylphenyl-bis(chlorodifluoromethyl)carbinol. 4-(1-Chloroethyl)phenyl-bis(chlorodifluoromethyl)carbinol, 46 grams, was added to 6 grams of NaOH in 225 ml of 50% ethanol. The mixture was heated to 40–50° and the extent of reaction was followed by the titration of aliquots. After 90 minutes the ethanol was distilled at 10 mm Hg pressure and the remaining mixture was extracted with ether. Distillation was used to separate 15 grams (36.7%) of 4-vinylphenyl-bis(chlorodifluoromethyl)carbinol, bp 75–77°/0.5 mm, n_D^{20} 1.5118; ir (neat) 2.80 (hindered OH), 3.22, 3.27 (=CH— and $=CH_2$), 6.15 (conjugated C=C), 8.40, 8.7, 9.04 (CF and/or COH), 10.1, 10.9 (—CH=CH_2), 5.23, 5.5, 12.45 (1,4 disub. arom.), 13.05, 13.8 (CCl); nmr ($CDCl_3$) δ3.8 (s, 1, OH), 5.3 and 5.8 (m, 2, $=CH_2$), 6.7 (m, 1, =CH—), 7.2–7.7 (m, 4, ArH).

Anal. Calcd. for $C_{11}H_8Cl_2F_4O$: C, 43.60; H, 2.66; Cl, 23.40. Found: C, 43.31; H, 2.96; Cl, 23.18.

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Some 2,5- and 5,6-Dihalonicotinic Acids and Their Precursors

FRANK L. SETLIFF

Department of Chemistry, University of Arkansas at Little Rock, Little Rock, Ark. 72204

The preparation of several new 2,5- and 5,6-dihalonicotinic acids (2,5- and 5,6-dihalo-3-pyridinecarboxylic acids) by oxidation of the corresponding dihalo-3-picolines is described. Experimental and spectral data for the acids and their precursors are presented.

The pharmacological significance of nicotinic acid (niacin) has been recognized for decades (*4*). Since introduction of halogen atoms into biologically active compounds often increases activity, and since relatively few dihalonicotinic acids have been reported, we were prompted to prepare several 2,5- and 5,6-dihalonicotinic acids incorporating bromine, chlorine, and fluorine in a variety of combinations.

A recent note (*2*) described the synthesis of 3-bromo-2-chloro-5-methylpyridine (Ib) and 3-bromo-2-fluoro-5-methylpyridine (Ic) via diazotization of 2-amino-3-bromo-5-methylpyridine (Ia) in hydrochloric and fluoboric acid, respectively. We now observe that diazotization of Ia as the hydrobromide perbromide using the procedure of Craig (*1*) provides 2,3-dibromo-5-methylpyridine (Id) in adequate yield.

The extension of this preparative scheme to the synthesis of the analogous 2,5-dihalo-3-picolines has been equally successful. Diazotization of 2-amino-3-methyl-5-bromopyridine (Ie), available by bromination of 2-amino-3-methylpyridine, in hydrochloric, fluoboric, and hydrobromic acids, provides substantial yields of the 2-chloro- (If), 2-fluoro- (Ig), and 2-bromo- (Ih) derivatives, respectively.

	I				II		
	R_1	R_2	R_3		R_1	R_2	R_3
a.	NH_2	Br	CH_3	*a.*	Cl	Br	CO_2H
b	Cl	Br	CH_3	*b.*	F	Br	CO_2H
c.	F	Br	CH_3	*c.*	Br	Br	CO_2H
d.	Br	Br	CH_3	*d.*	Cl	CO_2H	Br
e.	NH_2	CH_3	Br	*e.*	F	CO_2H	Br
f.	Cl	CH_3	Br	*f.*	Br	CO_2H	Br
g.	F	CH_3	Br				
h.	Br	CH_3	Br				

Permanganate oxidation of all the dihalo-3-picolines mentioned above led to the corresponding dihalonicotinic acids, IIa through IIf. The rather low yields are not surprising, in view of a previous report (*3*) which indicates

Table I. Experimental and Spectral Data for Dihalonicotinic Acids and Their Precursors

Cpd.[a]	Yield, %	M.P., °C	Recryst. Solvent	IR[b], ν, Cm^{-1}	Solvent[c]	Proton NMR Chemical Shifts, PPM, δ H_4	H_6	CH_3	Other[d]
Ib	46	67–69	Ligroine	1415, 1375, 1135, 1030, 1020, 884, 863, 710, 633	C	8.02	8.28	2.36	...
Ic	40	54–55	Ligroine	1595, 1460, 1265, 1040, 900, 885, 757, 725, 670	A	8.08	8.08	2.35	...
Id	58	52–54	MeOH-H_2O	1410, 1370, 1255, 1110, 1015, 887, 854, 704, 597, 525	C	7.78	8.16	2.30	...
Ie	72	90–92	Ligroine	1635, 1465, 901, 892, 753, 641, 540	C	7.31	7.82	1.95	NH_2, 4.88
If	35	40–41	MeOH-H_2O	1450, 1390, 1100, 1065, 885, 720, 690, 495	A	8.00	8.40	2.41	...
Ig	53	62–64	Ligroine	1460, 1425, 1240, 1136, 891, 755, 730, 633	C	7.77	8.13	2.31	...
Ih	41	41–42	MeOH-H_2O	1449, 1385, 1100, 1052, 1030, 972, 713, 680	C	7.71	8.30	2.48	...
IIa	50	170–72	Water	1710, 1575, 1405, 1362, 1275, 1138, 1115, 1031, 856, 763	A	8.61	8.95	...	...
IIb	25	169–71	Mecy.[e]	1705, 1575, 1415, 1290, 1260, 1040, 893, 770, 683, 633	D	8.66	8.66	...	...
IIc	45	173–74	Water	1725, 1568, 1280, 1110, 1025, 850, 763	D	8.51	8.80	...	...
IId	25	179–80	Water	1725, 1563, 1545, 1408, 1260, 1220, 1110, 1087, 910, 778, 720, 582	D	8.48	8.73	...	...
IIe	28	141–42	Mecy.[e]	1710, 1590, 1452, 1300, 1255, 1225, 1105, 1078, 918, 788, 670	D	8.55	8.55	...	...
IIf	30	174–75	Water	1725, 1563, 1538, 1400, 1260, 1220, 1110, 1087, 1041, 715	D	8.40	8.73	...	...

[a] All compounds except Ib and Ic are new, subjected to C, H, and N analysis, results editorially reviewed and found within acceptable limits. [b] Only most intense absorption bands reported. [c] A = acetone d_6; C = $CDCl_3$; D = DMSO d_5. [d] Carboxyl protons not visible in spectra of nicotinic acids. [e] Methylcyclohexane.

poor oxidative conversion of poly ring-halogenated pyridine compounds to their halocarboxylic acid derivatives.

Pertinent experimental and physical data for the compounds described here are presented in Table I.

EXPERIMENTAL

Elemental analyses were performed by the Heterocyclic Chemical Corp., Harrisonville, Mo., or Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained in potassium bromide disks on a Perkin-Elmer 337 spectrophotometer, and proton NMR spectra were obtained on a Varian A-60 instrument with tetramethylsilane as an internal standard.

2-Amino-5-bromo-3-methylpyridine (Ie). Bromination of 2-amino-3-methylpyridine at 80–90° in acetic acid was carried out by a procedure identical with that described for the preparation of Ia from 2-amino-5-methylpyridine (*2*).

5-Bromo-2-chloro-3-methylpyridine (If). Diazotization of Ie in concentrated hydrochloric acid was done in a fashion analogous to the preparation of Ib from Ia (*2*), except that the crude product was isolated by steam distillation. (We have subsequently found that steam distillation also is the preferred method of isolating Ib.)

5-Bromo-2-fluoro-3-methylpyridine (Ig). Diazotization of Ie in 48% fluoboric acid and subsequent workup were carried out as in the conversion of Ia to Ic (*2*).

2,3-Dibromo-5-methylpyridine (Id) and 2,5-Dibromo-3-methylpyridine (Ih). The Craig procedure (*1*) was employed for the preparation of these compounds. The appropriate aminobromopicoline (Ia or Ie) (11.6 grams, 0.0875 mole) was dissolved in 150 ml of 48% hydrobromic acid and cooled to 0° with mechanical stirring. Bromine (20 ml) was then added dropwise to the cold solution with continued stirring and temperature control at 0°. The resulting slurry of the orange hydrobromide perbromide was diazotized at 0° by the dropwise addition of a solution of 25 grams of sodium nitrite in 40 ml of water over a period of 90 minutes with continued stirring. After being stirred an additional 20 minutes at 0°, the dark solution was made basic with 25% sodium hydroxide at ice bath temperature, and the excess bromine was discharged by adding a 10% sodium bisulfite solution. The resulting light yellow solution, containing a dense oily phase, was then subjected to steam distillation until no more volatile solid distilled. The solid (Id or Ih) was filtered and recrystallized (Table I).

2,5- and 5,6-Dihalonicotinic Acids. The appropriate dihalo-3-picoline (0.02 mole) and potassium permanganate (0.05 mole) were added to 300 ml of water and heated under reflux for 2 hours. After traces of unreacted starting material were removed by steam distillation, the manganese dioxide was removed by filtration, and the clear filtrate was concentrated to a volume of 10 to 15 ml on a rotary evaporator. Acidification with 3 to 4 ml of concentrated hydrochloric acid afforded the crude dihalonicotinic acid which was recrystallized as described in Table I. The yield percentages were calculated on the basis of the amount of reacted starting material.

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