

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

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The preparation of 5-fluoro-6-iodo and 5-bromo-6-iodonicotinic acid by iodide displacement of the corresponding 6-chloro derivatives is described. The synthesis of 5-fluoro-2-iodonicotinic acid and its oxidative precursor 5-fluoro-2-iodo-3-picoline is also presented. Experimental and spectral data for all new compounds are given.

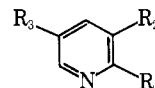
In previous communications (3, 5) we reported the synthesis of a number of dihalonicotinic acids of potential medicinal interest. However, none of these contained iodine, an element of known physiological importance. We now wish to report the preparation and characterization of three iodine-containing dihalonicotinic acids, namely, the 5-fluoro-6-iodo, 5-bromo-6-iodo, and 5-fluoro-2-iodo derivatives VIII, X, and VI, respectively.

The fluoroiodo acid VIII and the bromoiodo acid X were obtained in adequate yields by treatment of the corresponding fluorochloro acid VII (5) and bromochloro derivative IX (3) with sodium iodide in refluxing methyl ethyl ketone. Although all attempts to prepare acid VI directly by this iodide-chloride exchange procedure proved unrewarding, its synthesis was effected by a multistep route. 2-Iodo-3-methyl-5-nitropyridine (II) was prepared from 2-chloro-3-methyl-5-nitropyridine (I) (1) by treatment with sodium iodide and hydriodic acid in boiling methyl ethyl ketone.

Reduction of II to the iodoaminopicoline III was accomplished with aqueous iron powder. Diazotization of III by the modified Schiemann procedure (2, 4) afforded the stable diazonium hexafluorophosphate IV (57% yield, mp 88°C, dec), which was then thermally decomposed in hot mineral oil (108°C) to produce V. The diazotization-decomposition procedure employed was analogous to that previously described (4). Oxidation of V in neutral potassium permanganate by standard procedure (3, 5) yielded VI, albeit in low yield.

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Elemental analyses (C, H, N, I) for all new compounds in agreement with theoretical values were obtained and submitted for review. Experimental and physical data for the new compounds described are presented in Table I.



	R ₁	R ₂	R ₃
I	Cl	CH ₃	NO ₂
II	I	CH ₃	NO ₂
III	I	CH ₃	NH ₂
IV	I	CH ₃	N ₂ ⁺ PF ₆ ⁻
V	I	CH ₃	F
VI	I	CO ₂ H	F
VII	Cl	F	CO ₂ H
VIII	I	F	CO ₂ H
IX	Cl	Br	CO ₂ H
X	I	Br	CO ₂ H

Experimental

Elemental analyses were performed by the Heterocyclic Chemical Corp., Harrisonville, Mo. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained in potassium bromide disks (unless otherwise indicated) on a Perkin-Elmer 337 spectrophotometer. Nuclear magnetic resonance spectra were obtained at 60 MHz on a Jeolco C-60 HL instrument with tetramethylsilane as an internal standard.

5-Fluoro-6-iodonicotinic acid (VIII). 6-Chloro-5-fluoronicotinic acid (5) (1.00 gram; 0.0057 mole) and sodium iodide (2.0 grams) were added to methyl ethyl ketone (25 ml), and the resulting solution was stirred under reflux for 24 hr. The precipitated sodium chloride was removed by filtration, and the filtrate was evaporated to dryness (air blower). The residue was leached with 10% sodium bisulfite solution (15 ml), and the solid was collected and recrystallized (Table I).

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

Compd	Yield, %	Mp, °C	I _r , ^a ν, cm ⁻¹	Proton nmr, ppm δ ^b		
				H ₄	H ₆	Other
II	49	114–15 ^c	3150, 1625, 1560, 1510, 1470, 1445, 1375, 1030, 790, 670	8.33 d	9.08 d	CH ₃ , 2.58 s
III	40	98–100 ^c	3400, 3300, 1625, 1575, 1450, 1390, 1375, 1025, 857, 580	6.97 d	7.90 d	CH ₃ , 2.35 s NH ₂ , 3.78 b
V	21 ^d	Bp 68–70 (10 mm)	1600, 1575, 1470, 1400, 1280, 630 ^e	7.55 d	8.60 d	CH ₃ , 2.50 s
VI	10	162–4 ^c (dec)	1720, 1560, 1410, 1285, 1225, 900, 625	8.30 d'	8.88 d	CO ₂ H ^f
VIII	45	184–5 ^g (dec)	1670, 1575, 1395, 1285, 1160, 1025, 747, 572, 478	8.10 d'	8.93 m	CO ₂ H, ^h 6.47 b
X	48	173–4 ^g (dec)	1710, 1565, 1350, 1278, 1182, 1090, 1020, 840, 765, 710	8.53 d	9.00 d	CO ₂ H, ^h 6.76 b

^a Only most intense absorption bands reported. ^b CDCl₃ as solvent for compounds III, II, and V. Acetone d₆ as solvent for compounds VI, VIII, and X. All signals were observed to be in the correct area ratio. s = singlet, d = doublet, d' = doublet of doublets, m = multiplet, b = broad. ^c Recrystallized from methylcyclohexane. ^d Overall from the amine. ^e Liquid film sample. ^f This carboxyl proton not visible. ^g Recrystallized from water. ^h High field signals apparently due to protonated ring nitrogen as the zwitterion. Signal exchangeable with D₂O.

5-Bromo-6-iodonicotinic acid (X). 5-Bromo-6-chloronicotinic acid (3) (1.18 grams; 0.005 mole) and sodium iodide (2.0 grams) were heated under reflux in methyl ethyl ketone (20 ml) for 48 hr. The product was isolated by the same procedure used for VIII.

2-Iodo-3-methyl-5-nitropyridine (II). A mixture of the chloronitropicoline I (1) (10.0 grams; 0.058 mole), sodium iodide (30.0 grams), and 57% hydriodic acid (6 ml) in methyl ethyl ketone (150 ml) was stirred under reflux for 4 hr. The precipitated sodium chloride was removed by filtration, and the filtrate was evaporated to dryness with an air blower. The residue was made basic with 5% sodium hydroxide and then leached with 10% sodium bisulfite solution. The solid was collected and recrystallized (Table I).

5-Amino-2-iodo-3-methylpyridine (III). To a mechanically stirred suspension of iron powder (8.0 grams) in water (60 ml) maintained at 90°C was added 5.0 grams (0.019 mole) of II over an interval of 30 min. After an ad-

ditional 30 min of rapid stirring, the hot mixture was quickly filtered. The residue in the reaction flask was extracted with a 60-ml portion of boiling water and again filtered. The aqueous filtrates deposited crude III on cooling. Purification was achieved as described in Table I.

Acknowledgment

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Literature Cited

- (1) Hawkins, G., Roe, A., *J. Org. Chem.*, **14**, 328 (1949).
- (2) Rutherford, K., Redmond, W., Rigamonti, J., *ibid.*, **26**, 5149 (1961).
- (3) Setliff, F. L., *J. Chem. Eng. Data*, **15**, 590 (1970).
- (4) Setliff, F. L., *Org. Prep. Proc. Int.*, **3**, 217 (1971).
- (5) Setliff, F. L., Rankin, G. O., *J. Chem. Eng. Data*, **17**, 515 (1972).

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Correction

For the paper, "Binary Gaseous Diffusion Coefficients. I. Methane and Carbon Tetrafluoride with *n*-Hexane, *n*-Heptane, *n*-Octane, and 2,2,4-Trimethylpentane at One-Atmosphere Pressure at 10–70°C," by Emmerich Wilhelm and Rubin Battino [*J. Chem. Eng. Data*, **17** (2), 187 (1972)], the corrected binary diffusion coefficients, D_{12} ($\text{cm}^2/\text{sec}^{-1}$) at 1-atm pressure, are listed below. (The values reported in Table I were at the experimental pressure and not corrected to 1 atm.)

$t, ^\circ\text{C}$	$\text{CH}_4 + n\text{-Hexane}$	$\text{CF}_4 + n\text{-Hexane}$
10	0.0752	0.0388
25	0.0821	0.0429
40	0.0920	0.0485
55	0.0999	0.0522
	$\text{CH}_4 + n\text{-Heptane}$	$\text{CF}_4 + n\text{-Heptane}$
10	0.0714	0.0375
25	0.0791	0.0382
40	0.0838	0.0428
55	0.0911	0.0470
70	0.0991	0.0508
	$\text{CH}_4 + n\text{-Octane}$	$\text{CF}_4 + n\text{-Octane}$
10	0.0657	0.0274
25	0.0721	0.0356
40	0.0782	0.0422
55	0.0827	0.0435
70	0.0912	0.0467
	$\text{CH}_4 + \text{Isooctane}$	$\text{CF}_4 + \text{Isooctane}$
10	0.0662	0.0371
25	0.0727	0.0359
40	0.0770	0.0393
55	0.0867	0.0430
70	0.0948	0.0456