

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

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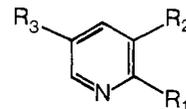
The preparation of 2,5-dichloro-, 2-chloro-5-iodo-, 5,6-dichloro-, and 6-chloro-5-iodonicotinic acid by oxidation of the appropriate dihalopicoline is described. The syntheses of the dihalopicolines are also presented. The generation of 5-chloro-6-iodonicotinic acid by iodide displacement of 5,6-dichloronicotinic acid is described. Experimental and spectral data for all new compounds are reported.

In recent years halo- and dihalonicotinic acids and their derivatives have received attention as potential hypolipidemic agents (1-4). We have previously reported the synthesis of a variety of dihalonicotinic acids of potential medicinal interest (6-8). In this communication we report the synthesis of dihalonicotinic acids IV, V, IX, and X by permanganate oxidation of the corresponding dihalopicolines II, III, VII, and VIII, respectively. Acid XI was generated by prolonged reflux of acid IX with sodium iodide in methyl ethyl ketone.

2,5-Dichloro-3-picoline (II) and 2-chloro-5-iodo-3-picoline (III) were obtained via diazotization of 5-amino-2-chloro-3-picoline (I) (7). 5,6-Dichloro-3-picoline (VII) and 6-chloro-5-iodo-3-picoline (VIII) were produced in analogous fashion from 5-amino-6-chloro-3-picoline (VI) (9).

Elemental analyses (C, H, N) for all new compounds in agreement with theoretical values were obtained and submitted for review. Experimental and physical data for compounds reported herein are presented in Table I. With the exception of 5,6-dichloronicotinic acid (IX), all compounds described in Table I are previously unreported. Acid IX had been observed by Meyer and Graf (5) in low yield by direct

chlorination of nicotinic acid with thionyl chloride. However, it seems appropriate to report its spectral data at this time.



	R ₁	R ₂	R ₃
I	Cl	CH ₃	NH ₂
II	Cl	CH ₃	Cl
III	Cl	CH ₃	I
IV	Cl	CO ₂ H	Cl
V	Cl	CO ₂ H	I
VI	Cl	NH ₂	CH ₃
VII	Cl	Cl	CH ₃
VIII	Cl	I	CH ₃
IX	Cl	Cl	CO ₂ H
X	Cl	I	CO ₂ H
XI	I	Cl	CO ₂ H

Experimental

Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained 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.

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

Compd	Yield, %	Mp, °C	IR, ^a ν , cm ⁻¹	Proton NMR, ppm, δ ^b		
				H ₄	H ₆	Other
II	62	40-41 ^c	1544, 1449, 1388, 1104, 1063, 892, 714, 689	7.57 d	8.20 d	CH ₃ , 2.40 s
III	86	52-53 ^c	1527, 1443, 1369, 1086, 1052, 873, 714, 558	7.87 d	8.43 d	CH ₃ , 2.37 s
IV	32	154-156 ^d	1724, 1550, 1408, 1219, 1052, 917, 781, 609	8.33 d	8.57 d	CO ₂ H, ^e 4.43 b
V	30	212-213 ^d	1724, 1538, 1409, 1257, 1219, 1041, 840, 719	8.53 d	8.77 d	CO ₂ H, ^e 5.17 b
VII	68	45-47 ^c	1555, 1418, 1136, 1035, 884, 714, 633, 540	7.60 d	8.13 d	CH ₃ , 2.37 s
VIII	74	59-61 ^c	1567, 1398, 1098, 1010, 869, 709, 628, 523	7.96 d	8.33 d	CH ₃ , 2.33 s
IX	34	160-161 ^{d,f}	1724, 1574, 1412, 1285, 1257, 1038, 760, 567	8.43 d	8.87 d	CO ₂ H, ^e 4.76 b
X	38	198-200 ^d	1700, 1567, 1366, 1273, 1257, 1190, 1030, 840, 763	8.73 d	8.91 d	CO ₂ H, ^e 4.33 b
XI	25	167-169 ^d	1724, 1574, 1360, 1257, 1098, 917, 763, 716	8.27 d	8.80 d	CO ₂ H, ^e 4.30 b

^a Only the most intense absorption bands are reported. ^b CDCl₃ as solvent for compounds II, III, VII, and VIII. Acetone d₆ as solvent for compounds IV, V, IX, X, and XI. All signals were observed to be in the correct area ratio. s = singlet, d = doublet, b = broad. ^c Recrystallized from methanol-water. ^d Recrystallized from water. ^e High field signals apparently due to protonated ring nitrogen as the zwitterion. Signal exchangeable with D₂O. ^f Lit (5), mp 160-161°.

2,5-Dichloro-3-picoline (II). A stirred solution of 5-amino-2-chloro-3-picoline (I) (3.0 g, 0.021 mol) (7) in concentrated hydrochloric acid (153 ml) was diazotized at 0–5 ° by the slow, dropwise addition of a solution of sodium nitrite (8.3 g) in water (23 ml). Copper powder (16.6 g) was cautiously added to the freshly diazotized solution, and the mixture was allowed to reach room temperature where stirring was continued for 2½ h. The solution was again cooled to ice bath temperature and slowly neutralized with chilled 30% sodium hydroxide. Indirect steam distillation of the neutralized solution afforded the dihalopicoline II as a white solid. Further purification was achieved by recrystallization (Table I).

2-Chloro-5-iodo-3-picoline (III). A stirred solution of I (2.0 g, 0.014 mol) in concentrated hydrochloric acid (7 ml) was diazotized at 0 ° by the slow, dropwise addition of sodium nitrite (1.7 g) in water (4 ml). The freshly diazotized solution was poured into a solution of potassium iodide (8.0 g) in water (6 ml). The resulting mixture was warmed on a steam cone for 5 min, cooled to room temperature, and made basic with 25% sodium hydroxide. Sodium bisulfite was added to the dark suspension which was then stirred overnight. The dihalopicoline III was isolated by indirect steam distillation and purified as described in Table I.

5,6-Dichloro-3-picoline (VII) and 5-iodo-6-chloro-3-picoline (VIII). These compounds were prepared by diazotization of 5-amino-6-chloro-3-picoline (VI) (9) by procedures identical to those employed in the preparation of II and III from I.

2,5-Dichloronicotinic acid (IV), 2-chloro-5-iodonicotinic acid (V), 5,6-dichloronicotinic acid (IX), and 6-chloro-5-

iodonicotinic acid (X). These dihaloacids were prepared by oxidation of the appropriate dihalopicoline (II, III, VII, and VIII, respectively) using potassium permanganate. The general procedure employed has been previously described (6–8).

5-Chloro-6-iodonicotinic acid (XI). A mixture of IX (0.82 g, 0.004 mol), sodium iodide (2.0 g), and methyl ethyl ketone (25 ml) was heated under reflux for 5 days. The precipitated sodium chloride was removed by filtration, and the filtrate was evaporated to dryness. The residual dark solid was leached with 10% sodium bisulfite solution (20 ml) and then recrystallized (Table I) to give pure XI.

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Physical Properties of Some Tertiary Amides

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Thirteen tertiary amides were prepared, and their densities and refractive indices determined. From the measured refractive indices, molar refractivities were calculated and compared with molar refractivities calculated from tables utilizing additive values.

During the course of an investigation of the reduction of some tertiary amides, it was necessary to prepare the amides to be studied. Since the compounds were made from the interaction of amines and acids or acid derivatives, the standard procedure of identifying an amide by hydrolyzing it to an acid and an amine was felt to be inadequate; accordingly, the densities, refractive indices, and molar refractivities of the amides were determined.

The methods used to prepare these amides are described elsewhere (1). (Supplemental information on the preparation of compounds and methods of determining data has been filed with the ACS Microfilm Depository Service.) Table I lists the observed values of the amides, as well as a tabulation of values calculated from the observed values or, in the case of

calculated molar refractivity, values obtained from the Lorenz-Lorentz equation using standard tables and methods (2, 4, 6).

Experimental

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Boiling points were determined during distillation and are reported both corrected and uncorrected. Determination of density was performed using a pycnometer which held 2.0086 g of water at 4.0 °C (6), and refractive indices were measured with a Bausch and Lomb Abbe-3L refractometer connected to a Lauda-thermostated bath utilizing a dry ice heat exchanger charged with ice-water instead of dry ice-isopropanol and connected as illustrated on page 23 of Lauda Bulletin BR 215-B. The prism temperature was maintained at 20.0 °C. M_r (%) was calculated from the equation:

$$\left| \frac{M_r(\text{found}) - M_r(\text{calculated})}{M_r(\text{calculated})} \right| \times 100$$