H, cis (CH=C)), a quartet ($J \simeq 1$ Hz, $\delta$ 5.30, 1 H, trans CH=C), and a multiplet at $\delta$ 6.93–7.92 (10 H, aromatic protons).

***Synthesis of 1,1-Diphenyl-3-aryl-4-oxa-5-(2-propenyl)-1-phosphoniacyclohena-2.5-dienes (3a–d). General.*** The starting bromo ketone **2** (0.01 mol) was dissolved in 100 mL of toluene and 0.01 mol of alkynylphosphine **1** was added to this solution. The reaction mixture was placed in an oil bath at 65 °C for 1 h and then allowed to cool to room temperature; white crystals started separating even before the reaction mixture cooled to room temperature. The reaction mixture was allowed to stay overnight at room temperature and then it was filtered to obtain the desired product in 60–70% yield. The product was recrystallized from acetone; the melting points, infrared (KBr), and NMR ($CDCl_3$) data are listed below. **3a:** mp 228–230 °C; IR, strong absorption bands at 2980, 1630, 1605, 1580, 1440, 1290, 1130, 1120, 1110, 840, 750, 690, and 520 $cm^{-1}$; NMR, broad singlet ($\delta$ 2.27, 3 H, $CH_3$), narrowly split quartet ($\delta$ 5.75, $H_{(1)}$), broad singlet ($\delta$ 6.25, $H_{(2)}$), quartet ($J = 3$ Hz, $\delta$ 6.70, $H_{(3)}$), quartet ($J = 3$ Hz, $\delta$ 7.20, $H_{(4)}$), and a multiplet at $\delta$ 7.52–8.17 (15 H, aromatic). **3b:** mp 233–235 °C; IR, strong absorptions at 2990, 1630, 1605, 1490, 1440, 1290, 1275, 1115, 1105, 1095, 1010, 840, 830, 820, 755, 715, 690, and 515 $cm^{-1}$; NMR: broad singlet ($\delta$ 2.20, 3H, $CH_3$), narrowly split multiplet ($\delta$ 5.70, $H_{(1)}$), broad singlet ($\delta$ 6.20, $H_{(2)}$), quartet ($J = 3$ Hz, $\delta$ 6.70, $H_{(3)}$), quartet ($J = 3$ Hz, $\delta$ 7.25, $H_{(4)}$), and a multiplet at $\delta$ 7.33–8.28 (14 H, aromatic). **3c:** mp 243–246 °C, IR, strong absorption at 2985, 1630, 1600, 1575, 1515, 1540, 1290, 1270, 1180, 1130, 1120, 835, 690, and 530 $cm^{-1}$; NMR, broad singlet ($\delta$ 2.25, 3 H, $CH_3C$), singlet ($\delta$ 3.88, 3 H, $CH_3O$), multiplet ($\delta$ 5.70, $H_{(1)}$), multiplet ($\delta$ 6.22, $H_{(2)}$), quartet ($J = 3$ Hz, $\delta$ 6.55, $H_{(3)}$), quartet ($J = 3$ Hz, $\delta$ 6.87, $H_{(4)}$), doublet ($J = 9$ Hz, 2 H, aromatic proton ortho to the methoxy group), and multiplet at $\delta$ 7.77–8.17 (12 H, aromatic). **3d:** mp 282–285 °C; IR, strong absorptions at 2970, 1630, 1605, 1440, 1305, 1120, 840, 765, 745, 725, 700, 685, and 530 $cm^{-1}$; NMR, broad singlet ($\delta$ 2.23, 3 H, $CH_3$), multiplet ($\delta$ 5.73, $H_{(1)}$), multiplet ($\delta$ 6.25, $H_{(2)}$), quartet ($J$ = Hz, $\delta$ 6.60, $H_{(3)}$), quartet ($J = 3$ Hz, $\delta$ 7.10, $H_{(4)}$), and a multiplet at $\delta$ 7.33–8.25, (19 H, aromatic).

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

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

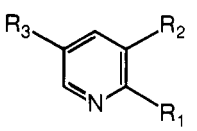
Compounds possessing hypolipidemic activity are the subject of extensive pharmaceutical research. Halo and dihalonicotinic acids and their derivatives have received attention as potential hypolipidemic agents (*1–4*), and in this communication we wish to report the preparation and characterization of four new dihalonicotinic acids as an extension of our previous work (*5–8*).

Dihalonicotinic acids IV, V, IX, and X were generated by oxidation of dihalopicolines II, III, VII, and VIII, respectively. 2-Bromo-5-chloro-3-picoline (II) and 2-bromo-5-iodo-3-picoline (III) were obtained by diazotization of 5-amino-2-bromo-3-picoline (I) (*9, 10*). 6-Bromo-5-chloro-3-picoline (VII) and 6-bromo-5-iodo-3-picoline (VIII) were prepared in analogous fashion from 5-amino-6-bromo-3-picoline (VI) (*9, 10*).

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.

### Experimental Section

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




I, $R_1$ = Br; $R_2$ = $CH_3$; $R_3$ = $NH_2$
II, $R_1$ = Br; $R_2$ = $CH_3$; $R_3$ = Cl
III, $R_1$ = Br; $R_2$ = $CH_3$; $R_3$ = I
IV, $R_1$ = Br; $R_2$ = $CO_2H$; $R_3$ = Cl
V, $R_1$ = Br; $R_2$ = $CO_2H$; $R_3$ = I
VI, $R_1$ = Br; $R_2$ = $NH_2$; $R_3$ = $CH_3$
VII, $R_1$ = Br; $R_2$ = Cl; $R_3$ = $CH_3$
VIII, $R_1$ = Br; $R_2$ = I; $R_3$ = $CH_3$
IX, $R_1$ = Br; $R_2$ = Cl; $R_3$ = $CO_2H$
X, $R_1$ = Br; $R_2$ = I; $R_3$ = $CO_2H$

obtained on a Perkin-Elmer 337 spectrophotometer with samples prepared as KBr disks. Proton nuclear magnetic resonance spectra were obtained at 60 MHz on a Jeolco C-60 HL instrument with tetramethylsilane as an internal standard.

***2-Bromo-5-chloro-3-picoline (II).*** A stirred solution of 5-amino-2-bromo-3-picoline (I) (1.85 g, 0.01 mol) (*9, 10*) in a mixture of concentrated hydrochloric acid (8 mL) and water (4 mL) was diazotized at 0 °C by the slow, dropwise addition of a solution of sodium nitrite (2.0 g) in water (5 mL) over a period of 15 min. Copper powder (8 g) was cautiously added to the freshly diazotized solution, and the resulting mixture was neutralized with 25% sodium hydroxide (9 mL). Indirect steam distillation of the orange neutral suspension afforded the dihalopicoline II as a white volatile solid. Further purification was achieved by recrystallization (Table I).

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**Table I. Experimental and Spectral Data for Dihalonicotinc Acids and Their Precursors[g]**

| Compd | Yield, % | Mp, °C | IR,[a] $\nu$, $cm^{-1}$ | Proton, NMR, ppm $\delta$[b] | | |
|---|---|---|---|---|---|---|
| | | | | $H_4$ | $H_6$ | Other |
| II | 60 | 30–31[c] | 1445, 1388, 1092, 1030, 876, 712, 678, 487 | 7.53 m | 8.20 m | $CH_3$, 2.40 s |
| III | 76 | 49–50[d] | 1453, 1388, 1351, 1149, 1087, 1053, 1032, 1012, 959, 708, 670 | 7.77 m | 8.38 b | $CH_3$, 2.38 s |
| IV | 43 | 163–164[e] | 1721, 1545, 1402, 1222, 1190, 1090, 1036, 716 | 8.20 m | 8.57 m | $CO_2H$,[f] 5.13 b |
| V | 16 | 197–198[e] | 1709, 1526, 1398, 1219, 1075, 1030, 838, 774, 705 | 8.44 m | 8.73 m | $CO_2H$,[f] 4.70 b |
| VII | 53 | 43–44[c] | 1390, 1374, 1160, 1019, 869, 704, 666, 592, 534 | 7.60 m | 8.13 m | $CH_3$, 2.38 s |
| VIII | 62 | 79–80[c] | 1393, 1364, 1096, 1028, 1010, 872, 843, 707, 517 | 7.90 m | 8.13 m | $CH_3$, 2.27 s |
| IX | 55 | 162–163[e] | 1709, 1550, 1404, 1346, 1250, 1111, 1021, 869, 762 | 8.36 m | 8.83 m | $CO_2H$,[f] 5.63 s |
| X | 23 | 187–188[e] | 1718, 1565, 1393, 1245, 1010, 823, 763, 704 | 8.67 m | 8.87 m | $CO_2H$,[f] 4.43 s |

[a] Only the most intense absorption bands are reported. [b] $CDCl_3$ as solvent for compounds II, III, VII, and VIII; acetone-$d_6$ solvent for compounds IV, V, IX, and X. Signals were observed to be in the correct area ratio. Key: s = singlet, m = ill-defined multiplet, b = broad. [c] Recrystallized from methanol–water. [d] Recrystallized from methanol. [e] Recrystallized from water. [f] High-field signals apparently due to protonated ring nitrogen as the zwitterion. Signal exchangeable with $D_2O$. [g] Elemental analyses in agreement with theoretical values were obtained and submitted for review.

***6-Bromo-5-chloro-3-picoline (VII).*** This compound was prepared by diazotization of 5-amino-6-bromo-3-picoline (VI) (*9, 10*) by a procedure indentical with that described above for the conversion of I to II.

***2-Bromo-5-iodo-3-picoline (III).*** A stirred solution of 5-amino-2-bromo-3-picoline (I) (2.60 g, 0.014 mol) (*9, 10*) in a mixture of concentrated hydrochloric acid (7 mL) and water (4 mL) was diazotized at 0 °C by the dropwise addition of a solution of sodium nitrite (1.7 g) in water (4 mL). The freshly diazotized solution was immediately poured into a solution of potassium iodide (8 g) in water (6 mL). The resulting dark mixture was warmed at 75 °C for 5 min (steam cone), cooled to 10 °C, and then slowly neutralized with 25% sodium hydroxide (9 mL). A solution of sodium bisulfite (5 g) in water (10 mL) was then added and the resulting suspension stirred at room temperature for 1 h. After addition of water (200 mL) the suspension was subjected to indirect steam distillation affording the product III as a white volatile solid. Recrystallization from methanol (3–4 mL) produced an analytical sample (Table I).

***6-Bromo-5-iodo-3-picoline (VIII).*** Preparation of this compound was achieved by the diazotization of 5-amino-6-bromo-3-picoline (VI) (*9, 10*) in an identical fashion with the aforementioned conversion of I to III.

***2-Bromo-5-chloronicotinic Acid (IV), 2-Bromo-5-iodonicotinic Acid (V), 6-Bromo-5-chloronicotinic Acid (IX), and 6-Bromo-5-iodonicotinic Acid (X).*** These dihalo acids were prepared by the oxidation of the appropriate dihalopicoline (II, III, VII, and VIII, respectively) using potassium permanganate. The standard general procedure employed has been described previously (*5, 6*).

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