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

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The preparation of 2-chloro- and 2-bromo-5-fluoronicotinic acid and 6-chloro- and 6-bromo-5-fluoronicotinic acid by oxidation of the corresponding dihalo-3-picolines is described. Experimental and spectral data for the acids, two of the dihalopicolines, and their amino-halo precursors are also presented.

The medicinal value of nicotinic acid as an antipellagra factor and a vasodilator is well recognized. Since introduction of halogen atoms into physiologically active compounds often increases activity, we have continued our efforts (*3*) toward the preparation of halo-substituted nicotinic acids. In this paper we describe the preparation of four new dihalonicotinic acids IIa through IId.

The corresponding dihalo-3-picolines Ia through Id served as precursors for the acids. The preparation of Ia and Ib has been described previously (*4*), and the synthesis of Ic and Id is described herein.

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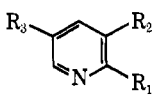
Dissolving-metal reduction of both 2-chloro-3-methyl-5-nitropyridine (*1*) using tin and hydrochloric acid and of 2-bromo-3-methyl-5-nitropyridine (*5*) using iron and acetic acid resulted in the previously unreported amines Ie and If, respectively. The procedures employed for these reductions were identical to those described for the conversion of 2-chloro-5-methyl-3-nitropyridine and 2-bromo-5-methyl-3-nitropyridine to their corresponding amines (*4*). Diazotization of amines Ie and If, using the modified Schiemann procedure (*2*), yielded the respective stable diazonium hexafluorophosphates Ig (99% yield, mp 99°C, dec) and Ih (95% yield, mp 90°C, dec), which were then thermally decomposed in hot mineral oil (110°C) to produce Ic and Id, respectively. The diazotization-

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



I

a. $R_1 = Cl; R_2 = F; R_3 = CH_3$
b. $R_1 = Br; R_2 = F; R_3 = CH_3$
c. $R_1 = Cl; R_2 = CH_3; R_3 = F$
d. $R_1 = Br; R_2 = CH_3; R_3 = F$
e. $R_1 = Cl; R_2 = CH_3; R_3 = NH_2$
f. $R_1 = Br; R_2 = CH_3; R_3 = NH_2$
g. $R_1 = Cl; R_2 = CH_3; R_3 = N_2^+PF_6^-$
h. $R_1 = Br; R_2 = CH_3; R_3 = N_2^+PF_6^-$

II

a. $R_1 = Cl; R_2 = F; R_3 = CO_2H$
b. $R_1 = Br; R_2 = F; R_3 = CO_2H$
c. $R_1 = Cl; R_2 = CO_2H; R_3 = F$
d. $R_1 = Br; R_2 = CO_2H; R_3 = F$

Compd	Yield, %	Mp, °C	Ir, ν, cm^{-1}[a]	Proton nmr, ppm δ[b]		
				H_4	H_6	Other
Ie	68	93-4[c]	3325, 3180, 1610, 1480, 1425, 1175, 1060, 865, 628	6.90 d	7.77 d	NH_2, 3.70 b CH_3, 2.33 s
If	35	98-100[c]	3200, 1640, 1590, 1465, 1400, 1030, 865, 600	7.03 d	7.87 d	NH_2, 3.75 b CH_3, 2.43 s
Ic	50[d]	40-1[e]	1583, 1450, 1400, 1290, 1065, 882, 717, 630, 474	7.36 m	8.14 d	CH_3, 2.41 s
Id	26[d]	Bp 70-2 (9 mm)	1450, 1390, 1280, 1125, 1045, 878, 712, 596[f]	7.46 m	8.30 d	CH_3, 2.47 s
IIa	25	182-3[g]	1680, 1590, 1455, 1420, 1295, 1200, 1120, 1065, 770, 758, 590, 530	8.50 d′	9.08 d	CO_2H,[h] 6.27 s
IIb	35	192-3[g]	1675, 1550, 1400, 1285, 1160, 1040, 810, 495	8.17 d′	9.00 d	CO_2H,[h] 7.50 b
IIc	41	146-7[g]	1700, 1570, 1415, 1300, 1258, 910, 760, 667	8.30 d′	8.77 d	CO_2H,[h] 6.80 s
IId	31	154-5[g]	1733, 1570, 1410, 1290, 1240, 900, 745, 625	8.17 d′	8.67 d	CO_2H,[h] 6.70 b

[a] Only most intense absorption bands reported. [b] $CDCl_3$ solvent for compounds Ic through If, acetone d_6 solvent for compounds IIa through IId. 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] Recrystallized from ligroin. [f] Liquid film sample. [g] Recrystallized from water. [h] High field signals apparently due to protonated ring nitrogen. Signal exchangeable with D_2O.

decomposition procedures utilized were analogous to those described for the preparation of Ia and Ib from their corresponding amines (4). Oxidation of the dihalo-3-picolines in neutral potassium permanganate afforded the desired dihalonicotinic acids.

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 the compounds described are presented in Table I.

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 (nmr) spectra were obtained at 60 MHz on either a Varian A-60 or a Jeolco C-60 HL instrument with tetramethylsilane as an internal standard.

2,5- and 5,6-Dihalonicotinic Acids. The appropriate dihalo-3-picoline (0.007 mole) and potassium permanganate (0.02 mole) were added to water (100 ml) and refluxed for 2 hr. 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 approximately 10 ml on a rotary evaporator. Acidification with concentrated hydrochloric acid afforded the crude dihalonicotinic acid which was recrystallized from water. The yield percentages were calculated on the basis of the amount of reacted starting material.

ACKNOWLEDGMENT

We thank R. F. Borne for obtaining the proton nmr spectra.

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RECEIVED for review March 31, 1972. Accepted July 11, 1972.

Synthesis and Spectral Data for Bithiazole Derivatives

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Nine bithiazole derivatives were synthesized by the interaction of rubeanic acid with α-haloketones. Uv, ir, and nmr data for the bithiazoles are presented.

Nine bithiazole derivatives were synthesized by the method of Karrer et al. (2), by the interaction of 1 mole of rubeanic acid (dithio-oxamide) with 2 moles of α-haloketones in alcoholic solutions. The α-haloketones used were: 2-bromoacetylfluorene, *p*-hydroxyphenacylbromide, *p*-nitrophenacylbromide, 2-bromo-1-tetralone, 2-bromocyclohexanone, 3-chloroacetylacetone, 5-bromoacetylindane, 3-bromoacetylindole, and 2-bromoacetylfuran. The structure and physical properties of the synthesized bithiazoles are given in Table I.

The direct preparation of substituted bithiazoles from a mixture of the ketone, rubeanic acid, and the oxidizing agent (bromine, iodine, or sulfuryl chloride) was not successful even when employing differing experimental conditions. In the condensation of thiourea with ketones, in the presence of an oxidizing agent, and in the synthesis of 2-aminothiazoles, formamidine disulfide $(-S-C(=NH)-NH_2)_2$, the oxidation product of thiourea, is thought to be the intermediate, since heating with certain ketones gives 2-aminothiazoles (5, 6). Similarly, one expects that a similar intermediate is formed when rubeanic acid is treated with an oxidizing agent. When it was attempted to prepare such an intermediate, negative results were obtained due to the fact that the expected formamidine disulfide does never appear to be formed as an intermediate compared with the corresponding thiourea. On the contrary, α-bromoketones condensed successfully with rubeanic acid in alcoholic solutions. On the other hand, some α-haloketones, not mentioned in Table I, such as bromoacetone, bromoethylmethylketone, and α-bromoethylacetate, condensed poorly with rubeanic acid even on prolonged heating. 3-Chloroacetylacetone condensed more easily with rubeanic acid than its bromo analog, giving better yields. The uv, ir, and nmr data for the synthesized bithiazoles are given in Tables II and III.

EXPERIMENTAL

Melting points were taken by a Kofler Hot Bench, and are uncorrected. Elemental analyses were performed by Alfred Bernhardt's Laboratories, Ruhr, Germany. Ultraviolet absorption spectra were recorded by a Unicam sp800B ultraviolet spectrophotometer. Infrared spectra were recorded by a Perkin-Elmer Model 137B infracord spectrophotometer as Nujol mulls. Nuclear magnetic resonance spectra were measured on a Varian A60A spectrometer, as solutions in deuterated dimethylsulfoxide (DMSO-d_6) or trifluoroacetic acid (TFA) with tetramethylsilane (TMS) as the internal reference. All τ-values are correct to 0.01 τ unit.

Materials. Rubeanic acid (dithiooxamide) was a British Drug House (BDH) product and was recrystallized from ethanol. α-Haloketones were prepared by the procedure described in an earlier paper (3).

General Procedure for Preparation of Bithiazoles. Rubeanic acid (0.1 mole) in ethanol or glacial acetic acid (500 ml) was mixed with an alcoholic solution of α-haloketone (0.2

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