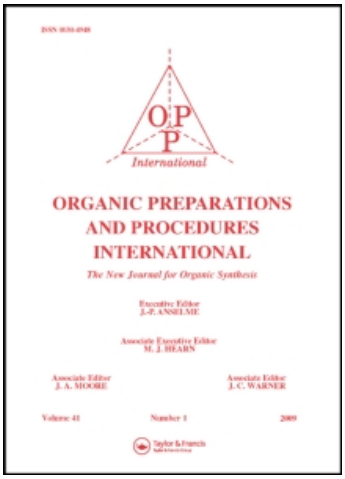

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THE SYNTHESIS OF TWO NEW 2,3-DIHALO-5-METHYLPYRIDINES

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THE SYNTHESIS OF TWO NEW 2,3-DIHALO-5-METHYLPYRIDINES

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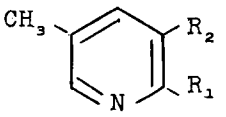
Our interest in 2,3-dihalopyridines[1] as potential progenitors of 2,3-dehydropyridines (2,3-pyridynes) prompted the preparation of 2-chloro-3-fluoro-5-methyl pyridine (X) and 2-bromo-3-fluoro-5-methylpyridine (XI). We now describe the preparation of these compounds and their previously unknown precursors.



I. $R_1 = NH_2$; $R_2 = H$
II. $R_1 = NH_2$; $R_2 = NO_2$
III. $R_1 = OH$; $R_2 = NO_2$
IV. $R_1 = Cl$; $R_2 = NO_2$
V. $R_1 = Br$; $R_2 = NO_2$
VI. $R_1 = Cl$; $R_2 = NH_2$
VII. $R_1 = Br$; $R_2 = NH_2$
VIII. $R_1 = Cl$; $R_2 = N_2^+PF_6^-$
IX. $R_1 = Br$; $R_2 = N_2^+PF_6^-$
X. $R_1 = Cl$; $R_2 = F$
XI. $R_1 = Br$; $R_2 = F$

2-Amino-5-methylpyridine (I) served as starting material for both X and XI and was first nitrated to produce the 3-nitro derivative (II).[2] Diazotization and subsequent hydrolysis of II in

dilute sulfuric acid afforded the pyridone III[2] which was converted to the chloride IV[3] or bromide V[4] with phosphorus oxychloride or phosphorous tribromide and phosphorus oxybromide, respectively. Reduction of IV with tin and hydrochloric acid yielded the amine VI. Similarly, reduction of V with iron and acetic acid afforded amine VII. Diazotization of VI and VII employing the modified Schiemann method[5] produced the stable diazonium hexafluorophosphates VIII and IX, which were isolated and subsequently decomposed thermally to yield the respective dihalides X and XI.

The proton magnetic resonance spectra of new compounds VI, VII, X and XI exhibit an interesting feature. In these compounds the methyl protons are coupled to the two adjacent ring protons as evidenced by the appearance of multiplets for the latter and a ragged singlet for the former. We have observed similar coupling in other 2,3-dihalopyridines, and oxidation of the methyl group in these compounds results in the appearance of the ring protons as the expected doublets in the dihalonicotinic acids thus produced.[6]

In compounds X and XI there appears to be coupling of the H_4 proton with fluorine as the signal for this proton appears as a highly split signal (1:1 doublet of multiplets).

EXPERIMENTAL

General information. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined using KBr pellets of the compounds (unless otherwise specified) on a Perkin Elmer 337 instrument. Proton nmr spectra of the compounds were determined in deuteriochloroform solution on a Varian A-60 instrument with tetramethylsilane as an internal standard. Elemental analyses were performed by the Heterocyclic Chemical Corporation, Harrisonville, Missouri.

3-Amino-2-chloro-5-methylpyridine (VI). Finely powdered tin (10.0 g, 0.084 g at wt) and 2-chloro-5-methyl-3-nitropyridine[3] IV, (7.0 g, 0.04 mole) were thoroughly mixed and treated with concentrated hydrochloric acid (23 ml) in approximately 5 ml portions. The mixture was then heated at 85° (steam bath) with frequent agitation for 90 min, cooled, diluted with water (25 ml) and poured into precooled 25% sodium hydroxide (300 ml). The resulting slurry was extracted with two 100 ml portions of chloroform, and the chloroform extracts were filtered and evaporated affording the crude product. Recrystallization from methylcyclohexane afforded the pure amine (4.4 g, 70%) as light yellow leaflets, mp 88-89°.

Anal. Calcd for $C_6H_7N_2Cl$: C, 50.50; H, 4.91; N, 19.65. Found: C, 50.73; H, 5.00; N, 19.87.

IR: 3460, 3310, 3175, 1620, 1595, 1439, 1382, 1320, 1269, 1228, 1170, 1098, 1047, 848, 730, 717, 625, 482, 476 cm^{-1}.

NMR: δ 7.58 (multiplet, H_6); 6.86 (multiplet, H_4); 4.22 (broad, NH_2); 2.2 (ragged singlet, CH_3).

3-Amino-2-bromo-5-methylpyridine (VII). A mixture of 2-bromo-5-methyl-3-nitropyridine[4] V, (9.0 g; 0.0415 mole), 11.7 g of iron filings (40 mesh), and glacial acetic acid (90 ml) was heated at 95° for 9 hr. The reaction mixture was cooled, diluted with water (50 ml), and poured slowly into 300 ml 25% sodium hydroxide maintained at 15°. The resulting slurry was extracted with three 100 ml portions of chloroform, and the resulting

emulsion was broken by filtration. Evaporation of the chloroform provided 5.05 g of yellow-orange solid, mp 97-105°. Crystallization from methylcyclohexane afforded pure VII as light yellow crystals, mp 106-107°, 4.40 g (57%).

Anal. Calcd for $C_6H_7N_2Br$: C, 38.52; H, 3.77; N, 14.98. Found: C, 38.56; H, 3.79; N, 14.92.

IR: 3450, 3290, 3162, 1615, 1590, 1428, 1375, 1315, 1262, 1100, 1162, 1090, 1030, 967, 842, 725, 710, 581, 468 cm^{-1}.

NMR: δ 7.62 (multiplet, H_6); 6.85 (multiplet, H_4); 4.10 (broad, NH_2); 2.2 (ragged singlet, CH_3).

2-Chloro-3-fluoro-5-methylpyridine (X). 3-Amino-2-chloro-5-methylpyridine VI, (4.0 g, 0.028 mole) was dissolved in a mixture of concentrated hydrochloric acid (14 ml) and water (20 ml), and the resulting solution was cooled to -5°. Diazotization at -5° to 0° was accomplished by the dropwise addition of a solution of sodium nitrite (3.35 g) in water (8 ml). Hexafluorophosphoric acid (15 ml) was added to the cold solution causing instantaneous precipitation of the diazonium hexafluorophosphate VIII. The white diazonium salt was filtered, washed with ether, and dried in vacuo yielding 7.5 g (89%) of material, dec. 82°. The salt was added in small portions over a 10 min period to 50 ml of preheated (95°) mineral oil contained in a 3-necked flask to which two efficient condensers had been attached. The content of the flask was kept at 95° for an additional 5 min, cooled to 15°, and neutralized with 15% sodium carbonate solution (50 ml).

Steam distillation of the alkaline reaction mixture afforded a pale yellow oil which was extracted with ether (100 ml). The ether extract was dried over anhydrous sodium sulfate and distilled. After removal of the volatile solvent, 1.8 g (44%) of the dihalopicoline distilled (bp 90-92°/25 mm), and later solidified on standing.

Anal. Calcd for C_6H_5NFCl: C, 49.48; H, 3.44; N, 9.61. Found: C, 49.50; H, 3.32; N, 9.38.

IR (liquid film): 3030, 2940, 1595, 1565, 1435, 1405, 1295, 1195, 1150, 1062, 870, 715, 707, 638, 575, 553, 488 cm^{-1}.

NMR: δ 8.08 (slightly broad and ill defined multiplet, H_6); 7.33 (doublet of multiplets, H_4); 2.40 (ragged singlet, $C\underline{H}_3$)

2-Bromo-3-fluoro-5-methylpyridine (XI). The bromoaminopicoline VII (3.74 g, 0.02 mole) was dissolved in a mixture of 13 ml concentrated hydrochloric acid and 20 ml water and cooled to -5°. Diazotization of the cold solution was achieved by the slow, dropwise addition of a solution of sodium nitrite (3.5 g) in water (10 ml). The addition of 16 ml of 65% hexafluorophosphoric acid to the cold solution caused precipitation of the diazonium hexafluorophosphate IX. The white salt was filtered and subsequently washed with cold ether and air-dried to yield 6.1 g (88%) of material, dec. 79°. The salt was thermally decomposed in preheated mineral oil (100°) in a manner previously described for the decomposition of VIII. Neutralization of the decomposition mixture with 15% sodium carbonate solution follow-

ed by indirect steam distillation of the alkaline mixture provided crude XI as an oil which slowly solidified on standing. Recrystallization from ligroin (bp 60-90°) afforded 1.55 g (42%) of pure XI as a white solid, mp 32-33°.

Anal. Calcd for C_6H_5NFBr: C, 37.90; H, 2.65; N, 7.36 Found: C, 38.04; H, 2.86; N, 6.96

IR: 3028, 2930, 2860, 1590, 1440, 1400, 1292, 1190, 1038 1041, 865, 705, 597, 567, 547, 478 cm^{-1}.

NMR: δ 8.08 (slightly broad and ill defined multiplet, H_6); 7.29 (doublet of multiplets, H_4); 2.34 (ragged singlet, $C\underline{H}_3$)

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