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New 2,3-Dihalopyridines. Potential Precursors for 2,3-Dehydropyridine. (1)

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One of the most desirable methods for the generation of the highly labile dehydrobenzene (benzynes) involves the action of an appropriate dehalogenating agent on an *ortho*-dihalobenzene (5). This procedure has been corroborated in the heterocyclic series by the successful generation of 3,4-dehydropyridine (3,4-pyridyne) (6) and 2,3-dehydropyridine (2,3-pyridyne) (7) by the respective treatment of 3-bromo-4-chloropyridine and 3-bromo-2-chloropyridine with lithium amalgam at 20° (8). However, the low yield of products resulting from the trapping of these highly reactive dehydropyridines as opposed to the high yield of analogous products formed from dehydrobenzene generated from the action of lithium amalgam on *o*-bromofluorobenzene is noteworthy. These facts suggest that an appropriate bromofluoropyridine or even a fluorochloropyridine might conceivably serve as a more desirable precursor for either a 3,4- or a 2,3-dehydropyridine. We wish to report the preparation of some new 2,3-dihalopyridines which could serve in the latter capacity.

Bromination of 2-amino-5-methylpyridine (I) in acetic acid at 90° proceeded rapidly to yield a single product, (68%) characterized as 2-amino-3-bromo-5-methylpyridine (II) (9). The absence of n.m.r. absorption assignable to the proton in position 3 ($\tau = 3.74$) in II as compared to the appearance of this signal in the spectrum of I confirmed that bromination occurred in the 3-position.

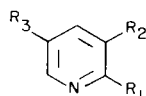
Diazotization of II directly in 40% fluoboric acid (Method A) by the Schiemann method (10) yielded the hitherto unknown 3-bromo-2-fluoro-5-methylpyridine (III)

and 3-bromo-5-methyl-2-(1H)pyridone (IV) in 40% and 31% yields respectively. That the formation of IV may be attributed to the hydrolysis of initially formed III was established by independent experiment. Treatment of pure III with 40% fluoboric acid under the conditions described for Method A resulted in the formation of IV in 38% yield (11). If diazotization of II is carried out directly in hexafluorophosphoric acid (12) by a modified Schiemann method (Method B) the fluorobromopyridine III is obtained in slightly better (45%) yield together with only trace amounts of the pyridone IV.

3-Bromo-2-chloro-5-methylpyridine (V) was conveniently prepared in 46% yield by diazotization of II in hydrochloric acid at 0°. We observed that careful temperature control is of utmost importance in this reaction since significant amounts of IV are formed also if the diazotization temperature is allowed to rise above 5° (13). However, the steam volatility of V permits its separation from any pyridone contamination.

Our route to the previously unreported 2-chloro-3-fluoropyridine (VI) involved initial tin and hydrochloric acid reduction of commercially available 2-chloro-3-nitropyridine to 3-amino-2-chloropyridine in 55% yield (14). Subsequent diazotization of the aminopyridine in hydrochloric acid followed by addition of hexafluorophosphoric acid, (12) yielded the stable solid diazonium hexafluorophosphate (VII) in 86% yield. Decomposition of VII in preheated mineral oil proceeded smoothly to yield VI.

TABLE I



	R ₁	R ₂	R ₃		R ₁	R ₂	R ₃
I	NH ₂	H	CH ₃	V	Cl	Br	CH ₃
II	NH ₂	Br	CH ₃	VI	Cl	F	H
III	F	Br	CH ₃	VII	Cl	N ₂ ⁺ PF ₆ ⁻	H
IV	OH	Br	CH ₃	VIII	F	Cl	H

The preparation of 3-chloro-2-fluoropyridine (VIII) was effected in 31% yield by the treatment of 2,3-dichloropyridine with potassium fluoride in dimethyl sulfoxide (15). This conversion has since been reported in improved yield (56%) by employing dimethyl sulfone as a solvent medium (16).

EXPERIMENTAL (17)

2-Amino-3-bromo-5-methylpyridine (II).

2-Amino-5-methylpyridine (I) (108.0 g., 1.0 mole) and glacial acetic acid (300 ml.) were combined and heated at 80° until solution was effected. Bromine (160 g., 55 ml., 1.0 mole) in acetic acid (55 ml.) was slowly added to the stirred mixture; the temperature was maintained between 90-100° by controlling the rate of addition. Upon completion of bromine addition, the reaction mixture was stirred additional 0.5 hour at steam bath temperature, then cooled to room temperature, and excess bromine destroyed by addition of a 10% sodium bisulfite solution (95 ml.). The solution was then neutralized with concentrated ammonium hydroxide while maintaining the reaction mixture at room temperature. The resulting brown solid was collected and air dried to give a crude yield of 185 g. The solid was recrystallized from ligroin (density 0.70), accompanied by treatment with Norite-A (20 g.); the resulting yellow needles were collected by filtration and dried to yield II (126 g., 68%), m.p. 71-72°.

Anal. Calcd. for $C_6H_7BrN_2$: C, 38.52; H, 3.77; Br, 42.72; N, 14.98. Found: C, 38.78; H, 3.63; Br, 42.46; N, 14.70.

The infrared spectrum (potassium bromide) exhibited strong bands at 2.88, 2.95, 3.04, 3.17, 6.20, 6.79, 7.18, 8.29, 9.53, 11.11, and 11.27 microns. The n.m.r. spectrum (deuteriochloroform) showed signals at τ 2.27 and 2.58 (2H, multiplet, 4- and 6-ring protons), 4.82 (2H, singlet, NH_2), and 7.84 (3H, singlet, CH_3) (18).

3-Bromo-2-fluoro-5-methylpyridine (III) (Method A).

2-Amino-3-bromo-5-methylpyridine (37.4 g., 0.2 mole) was dissolved in 40% fluoboric acid (230 ml.) and cooled by an external ice-salt bath to -10°. Solid sodium nitrite (13.9 g., 0.2 mole) was added to the stirred solution keeping the temperature below 0°. Upon completion of nitrite addition, the reaction mixture was stirred for an additional 0.5 hour at ice-bath temperature, then heated to 50° to ensure complete decomposition of the diazonium fluoborate. The mixture was cooled, made alkaline with 10% sodium carbonate solution, and steam distilled. An oil, which later solidified, appeared in the distillate and yielded colorless plates of III (15.0 g., 40%) m.p. 54-55°.

Anal. Calcd. for C_6H_5BrFN : C, 37.90; H, 2.65; N, 7.37. Found: C, 37.88; H, 2.79; N, 7.11.

The infrared spectrum (potassium bromide) showed strong bands at 6.29, 6.88, 7.24, 7.93, 8.46, 9.45, 11.06, and 11.28 microns.

3-Bromo-5-methyl-2-(1H)-pyridone (IV).

The pot residue from the steam distillation of III yielded, on cooling, a crystalline precipitate. The precipitate was filtered and recrystallized from water yielding 12.0 g. (31%) of IV as pale-yellow needles, m.p. 155-156°.

Anal. Calcd. for C_6H_6BrNO : C, 38.32; H, 3.22. Found: C, 38.44; H, 3.09.

The infrared spectrum (potassium bromide) showed strong bands at 6.05, 6.16, 6.51, 6.84, 7.49, 7.97, 8.26, 9.54, 11.19, 11.76, 12.46, and 13.29 microns.

In a control experiment a solution of pure III (5.0 g., 0.038 mole) in 40% fluoboric acid (50 ml.) was warmed to 50° for 20

minutes. Neutralization of the reaction mixture with 10% sodium carbonate followed by steam distillation yielded 2.1 g. of unchanged III. The pot residue yielded 1.9 g. (38%) of the pyridone IV.

3-Bromo-2-fluoro-5-methylpyridine (III) (Method B).

By a procedure analogous to Method A, II (28 g., 0.15 mole) on diazotization at 0° in a mixture of 65% hexafluorophosphoric acid (100 ml.) (19) and water (100 ml.) yielded 12.9 g. (45%) of III, m.p. 54-55°.

3-Bromo-2-chloro-5-methylpyridine (V).

A solution of 2-amino-3-bromo-5-methylpyridine (10.0 g., 0.053 mole) in a mixture of concentrated hydrochloric acid (50 ml.) and water (30 ml.) was carefully diazotized at 0° over a 30 minutes period by the dropwise addition of a solution of sodium nitrite (3.6 g., 0.053 mole) in water (30 ml.). Neutralization of the reaction mixture with cold concentrated ammonium hydroxide precipitated V which was recrystallized from aqueous ethanol to give 5.1 g. (46%) of pure product m.p. 67-69°.

Anal. Calcd. for C_6H_5BrClN : C, 34.88; H, 2.44; N, 6.79. Found: C, 34.96; H, 2.55; N, 6.59.

The infrared spectrum (carbon tetrachloride) exhibited intense absorption at 7.09, 7.31, 8.70, and 9.69 microns. A double maximum was found at 11.33 and 11.45 microns. Additional absorption occurred at 3.45, 8.40, and 13.95 microns.

3-Amino-2-chloropyridine.

2-Chloro-3-nitropyridine (47.4 g., 0.3 mole) and fine grain 40 mesh tin metal (72 g., 0.61 g. at. wt.) were thoroughly mixed and treated with concentrated hydrochloric acid (120 ml.); the acid was added in 10 ml. portions over a period of 45 minutes with efficient stirring, while maintaining the temperature between 50° and 80°. Upon completion of the acid addition, the solution was held at 85° for 2 hours. The mixture was then cooled to room temperature, diluted with water (250 ml.), and poured, with stirring, into an excess of 50% sodium hydroxide solution, which had been precooled to 15°. During the neutralization the temperature was maintained below 20°. The resulting slurry was shaken with chloroform (250 ml.), and the two-phase system filtered. The chloroform layer of the filtrate was separated and the solvent removed under reduced pressure leaving 23.5 g. of tan solid. The crude amine was recrystallized from petroleum ether (b.p. 60-90°) accompanied by decolorization treatment (Norite) to yield 21.2 g. (55%) of 3-amino-2-chloropyridine, which separated as colorless needles, m.p. 79-80° (lit. (20) m.p. 79-80°).

2-Chloro-3-fluoropyridine (VI).

3-Amino-2-chloropyridine (51.4 g., 0.4 mole) was dissolved in a mixture of concentrated hydrochloric acid (200 ml.) and water (350 ml.) and cooled to 0°. To the cold solution was added dropwise, with stirring, a solution of sodium nitrite (30.8 g., 0.44 mole) in water (60 ml.) over a period of 40 minutes keeping the temperatures below 5°. To the cold solution of the diazonium chloride was added 65% hexafluorophosphoric acid (200 ml.). The precipitated yellow diazonium hexafluorophosphate (VII) was filtered, washed successively with ice-cold 100 ml. portions of water, methanol, and ether, and air-dried. The diazonium salt (50.1 g., 85% from the amine) decomposed at 92°.

Decomposition was best performed in heavy mineral oil preheated to 95°. The diazonium salt was added by means of a Gooch rubber connecting tube from an Erlenmeyer flask to the hot mineral oil (300 ml.) contained in a 1-liter, three-necked, round bottom flask equipped with two efficient condensers. Decomposition was performed under a well-ventilated hood, and the salt addition required 40 minutes. The content of the flask was cooled

to 15° and made slightly alkaline with a 50% sodium carbonate solution. Steam distillation of the alkaline solution yielded a pale yellow oil which was removed. The aqueous distillate was saturated with sodium chloride, extracted with ether (50 ml.), and the oil and ether extract combined and dried over anhydrous sodium sulfate. Distillation gave 20.8 g. (41%) of 2-chloro-3-fluoropyridine as a colorless liquid, b.p. 84-85° (55 mm.); n_D^{27} 1.5022.

Anal. Calcd. for C₅H₃ClFN: C, 45.66; H, 2.28; N, 10.64. Found: C, 45.57; H, 2.44; N, 10.51.

The infrared spectrum (carbon tetrachloride) showed intense absorption at 6.31, 7.88, 8.25, 8.90, 9.22, 13.85, and 14.25 microns. A double maximum was evident at 6.90 and 7.05 microns. Additional absorption occurred at 3.29, 8.05, 8.49, 9.51, and 11.95 microns.

3-Chloro-2-fluoropyridine (VIII).

2,3-Dichloropyridine (50.0 g., 0.34 mole), powdered, anhydrous, potassium fluoride (39.4 g., 0.68 mole), and dimethyl sulfoxide (200 ml.) were combined and the colorless, heterogeneous mixture heated at 165° for 72 hours with vigorous mechanical stirring. The resulting black, heterogeneous mixture was cooled, poured onto crushed ice, and steam distilled. The steam volatile oil, (41.2 g.), was removed from the distillate and dried over anhydrous sodium sulfate. Fractionation of the crude material yielded 13.5 g. (31%) of colorless VIII (b.p. 59-60.5° (12 mm.); lit. (16) b.p. 94-95° (100 mm.).

Anal. Calcd. for C₅H₃ClFN: C, 45.66; H, 2.28; Cl, 26.97. Found: C, 45.78; H, 2.50; Cl, 27.10.

The infrared spectrum (chloroform) exhibited absorption at 6.30, 6.38, 6.91, 7.15, 7.69, 7.91, 8.14, 8.62, 8.78, 9.32, 9.53, 11.68, and 14.58 microns.

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- (13) The formation of IV at higher temperature is undoubtedly due to competitive diazonium chloride hydrolysis.
- (14) The only previous report of this reduction indicated a poor yield (11%) of product when an iron and acetic acid reducing medium was employed.
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