Anal. Calcd. for $C_5H_3Cl_2N_5$: C, 29.4; H, 1.5; N, 34.3. Found: C, 29.4; H, 1.3; N, 33.7.

Reduction of 2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII) with Raney Nickel to Yield 2-Chloropurine.—2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII, 250 mg.) was dissolved in 40 ml. of 2-ethoxyethanol to which was added 3 g. of Raney nickel, and the solution was refluxed for 2 hr. The ultraviolet absorption spectra and paper chromatographic data in solvents A, B, and C run on the filtrate of the reaction mixture showed 2-chloropurine[16] as the only purine derivative present.

2-Chloro-6,8-dimercapto-9-(tetrahydro-2′-pyranyl)purine (XIII).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 1 g.) was added to 1.03 g. of sodium sulfide (containing 2.7 mole equivalents of water) in 15 ml. of ethanol. The solution was stirred for 3 hr. at room temperature; the mixture was then filtered and the ethanol evaporated at 50° under reduced pressure. The yellow, gummy product was similarly evaporated several times with 50 ml. of benzene until a powdery solid remained. This substance was then dissolved in benzene and methanol, treated with charcoal, filtered, and evaporated to dryness to yield 0.95 g. (96.7%) of a yellow powder, m.p. > 300°.

Anal. Calcd. for $C_{10}H_{11}ClN_4OS_2$: C, 39.6; H, 3.6; N, 18.5. Found: C, 39.7; H, 3.3; N, 18.5.

2,6-Dichloro-8-hydroxy-9-(tetrahydro-2′-pyranyl)purine (XIV).—9-(Tetrahydro-2′-pyranyl)-2,6,8-trichloropurine (IV, 5 g.) was dissolved in 500 ml. of anhydrous *p*-dioxane containing 48.8 ml. of 0.9965 *N* sodium hydroxide. The solution was stirred for 22 hr. at room temperature, and the excess *p*-dioxane was removed under vacuum. Water was added to the residue, and a small amount of precipitate which formed was filtered. The filtrate was acidified to pH 1 with 1 *N* hydrochloric acid, and the solid that appeared was filtered, triturated, and washed with water, and dried to yield 2.0 g. (42.6%) of a pure white powder, m.p. > 300°, which could not be recrystallized successfully.

Anal. Calcd. for $C_{10}H_{10}Cl_2N_4O_2$: C, 41.5; H, 3.5; N, 19.4. Found: C, 41.3; H, 3.7; N, 19.5.

Hydrolysis of XV with hydriodic acid as for VI gave 8-hydroxypurine identified by ultraviolet absorption spectra and R_f values in solvents[24] A, B, and D.

Acknowledgment.—The authors are indebted to Brian M. Lynch, Saint Francis Xavier University, Antigonish, Nova Scotia, for helpful suggestions and discussions relative to this work.

(24) Solvent A, *i*-PrOH:H_2O::6:4—descending; B, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—descending; C, *n*-BuOH saturated with H_2O plus 1% NH_4OH—descending; D, *i*-PrOH:DMF:NH_4OH::65:25:10—descending; E, 5% NH_4HCO_3 in H_2O—descending; F, 5% Na_2HPO_4 in H_2O saturated with isoamyl alcohol—descending; G, *n*-BuOH saturated with H_2O—descending; H, EtOH:H_2O::7:3—ascending; I, *n*-BuOH:H_2O:HOAc (glacial)::5:4:1—ascending; J, $(NH_4)_2SO_4$:1 *N* NaOAc:*i*-PrOH::40:9:1—ascending.

Aromatic Fluorine Compounds. XI. Replacement of Chlorine by Fluorine in Halopyridines

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The α-halogenated pyridines react with potassium fluoride in various solvents to give replacement of the α-halogen by fluorine. A 50% yield of 2-fluoropyridine was obtained from 2-chloropyridine by heating with potassium fluoride in dimethyl sulfone or tetramethylene sulfone for twenty-one days; 2-bromopyridine gave a similar yield with a heating period of only seven days. The α-halogens of the polyhalopyridines undergo the exchange reaction more readily than do the halogens of the α-monohalopyridines. The proposed structures of the fluoropyridines are supported by alternate syntheses and by n.m.r. studies.

It previously has been found by Finger and coworkers that chlorine in certain positions in polychlorobenzenes[5] can be replaced by fluorine using the potassium fluoride exchange reaction. For example, hexachlorobenzene will react with potassium fluoride to give 1,3,5-trichloro-2,4,6-trifluorobenzene as a major product,[5] and small amounts of dichlorotetrafluorobenzene and chloropentafluorobenzene.[6] This shows that chlorine is not only a strong activating group from the *meta* position as expected in nucleophilic reactions,[7] but is also a significant activator even from the *ortho* and *para* positions.

In this study halogen activation has been demonstrated also in the polychloropyridines. A second halogen atom (chlorine or bromine) either adjacent to or opposite an α-chlorine on the pyridine ring gives increased lability to atoms in the α-position for reaction with potassium fluoride. These findings make it possible to synthesize many fluoropyridines more simply than can be done by the multi-step Schiemann operations.

Several years ago in the early stages of this study progress was slow with the reaction media then in use,[8] until it was discovered that dimethyl sulfone[9] was a better solvent medium for many exchange reactions. Unfortunately early work with 2-chloropyridine[9-11] and potassium fluoride led to the belief that activation by a ring nitrogen alone was insufficient for an exchange reaction; however, it has now been established that on prolonged heating 2-fluoropyridine (I) can be obtained in a significant yield. For instance, heating a mixture of 2-chloropyridine and potassium fluoride in dimethyl sulfone for twenty-one days gave a 50% yield of 2-fluoropyridine.[12] 2-Bromopyridine in dimethyl sulfone

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(3) N.m.r. discussion and data by H. S. G., Noyes Laboratory, University of Illinois. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for partial support of this research.

(4) Exchange studies on 2-chloropyridine by J. H., Tulane University, New Orleans, La.

(5) G. C. Finger, C. W. Kruse, R. H. Shiley, R. H. White, and H. A. Whaley, Abstracts, Organic Chemistry Division, XVIth International Congress of Pure and Applied Chemistry, Paris, July, 1957, p. 303. Also unpublished results.

(6) J. T. Maynard, *J. Org. Chem.*, **28**, 112 (1963).

(7) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(8) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956).

(9) L. D. Starr and G. C. Finger, *Chem. Ind.* (London), 1328 (1962).

(10) G. C. Finger and L. D. Starr, *J. Am. Chem. Soc.*, **81**, 2674 (1959).

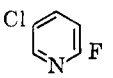
(11) J. Hamer, W. J. Link, A. Jurjevich, and T. L. Vigo, *Rec. trav. chim.*, **81**, 1058 (1962).

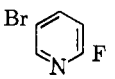
(12) A similar result was obtained with tetramethylene sulfone ("Sulfolane") as a reaction solvent.

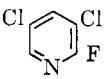
gave a similar yield in seven days. Somewhat greater activation exists in 2,6-dichloropyridine as a 52% of the difluoro analog was reported,[13] for a heating period of one hundred hours in dimethyl sulfone.

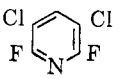

I


II


IIIa


IIIb


IV


V

The other halopyridines which were studied also showed α-chlorine or bromine replacement by fluorine, giving compounds II–V. The 4-halopyridines were not studied because of their reported thermal instability.[14]

It was found that heating 2,5-dichloropyridine with potassium fluoride in dimethyl sulfoxide gave both 5-chloro-2-fluoropyridine (IIIa) and 5-chloro-2-methylthiopyridine; the latter compound was obtained in the larger amount. In the absence of potassium fluoride neither 2,5-dichloropyridine nor 5-chloro-2-fluoropyridine reacted with dimethyl sulfoxide to give the thioether which apparently resulted from the reaction of some intermediate with the solvent. The use of dimethyl sulfone,[9] however, avoided this difficulty, as the sulfone structure prevented the sulfur from acting as an effective nucleophile. Furthermore, this solvent gave a much higher yield of the desired 5-chloro-2-fluoropyridine. From this example it is seen, that in certain cases, dimethyl sulfone is a superior solvent in that it affords higher yields and minimizes side reactions involving the solvent.

Dimethyl sulfone was found to be a satisfactory reaction medium in the remainder of the exchange reactions which were studied. That the 2-chlorine in 2,5-dichloropyridine was replaced was confirmed by the Schiemann conversion of 2-amino-5-chloropyridine to 5-chloro-2-fluoropyridine which was identical with that obtained from 2,5-dichloropyridine. The same 2-chlorine replacement was observed with 5-bromo-2-chloropyridine. The replacement of the 2-chlorine by fluorine in 2,3-dichloropyridine and 2,3,5-trichloropyridine was possible with potassium fluoride in dimethyl sulfone and gave 3-chloro-2-fluoropyridine (II) and 3,5-dichloro-2-fluoropyridine (IV), respectively. These examples illustrate that a chlorine adjacent to the chlorine which is being replaced provides increased activation and does not interfere sterically with the replacement. 2-Amino-3,5-dichloropyridine subjected to the Schiemann synthesis gave 3,5-dichloro-2-fluoropyridine which served as an authentic reference sample. The infrared spectrum of this material and that from the exchange reaction were identical.

The reaction of 2,3,5,6-tetrachloropyridine with potassium fluoride in dimethyl sulfone, which gave a 33% yield of 3,5-dichloro-2,6-difluoropyridine (V) in only twenty-four hours of heating is of special interest as it provided further convincing evidence not only of the exchangeability of the α-chlorine atoms but also of the activating influence of adjacent chlorine atoms. By contrast, 2,6-dichloropyridine gave a 50% yield of 2,6-difluoropyridine in one hundred hours.[11] As two chlorines were replaced, presumably stepwise, it appeared that the introduction of the first fluorine did not cause the deactivation[7] which might have been expected in the replacement of the second chlorine atom.

The structures proposed for II and V are supported by their n.m.r. spectra, in comparison with the spectrum of the related compound of known structure, 3,5-dichloro-2-fluoropyridine (IV).[15]

The proton spectrum of IV corresponds to the ab part of an abx system.[16,17a] Analysis of this spectrum is straightforward; there is one splitting common to the resonance lines from both protons. This is J_{46}^{HH}; the observed coupling of 2.45 c.p.s. agrees well with the value of 1.9 c.p.s. found in pyridine.[17b] The two values found for the H–F coupling are 7.60 and 1.45 c.p.s. Of these, the 7.60-c.p.s. value is assigned as J_{24}^{FH} and 1.45 c.p.s., as J_{26}^{FH}. This is based upon the similarity in the H–H coupling constants for benzene[16] and pyridine[17b] in combination with the 6.3- to 8.3-c.p.s. range found for the *meta* H–F coupling in fluorobenzenes.[16]

The proton spectrum of V is a simple 1:2:1 triplet which shows that the two fluorine atoms in the molecule are equivalent. The 7.75 c.p.s. H–F coupling constant agrees well with the corresponding value of 7.60 c.p.s. for J_{24}^{FH} in IV. However, this alone is not proof that V has the structure shown. In fact, in the fluorobenzenes it was found that the *ortho* H–F coupling ranges from 7.8 to 10.1 c.p.s., which overlaps the range for *meta* H–F coupling. Therefore, in principle the same proton spectrum might result if V were 2,6-dichloro-3,5-difluoropyridine. However, on the basis of the general chemical data, the latter possibility is excluded.

The correctness of this approach is borne out by the detailed analysis[18] made of the much more complicated proton spectrum of II, for which the coupling constants obtained agree with those found in IV and V, and for which the proton chemical shifts are similar to those in pyridine.[17b] The proton spectrum of II indicates the presence of three nonequivalent protons, and the values found for the H–H and H–F coupling constants eliminate all structures other than II.

Experimental[19]

Procedure A. Fluoropyridines by Halogen Exchange.—The fluoropyridines were prepared in dimethyl sulfoxide[10,20] or dimethyl sulfone[9,20] by the action of anhydrous potassium fluoride, usually 2 moles of potassium fluoride for each atom of halogen to

(13) A private communication by G. C. F. to Dr. W. J. Link suggested the use of dimethyl sulfone as a solvent. This materially assisted the Tulane group in obtaining 2-fluoropyridine and 2,6-difluoropyridine[11] by the exchange reaction.

(14) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939).

(15) The n.m.r. spectra of compounds II, IV, and V were observed with a Varian Associates Model A-60 high resolution spectrometer. Compounds IV and V were run in saturated solutions of carbon tetrachloride and II as the pure liquid, all at room temperature.

(16) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957).

(17) J. A. Pople, W. G. Schneider, and H. G. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959; (a) p. 132; (b) p. 266.

(18) H. S. Gutowsky and R. A. Meinzer, paper to be submitted to *J. Mol. Spectry.* See also the recent article, W. Brugel, *Z. Elektrochem.*, **66**, 159 (1962), which summarizes the proton spectra of a large number of substituted pyridines, including that of 2-fluoropyridine.

(19) Unless otherwise specified, all melting and boiling points are uncorrected.

(20) These solvents are commercially designated as DMSO and $DMSO_2$, respectively.

be replaced, on the appropriate halopyridine; good stirring is essential throughout the reaction. With dimethyl sulfone (m.p. 109°) the halopyridine and solvent were heated together until the latter melted and solution was complete. When the temperature reached about 110°, the potassium fluoride was added and the mixture heated to the desired reaction temperature. This temperature was maintained until the reaction was sensibly complete as verified by the usual probe test, then the mixture was cooled, diluted with warm water, and steam distilled. The product was separated from the distillate by extraction with ether or chloroform or by filtration, whichever was appropriate, and purified by distillation or recrystallization.

Procedure B. Fluoropyridines by the Schiemann Reaction.—The aminopyridine was added in small portions to 50% fluoboric acid. Powdered Dry Ice was added as needed to prevent excessive heating. If the amine did not dissolve readily, the amine–fluoboric acid mixture was heated (*ca.* 40–65°) until the amine dissolved completely and then cooled to 0°. The fluoborate salt of the amine separated during cooling. Powdered sodium nitrite was slowly added to this slurry and ether was added as needed to control foaming. The mixture was stirred for approximately 30 min. at 0°, then heated to 50°, cooled to 0°, poured onto ice, neutralized with sodium carbonate, and steam distilled. The product was collected and purified as described in procedure A.

2-Fluoropyridine (I).—(1) **From 2-Chloropyridine.**—A mixture of 2-chloropyridine (34.1 g., 0.3 mole), anhydrous potassium fluoride (35 g., 0.6 mole), and dimethyl sulfone (138 g.) heated for 510 hr. (*ca.* 21 days) at 200–210° by procedure A gave a yield of 14.4 g. or 49.5% of 2-fluoropyridine, b.p. 126–7°, $n^{23.5}D$ 1.4663 (lit.[21] b.p. 125°, $n^{20}D$ 1.4678). With tetramethylene sulfone ("Sulfolane") as a solvent, a yield of 58% was obtained.

(2) **From 2-Bromopyridine.**—A mixture of 2-bromopyridine (158 g., 1 mole), potassium fluoride (116 g., 2 moles), and dimethyl sulfone (450 g.) was heated at 200° by procedure A. After 2 days of heating, additional potassium fluoride (58 g., 1 mole) was added, and heating was continued for a total reaction time of 7 days. Yield of pure 2-fluoropyridine, 41 g. (42%), b.p. 124–125°.

3-Chloro-2-fluoropyridine (II).—A mixture of 2,3-dichloropyridine (14.8 g., 0.1 mole), anhydrous potassium fluoride (11.6 g., 0.2 mole), and dimethyl sulfone (30 g.) was heated at 192–201° for 48 hr. by procedure A to give 3-chloro-2-fluoropyridine; yield, 8.64 g. (65%), b.p. 92–96° (100 mm.). A second distillation gave a purified product; yield, 7.49 g. (56%), b.p. 94–95° (100 mm.), $n^{25}D$ 1.5020.

Anal. Calcd. for C_5H_3ClFN: C, 45.65; H, 2.30; N, 10.65; Cl, 26.95. Found: C, 45.58; H, 2.35; N, 10.48; Cl, 26.91.

5-Chloro-2-fluoropyridine (IIIa).—(1) A mixture of 2,5-dichloropyridine (45.0 g., 0.304 mole), anhydrous potassium fluoride (35.3 g., 0.608 mole), and dimethyl sulfoxide (180 ml.) upon heating at 170–175° for 52 hr. by procedure A gave a product which was distilled into two crude fractions: (1) 13.07 g., b.p. 84–95° (100 mm.); (2) 26.37 g., b.p. 118–130° (40–45 mm.). Fraction 1 was redistilled to give 5-chloro-2-fluoropyridine; yield, 11.59 g. (29%), b.p. 81–83.5° (100 mm.), $n^{25}D$ 1.4973.

Fraction 2 was distilled two more times to give 5-chloro-2-methylthiopyridine; yield, 19.37 g. (39%), b.p. 129–130° (40 mm.), $n^{25}D$ 1.6000.

Anal. Calcd. for C_6H_6ClNS: C, 45.15; H, 3.79; Cl, 22.21; S, 20.08. Found: C, 45.37; H, 3.76; Cl, 22.00; S, 20.35.

(2) A mixture of 2,5-dichloropyridine (45.0 g., 0.034 mole), anhydrous potassium fluoride (35.3 g., 0.608 mole), and dimethyl sulfone (180 g.) upon heating at 194–205° for 24 hr. by procedure. A gave 5-chloro-2-fluoropyridine; yield, 27.9 g. (70%), b.p. 88° (100 mm.), $n^{25}D$ 1.4970.

(3) 2-Amino-5-chloropyridine (40.0 g., 0.311 mole), 50% fluoboric acid (800 ml.), and powdered sodium nitrite (32.2 g., 0.464 mole) by procedure B gave 5-chloro-2-fluoropyridine; yield, 37.6 g. (61%), b.p. 86–89° (100 mm.), $n^{25}D$ 1.4948. A center cut [b.p. 89° (100 mm.), $n^{25}D$ 1.4943] from a distillation was used for analysis.

Anal. Calcd. for C_5H_3ClFN: C, 45.65; H, 2.30; Cl, 26.95. Found: C, 45.45; H, 2.18; Cl, 26.84.

5-Bromo-2-fluoropyridine (IIIb).—(1) A mixture of 5-bromo-2-chloropyridine (17.0 g., 0.088 mole), anhydrous potassium fluoride (10.3 g., 0.18 mole), and dimethyl sulfone (70 g.) upon heating at 204° for 24 hr. by procedure A gave 5-bromo-2-fluoropyridine; yield, 10.68 g. (68%), b.p. 62–63° (15 mm.), $n^{25}D$ 1.5300.

(2) 2-Amino-5-bromopyridine (17.3 g., 0.1 mole), 50% fluoboric acid (400 ml.), and powdered sodium nitrite by procedure B gave 5-bromo-2-fluoropyridine; yield, 10.76 g. (61%), b.p. 63° (15 mm.), $n^{25}D$ 1.5293–1.5296. A center cut, $n^{25}D$ 1.5294, from this distillation was used for analysis.

Anal. Calcd. for C_5H_3BrFN: C, 34.12; H, 1.72; Br, 45.41; N, 7.96. Found: C, 34.27; H, 1.75; Br, 45.24; N, 7.85.

3,5-Dichloro-2-fluoropyridine (IV).—(1) A mixture of 2,3,5-trichloropyridine (20.0 g., 0.11 mole), anhydrous potassium fluoride (12.8 g., 0.22 mole), and dimethyl sulfone (65 g.) upon heating at 200–205° for 24 hr. by procedure A gave a colorless solid (8.6 g., m.p. 29–37.5°) which was filtered from the steam distillate. This was sublimed to give 5.31 g. of pure 3,5-dichloro-2-fluoropyridine, m.p. 41–42°. The filtrate from the steam distillation upon extraction with ether and working up in the usual manner gave 1.6 g. of residue which was sublimed and recrystallized from ethanol and water to give an additional 0.66 g. of 3,5-dichloro-2-fluoropyridine, m.p. 42–43°. The total yield was 5.97 g. (33%).

(2) 2-Amino-3,5-dichloropyridine (10.0 g., 0.06 mole), 50% fluoboric acid (200 ml.), and powdered sodium nitrite (6.35 g., 0.09 mole) by procedure B gave 3,5-dichloro-2-fluoropyridine as a white solid; yield, 5.0 g. (49%) m.p. 42–43°. Recrystallization from petroleum ether did not alter the melting point.

Anal. Calcd. for $C_5H_2Cl_2FN$: C, 36.18; H, 1.21; N, 8.44; Cl, 42.72. Found: C, 36.19; H, 1.17; N, 8.44; Cl, 42.57.

3,5-Dichloro-2,6-difluoropyridine (V).—A mixture of 2,3,5,6-tetrachloropyridine[22] (10.0 g., 0.046 mole), anhydrous potassium fluoride (10.7 g., 0.184 mole), and dimethyl sulfone (30 g.) by procedure A with heating at 205° for 24 hr. gave a small amount of a semisolid which was extracted from the steam distillate with ether. After the ether was dried and evaporated, the residue (3.84 g.) was sublimed to give 3,5-dichloro-2,6-difluoropyridine as a white solid; yield, 2.8 g. (33%), m.p. 45–46.3°. Recrystallization from petroleum ether and sublimation did not significantly alter the melting point.

Anal. Calcd. for $C_5HCl_2F_2N$: C, 32.64; H, 0.55; Cl, 38.54; N, 7.61. Found: C, 32.57; H, 0.50; Cl, 38.43; N, 7.63.

(21) A. E. Chichibabin and N. D. Rjazancev, *J. Russ. Phys. Chem. Soc.*, **47**, 1571 (1915).

(22) The authors thank the Dow Chemical Co., Midland, Mich., for this compound.