With (S)-2-Phenyl-1-butoxymagnesium Bromide in Ether–Benzene, 1 Hr. The alcoholate was prepared from an ether solution of *n*-propylmagnesium bromide (31 ml, 1.6 *N*, 0.050 mol), (+)-(*S*)-2-phenyl-1-butanol, $\alpha^{25}D$ +14.9° (neat), 90% e.e. (8.25 g, 0.055 mol), in dry benzene. Solvent composition was adjusted by distillation to 55–56°. Trifluoromethyl phenyl ketone (8.50 g, 0.048 mol) dissolved in a small amount of dry benzene was added to provide a clear solution which formed a precipitate while the reaction mixture was stirred for 1 hr. Work-up gave four fractions: 2.3 g, bp 32–70° (10 mm); 3.2 g, bp 70–90° (10 mm); 1.2 g, bp 90–105° (10 mm); and 3.9 g, bp 86–90° (1 mm). Preparative glpc of the second fraction provided trifuloromethylphenylcarbinol, $\alpha^{26}D$ −4.0° (neat, l = 1), 9.7% e.e., and a sample of 2-phenylbutanal, $\alpha^{27}D$ 0.000° (neat). Preparative glpc of the fourth fraction provided (+)-(*S*)-2-phenyl-1-butanol, $[\alpha]^{27}D$ +14.25° (neat), 86% e.e.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—(+)-(*S*)-2-Phenylbutanoic acid, 4286-15-1; (−)-(*R*)-2-phenylbutanoic acid, 938-79-4; (+)-(*S*)-2-phenyl-1-butanol, 33442-47-6; trifluoromethyl phenyl ketone, 434-45-7; 2-methylbutanal, 96-17-3; 2,2,2-trifluoro-1-phenyl-ethanol-*1-d*, 2793-54-6; *n*-propyl bromide, 106-94-5; (−)-(*S*)-2-methyl-1-butanol, 1565-80-6; (−)-trifluoromethylphenylcarbinol, 10531-50-7.

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Preparation and Aluminum Chloride Induced Rearrangement of Cyclopropylpyridines

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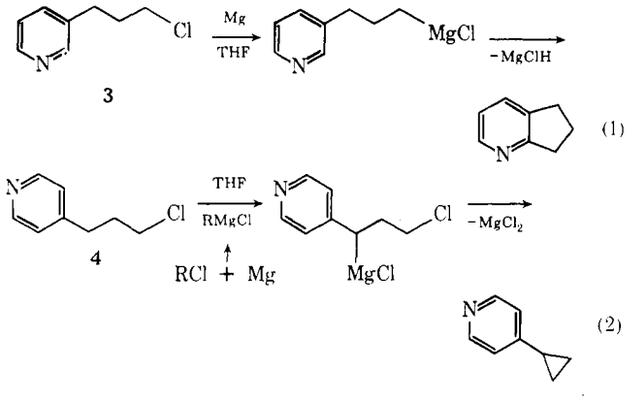
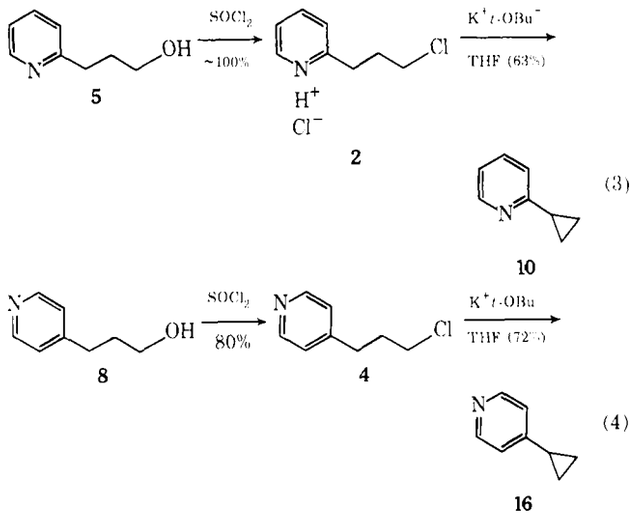
A convenient, two-step preparation of both 2- and 4-cyclopropylpyridines from the corresponding 3-(2- or 4-pyridyl)propanols consists of treatment with thionyl chloride and dehydrohalogenation of the resulting chlorides with potassium *tert*-butoxide. The analogous 3-(3-pyridyl)propanol was converted to *trans*-3-propenylpyridine by a similar procedure. Although the 2- and 4-cyclopropylpyridines were remarkably stable to strong bases, mineral acids, heat, and ultraviolet radiation, they did decompose at *ca.* 400° and were especially reactive toward anhydrous aluminum chloride at 25–45°. Thermally, the 2 isomer yielded 2-picoline, 2-*n*-propylpyridine, ethylene, acetylene, and polymeric material. In the presence of aluminum chloride, both the 2 and 4 isomers gave the corresponding *trans*-propenyl-, isopropenyl-, (2-chloropropyl)-, and (1-chloro-2-propyl)pyridines.

A recent study[1] of the carbocyclization reactions of pyridine derivatives has uncovered two novel reactions of synthetic potential: (1) the first formation of carboannulated pyridine derivatives by intramolecular nucleophilic attack[2] (eq 1); and (2) the detection of 4-cyclopropylpyridine from the reaction of 4-(3-chloropropyl)pyridine with magnesium metal (eq 2). Since the existing syntheses of cyclopropylpyridines are limited in number and in scope, the dechlorometalative closure to the cyclopropane, depicted in eq 2, seemed worth developing as a new synthetic method. Many of the known methods involve more steps or are low yielding.[3] Another approach, namely, the addition of diazoalkanes[4] or sulfonium methylides[5] to vinylpyridines, gives good yields and is convenient, if the appropriate pyridine starting material is available.



The cyclization of 2- and 4-(3-chloropropyl)pyridines by base has proved to be an advantageous route to the respective cyclopropylpyridines, because the conversion of the commercially available propanols to the chloropropanes and thence to the cyclopropanes requires only two steps and gives good overall yields. The enhanced acidity of the methylene groups α to the ring permits a facile formation of the anionic center needed for ring closure (*cf.* eq 2). With the use of 2 equiv of potassium *tert*-butoxide these reactions could be carried out on the isolated, but unpuri-

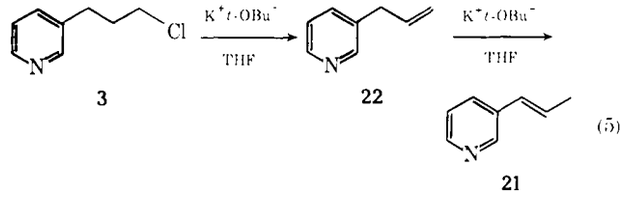
fied, hydrochloride salts (*e.g.*, **2**), thus further simplifying the procedure. In fact, for the 2-(3-chloropropyl)pyridine preparation, the use of **2** prevents altogether the ready tendency of the free pyridine base to undergo intramolecular quaternization to the known 1,2-dihydro-3*H*-pyrrocolinium salt.[6]



5 2 10 (3)

8 4 16 (4)

The foregoing method would be potentially applicable to any 2- or 4-alkylpyridines which could be transformed to the requisite propanols by base-catalyzed reaction with ethylene oxide. That the method fails with 3-(3-chloropropyl)pyridine (**3**) should not be surprising; the lowered acidity of the methylene group α to the ring means that a straightforward dehydrochlorination can compete readily. The observed product, *trans*-3-(1-propenyl)pyridine (**21**), has also been shown to form readily when pure 3-allylpyridine (**22**) is treated with this base in THF.[7]

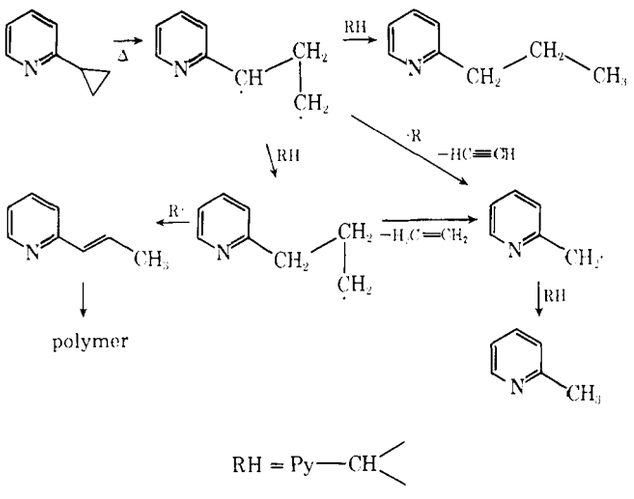


3 22 21 (5)

The ready formation of these cyclopropylpyridines raised the converse point, namely, how resistant such rings would be to rupture. As in recent work,[5] further attempts to cleave **10** or **16** by prolonged treatment with potassium *tert*-butoxide led to no nucleophilic rupture. Similarly, attempts with strong mineral acids or irradiation at 254 nm in benzene or cyclohexane solution showed the ring to be inert. Only by heating 2-cyclopropylpyridine in the vicinity of 400° could rupture be achieved, but then the decomposition was profound. In addition to a black, polymeric glass, the observed products were 2-picoline, 2-*n*-propylpyridine, ethylene, and acetylene, suggestive of a homolytic bond rupture[8] (Scheme I).

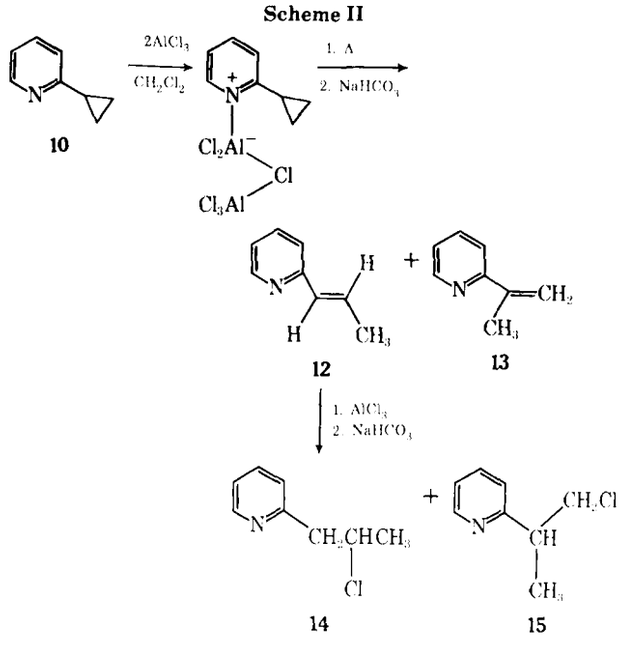
In light of the resistance of **10** and **16** to cleavage, especially by strong acids, it is therefore remarkable that both derivatives underwent rapid cyclopropyl ring opening with 2 equiv of anhydrous aluminum chloride at 25–45°. The reaction does not appear to be caused just by adventitious hydrogen chloride and catalytic amounts of $AlCl_3$, for both **10** and **16** were recovered unchanged when heated with 1 equiv of $AlCl_3$. The products obtained upon hydrolytic work-up were analogous in both cases: the corresponding *trans*-propenyl- and isopropenylpyridines, as well as the (2-chloropropyl)- and (1-chloro-2-propyl)pyridines

Scheme I



RH = Py—CH

Scheme II

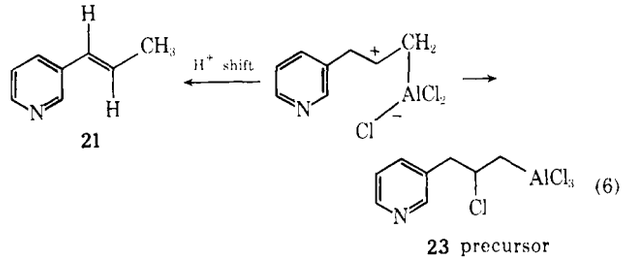


10 12 13 14 15

(Scheme II for 2-cyclopropylpyridine). When the cleavage reaction was conducted at 25°, the proportion of the chloro compounds (**14** and **15**) was higher than at 45°. This finding suggests that aluminum salts of **14** and **15** are the initially formed reaction products from **10**, but that higher temperatures cause partial dechloralumination to produce **12** and **13** (*vide supra*).

By treating pure **12** with 2 equiv of $AlCl_3$ it was shown that some **14** could be isolated. It is important to note, however, that no formation of **13** or **15** was observed from **12**. This experiment rules out the formation of the isopropylpyridines in a reaction other than the ring opening of 2-cyclopropylpyridine. Also pertinent is the behavior of a typical allylpyridine, such as the 3 isomer (**22**), toward anhydrous aluminum chloride. The observed isomerization and addition products are consistent with initial chloralumination and Lewis acid catalyzed isomerization. The conversion of **22** into **21** and **23** leaves open the possibility that, in the isomerization of cyclopropylpyridines, the 2- and 4-allylpyridines may actually be precursors to the propylpyridine derivatives, such as **12** and **14**.

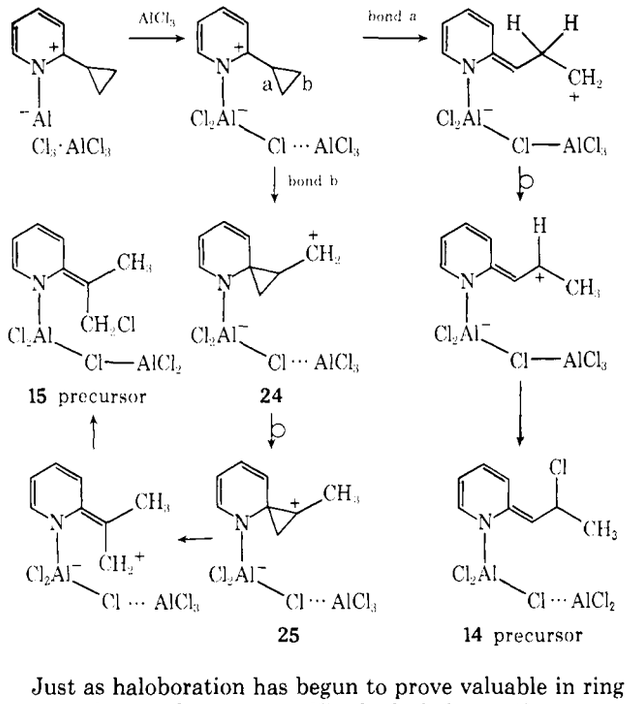
With this reservation in mind, then, the following mechanism (Scheme III) can be formulated in accordance with the experimental data: (a) the 1:1 pyridine–$AlCl_3$ complex



(6)

with a positive polarized α (with **16**, γ) position undergoes chloralumination; (b) rupture occurs principally at bond a, followed rapidly by a 1,2-hydride shift to yield the more stable carbonium ion, which is α to an enamine group;[9] (c) nucleophilic attack of chloride leads to the precursor of **14**; (d) a competing, minor, ring opening (bond b) leading to **24** could again be followed by a 1,2-hydride shift to yield a spiro cyclopropyl cation **25**, which could open up[10] to give a precursor to **15**. A precedent for such a cleavage of the cyclopropyl ring by anhydrous aluminum chloride is seen in the side-reaction cleavage of cyclopropylbenzene during an attempted Friedel–Crafts acylation.[11] In the case reported, however, hydrogen chloride may well have been a participant and, furthermore, no isopropyl products (analogous to **13** and **15**) were detected.[12]

Scheme III



Just as haloboration has begun to prove valuable in ring contraction and stereospecific hydrohalogenation reactions[13,14] so this facile chloralumination of strained carbon–carbon bonds deserves further study as a potentially useful synthetic reaction.

Experimental Section

All melting points were determined on a Thomas-Hoover, oil-bath, capillary apparatus and are uncorrected. Infrared spectra (ir) were recorded on Perkin-Elmer spectrophotometers, either Model 137 or Model 457. Proton magnetic resonance spectra (pmr) were obtained with Varian spectrometers, either Model A-60 or Model 3521A (100 MHz), on neat samples or on 10% solutions in pure solvents containing tetramethylsilane as an internal standard. Signals are reported on the δ scale in parts per million, followed by the relative proton intensities and the coupling constants (J) in hertz. Vapor phase chromatographic analysis (vpc) and isolations were carried out on an F & M chromatograph, Model 720, equipped with 12 ft × 0.25 in. dual columns of 10% silicone rubber (UC-W98) or Carbowax 20M on 60–80 mesh acid-washed firebrick. Mass spectra were recorded at Cornell University, Ithaca, N. Y., either on an AEI-MS-902 or on a Perkin-Elmer 270 spectrometer. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich.

All preparations and reactions involving air- or moisture-sensitive organometallic or heterocyclic intermediates were conducted under an atmosphere of dry, oxygen-free nitrogen, with adherence to published techniques.[15] The petroleum ether had a boiling range of 30–60°; the tetrahydrofuran was made absolute just before use; and the chloroform and methylene chloride used in the aluminum chloride reactions were dried over anhydrous $CaCl_2$ and then distilled.

Fractional distillations were performed with Nester-Faust spinning-band columns, of the 6-mm (i.d.) semimicro type, of either a 6-in. or 18-in. length, equipped with a Teflon spinning band and vacuum jacketing.

General Procedure for the Preparation of the 2-, 3-, and 4-(3-Chloropropyl)pyridines. To a stirred solution of 3-(3- or 4-pyridyl)-1-propanol (**7** and **8**) or 3-(2-pyridyl)-1-propanol hydrochloride (**6**) (0.50 mol) in 250 ml of dry chloroform was added, dropwise, 1.5 equiv of thionyl chloride (90.1 g, 0.76 mol) over a 30-min period (corrosive gas evolved). The dark solution was then refluxed for 1 hr (for the 2-substituted pyridine hydrochloride, 3 hr), cooled, and finally poured onto ice. The chilled biphasic system for **7** and **8** was made basic to litmus with an ice-cooled 50% solution of aqueous KOH. (*Cf.* below for **6**.) The organic layer was separated, the aqueous layer was extracted with 500 ml of $CHCl_3$, and the combined organic fractions were dried over anhydrous Ca_2SO_4.

A. 2-(3-Chloropropyl)pyridine (1). The reaction of thionyl chloride with 3-(2-pyridyl)-1-propanol (**5**), in accordance with the foregoing procedure, does yield 2-(3-chloropropyl)pyridine (**1**), if the work-up is prompt. The nmr spectrum ($CDCl_3$) of the undistilled, but fairly pure, product was clean: δ 9.73 (d, 1, H_6-Py), 8.00–8.97 (m, H_3-, H_4-, H_5-Py), 5.16 (t, 2, $-CH_2Cl$), 3.82 (t, 2, Py–CH_2–) and 2.63 (q, 2, $-CH_2$–). Soon, however, crystalline 1,2-dihydro-3*H*-pyrrocolinium chloride (**9**)[6] began to precipitate.

For further use of the chloride, it was best prepared and isolated as its hydrochloride. Thus, gaseous HCl was first passed into a $CHCl_3$ solution of **5** and the resulting partial solution of **6** was treated with thionyl chloride.

The work-up involved the evaporative removal of the solvent under reduced pressure to leave a light brown paste of **2**, which was then washed with dry benzene. The hygroscopic powder (~100%) could be stored under nitrogen until use: nmr ($CDCl_3$) of the Py–$CH_2CH_2CH_2Cl$, δ 3.65 (t), 2.65 (q), and 3.85 (t), respectively, for the hydrochloride salt.

B. 3-(3-Chloropropyl)pyridine (3). A 74% yield of this compound was obtained: bp 60–61° (0.4 mm); $n^{24.6}$D 1.5243; ir (neat) 1580 (m), 1420 (s), 1310 (m), 1290 (m), 1030 (s), 975 (m), 795 (s), and 718 cm^{-1} (s); nmr (neat) for Py–$CH_2CH_2CH_2Cl$, δ 2.77 (t), 2.00 (m), and 3.58, respectively; picrate mp 126–128° (platelets, EtOH).

Anal. Calcd for $C_8H_{10}ClN$: C, 61.74; H, 6.48. Found: C, 61.83; H, 6.44.

C. 4-(3-Chloropropyl)pyridine (4). An 80% yield was obtained: bp 64–66° (0.4 mm); $n^{23.2}$D 1.5250; ir (neat) 1600 (s), 1410 (s), 1300 (m), 1220 (m), 1065 (m), 990 (s), 875 (m), 833 (s), 795 (s), 758 (s), and 722 cm^{-1} (m).[16]

Reactions of the *x*-(3-Chloropropyl)pyridines with Potassium *tert*-Butoxide. To a solution of potassium *tert*-butoxide (5.88 g, 0.052 mol) in 100 ml of absolute tetrahydrofuran, which was chilled in an ice bath, was added a solution of 3- or 4-(3-chloropropyl)pyridine (7.78 g, 0.050 mol) in 50 ml of the solvent over a 20-min period. (In the case of the 2-substituted derivative, a slurry of **2** in THF was introduced and 2.5 equiv of potassium *tert*-butoxide was used.) The resulting mixtures were stirred at 25° under a nitrogen atmosphere for 24–36 hr. The reaction mixture was treated with 200 ml of water and extracted repeatedly with $CHCl_3$. The combined extracts were dried over anhydrous $MgSO_4$ and the solvent was carefully evaporated at 40° under reduced pressure.

A. 2-Cyclopropylpyridine (10).[17] Distillation of the product from **2** (bp 57–58°, 4.5 mm) yielded 7.3 g (63%) of colorless product: ir (neat) 3003 (s), 1599 (s), 1478 (s), 1454 (s), 1434 (s), 1214 (s), 1148 (s), 1102 (s), 1022 (s), 990 (s), 903 (s), 818 (s), 774 (s), and 747 cm^{-1} (s); nmr (neat) δ 8.43 (m, H_6-Py), 7.40 (m, H_4-Py), 6.93 (m, H_3- and H_5-Py), 1.95 (m, –CH of C_3H_5), and 1.00 (m, C_2H_4 of C_3H_5); picrate mp 130–132° (needles, EtOH).

The methiodide (**11**) was a colorless solid: mp 120–121° (EtOH); nmr (CF_3CO_2H) δ 8.73 (br d, H_6-Py), 8.37 (br d, H_4-Py), 7.42 (br t,

H_3- and H_5-Py), 4.55 (s, CH_3), 2.03–2.57 (m, CH of C_3H_5), and 1.73–1.90 (m, C_2H_4 of C_3H_5).

Anal. Calcd for $C_9H_{12}IN$: C, 41.39; H, 4.63; N, 5.36. Found: C, 41.37; H, 4.53; N, 5.32.

B. 3-(*trans*-1-Propenyl)pyridine (21). By dehalogenation of **3**, **21** was the only product detected by nmr and vpc analyses, as the mixture was monitored at 1, 2, 5, 8, 18, and 24 hr of reaction. Distillative work-up provided a 75% yield: bp 70–72° (5.8 mm); ir (neat) 3005 (s), 1570 (s), 1475 (s), 1395 (s), 1115 (m), 1028 (s), 965 (s), 825 (m), 774 (s), and 703 cm^{-1} (s); nmr (neat) δ 6.26 (m, CH=CH) and 1.74 (m, 3, CH_3); picrate mp 156–157° (needles, EtOH).

C. 4-Cyclopropylpyridine (16). This product was isolated from **4** in 72% yield: bp 61–62° (3.9 mm); ir (neat) 3012 (m), 1605 (s), 1492 (m), 1457 (m), 1407 (s), 1215 (m), 1048 (m), 1025 (m), 995 (s), 906 (s), and 810 cm^{-1} (s); nmr ($CDCl_3$) δ 8.78 (m, H_2- and H_6-Py), 1.85 (m, CH of C_3H_5), and 0.92 (m, C_2H_4 of C_3H_5); picrate mp 158–160° (needles, EtOH).[3]

Reactions of 2- and 4-Chloropropylpyridines with Anhydrous Aluminum Chloride. When either of the cyclopropylpyridines (465 mg, 3.9 mmol) was heated at reflux for 12 hr with 1 equiv of anhydrous aluminum chloride (freshly sublimed, 520 mg, 3.9 mmol) in 20 ml of pure methylene chloride, usual hydrolytic work-up yielded the unchanged cyclopropylpyridine (nmr and vpc analyses) in >90% recovery.

On the other hand, when each of the cyclopropylpyridines (3.64 g, 30.6 mmol) was treated with 2 equiv of anhydrous aluminum chloride (8.15 g, 61.1 mmol) a vigorous reaction took place. After a 12-hr reflux period the solution was poured into aqueous $NaHCO_3$ solution and the resulting suspension was filtered. The separated aqueous layer was extracted with three 25-ml portions of CH_2Cl_2, the organic fractions were combined and dried over anhydrous $MgSO_4$, and the solvent was removed on a rotary evaporator. The product residue amounted to 3.3–3.4 g and was shown by vpc analysis to contain ~5% of the cyclopropylpyridine and four new components.

A. 2-Cyclopropylpyridine. By a combination of nmr and vpc analyses this mixture was shown to consist of 77% *trans*-2-propenylpyridine (**12**), 9% 2-isopropenylpyridine (**13**), 6% 2-(2-chloropropyl)pyridine (**14**), 2% 2-(1-chloro-2-propyl)pyridine (**15**), and 5% **10**.

In another run conducted for 12 hr at 25° there was 20% of remaining **10** and the ratio of **12:13:14:15** was now 4:~0:2:1. Thus, the proportion of chloro derivatives isolated was higher than at 45°.

The products were separated by chromatography on a silica gel column (2.8 × 98 cm) prepared with petroleum ether. The eluting solvent was varied from petroleum ether through mixtures with benzene and finally CH_2Cl_2, as 470 25-ml fractions were collected automatically (Instrumentation Specialties Co.). The sequence of elution was **13**, **15**, **12**, and **14**. Identification follows from these data.

***trans*-2-Propenylpyridine (12):** bp 194–195°; ir (neat) 1585 (s), 1562 (m), 1472 (s), 1443 (m), 1438 (m), 972 (s), and 772 cm^{-1} (s); nmr (neat) δ 8.57 (m of d, H_6-Py), 7.30–7.65 (m, H_4-Py), 6.37–7.26 (m, H_3- and H_5-Py, CH=CH), and 1.80 (d, CH_3, J = 5.8 Hz).

2-Isopropenylpyridine (13): nmr (neat) δ 8.62 (m of d, H_6-Py), 6.96–7.80 (m, H_3-, H_4-, and H_5-Py), 5.88 (m, Py-C=C-H, cis to Py), 5.31 (m, Py-C=C-H, trans to Py), and 2.23 (m, CH_3). Weak couplings (0.5–1.5 Hz) were noted between geminal vinylic protons and between the vinylic and methyl protons.

A sample of 2-isopropenylpyridine (**13**) was prepared by heating 2-isopropylpyridine (5.63 g, 46.6 mmol) with *N*-bromosuccinimide (9.3 g, 46.6 mmol) in CCl_4 until complete consumption of the NBS. Filtration of the suspension and removal of the solvent and remaining 2-isopropyl pyridine (*in vacuo*) from the filtrate gave the crude bromo derivative, which was dissolved in anhydrous THF and treated with 1 equiv of potassium *tert*-butoxide at 0°. Usual work-up, according to that employed for the dehydrohalogenation of the *x*-(3-chloropropyl)pyridines, provided **13**.

2-(2-Chloropropyl)pyridine (14): Since **14** was contaminated with some **12**, only the saturated CH signals are pertinent: nmr δ 4.60 (sextet, -CHCl-, J = 6.8 Hz), 3.10 (d, $-CH_2-$, J = 6.8 Hz), and 1.47 (d, $-CH_3$, J = 6.8 Hz).

Treatment of a sample of **14** with potassium *tert*-butoxide in THF (*vide supra* for procedure) yielded only **12**.

2-(1-Chloro-2-propyl)pyridine (15): Although **15** was admixed with some **13**, the saturated CH signals served for identification: nmr δ 3.82 (q, $-CH_2Cl$, J = 6.8 Hz), 3.17 (sextet, CH, J = 6.8 Hz), and 1.33 (d, $-CH_3$, J = 6.8 Hz). That the diastereotopic methylene protons appear as a quartet is understandable; however, the diastereotopic methylene protons in **14** appear as a doublet. Nevertheless, the chemical shifts observed for the protons in **15** and in **14** correspond rather closely to calculated CH shifts for 1-chloro-2-phenylpropane and 2-chloro-1-phenylpropane, respectively. The calculated shifts were based upon values derived from known phenyl derivatives.[18]

B. 4-Cyclopropylpyridine (16). The reaction products from **16** and aluminum chloride had a marked tendency to change into a water-soluble gummy mass, so the exact proportion of components could not be obtained. However, analogous to **10**, the preponderant product was *trans*-4-propenylpyridine (**17**) and the minor products were the 4-isopropenyl-(**18**) and the corresponding 4-(chloropropyl)pyridine derivatives: *trans*-4-propenylpyridine, nmr δ 6.30 (m, Py-CH=CH-), 1.77 (d, CH_3, J = 5.0 Hz); 4-isopropenylpyridine (trace); 4-(2-chloropropyl)pyridine (**19**), nmr δ 4.27 (sextet, -CHCl-, J = 7.0 Hz), 2.90 (d, Py-CH_2-, J = 7.0 Hz), and 1.43 (d, CH_3, J = 7.0 Hz); 4-(1-chloro-2-propyl)pyridine (**20**), nmr δ 3.67 (d, $-CH_2Cl$), 2.90 (sextet, -CH-), and 1.24 (d, CH_3, J = 7.0 Hz).

Reaction of *trans*-2-Propenylpyridine with Anhydrous Aluminum Chloride. A solution of **12** (325 mg, 3.73 mmol) and anhydrous aluminum chloride (728 mg, 7.46 mmol) in 20 ml of CH_2Cl_2 was refluxed for 12 hr and worked up in the manner described for the cyclopropylpyridine–aluminum chloride reactions. By nmr analysis the product was shown to be a 9:1 mixture of starting material and 2-(2-chloropropyl)pyridine(**14**).

In contrast, passing dry HCl gas into a solution of **12** in CH_2Cl_2 for 2 hr or treating **12** with 12 *N* HCl led upon treatment with aqueous $NaHCO_3$ solution to unchanged **12**.

Attempted Cleavage Reactions of 2-Cyclopropylpyridine. The cyclopropane ring in **10** was inert to (a) treatment with 12 *N* HCl at 25° for 12 hr; (b) treatment with 36 *N* H_2SO_4 at 25° for 3 hr; (c) irradiation in dry benzene at 254 nm (low-pressure mercury lamps) for 40 hr or in cyclohexane for 20 hr; and (d) heating under nitrogen in a sealed tube at 315° for 12 hr.

2-Cyclopropylpyridine methiodide was thermally inert at 200° after 12 hr; at 300° it dissociated into **10** and CH_3I.

At 400° 2-cyclopropylpyridine underwent deep-seated decomposition after 3 hr to yield acetylene and ethylene (mass spectrum), 2-picoline, 2-*n*-propylpyridine, and a brittle, shiny black solid that contained nitrogen (by combustion, a $C_{12}H_7N$ ratio) and was insoluble in $CHCl_3$, EtOH, or CF_3COOH. The 2-picoline and 2-*n*-propylpyridine[19] were identified by nmr and vpc comparisons with authentic samples.

By comparison, 4-cyclopropylpyridine darkened after a 2-hr heating period to 400°, but no new gaseous or liquid component was detected. Spectral and chromatographic analyses showed only unchanged **16**.

Reaction of 3-Allylpyridine (22) with Anhydrous Aluminum Chloride. A solution of **22** (1.6 g, 13.5 mmol, distilled from barium oxide) and anhydrous aluminum chloride (3.6 g, 27 mmol) in 50 ml of CH_2Cl_2 was refluxed for 12 hr and worked up in the usual way. The 1.8 g of sweet-smelling liquid was shown by nmr analysis to be a mixture of *trans*-3-propenylpyridine (**21**) and 3-(2-chloropropyl)pyridine (**23**), nmr (neat) δ 4.21 (sextet, -CHCl-, J = 6.5 Hz), 2.90 (d, $-CH_2$, J = 6.5 Hz), and 1.39 (d, $-CH_3$, J = 6.5 Hz), in a 1.64:1.0 ratio.

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Registry No.—**1**, 52225-85-1; **2**, 17944-57-9; **3**, 21011-66-5; **3** picrate, 52225-86-2; **4**, 5264-02-8; **5**, 2859-68-9; **6**, 52225-87-3; **7**, 2859-67-8; **8**, 2629-72-3; **10**, 20797-87-9; **10** picrate, 41764-98-1; **11**, 52225-88-4; **12**, 52248-74-5; **13**, 6515-13-5; **14**, 52225-89-5; **15**, 52225-90-8; **16**, 4904-21-6; **16** picrate, 21011-78-9; **17**, 52248-75-6; **18**, 17755-30-5; **19**, 52225-91-9; **20**, 52225-92-0; **21**, 52248-76-7; **21** picrate, 52248-77-8; **22**, 7300-28-9; **23**, 52225-93-1; $AlCl_3$, 7446-70-0.

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Rearrangement of Anhydropyrimidine Nucleosides in Liquid Hydrogen Fluoride. Mechanism, Scope, and Synthetic Studies

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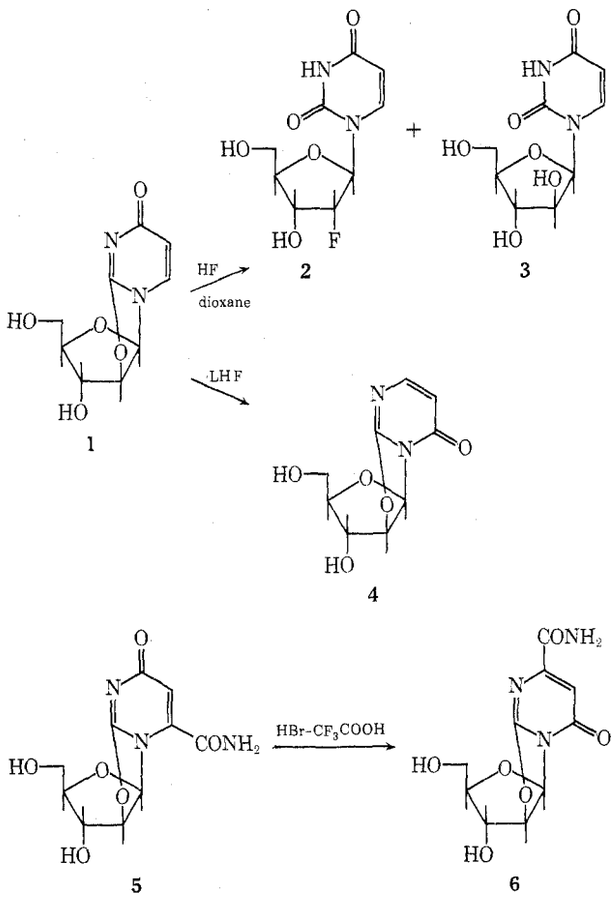
In contrast to the reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (1) with HF in dioxane which yields 2′-fluoro-2′-deoxyuridine (2), liquid hydrogen fluoride treatment of 1 resulted in rearrangement of the nucleosidic bond from N-1 to N-3. The mechanism proposed to account for the formation of 2,2′-anhydro-3-β-D-arabinofuranosyluracil (4) involves N-1–C-1′ bond cleavage of the protonated anhydro nucleoside with the formation of a resonance-stabilized carbonium ion in the carbohydrate portion of the molecule. Re-formation of the nucleosidic bond by electrophilic attack yields the thermodynamically more stable N-3 isomer. Other 2,2′-anhydropyrimidine nucleosides underwent similar rearrangement in liquid hydrogen fluoride, but 2,3′ and 2,5′-anhydro compounds were cleaved to the heterocyclic base. Cleavage of the anhydro bond of the rearranged nucleoside by aqueous base treatment yielded 3-β-D-arabinofuranosylpyrimidines. The di-*O*-benzoyl derivative of 4 (**20b**) served as a useful intermediate for the preparation of 3-β-D-ribofuranosyluracil (**21**) and 2′-deoxy-3-β-D-ribofuranosyluracil (**24**).

Aqueous acid or base hydrolysis of 2,2′-anhydropyrimidine nucleosides results in cleavage of the anhydro bond at C-2 of the pyrimidine nucleus with the formation of arabinosyl nucleosides.[1] In contrast, treatment of 2,2′-anhydro nucleosides under anhydrous conditions with hydrogen halides yields 2′-halogeno-2′-deoxyribofuranosylpyrimidine nucleosides. In this manner, 2′-chloro- and 2′-bromo-2′-deoxyuridine[2] have been obtained by reaction of 2,2′-anhydrouridine (1) with HCl in dioxane or HBr in trifluoroacetic acid, respectively. 2′-Chloro- and 2′-bromo-2′-deoxycytidine have been prepared from 2,2′-anhydrocytidine by reaction with hydrogen halides in DMF.[3] Treatment of 1 with hydrogen fluoride in dioxane solution gives 2′-fluoro-2′-deoxyuridine (2) in moderate yield.[2,4] Conflicting reports[3,5] exist as to the applicability of the HF–dioxane method for the preparation of the 2′-fluoro-2′-deoxy analog of cytidine from 2,2′-anhydrocytidine. The preparation of 2′-fluoro-2′-deoxycytidine from 2 by standard synthetic sequences has been reported.[4]

Fluorinated nucleoside 2 is desired in our laboratory as a precursor for the preparation of the corresponding 2′-fluorinated pyrimidine polynucleotides.[6,7] However, our large-scale preparations of 2, which are carried out essentially as reported,[2,4] contain a 3:2 ratio of 2 and 1-β-D-arabinofuranosyluracil (3). Nucleoside 3 is derived from 1 by hydrolytic cleavage, presumably from traces of moisture which are introduced into the mixture of 1 and dioxane during the addition of liquid hydrogen fluoride. Although 2 can readily be separated from 3 by acetylation[4] of the reaction products, our attempts to improve the yield of 2 were not successful. We therefore explored the reaction of 1 with neat liquid hydrogen fluoride (LHF) (Scheme I).

Treatment of 1 with LHF at elevated temperatures unexpectedly resulted in rearrangement of the nucleosidic linkage from N-1 of the uracil ring to N-3, with retention of the anhydro bond, to yield 2,2′-anhydro-3-β-D-arabinofuranosyluracil (4). We have previously reported the proof of

Scheme I



structure of this novel pyrimidine anhydro nucleoside.[8] The analogous rearrangement of 2,2′-anhydro-1-β-D-arabi-