Synthesis of 2-Chloro-5-hydroxynicotinonitrile: The Required Intermediate in the Total Synthesis of a Hydroxylated Metabolite of (*S*)-2-(3-*t*-Butylamino-2-hydroxypropoxy)-3-cyanopyridine

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A convenient method for the synthesis of 2-chloro-5-hydroxynicotinonitrile (**10**) *via* 5-amino-2-chloro-3-methylpyridine (**3**) is described. Subsequent conversions provided the basic metabolite **2** of (*S*)-2-(3-*t*-butylamino-2-hydroxypropoxy)-3-cyanopyridine (**1**). ^{13}C Nmr data is also presented to characterize 2-chloro-5-fluoro-3-methylpyridine (**5**), a by-product in the Schiemann reaction having unexpected ^{1}H and ^{19}F nmr spectra.

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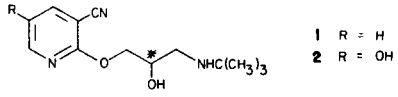
A continuing interest in functionalized pyridines (1) as intermediates leading to medicinally interesting compounds has led to an investigation of synthetic strategies suitable for the preparation of 2-chloro-5-hydroxynicotinonitrile. This compound, in particular, was required for the total synthesis of a putative metabolite of the antihypertensive agent (*S*)-2-(3-*t*-butylamino-2-hydroxypropoxy)-3-cyanopyridine (**1**) (2). During a detailed study of **1** in the rat, a basic monohydroxy metabolite was isolated from the bile (3). Based on ^{1}H nmr and mass spectral studies, this metabolite was tentatively identified as **2**, a derivative of **1** in which a hydroxy group had been introduced into the 5-position. Such hydroxylations of the aromatic ring have previously been observed with related systems (4). An unambiguous synthesis of **2** was therefore required to confirm the postulated structure.

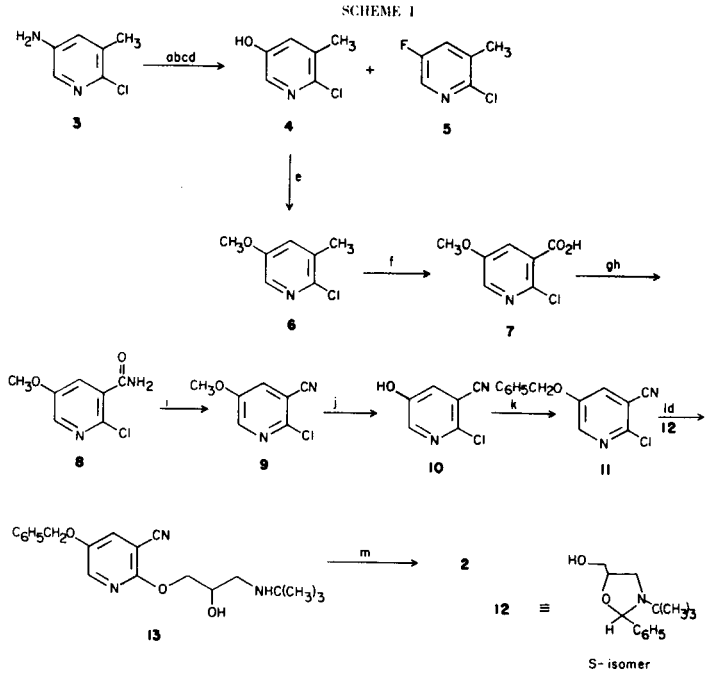
In previous communications (1), we have described methods for the synthesis of 5-substituted 2-bromonicotinic acid derivatives; however, these procedures were not amenable to the preparation of pyridines containing a 5-hydroxyl group. This limitation prompted a search for an alternate strategy. We now wish to report a convenient method for the preparation of 2-chloro-5-hydroxynicotinonitrile (**10**) and its conversion to the metabolite **2**.



1 R = H
2 R = OH

The synthetic sequence chosen is outlined in Scheme I and starts with 5-amino-2-chloro-3-methylpyridine (**3**), which was prepared according to the procedure of Hawkins and Roe (5). Diazotization of **3** using a modified Schiemann reaction (6) followed by decomposition of the intermediate diazonium salt in boiling acetic acid (7) gave **4** in 64% yield along with a second component identified as 2-chloro-5-fluoro-3-methylpyridine (**5**).

SCHEME I



(a) $NaNO_2$-HCl-65% HPF_6. (b) AcOH. (c) 10% NaOH. (d) H_3O^+. (e) NaH/DMF/CH_3I. (f) $KMnO_4$-H_2O. (g) $SOCl_2$, Δ. (h) aq. NH_3-0°. (i) $(C_6H_5)_3PO/(CF_3SO_2)_2O/CH_2Cl_2$. (j) $C_6H_5N \cdot HCl$/180-200°. (k) NaH/DMF/$C_6H_5CH_2Br$. (l) NaH/DMF/**12**. (m) 10% Pd on C/EtOH.

Unexpectedly, no coupling between the C_5-F and C_6-H was observed in the ^{1}H and ^{19}F nmr spectra of **5**. In order to confirm the structure of the fluoro derivative as **5**, ^{13}C nmr study was undertaken, the results of which are shown in Table I. Calculated ^{13}C chemical shifts *vis-à-vis* observed values are in agreement and the magnitude of the C-F couplings verifies that the carbon substituted by fluorine is flanked by the two C-H carbons. The zero 3-bond H-F coupling found with **5** is also in agreement with the results reported in the literature (8) for similar compounds. As a

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Table I

Observed and Calculated ^{13}C Chemical Shifts as well as C-F Coupling Constants

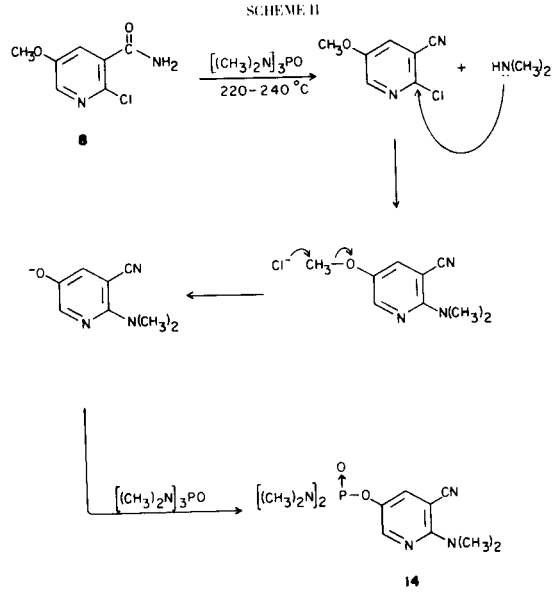
	C-2	C-3	C-4	C-5	C-6
Observed δ	146.2	134.2	126.4	158.7	134.8
Calculated δ	147.4	134.5	126.6	159.0	136.0
Observed J_{CF}	<1	4.3	19.8	256.0	25.4

final confirmation of structure, the high resolution mass spectrum of **5** exhibited the expected molecular ion at m/e 147.0062.

Treatment of **4** with sodium hydride and methyl iodide in DMF gave the ether **6** in nearly quantitative yield. Oxidation of **6** using potassium permanganate (9) provided the acid **7** in 35% yield. Conversion of **7** to the amide **8** was effected by treatment of the intermediate acid chloride with aqueous ammonia. Dehydration of **8** by the method of Hendrickson (10) gave an 86% yield of the nitrile **9**.

It is worthy to note that dehydration of **8** using hexamethylphosphoramide (11) failed to yield **9**, instead, compound **14** was isolated. Presumably, **14** arose through the series of transformations outlined in Scheme II.

SCHEME II



Demethylation of **9** using pyridine hydrochloride provided the 5-hydroxypyridine **10** in 70% yield which, on subsequent treatment with sodium hydride and benzyl bromide, gave the benzyl ether **11** in quantitative yield. This sequence of deprotection-protection was required since attempted oxidation of 5-benzyloxy-2-chloro-3-methylpyridine (**15**) by potassium permanganate resulted in attack of the benzyl ether yielding benzoic acid instead of 5-benzyloxy-2-chloronicotinic acid. In addition, we felt that the methyl group could not be retained throughout the sequence outlined in Scheme I because ultimate demethylation in the presence of the aminohydroxypropoxy side chain could result in indiscriminate cleavage of both ether linkages.

Incorporation of the aminohydroxypropoxy side chain was achieved through the reaction of **11** with (*S*)-2-phenyl-3-*t*-butyl-5-hydroxymethyloxazolidine (**12**) (2,12) and sodium hydride in DMF. Deprotection with mild acid afforded **13** in 70% yield. Debenzylation using 10% palladium on carbon gave **2** which was shown to be identical to the isolated metabolite by tlc, ^1H nmr and mass spectral studies (3).

EXPERIMENTAL

Infrared spectra were obtained on Perkin-Elmer Model 137 and 257 spectrophotometers. ^1H and ^{13}C nmr spectra were determined in the indicated solvent on Varian T-60 and CFT-20 instruments, respectively, using tetramethylsilane as an internal standard, and ^{19}F spectra were recorded on an EM-390 spectrometer at 84.67 MHz with fluorotrichloromethane as internal standard. Mass spectra were taken on an AEI MS-902 high resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The data were processed by a DS50 data acquisition system. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Silica gel 60, 70-230 mesh, (E. Merck, Darmstadt) was used for column chromatography. Solutions were dried over sodium sulfate and concentrated to dryness using a Buchi rotary evaporator under water aspirator pressure (20 mm).

2-Chloro-5-hydroxy-3-methylpyridine (**4**) and 2-Chloro-5-fluoro-3-methylpyridine (**5**).

To a solution of **3** (26.3 g., 0.18 mole) in 12*N* hydrochloric acid (90 ml.) and water (157 ml.) cooled at −10° to 0° was added dropwise a solution of sodium nitrite (13.9 g., 0.20 mole) in water (28 ml.). After the addition the solution was stirred for 10 minutes and then 65% HPF_6 (90 ml.) was added. The resulting mixture was filtered, washed with cold water, methanol and ether to yield 61.7 g. of diazonium salt, m.p. 104-105° dec. The solid was cautiously added through Gooch tubing to acetic acid (425 ml.) preheated to 105°. The addition was carried out over 1 hour with noticeable evolution of nitrogen. The solution was concentrated and the residue stirred for 1 hour with 10% sodium hydroxide solution (510 ml.). The aqueous solution was extracted with ether (3x), neutralized with concentrated hydrochloric acid and extracted with chloroform (3x). After concentration, the residue was crystallized from methanol-ligroin to yield 14.5 g. (56%) of **4**, m.p. 128-130°. A second crop weighing 2.24 g. (8%), m.p. 126-128°, was recovered from the mother liquor; ^1H nmr (deuteriochloroform): δ 2.35 (3H, s,), 7.15 (1H, d, J = 3), 7.9 (1H, d, J = 3) and 9.4 (1H, bs, exch).

Anal. Calcd. for C_6H_6ClNO: C, 50.19; H, 4.21; N, 9.76. Found: C, 50.30; H, 4.19; N, 9.66.

The ether layer (*vide supra*) was dried, filtered and concentrated. The residue was sublimed at 60° (1.6 mm) to yield 2.15 g. (8%) of **5**, m.p. 38-40°; ^{1}H nmr (deuteriochloroform): δ 2.35 (3H, s), 7.35 (1H, dd, J = 3 and 9) and 8.1 (1H, d, J = 3); ^{19}F nmr (fluorotrichloromethane): + 129.95 ppm (1F, d, J = 9). The exact mass was 147.0062 (Calcd. 147.0065).

2-Chloro-5-methoxy-3-methylpyridine (**6**).

Into a flame dried flask under nitrogen was placed DMF (150 ml.), sodium hydride (50% oil dispersion, 4.0 g., 0.08 mole) and **4** (11.7 g., 0.08 mole). The solution was stirred at 0-5° until the evolution of hydrogen ceased and then a solution of methyl iodide (5.6 ml., 0.09 mole) in DMF (50 ml.) was added dropwise. After the addition, the solution was allowed to stir at room temperature overnight. The resulting slurry was added to water and extracted with ether (3x). The organic layer was concentrated and the residue distilled at 85° (0.6 mm) to yield 12.8 g. of **6** (95%) as an oil; ^{1}H nmr (deuteriochloroform): δ 2.35 (3H, s), 3.8 (3H, s), 7.1 (1H, d, J = 3) and 7.9 (1H, d, J = 3); ms: m/e (M$^+$) 157.

Anal. Calcd. for C_7H_8ClNO: C, 53.24; H, 5.12; N, 8.89; Cl, 22.50. Found: C, 53.10; H, 5.18; N, 8.84; Cl, 22.36.

2-Chloro-5-methoxynicotinic Acid (**7**).

A mixture of **6** (5.0 g., 0.031 mole), water (400 ml.) and potassium permanganate (18.8 g., 0.12 mole) was heated at reflux for 1 hour. The resulting mixture was then filtered hot through super-cel, cooled and extracted with dichloromethane (3x). The organic layer was dried, filtered and concentrated to yield 1.1 g. of recovered **6**. The aqueous layer was acidified with 12*N* hydrochloric acid and concentrated to a small volume. The solid was filtered and recrystallized from 2-propanol/ether to yield 1.6 g. (35%) of **7**, m.p. 169-170°; ^{1}H nmr (DMSO-d_6): δ 3.95 (3H, s), 7.85 (1H, d, J = 3) and 8.3 (1H, d, J = 3); ir (nujol): 1740 cm^{-1}.

Anal. Calcd. for $C_7H_6ClNO_3$: C, 44.82; H, 3.22; N, 7.47. Found: C, 45.12; H, 3.12; N, 7.41.

2-Chloro-5-methoxynicotinamide (**8**).

A solution of **7** (10.6 g., 0.06 mole) and thionyl chloride (140 ml.) was heated at reflux for 3 hours. The resulting solution was concentrated and then added to cold (0-4°) aqueous ammonia (1 l.). After stirring for 15 minutes, the reaction mixture was concentrated and the residue extracted with hot acetonitrile (3x). The hot acetonitrile extract was filtered and concentrated to yield 21.2 g. (99%) of **8**, m.p. 129-132°; ^{1}H nmr (deuteriochloroform): δ 3.85 (3H, s), 6.6 (2H, bs, exch.), 7.7 (1H, d, J = 3) and 8.1 (1H, d, J = 3); ir (nujol): 3330 and 1650 cm^{-1}.

Anal. Calcd. for $C_7H_7ClN_2O_2$: C, 45.06; H, 3.78; N, 15.01. Found: C, 45.16; H, 3.62; N, 14.74.

2-Chloro-5-methoxynicotinonitrile (**9**).

Into a flame dried flask under nitrogen was placed triphenylphosphine oxide (12.0 g., 0.04 mole) and dichloromethane (80 ml.) and the mixture cooled to 0-4°. A solution of triflic anhydride (6.75 ml., 0.04 mole) in dichloromethane (80 ml.) was added dropwise. After the addition, the solution was stirred for 15 minutes and **8** (8.0 g., 0.04 mole) was added portionwise over 15 minutes. The mixture was allowed to warm to room temperature with stirring overnight, poured into saturated sodium carbonate solution and extracted with chloroform (3x). After concentration, the residue was chromatographed on silica gel and the product eluted with chloroform to yield 6.2 g. (86%) of **9**; ^{1}H nmr (deuteriochloroform): δ 3.9 (3H, s), 7.5 (1H, d, J = 3) and 8.3 (1H, d, J = 3); ir (nujol): 2250 cm^{-1}.

Anal. Calcd. for $C_7H_5ClN_2O$: C, 49.87; H, 2.99; N, 16.62. Found: C, 49.65; H, 2.88; N, 16.43.

N,N,N',N'-Tetramethylphosphorodiamidic Acid 2-*N,N*-dimethylamino-3-cyano-5-pyridyl Ester (**14**).

A solution of **8** (0.25 g., 0.0013 mole) and hexamethylphosphoramide (2 ml.) was heated at 220-240°. After 2 hours, the dark solution was poured into water and extracted with ether (3x). The organic layer was washed with water, saturated sodium chloride solution, dried, filtered and concentrated. The oily residue was characterized as **14**; ^{1}H nmr (deuteriochloroform): δ 2.6 (6H, s), 2.75 (6H, s), 3.2 (6H, s), 7.55 (1H, dd, J = 1 and 3) and 8.15 (1H, dd, J = 1 and 3); ir (neat): 2220 cm^{-1}; ms: m/e (M$^+$) 297.

2-Chloro-5-hydroxynicotinonitrile (**10**).

A mixture of **9** (3.1 g., 0.018 mole) and pyridine hydrochloride (90 g.) was heated at 200° with stirring until evolution of gases ceased. After 2 hours, the solution was poured onto ice and extracted with ether (3x). The organic layer was dried, filtered, and concentrated to yield 2.0 g. (70%) of **10**. An analytical sample of **10** was prepared by recrystallization from water, m.p. 182-184°; ^{1}H nmr (DMSO-d_6): δ 7.65 (1H, d, J = 3), 8.0 (1H, d, J = 3) and 8.7 (1H, bs, exch); ir (nujol): 2230 cm^{-1}; ms: m/e (M$^+$) 154.

Anal. Calcd. for $C_6H_3ClN_2O$: C, 46.62; H, 1.96; N, 18.13. Found: C, 46.62; H, 1.93; N, 18.17.

5-Benzyloxy-2-chloronicotinonitrile (**11**).

Into a flame dried flask under nitrogen was placed **10** (2.0 g., 0.013 mole), DMF (60 ml.), sodium hydride (50% oil dispersion, 0.75 g., 0.013 mole) and the mixture cooled to 0-4°. A solution of benzyl bromide (1.5 ml., 0.013 mole) in DMF (2 ml.) was then added and the solution allowed to stir at room temperature overnight. The mixture was poured into water and extracted with ether (3x). The organic layer was concentrated to yield 2.9 g. (100%) of **11**. An analytical sample of **11** was prepared by trituration with C_6H_{14}, m.p. 114-115°; ^{1}H nmr (deuteriochloroform): δ 5.2 (2H, s), 7.4 (5H, s), 7.5 (1H, d, J = 3) and 8.35 (1H, d, J = 3); ir (nujol): 2220 cm^{-1}; ms: m/e (M$^+$) 244.

Anal. Calcd. for $C_{13}H_9ClN_2O$: C, 63.82; H, 3.71; N, 11.45. Found: C, 64.00; H, 3.68; N, 11.23.

(*S*)-5-Benzyloxy-2-(3-*t*-butylamino-2-hydroxypropoxy)nicotinonitrile (**13**) Maleate Salt.

Into a flame dried flask under nitrogen was placed DMF (100 ml.), **12** (2,12) (2.5 g., 0.01 mole) and sodium hydride (50% oil dispersion, 0.5 g., 0.01 mole). The mixture was heated at 90° for 10 minutes, then cooled to 35° and a solution of **11** (2.5 g., 0.01 mole) in DMF (25 ml.) was added dropwise and allowed to stir at room temperature overnight. The mixture was poured into water and extracted with ether (3x). The organic layer was dried, filtered and concentrated. The residue was treated with 1*N* hydrochloric acid (150 ml.) and heated on a steam bath. After 15 minutes, the solution was cooled, extracted with ether (2x), poured into saturated sodium carbonate solution, and extracted with chloroform (3x). After concentration, the residue was crystallized as the maleate salt from 2-propanol/ether to yield 3.3 g. (70%) of **13**, maleate, m.p. 124-126°; ^{1}H nmr (DMSO-d_6): δ 1.3 (9H, s), 3.1 (2H, m), 4.2 (3H, m), 5.2 (2H, s), 6.05 (2H, s, olefinic protons of maleic acid), 7.4 (5H, bs), 8.1 (1H, d, J = 3) and 8.25 (1H, d, J = 3).

Anal. Calcd. for $C_{20}H_{25}N_3O_3 \cdot C_4H_4O_4$: C, 61.13; H, 6.19; N, 8.91. Found: C, 61.14; H, 6.15; N, 8.75.

(*S*)-2-(3-*t*-Butylamino-2-hydroxypropoxy)-5-hydroxynicotinonitrile (**2**).

Compound **13**, maleate, (2.27 g., 0.005 mole) was added to saturated sodium carbonate solution and extracted with chloroform (3x). After concentration, the residue was dissolved in ethanol (125 ml.) and 10% palladium on carbon (1.0 g.) was added under nitrogen. The mixture was placed on a Herschberg hydrogenation apparatus and after 108 ml. of hydrogen was consumed, the suspension was filtered through super-cel. The solution was concentrated, the residue was chromatographed on silica gel and the product eluted with 10% methanol-chloroform saturated with ammonia. The residue was triturated with acetonitrile to yield 0.38 g. (30%) of **2**, m.p. 85-90°; ^{1}H nmr (deuteriochloroform): δ 1.0 (9H, s), 2.55 (2H, m), 3.8 (1H, p), 4.25 (1H, d, J = 6), 5.0 (3H, bs, exch), 7.58 (1H, d, J = 3) and 7.98 (1H, d, J = 3); ir (nujol): 3300 and 2250 cm^{-1}; ms: m/e (M-15) 250.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.76; H, 7.27; N, 15.77.

5-Benzyloxy-2-chloro-3-methylpyridine (**15**).

Into a flame dried flask under nitrogen was placed **4** (2.9 g., 0.02 mole), DMF (20 ml.) and sodium hydride (50% oil dispersion, 1 g., 0.021 mole). The mixture was cooled to 0-4° and a solution of benzyl bromide (3.5 g.,

0.02 mole) in DMF (5 ml.) was added dropwise. After the addition, the solution was allowed to warm to room temperature overnight. The solution was then poured into water and extracted with ether (3x). The organic layer was dried, filtered, concentrated, and the residue distilled at 160-163° (0.6 mm) to yield 3.7 g. (79%) of **15**; ^{1}H nmr (deuteriochloroform): δ 2.35 (3H, s), 5.0 (2H, s), 7.15 (1H, d, J = 3), 7.35 (5H, bs) and 8.0 (1H, d, J = 3); ms: m/e (M^+) 233.

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