In summary, the study of the ^{13}C and ^{1}H NMR spectra of the perhydrobenzo[*c*]quinolizines (**2**) has enabled us to show that in this compound, as in the benzo-substituted analogue (**1**), the preferred conformation is the trans-cisoid-cis one. This is in agreement with the energies obtained by molecular-mechanics calculations. Once more,[24] it has been shown that an assignment of a *cis*-quinolizidine conformation, based upon the absence of strong Bohlmann absorptions in the infrared spectrum, should be made with due caution.

Experimental Section

The NMR spectra were recorded on Bruker HX 270 (^{1}H) and Bruker WH 90(^{13}C) pulsed-Fourier-transform spectrometers in $CDCl_3$ solutions as described previously.[1] The infrared spectra were recorded on a Perkin-Elmer 257 spectrometer as dispersions in KBr.

2-(2-Pyridylethyl)cyclohexanone Ethylene Ketal (8) was prepared as described by Ohki[2] using ~0.33 equiv of *p*-toluenesulfonic acid; yield 60%.

2-(2-Piperidylethyl)cyclohexanone Ethylene Ketal (9). To a solution of 10 g of **8** in 100 mL of absolute ethanol, 15 g of sodium was added in portions. This required about 2 h. Water was then added, and most of the ethanol was evaporated under vacuum. Extraction with benzene, drying over $MgSO_4$, and distillation gave 7.8 g (76%) of a colorless oil; bp 132 °C (0.8 mm).

Δ^{6a}- and $\Delta^{10(10a)}$-Dehydroperhydrobenzo[*c*]quinolizine (3a, b) was prepared as described by Ohki[2] by refluxing **9** in 20% HCl for 2 h. Distillation of the enamine at 70 °C (0.5 mm) yielded 71% of a colorless oil. The ^{1}H NMR (270 MHz, $CDCl_3$) indicated the vinylic proton of the $\Delta^{10(10a)}$ isomer at δ 4.6, integrating for about 10% of a proton. The ^{13}C spectrum (22.63 MHz, $CDCl_3$) showed two sets of signals in a 90:10 proportion. The literature[2,25] reports a 4:1 composition of the isomeric mixture.

Perhydrobenzo[*c*]quinolizine (Perhydropyrido[1,2-*a*]quinoline) (2). Method 1. Catalytic and $NaBH_4$ reductions of **3a** or **3b** were carried out under the previously described conditions.[2] The composition of the reaction mixture was determined on a Varian 1520 B gas chromatograph (5% SE 30 Chromosorb W, 160 °C column, 290 °C detector, and N_2 and H_2 flow rates of 25 mL/min).

Method 2. $LiAlH_4$ reduction of 500 mg of the perchlorate salt of **3a** or **3b** was carried out in 200 mL of dry tetrahydrofuran. After a 4-h reflux, water was added and most of the tetrahydrofuran was evaporated. After extraction with ether, drying over $MgSO_4$, and evaporation of the solvent, the residue was examined by GLC (Table I). The isomers were separated by column chromatography over Al_2O_3 (Fluka, Type 507 C, Activity I) with ether elution.

Method 3. Reduction with K-selectride (5 equiv of a 0.5 M solution in THF, Aldrich) of 1 g of the perchlorate salt of **3a** or **3b** in 50 mL of dry THF was carried out at −50 °C for 15 h. The reaction was worked up as described for the $LiAlH_4$ reduction, followed by an acid–base extraction.

About 20% unreduced enamine was further reduced by the PtO_2/H_2 procedure.

Acknowledgment. We wish to thank the Fonds voor Fundamenteel Kollektief Onderzoek and the Nationale Raad voor Wetenschapsbeleid for their contribution to the equipment of our laboratory.

Registry No.—**2,** isomer I, 64161-72-4; **2,** isomer II, 64161-73-5; **2,** isomer III, 64161-74-6; **3a,** 944-68-3; **3a**·$HClO_4$, 64114-15-4; **3b,** 944-67-2; **3b**·$HClO_4$, 64114-16-5; **8,** 1023-99-0; **9,** 1444-15-1.

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Use of α-Cyano Amines for the Regiospecific Synthesis of Multisubstituted Pyridines. Preparation of Nicotine Analogues[1]

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A general synthesis of 2-alkyl-3-acylpyridines and 2-alkyl-3-formylpyridines via [2,3] sigmatropic rearrangements of α-pyrrolidinyl-2-alkylpyridines is described. The initially obtained α-cyano amine can be hydrolyzed to an aldehyde, reductively cleaved to an amine, or alkylated and hydrolyzed to a ketone. These procedures are applied toward the synthesis of pyridine-substituted nicotine, nornicotine, and anabasine derivatives. In certain cases, the Stevens rearrangement product was observed along with the desired Sommelet–Hauser product, and studies indicated that sodium amide/NH_3 gave the largest preference for the latter rearrangement pathway.

The importance of the pharmacology of nicotine (**1**) and the nicotiana alkaloids is demonstrated by the intensive study they have received over the past century.[2] Some time ago Haglid reported that 6-methylnicotine (**3**) retained virtually full nicotinic activity, whereas 4-methylnicotine (**2**) displayed no activity on isolated muscle preparations.[3] This finding was rationalized by assuming that the 4-methyl group prevented the compound from adopting the conformation necessary for interaction with the receptor. As part of our interest in the structure, chemistry, and pharmacology of nicotine,[4,5] we

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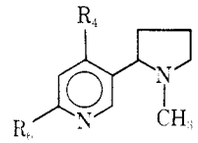
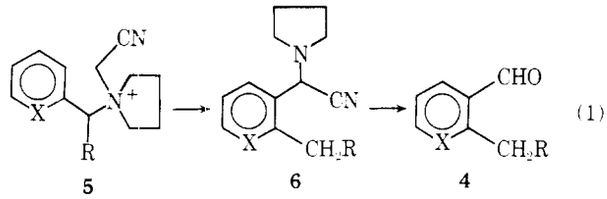
initiated a study directed toward the synthesis of 2-alkylnicotinoids so as to better assess the effect of substituents ortho to the pyrrolidine ring of nicotine.

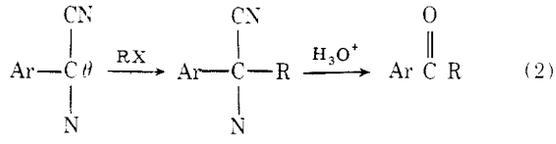


1, $R_4 = R_6 = H$
2, $R_4 = CH_3$; $R_6 = H$
3, $R_4 = H$; $R_6 = CH_3$

The most commonly used approach toward the regiospecific synthesis of polysubstituted pyridines involves the formation of the pyridine ring from appropriately substituted acyclic precursors.[6] However, the requirements of our desired pharmacological studies suggested that a synthetic strategy should involve a general route to 2-alkyl-3-acylpyridines. We now report a sequence of reactions leading to **4** (X = N) from readily available 2-picolyl halides involving α-cyano amines in which the α-cyano amines (**1**) serve as the migrating moiety in a Sommelet–Hauser rearrangement,[7] and (2) are utilized



(1)



(2)

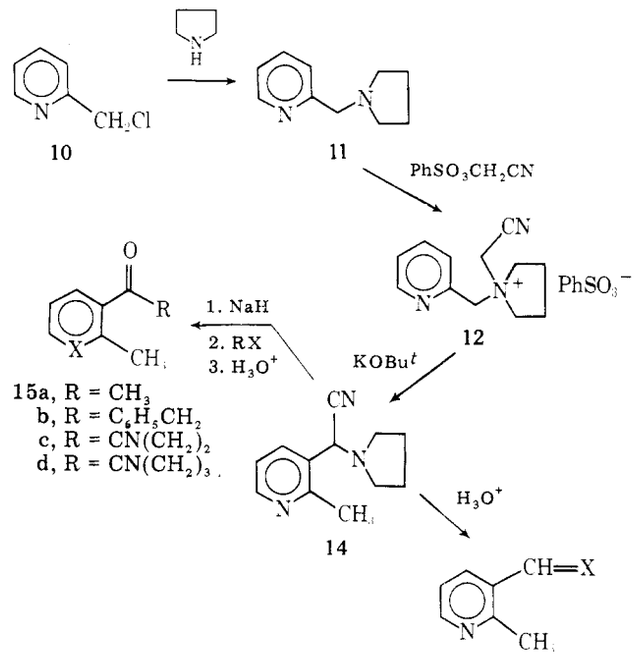
as acyl carbanion equivalents to effect alkylations. We also report the direct synthesis of the 1-methyl-2-(2-alkyl-3-pyridyl)pyrrolidine ring system using these procedures (cf. Scheme 8).

Results and Discussion

The only successful use of the Sommelet–Hauser rearrangement in pyridine chemistry is the formation of 4-dimethylaminomethyl-3-picoline (**7**) from trimethyl-3-picolylammonium chloride (**8b**).[7a] Under similar conditions, trimethyl-4-picolylammonium chloride (**8c**) gave no rearranged product and trimethyl-2-picolylammonium chloride (**8a**) gave 2-(1-dimethylaminoethyl)pyridine (**9**), the Stevens rearrangement product, in 12% yield.[7a] The existence of more than one acidic proton in **8a–c** results in the opportunity for competitive reaction pathways. Recently, Mander and Turner[8] described the [2,3] sigmatropic rearrangement of a variety of ylides derived from α-cyano amines, e.g., **5** → **4** (X = CH). This reaction appeared particularly attractive for use in the pyridine series, since the strongly electron-withdrawing cyano group should direct ylide formation away from the acidic picolyl position. Indeed, such a consideration is important for compounds having two sites bearing abstractable α-hydrogens, as is the case at hand.

Treatment of 2-chloromethylpyridine (**10**) with pyrrolidine gave 1-(2-picolyl)pyrrolidine (**11**) (93%) which could be converted to quaternary salt **12** (86%) with cyanomethyl benzenesulfonate in acetonitrile.[9] Reaction of **12** with either NaH or KOBu^t in THF–Me_2SO at −10 °C followed by acid hydrolysis gave (50%) 2-methylpyridine-3-carboxaldehyde (**13a**) isolated as its semicarbazone **13b**. Cyano amine **14**, the initial rearrangement product, was not isolated, but its formation was confirmed by the ^1H NMR spectrum of the crude reaction

Scheme I



13a, X = O
b, X = NH_2CONHN

product which exhibited three well-resolved pyridyl protons and a three-proton singlet at δ 2.65 in addition to the eight pyrrolidine protons.

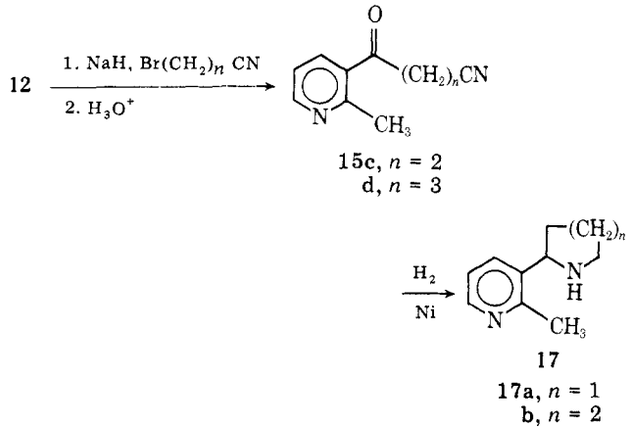
The flexibility of this reaction sequence was extended by utilizing the α-cyano amine moiety of **14** as an acyl carbanion equivalent.[10,11] Pyrrolidinium salt **12** was treated with 1 equiv of KOBu^t to bring about rearrangement as before. After the rearrangement was complete, as judged by TLC and ^1H NMR, 1 equiv of NaH or KH was added followed by 1 equiv of methyl iodide. Acid hydrolysis gave (78%) 2-methyl-3-acetylpyridine (**15a**). The corresponding benzyl ketone **15b** was obtained (87%) via alkylation with benzyl bromide (Scheme I). No evidence was obtained for pyridine nitrogen alkylation, although we have previously shown that nicotine itself is alkylated on both nitrogens when treated with methyl iodide.[5a]

Further investigation showed that the ylide formation–rearrangement–alkylation procedure could be simplified by using NaH in THF–Me_2SO to effect both rearrangement and alkylation. Thus, the pyrrolidine salt **12** was treated with 2 equiv of NaH and, after ylide formation, rearrangement, and anion formation, 3-bromopropionitrile was added. The crude reaction product after mild acid hydrolysis afforded the crystalline cyano ketone **15c** in 48% yield.

Cyano ketone **15c** is a key intermediate in the synthesis of pyridine-substituted nicotinoids, since the reductive cyclization of 3-pyridyl 2-cyanoethyl ketone (**16**) has been shown to yield myosmine and nornicotine, depending on reaction conditions.[10] Thus, hydrogenation of **15c** over Raney nickel in ethanol saturated with ammonia (Scheme II) led to a single product which was purified by distillation. This material, obtained in 36% overall yield from **11**, was identified as 2-methylnornicotine (**17a**) on the basis of spectroscopic and elemental analyses. The synthesis of 2-methylanabasine (**17b**) was accomplished in a similar fashion by the reductive cyclization of 2-methyl-3-pyridyl 3-cyanopropyl ketone (**15d**) obtained via alkylation of the rearranged cyanoamine **14** with 4-bromobutyronitrile.

Synthesis of 2-Ethyl 3-Substituted Pyridines. Pyridine-2-carboxaldehyde (**19**) was converted to α-cyano-α-(1-pyrrolidinyl)-2-picoline (**20**) (58%) by treatment with po-

Scheme II

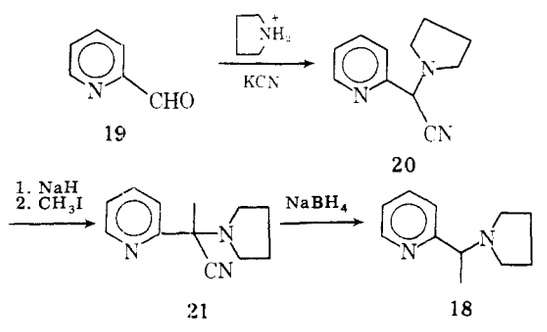


tassium cyanide and pyrrolidinium perchlorate. Methylation of **20** using NaH and methyl iodide gave **21,** which was converted to α-methyl-α-(1-pyrrolidinyl)-2-picoline **18** by reduction with $NaBH_4$ in ethanol (Scheme III).[12] The ^1H NMR spectrum of **18** exhibited a complex pair of multiplets for the pyrrolidine ring, a doublet and a quartet for the methyl and methine protons, and the normal splitting pattern of a 2-substituted pyridine.

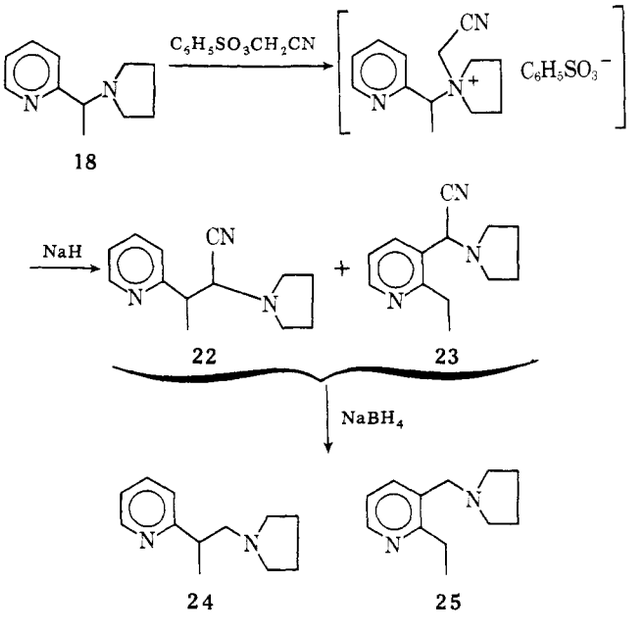
In contrast to the cyanomethylation of **11,** treatment of **18** with cyanomethyl benzenesulfonate did not give a crystalline product. Quaternization in Me_2SO or CH_3CN was followed by ^1H NMR. After salt formation was complete, the reaction mixture was exhaustively extracted with ether and the resulting product treated with NaH in THF–Me_2SO. The rearrangement was monitored by following the disappearance of the pyrrolidinium salt by TLC. Instead of obtaining a single product, however, two products were observed. Trituration of the crude reaction mixture with ether allowed the isolation of one of these as a crystalline material. A ^1H NMR spectrum of this substance eliminated the possibility that it was the [2,3] sigmatropic rearrangement product, in that four pyridyl protons were observed in a pattern consistent only with a 2-picoline derivative. The spectrum indicated that this material was 2-(1-pyrrolidinyl)-3-(2-pyridyl)butyronitrile (**22**), the Stevens rearrangement product. This assignment was confirmed by the remainder of the ^1H NMR spectrum which consisted of a doublet at δ 1.42 for the methyl group, a doublet at δ 4.32 for the β-hydrogen, and a doublet of quartets at δ 3.20 for the α-hydrogen. Infrared and elemental analyses and its subsequent conversion to amine **24** (see below) supported the assignment of **22.**

Identification of the second product, **23,** was accomplished subsequent to reductive decyanation of the crude product mixture with $NaBH_4$. GLC analysis of the total reduced material showed two products in about equal amounts. These two compounds were isolated by GLC and analyzed by ^1H NMR. The product of shorter retention time was found to be 1-(1-pyrrolidinyl)-2-(2-pyridyl)propane (**24**) derived via decyanation of **22.** The ^1H NMR resonances for the pyridyl protons of the longer retention-time product established it to be a 2,3-disubstituted pyridine, while the aliphatic region exhibited a triplet at δ 1.28, a quartet at δ 2.91, and a singlet at δ 3.68. This spectrum was consistent with 1-(2-ethyl-3-picolyl)pyrrolidine (**25**), the compound derived from Sommelet–Hauser rearrangement and reductive cleavage of the cyanide moiety. Identification of **25** allowed the assignment of **23** as the second rearrangement product. Thus, treatment of the quaternary salt derived from **18** with NaH led to a ca. 1:1 mixture of [2,3] sigmatropic rearrangement and [1,2] shift products (Scheme IV).

Scheme III



Scheme IV

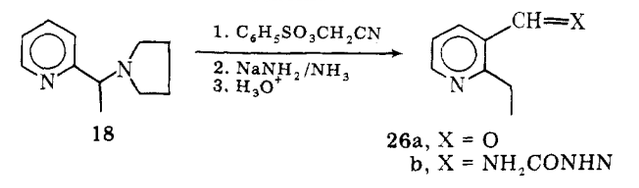


It has been shown that, where Stevens and Sommelet–Hauser rearrangements occur competitively, the use of sodium amide in liquid ammonia generally favors the latter reaction.[13] The reaction sequence **18** → **22** + **23** was repeated using sodium amide/NH_3, and the crude product was reduced with $NaBH_4$ as before. Analysis of the reduced product indicated the ratio of **25** to **24** had increased to 2:1. Other attempts to increase this ratio in favor of Sommelet–Hauser product were unsuccessful. It is worthy of note that Mander and Turner[8] observed ca. 10% phenylacetaldehyde, the Stevens reaction product, in the isomerization of **5** (X = CH, R = H), using $KOBu^t$ as the base.

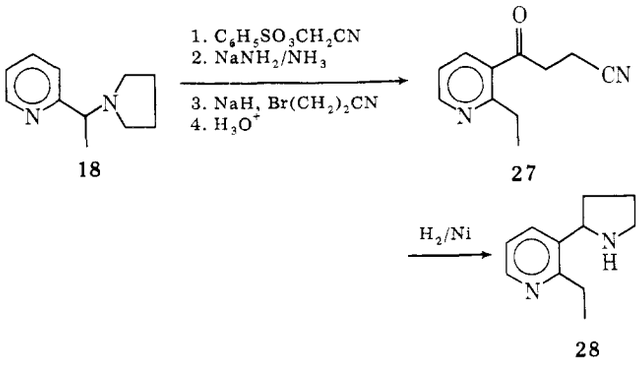
We next attempted to prepare 2-ethylpyridine-3-carboxaldehyde (**26a**). Treatment of **18** with cyanomethyl benzenesulfonate was carried out in acetonitrile. The derived salt was treated with sodium amide in liquid ammonia and the product hydrolyzed with aqueous acetic acid. The resulting crude product, which possessed an aldehyde group as shown by ^1H NMR, was treated with semicarbazide hydrochloride to give 2-ethylpyridine-3-carboxaldehyde semicarbazone (**26b**) (Scheme V). The derivative was isolated by preparative TLC and recrystallized to give a low yield (10%) of a crystalline solid which had spectral data consistent with **26b.**

The cyanomethylation of **18** was repeated, and the resulting salt was treated with sodium amide in liquid ammonia to ef-

Scheme V

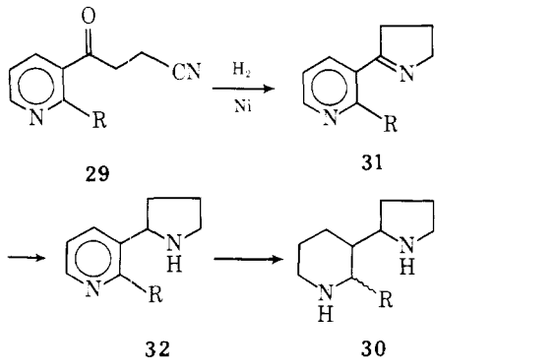


Scheme VI



18 27 28

Scheme VII



29 31 32 30

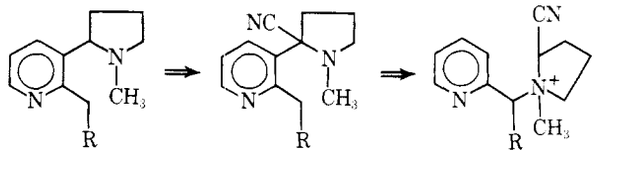
fect rearrangement, alkylated with 3-bromopropionitrile utilizing sodium hydride as the base, and hydrolyzed with aqueous acetic acid. The crude product was distilled giving a 21% yield (based on **18**) of the desired product, 2-ethyl-3-pyridyl 2-cyanoethyl ketone (**27**), as an oil of about 90% purity. The ^1H NMR spectrum exhibited a typical pattern for a 2,3-disubstituted pyridine, a pair of triplets at δ 3.23 and 2.78, and a quartet and triplet at δ 3.02 and 1.27. Hydrogenation of distilled **27** over Raney nickel gave 2-ethylnornicotine (**28**) (Scheme VI).

The reductive cyclization of **29** (R = H) must be performed with care as we have observed overreduction of the desired nornicotines to the corresponding piperidine derivatives **30.** Indeed, this sequence is somewhat problematical in that underreduction of **29** leads to mixtures of myosmine **31** (R = H) and nornicotine **32** (R = H),[10] while overreduction leads to **30** (R = H). However, we have found that for cyano ketones having substituents at C-2 of the pyridine ring (**29,** R = methyl or ethyl) the tendency for competitive pyridine reduction is not observed, presumably due to steric reasons. (Scheme VII).

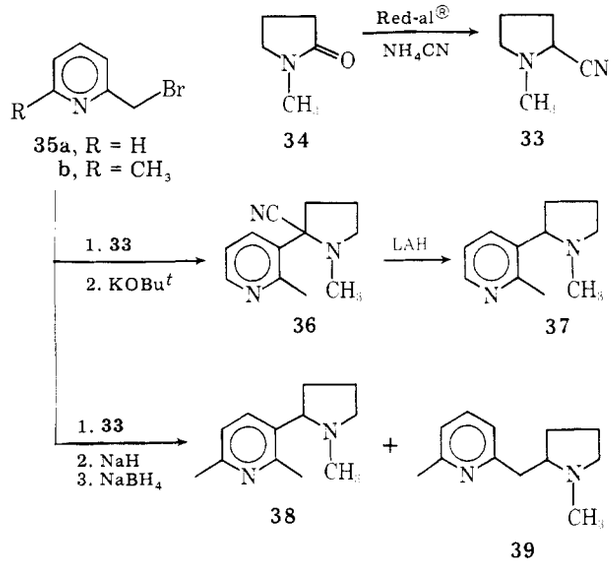
Direct Synthesis of Nicotinoids via [2,3] Pyrrolidine Rearrangement. With the now established utility of α-cyano amines as migrating moieties in the Sommelet–Hauser rearrangement and as acyl anion equivalents, an antithetical analysis for 2-alkylnicotines reveals an intriguing synthetic sequence as shown in Scheme VIII.

The required 1-methyl-2-cyanopyrrolidine (**33**) was prepared by treatment of 1-methyl-2-pyrrolidinone (**34**) with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al®)

Scheme VIII



Scheme IX



35a, R = H
b, R = CH_3

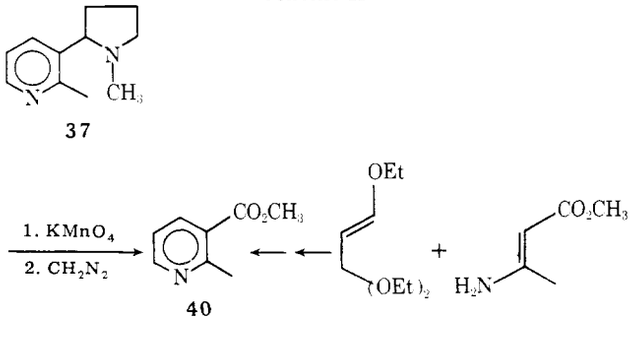
34 33 36 37 38 39

followed by aqueous ammonium cyanide (46%) (Scheme IX).[14] Reaction of **33** with 2-bromomethylpyridine (**35a**) in Me_2SO was followed by ^1H NMR until salt formation was complete. The Me_2SO solution was cooled, diluted with THF, and treated with $KOBu^t$. Rearrangement was monitored by TLC until no further salt remained. Isolation of the intermediate, 2-methyl-2′-cyanonicotine (**36**) was not pursued because of its observed lability.[14] Consequently, LAH reduction was carried out directly on the crude product after removal of Me_2SO. Distillation of the reduced product gave (20%) 2-methylnicotine (**37**). Spectral data and elemental analyses were consistent with the assigned structure. Synthesis of 2,6-dimethylnicotine (**38**) was carried out by the same procedure starting with 2-bromomethyl-6-methylpyridine (**35b**) (Scheme IX). In this case, a significant amount (~20%) of competitive Stevens rearrangement occurred to give α-(1-methyl-2-pyrrolidinyl)-2,6-dimethylpyridine (**39**).

Oxidation of 2-methylnicotine (**37**) was carried out as a further proof of its structure. Treatment of **37** with neutral aqueous $KMnO_4$ at 80 °C followed by esterification with diazomethane gave a product identical in all respects with methyl 2-methyl-3-nicotinate (**40**), prepared following a literature procedure[15] (Scheme X).

Conclusions. These procedures represent a synthetically useful methodology for the regiospecific formylation and acylation of 2-methylpyridines. The process has been extended to prepare 2-methylnicotinoids expeditiously. Of particular interest is the modification of the sequence such that the pyrrolidine ring functions initially as the amino portion of the cyano amine and ultimately as the pyrrolidine ring of the nicotinoid. Although we have thus far confined our studies to the pyrrolidine ring due to our interest in the synthesis of nicotine analogues, the reaction should also be applicable to systems containing heteroatoms other than nitrogen, such as

Scheme X



37 40

sulfur and phosphorus. The significant percentage of product due to Stevens rearrangement in the case of the acylation of 2-ethylpyridine is interesting and unfortunately detracts considerably from the reaction's synthetic utility. In that 2-picolines can be directly alkylated,[16] however, elaboration of the 2-methyl substituent can be performed at some stage following rearrangement. We have found this, in fact, to be a valid alternative, and details on this work will appear subsequently.

Experimental Section

^{1}H NMR spectra were recorded on a Varian XL-100 spectrophotometer operating at 100 MHz in the Fourier transform mode. Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. THF was distilled from LAH prior to use, and Me_2SO was distilled from CaH_2. Both solvents were stored over 4-Å molecular sieves. KOBu^t was freshly sublimed. All reactions were run under a dry N_2 atmosphere. Gas chromatography was carried out on a Bendix 2300 instrument using 5-ft 5% SE-30 on chromosorb G-HP columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(2-Picolyl)pyrrolidine (11). To a solution of 5.0 g (0.03 mol) of 2-chloromethylpyridine hydrochloride in 10 mL of Me_2SO was added 10 mL of pyrrolidine. The resulting solution was stirred for 3 h at 50 °C and then for 16 h at room temperature. The solution was diluted with ether and washed once with 50% KOH and three portions of saturated brine. The ether solution was dried (KOH) and filtered, and the solvent was removed. The residue was distilled, yielding 4.60 g (93%) of a light yellow oil: bp 57–59 °C/0.1 mm; lit.,[17] 106–8 °C/9 mm; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4, 3′,4′-H), 2.57 (m, 4, 2′,5′-H), 3.62 (s, CH_2), 7.45 (m, 3, 3,4,5-PyH), 8.62 (m, 1, 6-PyH).

1-Cyanomethyl-1-(2-picolyl)pyrrolidinium Benzenesulfonate (12). To 20.0 g (0.124 mol) of **11** in 100 mL of acetonitrile was added 1 equiv of cyanomethyl benzenesulfonate in 50 mL of acetonitrile at 25 °C with cooling. The reaction was stirred at room temperature for 18 h, and the acetonitrile was removed under reduced pressure. THF was added, and the product was collected by filtration and washed with THF and ether. After air drying, 38.5 g (86%) of colorless crystals was obtained: mp 118.5–120 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.17 (m, 4, pyrrolidine), 3.82 (m, 4, pyrrolidine), 4.82 (s, 2, $ArCH_2N$), 4.95 (s, 2, NCH_2CN), 6.59 (m, 8, aromatic), 7.59 (m, 1, pyridine).

Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.40; H, 5.89; N, 11.72; S, 8.82.

2-Methylpyridine-3-carboxaldehyde Semicarbazone (13b). A solution of 718 mg (2 mmol) of **12** in 6 mL of Me_2SO and 30 mL of THF was cooled to −10 °C and treated with 280 mg (2.5 mmol) of KOBu^t. The reaction mixture was stirred for 3 h and the bulk of the THF removed at the water pump at about 40 °C under reduced pressure. The residue was diluted with ice water and CH_2Cl_2, and 2.3 g of KOH was added. The basic solution was extracted with three portions of CH_2Cl_2. The organic extracts were combined, washed with saturated brine and dried (Na_2SO_4). Filtration followed by removal of the solvent gave 746 mg of a tan oil which was dissolved in 16 mL of THF and treated with an equal volume of 30% aqueous oxalic acid at reflux for 15 min. The THF was removed under reduced pressure and the aqueous solution neutralized with a slurry of 11 g of $NaHCO_3$ in ice water. The solution was extracted with two portions of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4). Filtration of the solution and evaporation of the solvent gave 231 mg of a dark brown oil. The major product was identified as **13a** from the ^{1}H NMR spectrum of the crude product. The product was dissolved in EtOH and treated with an aqueous solution of NaOAc and semicarbazide hydrochloride. Filtration of the solution gave 142 mg (31%) of **13b** as colorless crystals, mp 218–219 °C, lit.[15] 209 °C.

2-Methyl-3-acetylpyridine (15a). A solution of 1.48 g (4.15 mmol) **12** in 10 mL of Me_2SO was cooled to −10 °C and treated with 580 mg (5.2 mmol) of KOBu^t. The reaction mixture was stirred for 30 min at −10 °C and for an additional 30 min at room temperature. The mixture was cooled to −10 °C, and 740 mg (4.6 mmol) of a 25% dispersion of KH was added. The cooling bath was removed and the reaction mixture was stirred for 15 min and for an additional 15 min under reflux to ensure complete anion formation. The solution was then cooled to −10 °C and treated with 705 mg (5.0 mmol) of MeI. After addition of MeI was complete, the mixture was stirred at room temperature for 1 h and under reflux for 30 min. The reaction mixture was cooled and distributed between ether and a mixture of 50% KOH and saturated brine. The aqueous phase was extracted with ether, and the ether extracts were combined and washed once with saturated brine. The ether solution was dried ($CaSO_4$) and filtered, and the solvent was removed. The residual oil was treated with 6 mL of acetic acid, 3 mL of water, and 1 mL of THF. The solution was heated at 53 °C for 24 h, cooled, and treated with 10 g of K_2CO_3. Water was added to the basic slurry and the excess solids were removed by filtration. The filtrate was extracted with $CHCl_3$ and the $CHCl_3$ phase in turn extracted with 2 N HCl. The acidic phase was basified with solid K_2CO_3 and again extracted with $CHCl_3$. The crude product after solvent removal was distilled to give 400 mg (78.5%) of a clear liquid: bp 55–65 °C/0.05 mm; IR (neat) 1690 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3, $PyCH_3$), 2.74 (s, 3, $COCH_3$), 7.27 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.00 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.61 (dd, 1, J = 5, 2 Hz, 6-PyH). A sample of the product was treated with picric acid to give a crystalline dipicrate, mp 174–176 °C, lit. 174 °C.[18]

2-Methyl-3-phenylacetylpyridine (15b). The preparation of **15b** was accomplished using the same procedure described for the preparation of **15a**, except that NaH was used as the base and benzyl bromide served as the alkylating agent. The crude product, isolated as a crystalline solid (87%), was estimated to be 95% pure. Two recrystallizations from n-hexane gave a 37% yield of colorless crystals: mp 66–67 °C, lit.[19] 61–63 °C; IR (nm) 1695 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3, CH_3), 4.21 (s, 2, CH_2), 7.28 (m, 6, phenyl + 5-PyH), 7.99 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.61 (dd, 1, J = 5, 2, Hz, 6-PyH).

2-Methyl-2-pyridyl 2-Cyanoethyl Ketone (15c). A solution of 12.32 g (34.6 mmol) of **12** in 125 mL of Me_2SO was prepared and 290 mL of THF added. The solution was cooled to −10 °C, and 1.84 g (38.1 mmol) of a 50% NaH dispersion was added. The mixture was stirred at −5 to −10 °C for 30 min and allowed to warm to room temperature over 1.5 h. An additional 1.84 g (38.1 mmol) of NaH was added, and the mixture was heated under reflux for 30 min and then cooled to −10 °C. A solution of 5.1 g (38 mmol) of 3-bromopropionitrile in 25 mL of THF was added over a 30-min period, and the reaction was stirred for an additional 30 min, filtered, and concentrated under reduced pressure. The residue was dissolved in ether and washed three times with a saturated $NaCl$–K_2CO_3 solution. The organic phase was filtered, dried (Na_2SO_4), and concentrated to give 8.17 g of a brown oil. The crude product was hydrolyzed and isolated as described for **15a** above. Distillation (147 °C/0.1 mm) gave a yellow oil which crystallized on trituration with ether. The colorless crystals were collected and dried, giving 3.2 g (53%): mp 82–83.5 °C; IR (nm) 1675 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3, CH_3), 2.76 (t, 2, CH_2CH_2CN), 3.32 (t, 2, J = 8 Hz, CH_2CH_2CN), 7.28 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.00 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.65 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.13; H, 5.80; N, 16.13.

2-Methylnornicotine (17a). To a solution of 3.15 g (18 mmol) of **15c** in 180 mL of ethanol saturated with ammonia was added 10 g of freshly prepared Raney nickel W-2.[20] The mixture was hydrogenated in a Parr apparatus at ca. 50 psi for 15 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in hexane and dried ($CaSO_4$), filtered, concentrated, and distilled. The fraction boiling at 100–105 °C/0.175 mm was collected, giving 2.1 g (75%) of **17a:** IR (neat) 3295 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4, 3′, 4′-H), 2.53 (s, 3, CH_3), 3.10 (m, 2, 5′-H), 4.30 (t, 1, J = 7 Hz, 2′-H), 7.07 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.88 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.35 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.93; H, 8.75; N, 16.99.

2-Methylanabasine (17b). The preparation of 2-methyl-3-pyridyl 3-cyanopropyl ketone (**15d**) was carried out exactly as described for the preparation of **15c,** except that 4-bromobutyronitrile was used as the alkylating agent. The crude product was distilled (bp 140–144 °C/0.05 mm), giving (65%) a light yellow oil (**15d**) which resisted crystallization: ^{1}H NMR ($CDCl_3$) δ 2.08 (m, 2, $CH_2CH_2CH_2$), 2.54 (t, 2, J = 6 Hz, CH_2CN), 2.68 (s, 3, CH_3), 3.12 (t, 2, J = 7 Hz, $COCH_2$), 7.25 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.95 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.58 (dd, 1, J = 5, 2 Hz, 6-PyH).

A solution of 2.8 g (15 mmol) of **15d** in 150 mL of ethanol saturated with ammonia was prepared, and 10 g of freshly prepared Raney nickel W-2 was added. The mixture was hydrogenated for 20 h in a Parr apparatus at 67 psi. The reaction was worked up using the procedure outlined for **17a.** The product was isolated by distillation (108–112 °C/0.2 mm), giving 2.2 g (89%) of **17b:** IR (neat) 3290 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 5, piperidine), 2.38 (m, 3, piperidine), 3.79 (m, 2, piperidine), 2.54 (s, 3, CH_3), 7.08 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.47 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.43 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.04; H, 8.96; N, 15.81.

α-Methyl-α-(1-pyrrolidinyl)-2-picoline (18). To 25.0 g (133.5 mmol) of α-cyano-α-(1-pyrrolidinyl)-2-picoline (**20**), prepared by the reaction of pyridine-2-carboxaldehyde (**19**) with KCN and pyrrolidinium perchlorate,[21] in 75 mL of Me_2SO and 200 mL of THF was added 7.75 g (161 mmol) of NaH dispersion at −10 °C. The reaction mixture was stirred until no further gas evolution was noted, at which time 22.84 g (161 mmol) of MeI in 10 mL of THF was added over 10 min. After addition was complete, the reaction mixture was filtered and the precipitate washed with CH_2Cl_2. The filtrates were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give 24.75 g (92%) of crude product, α-cyano-α-methyl-α-(1-pyrrolidinyl)-2-picoline (**21**). The total crude nitrile was dissolved in 500 mL of 95% ethanol, cooled to 5 °C, and treated with 9.3 g (245 mmol) of $NaBH_4$. The reaction mixture was stirred at room temperature for 20 h, filtered, and rotary evaporated, giving a tan oil which was dissolved in hexane and dried (Na_2SO_4). The crude product was distilled (78–80 °C/0.2 mm), yielding 20.77 g (88%) of **18:** ^1H NMR ($CDCl_3$) δ 1.43 (d, 3, J = 6.5 Hz, CH_3), 1.77 (m, 4, 3′,4′-H), 2.50 (m, 4, 2′,5′-H), 3.44 (q, 1, J = 6.5 Hz, CH), 7.33 (m, 3, 3,4,5-PyH), 8.55 (m, 1, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.93; H, 9.23; N, 15.81.

Attempted Rearrangement of 18. A solution of 1.76 g (10 mmol) of **18** and 2.17 g (10.3 mmol) of cyanomethyl toluenesulfonate in 25 mL of Me_2SO was stirred overnight at room temperature and then at 45 °C for 2.5 h. The solution was cooled to −10 °C and 75 mL of THF and 602 mg (12.5 mmol) of 50% NaH dispersion were added. The reaction mixture was stirred at −10 °C for 2.5 h and then at room temperature overnight. Ether was added to precipitate the salts, the mixture was filtered, and solvent was removed in vacuo. A TLC of the crude product showed two major products. The residue was dissolved in ether and extracted into 2 N HCl, the acid solution was basified, and the aqueous solution was extracted with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated to give a brown oil which crystallized on trituration with ether. The solid was collected by filtration to give 135 mg (5%) of product, mp 109–112 °C, showing a single spot on TLC, corresponding to one of the major products in the reaction mixture. This product was identified as 2-(1-pyrrolidinyl)-3-(2-pyridyl)butyronitrile (**22**) on the basis of its spectral data: IR (nm) 2220 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 1.44 (d, 3, J = 7 Hz, CH_3), 1.65 (m, 4, 3′,4′-H), 2.60 (m, 4, 2′,5′-H), 3.12 (m, 1, CH_3CH), 4.32 (d, 1, J = 10 Hz, CNCH), 7.11 (m, 2, 3,5-PyH), 7.55 (m, 1,4-PyH), 8.52 (m, 1, 6-PyH).

Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.43; H, 8.06; N, 19.41.

Treatment of **18** with cyanomethyl toluenesulfonate followed by reaction with NaH was repeated as above. The crude product was isolated, dissolved in 35 mL of 95% EtOH, treated with an excess of $NaBH_4$, and stirred overnight. The mixture was filtered and concentrated. The residue was dissolved in ether and extracted with 2 N HCl. The acid solution was washed with ether, basified, and extracted with ether. The ether extracts were combined, dried (Na_2SO_4), and filtered, and the solvent was removed. Distillation of the residue gave 1.02 g of a colorless oil which was shown to be a 1:1 mixture of two components by GLC. The substance with shorter retention time was identified as 1-(1-pyrrolidinyl)-2-(2-pyridyl)propane (**24**): ^1H NMR ($CDCl_3$) δ 1.33 (d, 3, J = 7 Hz, CH_3), 1.74 (m, 4, 3′,4′-H), 2.52 (m, 4, 2′,5′-H), 2.80 (d, 2, J = 7 Hz, CH_2), 3.14 (m, 1, CH), 7.14 (m, 2, 3,5-PyH), 7.60 (m, 1, 4-PyH), 8.56 (m, 1, 6-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.69; H, 9.45; N, 15.02.

The second substance was identified as 1-(2-ethyl-3-picolyl)pyrrolidine (**25**): ^1H NMR ($CDCl_3$) δ 1.29 (t, 3, J = 8 Hz, CH_3), 2.72 (m, 4, 3′,4′-H), 2.59 (m, 4, 2′,5′-H), 2.92 (q, 2 H, J = 8 Hz, CH_3CH_2), 3.59 (s, 2, NCH_2), 7.10 (dd, 1, J = 8, 6 Hz, 5-PyH), 7.73 (dd, 1, J = 8, 1 Hz, 4-PyH), 8.46 (dd, 1, J = 6, 1 Hz, 6-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54, N, 14.72. Found: C, 75.91; H, 9.67; N, 14.59.

2-Ethylpyridine-3-carboxaldehyde Semicarbazone (26b). A solution of 1.00 g (5.67 mmol) of **18** in 3 mL of MeCN was cooled to 0 °C and treated with 1.12 g (5.67 mmol) of cyanomethyl benzenesulfonate in 3 mL of MeCN. The solution was stirred for 1 h at 0 °C and then for 11 days at room temperature. The solution was transferred to a 100-mL three-necked flask, and the solvent was removed in vacuo. About 50 mL of ammonia was condensed into the flask, the temperature was adjusted to −40 °C, and the mixture was stirred until a homogeneous solution resulted. The solution was treated with 280 mg (7.18 mmol) of $NaNH_2$, and the reaction mixture was stirred under reflux for 3 h. The ammonia was evaporated and the residue treated with a mixture of water and ether. The aqueous phase was further extracted with ether, and the ether extracts were combined, washed with aqueous KOH, and water, and dried (Na_2SO_4). The solution was filtered and concentrated, and the resulting crude product was hydrolyzed as before, using 6 mL of acetic acid, 3 mL of water, and 1 mL of THF to give a dark brown oil which showed two major components on TLC. An NMR spectrum of the crude product established the presence of an aldehyde. Treatment of the crude product with an aqueous solution of semicarbazide hydrochloride and NaOAc followed by preparative TLC ($CHCl_3$/EtOH/NH_4OH, 85:14:1) gave the crystalline semicarbazone. Recrystallization (H_2O) gave 110 mg (10%) of colorless **26b:** mp 176–177 °C; IR (nm) 1700 cm^{-1} (C=O); ^1H NMR (Acetone-d_6, 50 °C) δ 1.21 (t, 3, J = 7 Hz, CH_3), 2.07 (q, 2 H, J = 7 Hz, CH_2), 6.83 (s, 2, NH_2), 7.13 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.17 (s, 1, CH), 8.27 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.42 (dd, 1, J = 5, 2 Hz, 6-PyH), 10.17 (s, 1, NH).

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.23, H, 6.29; N, 29.15. Found: C, 56.54; H, 6.33; N, 29.07.

2-Ethylnornicotine (28). To 5.0 g (28.4 mmol) of **18** in 30 mL of MeCN was added 5.6 g (28.4 mmol) of cyanomethyl benzenesulfonate. The mixture was allowed to stand 3 days at room temperature, the solvent was removed, and the residue was subjected to continuous ether extraction. The resulting ether-insoluble material after drying was dissolved in 250 mL of anhydrous ammonia, the temperature was adjusted to −40 °C, and the mixture was stirred until homogeneous. The reaction mixture was treated with 1.45 g (37.2 mmol) of $NaNH_2$, stirred for 4 h at −40 °C, and allowed to warm to room temperature. Ether was added to the residue, and the resulting solution was washed with saturated brine, dried (Na_2SO_4), and concentrated to give 4.88 g of a tan oil. The oil was dissolved in 70 mL of Me_2SO and 300 mL of THF to which 1.48 g (30.8 mmol) of 50% NaH dispersion was added. The mixture was heated under reflux for 30 min and then cooled to −10 °C. A solution of 3.64 g (27.2 mmol) of 3-bromopropionitrile in 10 mL of THF was added over a 15-min period. After stirring for 1 h at room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in ether, washed with 10% K_2CO_3 and saturated brine, dried (Na_2SO_4), and concentrated to give 3.78 g of a tan oil. Hydrolysis as before using 30 mL of acetic acid, 15 mL of water, and 5 mL of THF followed by distillation (150–5 °C/0.05 mm) gave 1.1 g (21%) of **27:** ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 3.05 (m, 6), 7.25 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.95 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.63 (dd, 1, J = 5, 2 Hz, 6-PyH). A 500-mg (2.6 mmol) sample of **27** and 10 g of Raney nickel in 100 mL of EtOH saturated with ammonia was hydrogenated in a Parr apparatus at about 60 psi for 20 h and worked up as before. Isolation by preparative TLC ($CHCl_3$/EtOH/NH_4OH, 85:14:1) gave 125 mg (28%) of **28** as a light yellow oil. An analytical sample was obtained by preparative GLC: IR (neat) 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, J = 8 Hz, CH_2CH_3), 1.94 (m, 5, NH, 3′,4′-H), 2.88 (q, 2, J = 8 Hz, CH_2CH_3), 3.08 (m, 2, 5′-H), 4.37 (t, 1, J = 7 Hz, 2′-H), 7.40 (dd, 1, J = 6, 5 Hz, 5-PyH), 7.88 (dd, 1, J = 6, 2 Hz, 4-PyH), 8.12 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.07; H, 9.25; N, 16.01.

1-Methyl-2-cyanopyrrolidine (33). A solution of 75 g (0.76 mol) of 1-methyl-2-pyrrolidinone (**34**) in 900 mL of THF was cooled to 0 °C, and 117 mL (0.404 mol) of 70% Red-Al® solution was added over a 1-h period maintaining the temperature between −10 and 0 °C. After stirring for an additional hour at 0 °C and 1.5 h at room temperature, the solution was cooled to 10 °C and an ice-cold solution of 74.5 g (1.52 mol) of NaCN and 80.7 g (1.52 mol) of NH_4Cl in 625 mL of water was added. The mixture was stirred overnight at room temperature and heated under reflux for 30 min, and the organic phase was separated. The aqueous phase was filtered and extracted with two 200-mL portions of ether, and the combined organic extracts were washed with base. The ether solution was chilled and extracted with 1 equiv of ice-cold dilute HCl in two portions. The acidic phase, after washing with ether, was basified at <5 °C by addition to a 50% KOH solution, and the basic solution was extracted with ether. The ether extract was washed with saturated brine, dried (Na_2SO_4), concentrated, and distilled to give 38.26 g (46%) of a colorless oil: bp 79–82 °C/12 mm; lit.[22] 68–71 °C/12 mm; IR ($CHCl_3$) 2230, 2250 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 2.07 (m, 4, 3,4-H), 2.48 (s, 3, CH_3(= 2/75 (m, 2, NCH_2), 3.68 (t, 1, J = 5 Hz, CHCN).

2-Methylnicotine (37). An ethereal solution of 2-bromomethylpyridine (**35a**), obtained by treating 9.0 g (35.6 mmol) of 2-bromomethylpyridine hydrobromide with aqueous $NaHCO_3$, was added to 4.30 g (39 mmol) of 1-methyl-2-cyanopyrrolidine (**33**) in 100 mL of Me_2SO. The ether was removed at reduced pressure, and the solution was stirred at room temperature for 24 h. To the resulting solution was added 500 mL of THF and, after cooling to 20 °C, 4.0 g (35.8

mmol) of KOBu^t. The reaction mixture was stirred for 5 h at −20 °C, after which the solvents were removed under high vacuum at <50 °C. The residue was distributed between ether and ice water and the aqueous phase further extracted with ether. The combined extracts were washed with saturated brine and base, and dried (Na_2SO_4). The ethereal solution containing 3.74 g of a brown oil was adjusted to a volume of 60 mL and added to a slurry of 1.41 g (37 mmol) of LAH in 120 mL of ether maintained at 0 °C. The solution was stirred at 0 °C for 30 min, heated under reflux for 3 h, cooled to 0 °C, treated dropwise with 15 mL of saturated K_2CO_3, and again heated under reflux for 30 min. The mixture was filtered and the filtrate extracted with two 10-mL portions of 20% aqueous acetic acid. The combined acid extracts were basified and extracted with ether, and the combined ether extracts were washed with saturated brine and dried (Na_2SO_4). The solvent was removed and the residue was distilled (56–59 °C/0.1 mm), giving 1.22 g (19.5%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3, NCH_3), 2.58 (s, 3, $PyCH_3$), 3.32 (m, 2, 2′,5′$_{cis}$-H), 7.16 (dd, 1, J = 8, 6 Hz, 5-PyH), 7.87 (dd, 1, J = 8, 1 Hz, 4-PyH), 8.39 (dd, 1, J = 6, 1 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.04; H, 9.06; N, 15.68.

Oxidation of 2-Methylnicotine (37). A suspension of 55.6 mg (0.312 mmol) of 2-methylnicotine (**37**) in 55 mL of water was treated with small portions of $KMnO_4$ at 80 °C until no further oxidation was evident. The suspension was filtered, and the filtrate was acidified (HCl) and concentrated to dryness in vacuo. The residue was dissolved in a minimum amount of methanol, ten drops of diethylamine was added, and the solution was added to an etheral solution containing a slight excess of diazomethane. The solvent was removed, the residue was taken up in ether, and the solution was filtered and dried (Na_2SO_4). The resulting solution contained a single major product as shown by both GLC and TLC, which was identical in all respects to a sample of methyl 2-methylnicotinate (**40**) prepared by the method of Dornow and Bormann.[15]

2,6-Dimethylnicotine (38). To a solution of 22.09 g (82.7 mmol) of 2-bromomethyl-6-methylpyridine hydrobromide (**35b**) in 40 mL of water was added 40 mL of CH_2Cl_2 and 6.95 g (82.7 mmol) of $NaHCO_3$ at 0 °C. The organic portion was separated and the aqueous solution extracted with three portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated to ca. 35 mL, diluted with 50 mL of THF, again concentrated to ca. 35 mL, and then treated with a solution of 10 g (91 mmol) of 1-methyl-2-cyanopyrrolidine (**33**) in 100 mL of Me_2SO. After stirring overnight at room temperature, the Me_2SO was removed in vacuo to give a viscous yellow oil which was dissolved in 100 mL of Me_2SO and 500 mL of THF, cooled to −10 °C, and treated with 4.5 g (94 mmol) of a 50% NaH dispersion. The reaction mixture was stirred for 3.5 h at 0 °C, 16 h at room temperature, filtered, and concentrated in vacuo. The resulting oil was dissolved in ether, filtered to clarify, washed with basic saturated brine, and dried (Na_2SO_4). Removal of solvent gave 14.96 g of crude product which was dissolved in 300 mL of 95% EtOH and 4.7 g (124 mmol) of $NaBH_4$ was added. After stirring at 0 °C for 1 h and at room temperature for 2 h, the mixture was filtered, and the insolubles were washed with ethanol and ether. The combined filtrates were concentrated, and the residue was taken up in ether and filtered. The ether solution was extracted with 20% acetic acid, and the acid solution after washing with ether was treated with 11 mL of concentrated HCl and rotary evaporated. The residue was treated with base and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 12.88 g of a crude product which was distilled. The fraction boiling from 88–135 °C/0.25 mm was collected, giving 6.2 g of a colorless oil which was chromatographed on 200 g of basic alumina, activity grade I. Elution with 2% ethyl acetate in hexane gave 4.6 g of an oil which was distilled (63–64 °C/0.05 mm), yielding 3.8 g (25%) of pure **38**: ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 5, 3′,4′,5′$_{trans}$-H), 2.15 (s, 3, NCH_3), 2.48 (s, 3, $PyCH_3$), 2.51 (s, 3, $PyCH_3$), 3.28 (t, 2, J = 8 Hz, 2′,5′$_{cis}$-H), 6.99 (d, 1, J = 9 Hz, 5-PyH), 7.81 (d, 1, J = 9 Hz, 4-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.61; H, 9.62; N, 14.64.

Further elution of the column with 10–50% ethyl acetate in hexane gave 560 mg (~4%) of a light yellow oil which was essentially a single product. Analytical data obtained on a GLC trapped sample were consistent with α-(1-methyl-2-pyrrolidinyl)-2,6-dimethylpyridine (**39**): ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4, 3′,4′-H), 2.39 (s, 3, NCH_3), 2.52 (s, 3, $PyCH_3$), 2.65 (m, 2, CH_2), 3.14 (m, 2, 2′,5′$_{cis}$-H), 6.97 (m, 2, 3,5-PyH), 7.57 (AB q, 1, J = 8, 8 Hz, 4-PyH).

The compound was converted to the dipicrate in EtOH and recrystallized from water, mp 193–194 °C.

Anal. Calcd. for $C_{24}H_{24}N_8O_{14}$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.54; H, 3.58; N, 17.43.

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Registry No.—**10** HCl, 6959-47-3; **11,** 60032-62-4; **12,** 60032-56-6; **13a,** 60032-57-7; **13b,** 60032-58-8; **14,** 64114-17-6; **15a,** 1721-12-6; **15b,** 31251-53-3; **15c,** 60032-59-9; **15d,** 64114-18-7; **17a,** 64114-19-8; **17b,** 64114-20-1; **18,** 60032-60-2; **19,** 1121-60-4; **20,** 56752-65-9; **21,** 64114-21-2; **22,** 64114-22-3; **23,** 64114-23-4; **24,** 64114-24-5; **25,** 64114-25-6; **26a,** 64114-26-7; **26b,** 60032-61-3; **27,** 64114-27-8; **28,** 64114-28-9; **33,** 20297-37-4; **34,** 872-50-4; **35a,** 55401-97-3; **35a** HBr, 31106-82-8; **35b** HBr, 64114-29-0; **36,** 64114-30-3; **37,** 64114-31-4; **38,** 64114-12-1; **39,** 64114-13-2; **39,** dipricrate, 64114-14-3; pyrrolidine, 123-75-1; cyanomethyl benzenesulfonate, 10531-13-2; methyl iodide, 74-88-4; benzyl bromide, 100-39-0; 3-bromopropionitrile, 2417-90-5, 4-bromobutyronitrile, 5332-06-9; pyrrolidinium perchlorate, 22401-44-1; cyanomethyl toluenesulfonate, 14562-04-0.

References and Notes

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