terial was collected, washed with ethanol, and recrystallized from pyridine–water to give product: mp 229–232°; $\lambda_{max}^{dioxane}$ 265, 325, 339 mμ ($\epsilon \times 10^{-4}$ 9.23, 1.62, 1.68).

Anal. Calcd for $C_{30}H_{22}N_4O_2S_2$: C, 67.41; H, 4.15; N, 10.48. Found: C, 67.42; H, 3.99; N, 10.20.

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Registry No.—**2**, 6483-99-4; **3**, 13116-83-1; **4**, 13116-84-2; **5**, 13116-85-3; **6**, 13116-86-4; **7**, 13116-87-5; **8**, 13135-41-6; **9**, 13116-88-6; **10**, 13116-89-7; **11**, 13116-90-0; **12**, 13116-91-1; **13**, 13116-92-2; **14**, 13116-93-3; **16**, 13116-94-4.

Acylation and Other Reactions of 2- and 4-Pyridylacetonitriles[1]

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A study of the acylation reactions of 2- and 4-pyridylacetonitriles has shown that (a) the product from cold or hot acetic anhydride and 2-pyridylacetonitrile is the C-acetyl derivative **3**, (b) the product from cold acetic anhydride and 4-pyridylacetonitrile is the N-acetyl derivative **9**, (c) the product from hot acetic anhydride and 4-pyridylacetonitrile is the C,N-diacetyl derivative **10**, and (d) the C,N-diacetyl derivative **10** is convertible to the C-acetyl derivative **11** by alcoholysis. Alkylation of the C-acetyl compounds yields the O-alkyl derivative from **3** and the N-methyl derivative from **11**. In addition to the acylation reactions, the dimerization reaction and Knoevenagel reaction were carried out with 2-pyridylacetonitrile and the structures of the products were established.

As part of a program directed to a study of the intramolecular catalysis of α-carbanion formation some of the reactions of 2-pyridylacetonitrile and 4-pyridylacetonitrile have been investigated. Although these reactions failed to yield the desired catalysts they are, nevertheless, of some general interest.

2-Pyridylacetonitrile (**1**), which has been described previously,[3–9] was prepared by the action of cyanide on 2-chloromethylpyridine.[4,5,7–9] Although its structure appeared to be secure, a further confirmation was prompted by the recent observation[10] that 2-chloromethyl-3-benzylimidazole undergoes an SN2′, reaction with cyanide to yield 2-methyl-3-benzyl-4-cyanoimidazole. Evidence that the assigned structure is correct has been provided by an nmr spectrum which is in complete accord with 2-pyridylacetonitrile and by hydrolysis to 2-pyridylacetamide, a compound whose structure has been well established.[4,6,11] 4-Pyridylacetonitrile (**8**), also previously described,[4,7,9,12] was prepared by dehydration of 4-pyridylacetamide[13] or by the action of cyanide on 4-chloromethylpyridine.[7,9,12]

Reactions of 2-Pyridylacetonitrile.—When 2-pyridylacetonitrile (**1**) is heated with ethanolic sodium ethoxide it is converted to a solid material which possesses an elemental analysis identical with that of the starting material, a molecular weight twice that of the starting material, and spectral characteristics that are best accommodated by a dimer of structure **2** (presumably **2B** is the tautomer present in larger amount). The infrared spectrum of this compound contains bands characteristic for a nonhydrogen-bonded N–H as well as a hydrogen-bonded N–H,[14a] a band characteristic for a conjugated nitrile,[14b] and a band associated with an olefinic moiety;[14c] the nmr spectrum shows a two-proton singlet for the $PyC\mathit{H}_2C$ group,[15a] a six-proton multiplet for the pyridine H_3, H_4, and H_5, a two-proton multiplet for the pyridine H_6,[15b] and resonances at 3.33 and 3.5–3.8 ppm corresponding to almost two protons and possibly arising from N–H;[15c] the ultraviolet spectrum has the longest wavelength band at 320–324 mμ commensurate with a β-(2-pyridyl)vinylamine structure.[16]

Treatment of 2-pyridylacetonitrile with acetic anhydride–acetic acid yields a $C_9H_8N_2O$ compound as a pale yellow solid which is soluble in dilute acid and base.

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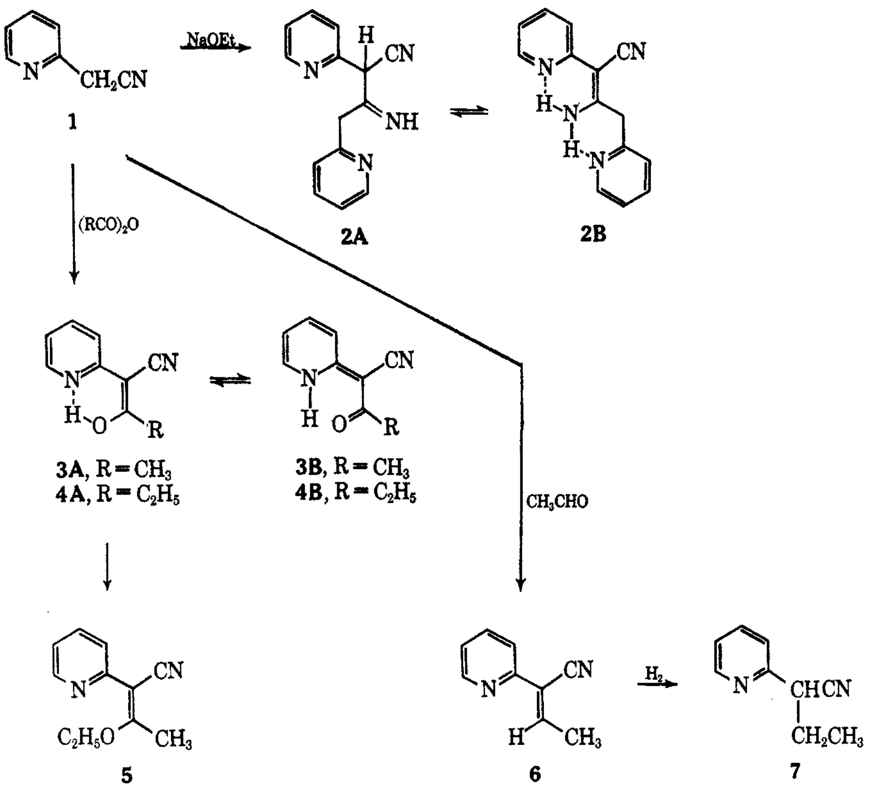
(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958: (a) p 248; (b) p 263; (c) p 34; (d) p 96; (e) p 132; (f) p 203; (g) p 125.

(15) (a) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery ("NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962–1963) report that $PyC\mathit{N}_2CONH_2$ (Spectrum No. 159) has a resonance at 3.72 ppm. (b) Bhacca, *et al.*,[15a] report that the spectra of pyridine (No. 96), 2-vinylpyridine (No. 154), and 2-pyridylacetamide (No. 159) show that the pyridine H_3 resonance occurs at 7.0–7.3 ppm, the pyridine H_4 resonance at 7.55–7.65 ppm, the pyridine H_5 resonance at 7.0–7.2 ppm, and the pyridine H_6 resonance at 8.5–8.6 ppm. (c) N–H resonances show a wide variation with respect to position and sharpness; a compound with certain structural similarities to **2B** is $NH_2C(CH_3)H{=}CHCO_2CH_3$ (ref 15a, No. 442), which possesses an extremely broad and barely discernible N–H resonance at *ca.* 6 ppm. (d) Bhacca, *et al.*,[15a] report that $C\mathit{H}_3COCH_2CONHC_6H_5$ (No. 256) has a resonance at 2.17 ppm, and $C\mathit{H}_3C({=}C)OCOCH_3$ (No. 175) has a resonance at 1.98 ppm. (e) Bhacca, *et al.*,[15a] report that $C\mathit{H}_3COCl$ (index) has a resonance at 2.67 ppm. (f) The chelated H in acetylacetone has a resonance near 15.5 ppm (L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 70).

(16) 1,2-Dihydronaphthalene absorbs at 259 mμ (ε 9449) and 3-methoxy-1,2-dihydronaphthalene absorbs at 272 mμ (ε 26,300) (W. Hückel, E. Vevera, and U. Wörffel, *Chem. Ber.*, **90**, 901 (1957)). A qualitatively similar and possibly quantitatively greater difference might be anticipated between 2-vinylpyridine which absorbs at 282 mμ (ε 7150) and a β-aminovinylpyridine (*e.g.* **2B**, that absorbs at 324 mμ (ε 18,100)).

SCHEME I



It forms an unstable hydrochloride, consumes 2 mole equiv of sodium hydroxide with the release of ammonia, rapidly decolorizes bromine in chloroform, rapidly decolorizes potassium permanganate in aqueous sodium carbonate, gives a deep blue-violet color with alcoholic ferric chloride, but fails to give a haloform test or form a carbonyl derivative. The infrared spectrum shows bands characteristic for a N···H–O structure,[14d] a conjugated nitrile,[14b] and an enol moiety;[14e] the nmr spectrum shows resonances characteristic for the pyridine ring,[15b] a methyl group attached to a completely substituted carbon,[15d] and a hydrogen involved in a chelate structure.[15f] Spectrophotometric determination indicates the compound to have a pK_A of 9.73. Undoubtedly, the compound possesses a second pK_A between 1 and 2 (see compound **11**), but it undergoes decomposition too rapidly in solutions of this acidity to allow this determination. These data are best accommodated by the structure **3A**, although the ultraviolet spectrum under certain conditions is not entirely commensurate with this formulation. Although spectra taken in aqueous base or in cyclohexane show a strong absorption at 312 mμ (a weak absorption at 377 mμ is also observed in cyclohexane solution) in accordance with that anticipated for the PyC=CO system present in **3A**, spectra taken in aqueous acid or in methanol show a strong absorption near 360 mμ suggestive of structure **3B** in which a longer system of conjugation is present. Apparently the position of the tautomeric equilibrium between **3A** and **3B** is rather sensitive to the pH of the solution and to the solvating capacities of the solvent; the preferential existence of **3B** in methanol suggests that this is the more polar of the two tautomers. Treatment of the silver salt of **3** with ethyl iodide yields an ethyl derivative for which the ultraviolet spectrum (intense band at 287 mμ; weak band at 362 mμ) and the nmr spectrum (bands characteristic for the pyridine ring) support the O-alkyl structure **5**. In a fashion comparable to that of acetic anhydride, propionic anhydride reacts with 2-pyridylacetonitrile to yield the next higher homolog **4**.

When heated with acetaldehyde and a base, 2-pyridylacetonitrile undergoes the expected Knoevenagel reaction to yield a compound which has an elemental analysis compatible with a $C_9H_8N_2$ formula, an infrared spectrum characteristic for an α,β-unsaturated nitrile,[14b] an nmr spectrum indicating the presence of a pyridine ring,[15b] and an ultraviolet spectrum characteristic for a vinylpyridine.[16] Commensurate with these data is the structure 2-(2′-pyridyl)-2-butenonitrile (**6**). Upon treatment with hydrogen in the presence of palladium-on-charcoal catalyst **6** undergoes smooth reduction to 2-(2′-pyridyl)butyronitrile (**7**). (See Scheme I.)

Reactions of 4-Pyridylacetonitrile.—The acetylation of 4-pyridylacetonitrile proves to be more complex than the acetylation of the 2 isomer. Whereas 2-pyridylacetonitrile reacts with acetic anhydride very slowly at room temperature, 4-pyridylacetonitrile (**8**) reacts immediately and deposits within 10 min an almost quantitative yield of yellow-orange crystals. This material, which possesses an analysis compatible with a $C_9H_8N_2O$ formula, is insoluble in aqueous sodium hydroxide, decolorizes bromine in chloroform solution, and yields an unstable hydrochloride. The infrared spectrum shows bands characteristic for a conjugated nitrile,[14b] a carbonyl group (see below), and an olefinic bond.[14c] The ultraviolet spectrum shows an intense absorption at 342 mμ indicative of a longer conjugated system than that present in a vinylpyridine.[16] The nmr spectrum shows a three-proton singlet from $CH_3C{=}O$,[15e] a one-proton singlet from H-C(CN)=, and four one-proton quartets at low field (the low-field pattern is quite different from that of compounds containing the pyridine nucleus).[15b] These data are best accommodated by the N-acetyl structure **9**, for which the resonance structures **9a**, **9b**, and **9c** are all possible contributors to the resonance hybrid. The infrared absorption at 1760 cm^{-1}, however, is more characteristic of an acylpyridinium structure[17] (*e.g.*, **9c**) than of an amide and suggests that **9c** is a relatively more important contributor than **9b**. The nonequivalence of the ring hydrogens in the nmr must be ascribed to restricted rotation around the cyanomethylidene group, as implied in resonance structures **9a** and **9b**.

When the reaction mixture of 4-pyridylacetonitrile and acetic anhydride is heated, the orange-yellow precipitate of **9** goes into solution, and a bright yellow compound crystallizes upon cooling. This material possesses an analysis compatible with a $C_{11}H_{10}N_2O_2$ compound and spectral data commensurate with structure **10**. The infrared spectrum shows bands characteristic for a conjugated nitrile,[14b] olefinic bonds,[14c] and an acylpyridinium carbonyl;[17] the ultraviolet spectrum shows intense absorption at 403 and 423 mμ indicative of an extended conjugated system; the nmr spectrum shows a six-proton pattern of resonances at high field (CH_3 protons) and a four-proton pattern of resonances at low field (ring protons). The high-field pattern, consisting of four singlets in the approximate ratio of 5:5:3:3, is interpretable as the resonances arising from the two nonequivalent methyl groups in **10A** and the two nonequivalent methyl groups in its conformer **10B** (present in unequal amounts). Although the low-field pattern consists of four broad bands without much fine structure, the positions and intensities can also be accommodated by the structures **10A** and **10B**.

Attempted recrystallization of the N,C-diacetyl compound (**10**) from 1-butanol yields a $C_9H_8N_2O$ compound as a colorless solid. The infrared spectrum of this material shows bands characteristic for an acidic H, a conjugated nitrile,[14b] and an olefinic bond;[14c] the ultraviolet spectrum, which is very similar to that of compound **4**, is pH dependent and allows the assignment of pK_A values of 8.40 and 1.76 to the compound; the nmr spectrum shows a three-proton singlet from $CH_3(O)C{=}C$, a one-proton band from an acidic H, and a four-proton unsymmetrical doublet at low field. The structure which seems to best fit these data is the C-acetyl compound **11** which, it is postulated, exists primarily in the tautomeric forms **11A** and **11B**. Conversion of **11** to a silver salt followed by treatment with methyl iodide yields a compound which is formulated as the N-methyl derivative **12** on the basis of its spectral characteristics. The infrared spectrum shows bands characteristic for an unsaturated nitrile[14b] and an unsaturated ketone;[14e] the ultraviolet spectrum shows an intense absorption at 362 mμ indicative of an extended system of conjugation (*e.g.*, a similar chromophore present in **4B**); the nmr spectrum shows a three-proton singlet from $\mathrm{C}H_3\mathrm{CO}$, a three-proton singlet from CH_3–N, and a four-proton pattern from the ring protons. (See Scheme II.)

The very appreciable water solubility of **12** also supports the N-methyl structure. The enhanced long-wavelength absorption of **3** in methanol was ascribed (see above) to the greater polarity of tautomer **3B** compared with **3A**. Alkylation of **3** yields the O-alkyl compound **5**, structurally related to the tautomer **3A**, and this compound is essentially water insoluble. Alkylation of **11**, on the other hand, yields the N-alkyl compound **12**, which is structurally related to the tautomer **11B**, and which, in accord with the polar solvent solubilities imputed to **3A** and **3B**, would be expected to be more water soluble than the O-alkyl compound.

Experimental Section[18]

2-Pyridylacetonitrile (**1**) was obtained as a colorless liquid: bp 124–127° (15 mm) (lit.[9] 118–120° (13 mm)), $\tilde{\nu}^{\text{liq}}$ (in cm^{-1}) 3100 (C–H), 3000 (C–H), 2280 (CN), 1585 (pyridine), 1565 (pyridine); nmr (CCl_4 in ppm) two-proton singlet at 3.91 ($\mathrm{C}H_2\mathrm{CN}$), three-proton multiplet at 7.05–7.81 (PyH_3, H_4, H_5), one-proton doublet at 8.47 (PyH_6).

As a check on the identity of this material, a solution of 5 g in 40 ml of water was treated with 10 g of Amberlite IRA-400 ion-exchange resin (in the base form), and the mixture was refluxed for 2 hr. The resin was removed by filtration, the water was removed by evaporation, and the residue was recrystallized from benzene to yield 2-pyridylacetamide as pale yellow needles, mp 119–120° (lit.[13] mp 120–121°).

4-Pyridylacetonitrile (**8**) was obtained as a colorless solid after recrystallization from petroleum ether (bp 40–60°): mp 46–49° (lit. 52–53°,[7] *ca.* 40°,[9] 36°[12]); $\tilde{\nu}^{\text{liq}}$ (in cm^{-1}) 3100 (C–H), 3000 (C–H), 2280 (CN), 1580 (pyridine), 1550 (pyridine); nmr ($CDCl_3$ in ppm) two-proton singlet at 3.82 ($\mathrm{C}H_2\mathrm{CN}$), two-proton doublet of quartets at 7.33 and 7.22 (PyH_3, H_5), two-proton doublet of doublets at 8.64 and 8.53 (PyH_2, H_6).

Dimerization of 2-Pyridylacetonitrile.—To a gently refluxing solution of sodium ethoxide (prepared from 2.3 g of sodium and 100 ml of ethanol), a solution of 11.8 g (0.1 mole) of 2-pyridylacetonitrile in 50 ml of absolute ethanol was added dropwise over a period of 30 min. The reaction mixture was refluxed an additional 2 hr and was then worked up to yield 11.0 g (96%) of crude material which, after recrystallization from methanol, gave **3-amino-2,4-di(2′-pyridyl)-2-butenonitrile** (**2B**) as colorless needles: mp 124–126°; $\tilde{\nu}^{\text{CHCl}_3}$ (in cm^{-1}), 3500 (N–H), 3320 (N–H···N), 2100 (C–H), 2205 (C═CCN), 1610 (C═C), 1580 (pyridine); $\lambda_{\text{max}}^{\text{aq HCl}}$ (ϵ) 250 mμ (shoulder) (10,400), 265 (12,200), 280 (shoulder) (10,400), 320 (12,300); $\lambda_{\text{max}}^{\text{aq NaOH}}$ (ϵ) 245 mμ (9300), 286 (11,900), 324 (18,100); nmr (DMSO-d_6) (in ppm) one-proton singlet at 3.33 (N–H), 0.8-proton multiplet at 3.5–3.8 (N–H), two-proton singlet at 4.15 (Py$\mathrm{C}H_2\mathrm{C}{=}\mathrm{C}$), six-proton multiplet at 6.9–7.9 (PyH_3, H_4, H_5), two-proton multiplet at 8.45 (PyH_6).

Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71; mol wt, 236. Found: C, 71.08; H, 5.16; N, 23.32; mol wt, 229.

Acetylation of 2-Pyridylacetonitrile.—Two 1.2-g samples of 2-pyridylacetonitrile were mixed with 5.0 g of acetic anhydride and kept at room temperature. One sample was worked up after 30 min and yielded 1.0 g of recovered starting material and a distillation residue which did not crystallize upon seeding with the acetylation product (described below). The other sample was allowed to stand for 10 days during which time crystals were deposited. Filtration yielded 0.95 g of yellow-orange crystals, mp 168–173°, and concentration of the mother liquors, followed by cooling, yielded an additional 0.43 g of crude product, mp 170–172°. Alternatively, a mixture of 5.9 g of 2-pyridylaceto-

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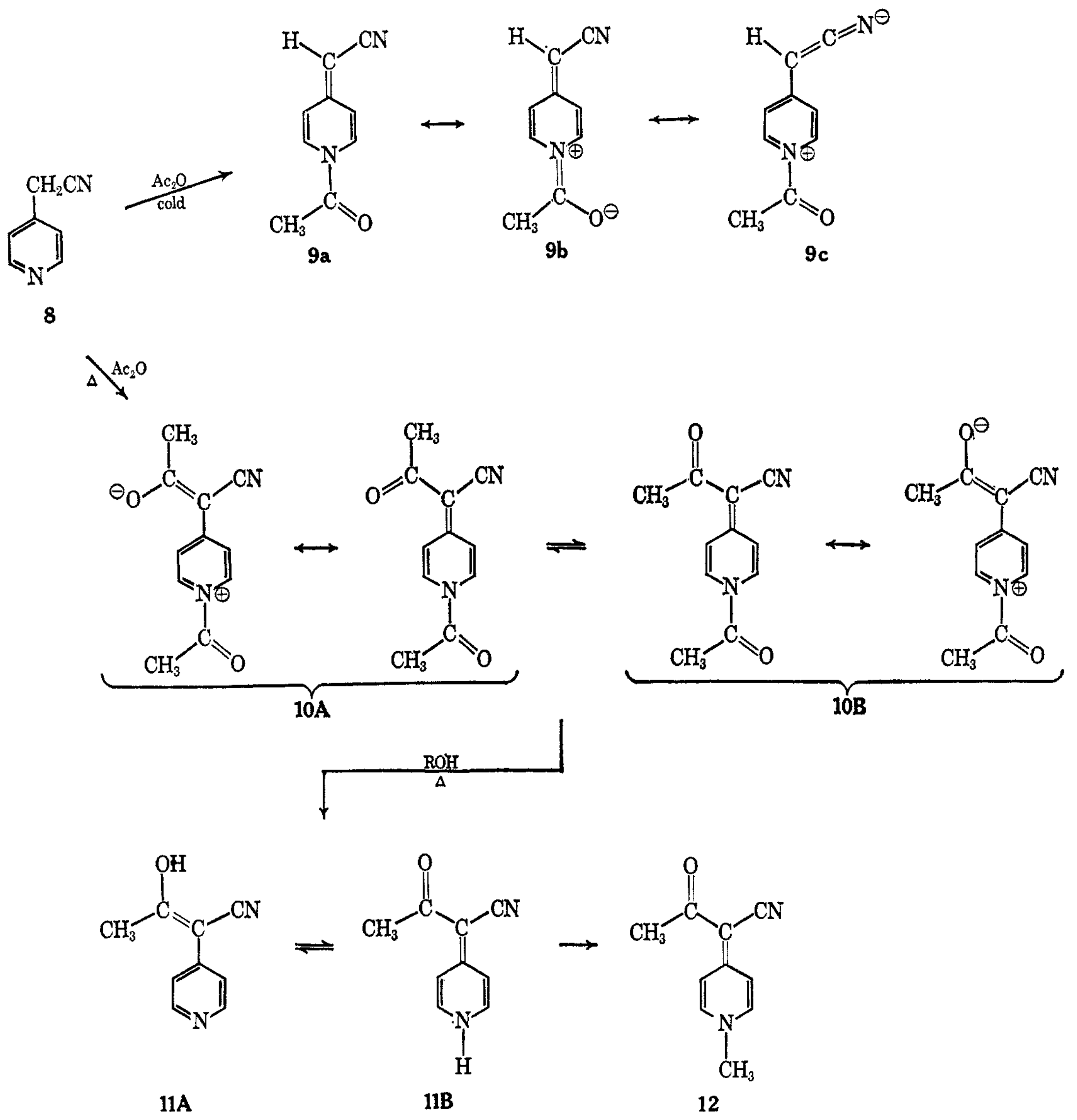
[17] Infrared data on acylpyridinium salts appear to be lacking in the literature. The similarity in chemical behavior between acylpyridinium compounds and acid chlorides, however, suggests that the carbonyl stretching frequencies are probably comparable; acyl chlorides absorb at 1770–1815 cm^{-1}.[14g]

[18] Melting points are corrected; boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer; the ultraviolet spectra were recorded on a Cary Model 11 and Model 14 spectrometer; the nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer. The nmr resonances are reported as parts per million downfield shift from tetramethylsilane, used as an internal reference. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria.

SCHEME II



nitrile, 5.5 g of acetic anhydride, and 3 g of glacial acetic acid was refluxed for 6 hr. Evaporation left 7.8 g (98%) of a brown solid, mp 145–155°, which was recrystallized from carbon tetrachloride, cyclohexane, or ethanol (with charcoal decolorization) to yield 2-(2′-pyridyl)-3-hydroxy-2-butenonitrile (**3A**) and/or its tautomer 2-(acetylcyanomethylidene)-1,2-dihydropyridine (**3B**) as yellow needles, mp 171–172°, which showed no melting point depression when admixed with the material obtained from the room temperature experiment; $\tilde{\nu}_{max}^{CHCl_3}$ (in cm^{-1}) 3050 (C–H), 2700–2900 (N···H–O), 2230 (C═CCN), 1630 (C═C–OH or C═C–C═O), 1570 (pyridine); $\lambda_{max}^{0.01\ N\ HCl}$ (ϵ) 238 mμ (10,300), 286 (11,900), 355 (12,500); $\lambda_{max}^{pH\ 11.5}$ (ϵ) 241 mμ (10,200), 312 (11,800); λ_{max}^{MeOH} (ϵ) 238 mμ (20,000), 294 (26,200), 363 (22,600); $\lambda_{max}^{cyclohexane}$ (ϵ) 267 mμ (11,800), 312 (13,800), 377 (2,800); pK_A from spectrophotometric determination = 9.73 ± 0.05; nmr ($CDCl_3$) (in ppm) three-proton singlet at 2.54 (C═C(CH_3)═O), one-proton triplet at 6.99 (PyH_5), one-proton doublet at 7.38 (PyH_3), two-proton multiplet at 7.7–8.0 (PyH_4, H_6), one-proton broad singlet at 16–17.8 (*H*OC═C, chelated).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49; mol wt, 141. Found: C, 67.47; H, 5.18; N, 17.28; mol wt, 147.

This material is slightly soluble in cold water and soluble in dilute hydrochloric acid, sodium hydroxide, and sodium carbonate, and forms a hydrochloride, mp 165–170°, which is quite unstable. It decolorizes a solution of bromine in chloroform, gives a strong blue-violet color with alcoholic ferric chloride, and fails to give a positive haloform test for (CH_3C═O).

Propionylation of 2-Pyridylacetonitrile.—A mixture of 5 g of 2-pyridylacetonitrile, 6 g of propionic anhydride, and 6 g of propionic acid was refluxed for 4 hr. The product, obtained as yellow needles after recrystallization from cyclohexane, had mp 108° and possessed spectral and chemical properties similar to those described for the acetyl analog and commensurate with the structure 2-(2′-pyridyl)-3-hydroxy-2-pentenonitrile (**4A**) and/or its tautomer 2-(propionylcyanomethylidene)-1,2-dihydropyridine (**4B**).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.45; H, 5.83; N, 15.87.

Acetylation of 4-Pyridylacetonitrile. A. N-Acetyl Derivative 9.—A 1.2-g (0.01 mole) sample of 4-pyridylacetonitrile was mixed with 5.0 g (0.05 mole) of acetic anhydride, and the mixture was allowed to stand at room temperature for 10 min. The yellow-orange crystals, which started forming immediately upon mixing, were removed by filtration, washed with ether, and dried under vacuum to yield 1.0 g (62%) of crude product, mp 147–152°. A second crop amounting to 0.4 g (25%) was obtained from the mother liquor, mp 127–135°. After three recrystallizations from 1-butanol orange-red crystals of 1-acetyl-4-cyanomethylidene-1,4-dihydropyridine (**9**) were obtained: mp 149–150°; $\tilde{\nu}_{max}^{CHCl_3}$ (in cm^{-1}) 3030 (C–H), 2215 (C═CCN), 1730 ($R_3N^+COCH_3$), 1660 (C═C or C═N); λ_{max}^{EtOH} (ϵ), 342 mμ (30,000); nmr ($CDCl_3$) (in ppm) three-proton singlet at 2.40 (CH_3C═O), one-proton singlet at 4.47 *H*C(CN)═C, one-proton quartet at 6.1 (ring H_5 or H_3), one-proton quartet at 6.44 (ring H_3 or H_5), one-proton quartet at 7.33 (ring H_2 or H_6), one-proton quartet at 7.46 (ring H_6 or H_2).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.06; N, 17.35.

This material is insoluble in cold, dilute sodium hydroxide or sodium carbonate solution and reacts rapidly with bromine to give a solid, mp 275–280° dec, which possesses an infrared spectrum very similar to that of 4-chloromethylpyridinium hydrochloride.

B. **N,C-Diacetyl Derivative 10.**—A 1.7-g (0.015 mole) sample of 4-pyridylacetonitrile was mixed with 7.5 g (0.075 mole) of acetic anhydride. Upon heating, the yellow-orange precipitate of the N-acetyl compound dissolved to give a clear solution. After 10 min the solution was cooled, whereupon a bright yellow material crystallized. This was removed by filtration and consisted of 1.8 g (62%) of 1-acetyl-4(acetylcyanomethylidene)-1,4-dihydropyridine (**10**), mp 210–225° dec. Recrystallization from chloroform gave the pure product as bright yellow blades: mp 225° dec; $\tilde{\nu}^{\text{KBr}}$ (in cm^{-1}) 3100 (C–H), 2200 (C=CCN), 1760 ($R_3N^+COCH_3$), 1670 (C=CO$^-$), 1650 (C=C), 1600 (C=C); nmr (DMSO-d_6) (in ppm) singlets at 1.82, 2.08, 2.20 and 2.57 accounting for six protons (CH_3), a doublet at 6.80, and singlets at 7.85 and 8.30 accounting for four protons (ring H).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.69; H, 4.55; N, 13.84.

C. **C-Acetyl Derivative 11.**—In an attempt to recrystallize the N,C-diacetyl compound **10** from 1-butanol, the solution changed color upon heating and deposited a brown material which was subsequently recrystallized from water to yield 2-(4′-pyridyl)-3-hydroxy-2-butenonitrile (**11A**) and/or its tautomer 4-(acetylcyanomethylidene)-1,4-dihydropyridine (**11B**) as small, glistening, colorless crystals: mp 268–269°; $\tilde{\nu}^{\text{KBr}}$ (in cm^{-1}) 2700 (acidic H), 2190 (C=CCN), 1630 (C=C–C=O), 1545 (pyridine); $\lambda_{\max}^{\text{pH 1}}$ (ϵ) 227 mμ (11,000), 320 (16,000), 355 (8200); $\lambda_{\max}^{\text{pH 5}}$ (ϵ) 233 mμ (15,400), 250 (shoulder), 356 (32,000); $\lambda_{\max}^{\text{pH 12}}$ (ϵ) 225 mμ (13,800), 245 (shoulder), 316 (21,000); pK_A from spectrophotometric determination = 8.40 and 1.76; nmr (DMSO-d_6) (in ppm) three-proton singlet at 2.16 (CH_3C=), one-proton broad singlet at 3.29 (acidic H), four-proton unsymmetrical doublet at 7.9 (PyH_2, H_3, H_5, H_6).

Anal. Calcd for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.35; H, 4.58; N, 17.40.

This material is only slightly soluble in most organic solvents; dimethyl sulfoxide and dimethylformamide are among the better solvents. It is readily soluble in dilute, aqueous sodium hydroxide, and sodium carbonate as well as in dilute acid.

Knoevenagel Reaction with Acetaldehyde.—A mixture of 18 g (0.15 mole) of 2-pyridylacetonitrile, 6.6 g (0.15 mole) of freshly distilled acetaldehyde, 1.2 g of piperidine, 1.8 g of acetic acid, and 100 ml of benzene was placed in a flask equipped with a Dean–Stark tube. After refluxing for 45 min the theoretical amount of water had been collected, whereupon the reaction mixture was cooled and worked up to yield 16 g (74%) of 2-(2′-pyridyl)-2-butenonitrile (**6**) as a colorless liquid: bp 70–71° (0.25 mm); $\tilde{\nu}_{\max}^{\text{liq}}$ (in cm^{-1}) 3100 (C–H), 2230 (C=CCN), 1630 (C=C), 1570 (pyridine); $\lambda_{\max}^{\text{heptane}}$ (ϵ) 241 mμ (11,500), 275 (6100); nmr (CCl_4 in ppm) three-proton doublet (J = 7 cps) at 2.18 ($CHCH_3$), one-proton quartet (J = 7 cps) at 7.19 (=$CHCH_3$), three-proton multiplet at 7.35–7.80 (PyH_3, H_4, H_5), one-proton doublet at 8.45 (PyH_6).

Anal. Calcd for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.21; H, 5.95; N, 19.06.

A 7.2-g (0.05 mole) sample of the above product was dissolved in 100 ml of ethanol, treated with 1 g of 10% palladium-on-charcoal catalyst, and subjected to hydrogenation at atmospheric pressure and room temperature. When the theoretical amount of hydrogen for 1 mole equiv had been absorbed (*ca.* 1.1 l.), the catalyst was removed by filtration and the solvent by evaporation, and the residue was distilled to give 6.5 g (88%) of 2-(2′-pyridyl)-butyronitrile (**7**) as a colorless liquid: bp 73–76° (0.5 mm); $\tilde{\nu}^{\text{liq}}$ (in cm^{-1}) 3030 (C–H), 2260 (CN), 1585 (pyridine), 1565 (pyridine); nmr (CCl_4) (in ppm) three-proton triplet (J = 7.8 cps) at 1.07 (CH_2CH_3), two-proton pattern of overlapping triplets (J = 7.8 and 6.8 cps) at 2.06 (CH–CH_2-CH_3), one-proton triplet (J = 6.8 cps) at 3.92 (CH–CH_2), three-proton multiplet at 7.1–7.9 (pyridine H_3, H_4, H_5), one-proton doublet at 8.52 (pyridine H_6).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.64; H, 6.83; N, 18.70.

Ethylation of C-Acetyl Derivative from 2-Pyridylacetonitrile.—A 3.2 g (0.02 mole) sample of 2-(2′-pyridyl)-3-hydroxy-2-butenonitrile (**3**) was dissolved in 20 ml of 1 *N* sodium hydroxide, and the solution was treated with 3.4 g (0.02 mole) of silver nitrate in 40 ml of water. The resulting silver salt was separated by filtration, washed with alcohol and ether, dried in a vacuum desiccator, and treated in ether suspension with 4.7 g (0.03 mole) of ethyl iodide. After removing the silver iodide by filtration, the solvent was evaporated, and the residue was recrystallized from petroleum ether (bp 63–69°) to give 2-(4′pyridyl)-3-ethoxy-2-butenonitrile (**5**) as pale yellow crystals: mp 81–82°; $\tilde{\nu}^{\text{KBr}}$ (in cm^{-1}) 3040 (C–H), 2220 (C=CCN), 1630 (C=C), 1585 (pyridine), 1560 (pyridine); $\lambda_{\max}^{\text{EtOH}}$ (ϵ), 265 mμ (12,200), 287 (14,400), 362 (1250); nmr ($CDCl_3$) (in ppm) three-proton triplet at 1.43 (CH_2CH_3), three-proton singlet at 2.51 (=CCH_3), two-proton quartet at 4.23 (CH_2CH_3), three-proton multiplet at 7.0–8.0 (PyH_3, H_4, H_5), one-proton singlet at 8.65 (PyH_6).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.91; H, 6.18; N, 14.96.

Methylation of C-Acetyl Derivative from 4-Pyridylacetonitrile.—A 1.6-g sample of 2-(4′-pyridyl)-3-hydroxy-2-butenonitrile (**11**) was treated as described above (methyl iodide in place of ethyl iodide) to produce 1-methyl-4-(acetylcyanomethylidene)-1,4-dihydropyridine (**12**) as pale yellow crystals after recrystallization from ethyl acetate: mp 216–217°; $\tilde{\nu}^{\text{KBr}}$ (in cm^{-1}) 3100 (C–H), 2200 (C=C–CN), 1660 (C=C–C=O), 1600 (C=C); $\lambda_{\max}^{\text{pH 5-9}}$ (ϵ) 235 mμ (15,400), 362 (35,000); $\lambda_{\max}^{\text{pH 1}}$ (ϵ) 230 mμ (12,800), 362 (22,400); nmr (DMSO-d_6) (in ppm) three-proton singlet at 2.35 (CH_3C=O), three-proton singlet at 4.03 (CH_3N), four-proton doublet at 7.95 (ring H).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 68.75; H, 5.79.

Registry No.—1, 2739-97-1; **2B,** 13427-04-8; **3A,** 13449-02-0; **3A** hydrochloride, 13427-05-9; **3B,** 13427-06-0; **3B** hydrochloride, 13441-16-2; **4A,** 13427-07-1; **4B,** 13444-35-4; **5,** 13427-08-2; **6,** 13427-09-3; **7,** 13427-10-6; **8,** 13121-99-8; **9a,** 13427-12-8; **9b,** 13427-13-9; **9c,** 13427-14-0; **10A,** 13444-36-5; **10A′,** 13427-15-1; **11A,** 13427-16-2; **11B,** 13427-17-3; **12,** 13427-18-4.

The Gattermann Reaction of 3,5-Dimethoxyphenylacetonitrile. A Synthesis of 6,8-Dioxyisoquinolines

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Treatment of 3,5-dimethoxyphenylacetonitrile with zinc cyanide and a hydrogen halide gave a 3-halo-6,8-dimethoxyisoquinoline. Structural confirmation of the products was obtained by hydrogenolysis to 6,8-dimethoxyisoquinoline, which was synthesized by an unambiguous route. Partial or complete demethylation of dimethoxyisoquinoline derivatives could be effected and a comparison of spectral data showed that 6,8-dihydroxyisoquinolines exist as hydroxy tautomers with no detectable contribution from quinolone forms.

During the course of synthetic studies directed toward mold metabolites of the isochromene group,[1] we have found that 3,5-dimethoxyphenylacetonitrile (**1**), when treated with zinc cyanide and either hydrogen chloride or hydrogen bromide under the usual conditions of the Gattermann reaction, affords a 3-halo-6,8-dimethoxy-

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(1) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworth and Co. Ltd., London, 1963, p 450; G. Büchi, J. D. White, and G. N. Wogan, *J. Am. Chem. Soc.*, **87**, 3484 (1965), and references cited.