# Preparation and Properties of Annelated Pyridines

Randolph P. Thummel* and Dalip K. Kohli

*Department of Chemistry, University of Houston, Houston, Texas 77004*

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A series of monoannelated pyridines has been prepared in which a five- or six-membered ring is fused at either the 2,3 or 3,4 position of the pyridine ring. Condensation reactions were employed to prepare a similar series of bisannelated molecules in which all possible combinations of five- and six-membered rings are fused to the pyridine nucleus. The $^1H$ and $^{13}C$ NMR spectra of these systems have been reported. As the size of a fused ring is decreased from six carbons to five, electron density decreases at the bridgehead carbons while increasing at the carbons ortho to the bridgehead. A proton attached to this ortho carbon is consequently deshielded and $J_{C-H}$ is seen to increase. Decreasing the size of a ring fused at the 2,3 position decreases the basicity of the molecule while the same change at the 3,4 position increases basicity. These observations are adequately explained by inductive effects due to rehybridization of the bridgehead carbon which occurs when the size of the fused ring is decreased.

In an earlier paper, we have examined the effects of fusing four- and five-membered rings onto the benzene nucleus.[1] In a series of compounds where two such rings are fused para to one another, the chemical shift of the aromatic proton ortho to the fused ring is found to shift upfield with increasing strain. This shift is attributed to a perturbation of the aromatic ring current rather than to inductive effects due to rehybridization at the bridgehead carbon atoms. A shift to longer-wavelength absorption in the ultraviolet spectrum is observed for para-fused benzenes as compared to meta-fused ones. The extinction coefficient of all fused benzenes is found to increase as the system becomes more symmetrical and more planar.

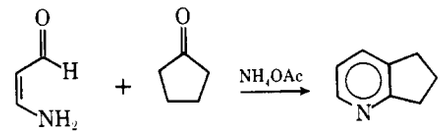
By comparison with the extensive studies of the effect of ring fusion on the benzene nucleus,[2] similar pyridine systems have been given only sparse consideration. Wilk and coworkers examined ultraviolet and fluorescence spectra of a series of 2,3-annelated quinolines.[3] They found that as the size of the fused ring was decreased from five carbons to four carbons to dimethyl the UV absorption shifted to shorter wavelength and became less intense. Markgraf examined the basicity and NMR spectra of these same compounds as well as some fused quinoxalines and discovered other well-defined systematic variations.[4] The various methyl-substituted pyridines have been much more extensively investigated with thorough consideration being given to their basicities,[5] ultraviolet,[6] and $^1H$ NMR spectra.[7]

There are several features of the pyridine nucleus which make it attractive for studies related to aromaticity. First, the nitrogen atom introduces an element of asymmetry which allows for comparison between positionally isomeric molecules (i.e., 2,3- vs. 3,4-annelated pyridines). Secondly, the heteroatom provides a convenient means for directly probing the aromatic nucleus via basicity studies or the formation of derivatives such as pyridinium salts or *N*-oxides. Thirdly, the resonance energy of pyridine has been calculated to be about 21 kcal/mol based on heats of atomization estimated from thermochemical data.[8] This value is substantially less than the value of 36 kcal/mol calculated for benzene. Thus, one might expect that it should be easier to perturb the aromaticity of pyridine than it would be to perturb it for benzene.

This paper will offer a thorough investigation of mono- and bisannelated pyridines where five- and six-membered rings have been fused to the pyridine nucleus.

## Synthesis of Annelated Pyridines

Annelated pyridines are most easily prepared by the condensation of cyclic ketones with an appropriate nitrogen-containing species to build up the pyridine ring. Thus, the Friedlander condensation of cyclopentanone and cyclohexanone with β-aminoacrolein (1) provides 2,3-fused pyridines

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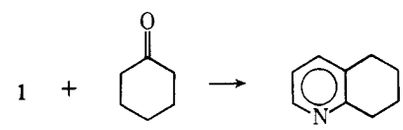


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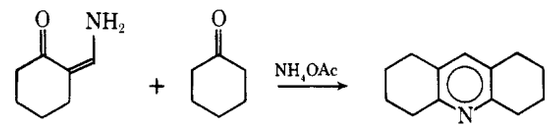
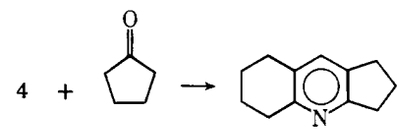
2 and 3.[9] Partial hydrogenation of isoxazole over a Raney nickel catalyst afforded a convenient source of β-aminoacrolein.[10] Hoping to extend the generality of this method, we prepared 4 and 5 by treating the appropriate α-formyl ketones with ammonia. Condensation of these β-amino-α,β-unsaturated ketones with cyclic ketones was expected to lead to meta-fused pyridines.

The major product observed upon condensation of 4 or 5 with cyclopentanone or cyclohexanone was a rearranged, para-fused pyridine (6–8). The identity of these materials was confirmed by their characteristic aromatic proton resonance at 7.02–7.30 ppm as well as by alternate synthesis of 6 and 8.[11]




4 6

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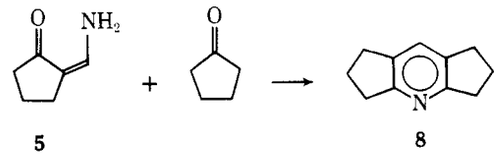
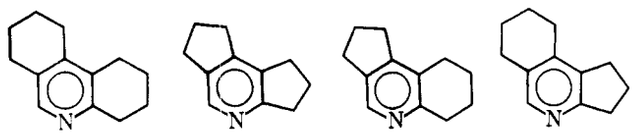



5 8

A similar rearrangement has been observed for acyclic β-amino-α,β-unsaturated ketones, while the corresponding aldehydes condense in a normal fashion.[12] Curran has observed the same behavior for condensations with 1,3-cyclohexanedione and dimedone.[13] He explains these results by invoking a prior equilibration giving rise to the enamine of the

1,3-dicarbonyl reaction partner. We are currently examining this mechanism more closely.

The meta-fused pyridines **9–12** were prepared by a condensation first reported by Chichibabin.[14] Two equivalents of cyclohexanones were found to react with formaldehyde and ammonia under acidic conditions to give predominantly **9** (54%). A similar reaction with cyclopentanone provided **10** in



**9** **10** **11** **12**

much lower yield. An equimolar mixture of cyclohexanone and cyclopentanone gave a complex mixture from which **11** and **12** could be isolated by preparative gas chromatography. The assignment of these two structures will be discussed in the following section. This same reaction employing 2-butanone led to the facile preparation of 2,3,4,5-tetramethylpyridine (**13**).

Catalytic hydrogenation of isoquinoline with platinum oxide in trifluoroacetic acid gave 5,6,7,8-tetrahydroisoquinoline (**14**).[15] Grignard cyclization of γ-(3-pyridyl)propyl chloride provided 3,4-trimethylenepyridine (**15**).[16] Finally, 2,3,5,6-tetramethylpyridine (**16**) was prepared from 2,6-dimethyl-3,5-dicarbethoxypyridine by the method of Tsuda and coworkers.[17]

## Spectral Properties

Pyridine chemical-shift assignments are greatly facilitated by the electronic influence which the nitrogen atom exerts on the various positions around the ring. Thus, the two and the six positions are the most deshielded due to the proximity of the electronegative heteroatom. The four position possesses significant positive character by resonance and is the next most deshielded. Atoms at positions three and five are least deshielded and are found at highest field. An additional feature facilitates assignment of carbon chemical shifts. Aromatic carbons bearing a hydrogen have shorter relaxation times and greater nuclear Overhauser enhancements, thus giving rise to more intense signals.

In Tables I and II are recorded the proton and carbon-13 chemical shifts for mono- and bisannelated pyridines, as well as appropriate dimethyl- and tetramethyl-substituted analogues. In the case of 3,4-substituted pyridines, **14, 15,** and **18**, C-2 is assigned to lower field than C-6 by analogy with assignments for 3-methylpyridine.[18] Assignments for an unsymmetrical pyridine such as **7** are facilitated by the observation of close agreement with the symmetrical analogues **6** and **8**. Pyridines **11** and **12** were assigned by similar analogy to compounds **9** and **10**. The fusion of a six-membered ring onto the pyridine nucleus results in chemical shifts very much like those of the corresponding methyl-substituted derivatives, as is illustrated by the similarity between the NMR data for compounds **3** and **17, 14** and **18, 6** and **16,** and **9** and **13**.

As the size of the fused ring is decreased from six to five carbons, a very consistent variation in pyridine chemical shifts is observed. The carbon-13 chemical-shift changes are tabulated in Table III. For a ring fused at the 2,3 position, both bridgehead carbons are observed to shift downfield with C-2 shifting 8.2–8.7 ppm and C-3 shifting 4.4–5.4 ppm. For 3,4-fused systems the shift is also downfield with C-3 shifting 7.1–7.5 ppm and C-4 shifting 7.2–8.3 ppm. At the pyridine ring positions ortho to the bridgehead carbons, the change is in the opposite direction, shifting upfield 1.5–3.1 ppm when the ortho carbon is bonded to a methylene and 3.2–5.2 ppm when

**Table I. NMR and Ultraviolet Spectral Data for Monoannelated Pyridines**

| Registry no. | | Chemical shifts (ppm) | | | | | | | | $\lambda_{max}$ (95% EtOH) ($\epsilon$) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_6$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | | | |
| 533-37-9 | **2** | | | 7.47 | 7.00 | 8.31 | 165.3 | 136.8 | 132.0 | 120.8 | 147.0 | 278 (2768) | 274 (3580) | 270 (3873) | 265 (3421) |
| 10500-57-9 | **3** | | | 7.31 | 6.98 | 8.31 | 157.1 | 132.1 | 136.7 | 120.7 | 146.4 | 276 (2180) | 271 (2556) | 268 (2851) | 264 (2491) |
| 583-61-9 | **17** | | | 7.37 | 7.00 | 8.29 | 156.7 | 131.0 | 136.6 | 120.8 | 146.1 | 271 (2417) | 265 (3182) | 259 (2767) | |
| 533-35-7 | **15** | 8.44 | | | 7.14 | 8.33 | 147.1 | 139.9 | 153.3 | 119.7 | 145.7 | 267 (1758) | 259 (2027) | 254 (1646) | |
| 36556-06-6 | **14** | 8.27 | | | 6.94 | 8.24 | 150.3 | 132.8 | 145.9 | 123.7 | 146.3 | 269 (1771) | 261 (2169) | 254 (1708) | |
| 583-58-4 | **18** | 8.28 | | | 6.99 | 8.26 | 149.6 | 131.6 | 145.0 | 124.1 | 146.9 | 267 (1842) | 259 (2248) | 255 (1947) | |

Table II. NMR and Ultraviolet Spectral Data for Bisannelated Pyridines

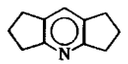
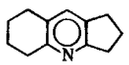
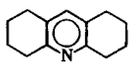
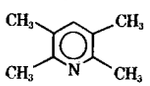
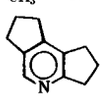
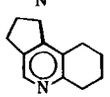
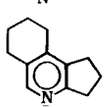
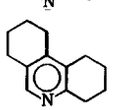
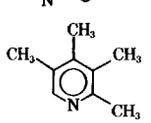
| Registry no. | | | Chemical shifts (ppm) | | | | | | $J_{C_{Ar}-H}$ (Hz) | $\lambda_{max}$ (95% EtOH) ($\epsilon$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $H_{Ar}$ | $C_2$ | $C_3$ | $C_4$ | $C_5$ | $C_6$ | | | | | |
| 34421-99-3 |  | 8 | 7.30 | 163.2 | 134.1 | 128.4 | 134.1 | 163.2 | 159.8 | 297 (4875) | 292 (7200) | 287 (7925) | 282 (6800) |
| 56717-25-0 |  | 7 | 7.15 | 162.4 | 133.9 | 132.8 | 129.0 | 154.6 | 155.2 | 295 (4805) | 289 (6603) | 285 (7000) | 281 (6217) |
| 1658-08-8 |  | 6 | 7.02 | 153.9 | 129.1 | 137.3 | 129.1 | 153.9 | 152.2 | 291 (3980) | 286 (5073) | 281 (5520) | 277 (4625) |
| 3748-84-3 |  | 16 | 7.10 | 153.1 | 128.1 | 138.5 | 128.1 | 153.1 | 152.6 | 281 (3388) | 275 (4518) | 272 (4556) | 267 (3743) |
| 7075-83-4 |  | 10 | 8.18 | 162.8 | 132.5 | 149.2 | 137.3 | 142.9 | 174.9 | 278 (2804) | 274 (2942) | 270 (2927) | |
| 62359-09-5 |  | 11 | 8.22 | 154.1 | 128.1 | 152.3 | 136.8 | 142.2 | 174.0 | 276 (2840) | 272 (2985) | 268 (3205) | |
| 62359-10-8 |  | 12 | 8.06 | 161.6 | 135.0 | 142.0 | 129.8 | 148.1 | 173.7 | 276 (4300) | 272 (4470) | | |
| 21199-79-1 |  | 9 | 8.06 | 153.4 | 129.6 | 144.0 | 129.6 | 146.9 | 172.2 | 279 (3064) | 276 (3321) | 271 (3423) | 267 (3013) |
| 18441-60-6 |  | 13 | 8.04 | 153.9 | 129.1 | 143.6 | 129.1 | 146.3 | 172.2 | 275 (2552) | 271 (2958) | 267 (4000) | 263 (2682) |

**Table III. Changes in Carbon-13 Chemical Shifts upon Decreasing Annelated Ring from Six Carbons to Five**

| Compd | Altered ring fusion | $\Delta C_2$ | $\Delta C_3$ | $\Delta C_4$ | $\Delta C_5$ | $\Delta C_6$ |
|---|---|---|---|---|---|---|
| 3 → 2 | 2,3 | −8.2 | −4.7 | +4.7 | −0.1 | −0.6 |
| 6 → 2 | 2,3 | −8.5 | −4.8 | +4.5 | +0.1 | −0.7 |
| 7 → 8 | 5,6 (2,3)[a] | −8.6 | −5.1 | +4.4 | −0.2 | −0.8 |
| 9 → 12 | 2,3 | −8.2 | −5.4 | +2.0 | −0.2 | −1.2 |
| 11 → 10 | 2,3 | −8.7 | −4.4 | +3.1 | −0.5 | −0.7 |
| 6 → 8 | 2,3 and 5,6 | −9.3 | −5.0 | +8.9 | −5.0 | −9.3 |
| 14 → 15 | 3,4 | +3.2 | −7.1 | −7.4 | +4.0 | +0.6 |
| 9 → 11 | 4,5 (3,4)[a] | +4.7 | −7.2 | −8.3 | +1.5 | −0.7 |
| 12 → 10 | 4,5 (3,4)[a] | +5.2 | −7.5 | −7.2 | +2.5 | −1.2 |
| 9 → 10 | 2,3 and 4,5 | −9.4 | −2.9 | −5.2 | −7.7 | +4.0 |

[a] Numbering patterns ($C_2$ and $C_6$, $C_3$ and $C_5$) in these molecules are reversed to preserve consistency throughout the table.

it is bonded to a hydrogen. The chemical shift of the hydrogen bonded to this ortho carbon is found to move downfield as the size of the fused ring is decreased from six carbons to five. Changes in proton and carbon chemical shifts at positions meta and para to the bridgehead vary only slightly when the annelated ring size is decreased, indicating that the influence of the fused ring is localized around the bridgehead and does not significantly affect the $\pi$ sextet as a whole. It should be noted that similar variations in carbon chemical shifts are observed between tetralin and indan.[19]

The chemical-shift effects appear to be additive. In going from **6** to **8**, C-4 is ortho to two rings, both of which have been decreased by one carbon. The chemical shift of C-4 moves upfield by 8.9 ppm, about twice the value observed when only one ring is altered. Furthermore, the effect of decreasing two rings in going from **9** to **10** can be reasonably well approximated by summation of the changes observed in going from **9** to **12** and in going from **9** to **11**. We calculate: $\Delta$C-2 = −8.9, $\Delta$C-3 = −3.9, $\Delta$C-4 = −6.3, $\Delta$C-5 = −7.4, and $\Delta$C-6 = +3.5 ppm.

All the evidence presented indicates that, as the size of a fused ring is decreased, there is an increase in electron density at the carbons ortho to the bridgehead, resulting in a significant polarization of this C–H bond. Thus, the ortho carbon becomes more shielded and its resonance moves upfield while the proton attached to it becomes more deshielded and moves to lower field. Furthermore, the coupling constant between the ortho carbon and hydrogen increases regularly along the series **16, 6, 7, 8** as well as along the series **9, 12, 11, 10,** indicating increased s character resulting from polarization of this bond. The downfield shift of the bridgehead carbon atoms with increasing strain indicates a decrease in electron density at these positions. All these effects are consistent with a rehybridization model proposed by earlier workers.[20] For aryl positions adjacent to a fused strained ring, Streitwieser claims that for the bridgehead carbons "the atomic orbitals used to construct the strained ring have higher p character. Hence, the remaining orbital has higher s character. The ortho carbon is thus bound to an orbital of higher electronegativity."[20b] As the size of the fused ring is decreased from six carbons to five, the electronegativity of this ortho carbon should increase. The expected effect of this would be to decrease shielding of the attached proton, shifting the carbon resonance to higher field and the proton resonance to lower field.

As regards to the UV data reported in Table II, only one trend bears mentioning. The positions of the maxima observed for the para bisannelated series **16, 6, 7, 8** move to longer wavelength with increasing strain while the extinction coefficients are seen to increase. The latter effect is analogous to what is observed for para bisannelated benzenes[1] and is explained by increased planarity leading to better Franck–Condon overlap between the ground and excited states of the molecule.

**Table IV. Basicities of Substituted Pyridines**

| Registry no. | | HNP[a] | $pK_a$ |
|---|---|---|---|
| | Methyl-Substituted Pyridines | | |
| 110-86-1 | Pyridine | 289 | 5.30[b] |
| 108-99-6 | 3-Methylpyridine | 269 | 5.85[b] |
| 108-89-4 | 4-Methylpyridine | 248 | 6.10[b] |
| | 2,3-Dimethylpyridine | 234 | 6.56[b] |
| | 3,4-Dimethylpyridine | 231 | 6.61[b] |
| 108-75-8 | 2,4,6-Trimethylpyridine | 186 | 7.63[b] |
| | 2,3,5,6-Tetramethylpyridine (**16**) | 169 | 7.91[b] |
| | 2,3,4,5-Tetramethylpyridine (**13**) | 180 | 7.78[b] |
| | Annelated Pyridines | | |
| | 2,3-Trimethylenepyridine (**2**) | 260 | 5.95 |
| | 5,6,7,8-Tetrahydroquinoline (**3**) | 229 | 6.65 |
| | 5,6,7,8-Tetrahydroisoquinoline (**14**) | 221 | 6.83 |
| | 3,4-Trimethylenepyridine (**15**) | 215 | 6.96 |
| | 2,3:5,6-Di(trimethylene)pyridine (**8**) | 239 | 6.42 |
| | 2,3-Trimethylene-5,6,7,8-tetrahydroquinoline (**7**) | 200 | 7.30 |
| | 1,2,3,4,5,6,7,8-Octahydroacridine (**6**) | 165 | 8.09 |
| | 3,4-Trimethylene-5,6,7,8-octahydroisoquinoline (**12**) | 198 | 7.35 |
| | 2,3:4,5-Di(trimethylene)pyridine (**10**) | 196 | 7.39 |
| | 1,2,3,4,7,8,9,10-Octahydrophenanthridine (**9**) | 180 | 7.75 |
| | 3,4-Trimethylene-5,6,7,8-octahydroquinoline (**11**) | 167 | 8.05 |

[a] Duplicate runs, ±2 mV, at 25 °C. [b] Reference 5a.

## Pyridine Basicities

The basicities for mono- and bisannelated pyridines are recorded in Table IV. The basicities were determined as half-neutralization potentials (HNP) by titration at 25 °C with 0.10 N perchloric acid in acetic acid with acetic anhydride as the solvent. The HNPs were determined for a series including pyridine and seven methyl-substituted derivatives of known basicity.[5a] A plot of HNP vs. $pK_a$ for these compounds resulted in a straight line from which the $pK_a$ values of the annelated pyridines could be determined.[5d,21]

The most dramatic effect is observed as the size of a ring fused to the 2,3 (or 5,6) position is decreased. Thus, the basicity of **2** ($pK_a$ = 5.95) is significantly less than that of its next higher homologue **3** ($pK_a$ = 6.65). Surprisingly, the fusion of a five-membered ring in the 3,4 position actually *increases* basicity such that **15** ($pK_a$ = 6.96) is more basic than **14** ($pK_a$ = 6.83) or 3,4-dimethylpyridine ($pK_a$ = 6.61). With two rings fused to the pyridine nucleus, the effects are even more impressive with the para bisannelated series **6** > **7** > **8** spanning 1.67 $pK_a$ units. The meta bisannelated pyridines are consistent with the observations made above. With a 2,3-fused six-membered ring and a 3,4-fused five-membered ring, 3,4-trimethylene-5,6,7,8-octahydroquinoline (**11**) is the most basic ($pK_a$ = 8.05), while 3,4-trimethylene-5,6,7,8-octahydroisoquinoline (**12**) with the opposite orientation is the least basic ($pK_a$ = 7.35). Pyridines **9** and **10** fall in between.

Again Streitwieser's arguments for the rehybridization of bridgehead carbons can be invoked to explain the decrease in basicity for compounds such as **2** and **8**.[4c,18] The lone pair of electrons on nitrogen is held more tightly when that atom is bonded to a carbon atom using an orbital of higher s character. A possible explanation for the increased basicity observed for 3,4-fused pyridines such as **15** and **11** might be that the nitrogen atom is now adjacent to an electron-enriched carbon (higher field chemical shift), C-2, which could help to stabilize

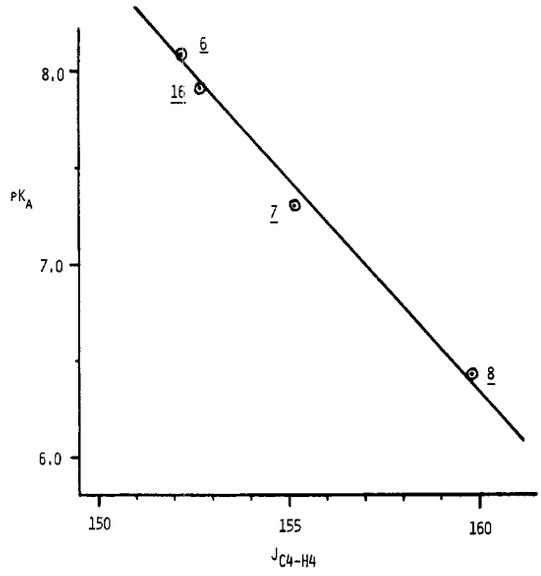



**Figure 1.**

an incipient positive charge.

The fact that this ortho rehybridization effect functions for nitrogen to about the same degree as it does for carbon is supported by the graph shown in Figure 1. The electron distribution or polarity of the C-4–H-4 bond is directly reflected by the C–H coupling constant observed for this bond, just as the availability of the lone pair of electrons on nitrogen is reflected by the basicity of the molecule. In the para bisannelated pyridines, where the ortho effect should be equivalent at N and C-4, these parameters are linearly related as is evidenced by a plot of $pK_a$ vs. $J_{C(4)-H(4)}$.

## Experimental Section

Proton and carbon magnetic resonance spectra were obtained on a Varian Associates XL-100 spectrometer and chemical shifts are reported in ppm downfield from TMS. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Cary 14 spectrometer. All melting points are uncorrected.

**β-Aminoacrolein.** A solution of 5 g (0.073 mol) of isoxazole[22] in 100 mL of anhydrous methanol containing 1.0 g of Raney nickel was hydrogenated at 40 psi until a theoretical volume of hydrogen had been absorbed and hydrogen uptake had ceased. The reaction mixture was filtered to remove the catalyst and the solvent was evaporated to give 4.2 g (82%) of a yellow solid, mp 96–97 °C. Recrystallization from chloroform–petroleum ether (1:1) gave crystals of β-aminoacrolein, mp 104–105 °C, lit.[23] mp 105–106 °C.

**2-Aminomethylenecyclopentanone (5).** Into a solution of 1.0 g (8 mmol) of 2-oxocyclopentanecarboxaldehyde[24] in 10 mL of chloroform was passed a slow stream of ammonia gas for 20 min such that the temperature of the solution did not rise appreciably. The reaction mixture was allowed to stand overnight, then dried over $MgSO_4$, and filtered, and the solvent was removed under vacuum to give 0.96 g of a dark-yellow solid which was recrystallized from chloroform–petroleum ether (1:1) to give light-yellow crystals, mp 109–110 °C, which darkened upon standing: NMR ($CDCl_3$) δ 7.32 (t, =CH (cis), $J$ = 10 Hz), 6.72 (t, =CH (trans), $J$ = 10 Hz), 4.9 (broad s, $NH_2$), 2.6–1.8 ppm (m, 6 H); upon addition of $D_2O$, the two triplets collapse to singlets and the signal at 4.9 disappears; IR (KBr) 3400–2900 (b), 2400, 1680 (b), 1120, 915, 875, and 635 $cm^{-1}$.

**2-Aminomethylenecyclohexanone (4).** Treatment of 5.0 g (0.04 mol) of 2-oxocyclohexanecarboxaldehyde[25] in 25 mL of chloroform as described above led to the isolation of 2.5 g (50%) of 4 after recrystallization from acetone, mp 104–105 °C, lit.[26] mp 110–111 °C.

**Friedländer Condensations.** To an equimolar mixture of the β-amino-α,β-unsaturated carbonyl compound and the appropriate ketone was added 10–30 mg of ammonium acetate and the mixture was heated to 120 °C for 12–20 h. After cooling, the mixture was triturated with ether and the ether-soluble portion was dried over $MgSO_4$ and filtered; the solvent was removed under vacuum. The dark crude oil obtained was first purified by vacuum distillation and then by chromatography on silica gel, eluting with ether–petroleum ether (2:5).

**2,3-Trimethylenepyridine (2).** Reaction of 3.0 g of β-aminoacrolein with 3.53 g of cyclopentanone provided 0.80 g (16%) of **2**, bp 38–40 °C (0.2 mm), lit.[9b] bp 87–88 °C (11 mm): NMR ($CDCl_3$) δ 8.31 (d, $H_6$, $J_{6,5}$ = 5.0 Hz), 7.47 (d, $H_4$, $J_{4,5}$ = 7.5 Hz), 7.00 (d of d, $H_5$, $J_{5,4}$ = 7.5 Hz, $J_{5,6}$ = 5.0 Hz), 2.96 (2 overlapping t, 4 H), and 2.10 ppm (m, 2 H); IR (thin film) 3050, 2963, 2853, 1720, 1597, 1586, 1430, 1267, 790, and 725 $cm^{-1}$.

**5,6,7,8-Tetrahydroquinoline (3).** Reaction of 3.0 g of β-aminoacrolein with 4.03 g of cyclohexanone provided 1.15 g (21%) of **3**, bp 45–47 °C (0.25 mm), lit.[9a] bp 98–99 °C (12 mm): NMR ($CDCl_3$) δ 8.31 (d, $H_6$, $J_{6,5}$ = 4.8 Hz), 7.31 (d, $H_4$, $J_{4,5}$ = 7.5 Hz), 6.98 (d of d, $H_5$, $J_{5,4}$ = 7.5 Hz, $J_{5,6}$ = 4.8 Hz), 2.89 (t, 2 H), 2.73 (t, 2 H), and 1.80 ppm (m, 4 H); IR (thin film) 3064, 2945, 2872, 1720, 1590, 1455, 1430, 1265, 785, and 730 $cm^{-1}$.

**2,3:5,6-Di(trimethylene)pyridine (8).** Reaction of 0.5 g (4.5 mmol) of **5** with 0.38 g (4.5 mmol) of cyclopentanone in the presence of 10 mg of ammonium acetate provided 0.63 g of material which after distillation showed a major peak at 21-min retention time by VPC (10 ft × ⅛ in. 10% Carbowax 20M on Chromosorb W 60/80 at 150 °C and 30 mL/min). Isolation of this peak provided a white-crystalline material, mp 86–87 °C, which was found to be identical with authentic **8** prepared by the method of Colonge and co-workers[11] (mp 87 °C): NMR ($CDCl_3$) δ 7.30 (s, Ar H), 2.95 (t, 4 H), 2.87 (t, 4 H), and 2.10 ppm (quintet, 4 H); IR (thin film) 2950, 2850, 1605, 1570, 1442, 1415, 1305, 1230, 1215, and 730 $cm^{-1}$.

**1,2,3,4,5,6,7,8-Octahydroacridine (6).** Reaction of 2.0 g (16 mmol) of **4** with 1.57 g (16 mmol) of cyclohexanone in the presence of 20 mg of ammonium acetate provided 3.14 g of a brown oil which was distilled, bp 95–98 °C (0.4 mm), to yield 0.79 g (26%) of a crystalline material, mp 69–70 °C, which was found to be identical with authentic **6** prepared by the method of Colonge and co-workers[11] (mp 69 °C): NMR ($CDCl_3$) δ 7.02 (s, Ar H), 2.85 (t, 4 H), 2.70 (t, 4 H), and 1.85 ppm (m, 8 H); IR (thin film) 2930, 2860, 1660, 1640, 1607, 1450, 1250, 985, 936, 820, and 710 $cm^{-1}$.

**2,3-Trimethylene-5,6,7,8-tetrahydroquinoline (7).** Reaction of 3.2 g (0.026 mol) of **4** with 2.2 g (0.026 mol) of cyclopentanone in the presence of 30 mg of ammonium acetate provided 4.40 g of a brown oil which was distilled to yield 0.96 g of crude product, bp 84 °C (0.5 mm), lit.[27] bp 160–161 °C (17 mm). This material was purified by column chromatography to provide 0.35 g (8%) of a colorless oil which was identified as **7**: NMR ($CDCl_3$) δ 7.15 (s, Ar H), 3.0–2.7 (overlapping triplets, 8 H), 2.06 (quintet, 2 H), and 1.84 ppm (m, 4 H); IR (thin film) 2935, 2860, 1610, 1575, 1450, 1420, 1227, 920, and 750 $cm^{-1}$.

**3,4-Trimethylenepyridine (15).** The procedure of Eisch and Russo[16] was followed. To a mixture of 1.34 g (0.055 mol) of magnesium metal in 25 mL of dry THF was added over 1 h a solution of 7.80 g (0.05 mol) of γ-(3-pyridyl)propyl chloride[28] in 60 mL of dry THF. The reaction mixture was stirred vigorously and heated with a heat gun at 5-min intervals during addition. After the mixture was stirred for 20 h at 25 °C, hydrolysis was carried out by the addition of 7.8 mL of saturated ammonium chloride solution with vigorous stirring. The mixture was suction filtered and the salts were washed well with THF. The filtrate was dried over $K_2CO_3$ and filtered again, and the solvent was evaporated to yield 4.0 g of liquid which showed three peaks in the ratio of 7:1:2 by VPC (10 ft × ⅛ in. 10% Carbowax 20M + 10% KOH on Chromosorb W 60/80 at 150 °C and 30 mL/min). This material was distilled into four fractions, bp 40–90 °C (8 mm). The fourth fraction weighed 0.80 g and contained 50% of the longest retention time peak. This peak was isolated by preparative gas chromatography and shown to be 3,4-trimethylenepyridine: NMR ($CDCl_3$) δ 8.44 (s, $H_2$), 8.33 (d, $H_6$, $J_{6,5}$ = 4.9 Hz), 7.14 (d, $H_5$, $J_{5,6}$ = 4.9 Hz), 2.91 (two overlapping triplets, 4 H), and 2.10 ppm (quintet, 2 H); IR (thin film) 3040, 2960, 2855, 1605, 1577, 1491, 1430, 1180, 827, and 721 $cm^{-1}$.

**5,6,7,8-Tetrahydroisoquinoline (14).** The procedure of Vierhapper and Eliel[15] was followed. To a solution of 2.15 g (16.6 mmol) of isoquinoline (stirred over Raney nickel, filtered, and distilled) dissolved in 15 mL of ice-cold trifluoroacetic acid was added 250 mg of platinum oxide and the mixture was hydrogenated at 50 psi. After 2 equiv of hydrogen had been absorbed, the solution was filtered, diluted with 20 mL of water, and carefully made basic with 50% NaOH. The basic solution was extracted with ether, the ether extracts were dried over KOH, and the solvent was evaporated to yield 1.50 g (68%) of a colorless liquid, bp 68–71 °C (1.5 mm). VPC analysis (10 ft × ⅛ in. 10% Carbowax 20M and 10% KOH on Chromosorb W 60/80 at 145 °C and 30 mL/min) showed the presence of 10% unreduced quinoline. Final purification could be effected only by preparative VPC: NMR ($CDCl_3$) δ 8.31 (d, $H_2$, $J_{2,3}$ = 4.8 Hz), 7.31 (d, $H_4$, $J_{4,3}$ = 7.5 Hz), 6.98 (d of d, $H_3$, $J_{3,4}$ = 7.5 Hz, $J_{3,2}$ = 4.8 Hz), 2.89 (t, 2 H, $H_8$),

2.73 (t, 2 H, $H_5$), and 1.8 ppm (m, 4 H); IR (thin film) 3028, 2940, 2868, 1608, 1570, 1440, 1420, 1295, 830, and 720 $cm^{-1}$.

**Meta bisannelated pyridines** were prepared by the method of Chichibabin.[14] A mixture of the ketone (or ketones), ammonium acetate, 38% aqueous formaldehyde, and 28% ammonium hydroxide was heated at 150–200 °C for 8–15 h. The reaction mixture was cooled and extracted four times with ether. The combined ether extracts were then extracted four times with 10% HCl. The acidic solution was cooled in ice, made basic with sodium hydroxide pellets, and extracted four times with ether. The ether extracts were dried over sodium sulfate and filtered, and the solvent was evaporated to provide a dark oil which was fractionally distilled. Further purification was effected by column chromatography or preparative VPC.

**1,2,3,4,7,8,9,10-Octahydrophenanthridine (9).** A mixture of 49 g (0.5 mol) of cyclohexanone, 75 g of ammonium acetate, 40 g of 38% aqueous formaldehyde, and 13 mL of 28% ammonium hydroxide was heated at 180–200 °C overnight and worked up in the manner described above. Distillation provided 25 g (54%) of **9**, bp 110 °C (0.5 mm). VPC analysis (10 ft × ⅛ in. 10% Carbowax 20M and 10% KOH on Chromosorb W 60/80 mesh at 150 °C and 30 mL/min) showed this material to be 98% of a single component: NMR ($CDCl_3$) δ 8.06 (s, Ar H), 2.85–2.50 (four overlapping triplets, 8 H), and 1.79 ppm (m, 8 H); IR (thin film) 2940, 2870, 1592, 1470, 1415, 1325, 1250, 932, 830, and 730 $cm^{-1}$.

**2,3:4,5-Di(trimethylene)pyridine (10).** A mixture of 50 g (0.595 mol) of cyclopentanone, 60 g of glacial acetic acid (in place of ammonium acetate), 22 g of 38% aqueous formaldehyde, and 55 g of 28% ammonium hydroxide was heated at 180–200 °C overnight and worked up in the manner described above. Fractional distillation provided a small amount of material, bp 93–94 °C (0.3 mm), which VPC analysis (10 ft × ⅛ in. 10% Carbowax 20M on Chromosorb W 60/80 at 150 °C and 30 mL/min) showed to be contaminated by the symmetrical isomer **8**. Chromatography on silica gel eluting with ether–petroleum ether (2:3) provided 20 mg of pure **8** (mp 84–85 °C) and 0.66 g of **10** as a colorless oil (pure by VPC): NMR ($CDCl_3$) δ 8.18 (s, Ar H), 2.95–2.70 (four overlapping triplets, 8 H), 2.08 (quintet, 2 H), and 2.05 ppm (quintet, 2 H); IR (thin film) 2950, 2850, 1617, 1580, 1470, 1440, 1395, and 750 $cm^{-1}$.

**3,4-Trimethylene-5,6,7,8-octahydroquinoline (11) and 3,4-Trimethylene-5,6,7,8-octahydroisoquinoline (12).** A mixture of 49 g (0.5 mol) of cyclohexanone, 42 g (0.5 mol) of cyclopentanone, 75 g of ammonium acetate, 40 g of 38% aqueous formaldehyde, and 11.5 g of 28% ammonium hydroxide was heated at 200 °C overnight and worked up in the manner described above. Simple distillation provided 15 g of material which was carefully fractionated to provide 2.37 g of a mixture of bisannelated pyridines, bp 108–110 °C (0.4 mm). This fraction was chromatographed on silica gel eluting with ether–petroleum ether (2:3) to provide 1.33 g of material which showed only two peaks in the ratio 74:26 by VPC (10 ft × ⅛ in. 10% Carbowax 20M and 10% KOH on Chromosorb W 60/80 at 150 °C and 30 mL/min). Both peaks were isolated pure by preparative VPC and structural assignments were made based on $^1H$ and $^{13}C$ NMR as described in the text. The major peak was assigned as **11**: NMR ($CDCl_3$) δ 8.22 (s, Ar H), 3.0–2.5 (four overlapping triplets, 8 H, Ar $CH_2$), 2.07 (quintet, 2 H), and 1.83 ppm (m, 4 H); IR (thin film) 2940, 2870, 1604, 1581, 1470, 1412, 1199, 925, 887, and 830 $cm^{-1}$. The minor peak was assigned as **12**: NMR ($CDCl_3$) δ 8.06 (s, Ar H), 3.0–2.6 (four overlapping triplets, 8 H, Ar $CH_2$), 2.09 (quintet, 2 H), and 1.80 ppm (m, 4 H); IR (thin film) 2870, 2830, 1600, 1573, 1481, 1440, 1402, 928 and 820 $cm^{-1}$.

**2,3,4,5-Tetramethylpyridine (13).** A mixture of 36 g (0.5 mol) of 2-butanone, 20 g of 38% aqueous formaldehyde, 37.5 g of ammonium acetate, and 6 mL of 28% ammonium hydroxide was heated at 150 °C overnight and worked up in the manner described above. Fractional distillation provided 3.5 g of material, bp 70–76 °C (5 mm) which showed one major peak by VPC (10 ft × ⅛ in. 10% Carbowax 20M and 10% KOH on Chromosorb W 60/80 at 148 °C and 30 mL/min). Further purification by chromatography on silica gel, eluting with ether (2:3), provided pure **13** as a colorless liquid: NMR ($CDCl_3$) δ 8.04 (s, Ar H), 2.45 (s, 3H), and 2.15 ppm (broad s, 9 H); IR (thin film) 2988, 2940, 2920, 1590, 1450, 1395, 1210, 1005, 750, and 730 $cm^{-1}$.

**2,3,5,6-Tetramethylpyridine (16).** The procedure of Tsuda and co-workers was followed.[17] Reduction of 2,6-dimethyl-3,5-dicarbethoxypyridine[29] with lithium aluminum hydride provided the corresponding diol which was converted to the dichloride with thionyl chloride. Catalytic hydrogenation of the dichloride provided **16**, mp 76–77 °C, lit.[17] mp 76 °C: NMR ($CDCl_3$) δ 7.10 (s, Ar H), 2.41 (s, 6 H), and 2.18 ppm (s, 6 H); IR (KBr) 2930, 2865, 1610, 1440, 1260, 1022, 800, and 733 $cm^{-1}$.

**Basicity Measurements.** Basicities were determined according to the method of Markgraf and Katt[4c] by potentiometric titration with a Radiometer RTS622 recording titration system fitted with a glass indicator electrode and a saturated calomel reference electrode, previously equilibrated with acetic anhydride for 48 h. Titrations were carried out at 25.00 ± 0.05 °C under a nitrogen atmosphere in a water-jacketed cell connected to a constant-temperature bath and fitted with a neoprene cover drilled to accommodate two electrodes, buret, thermometer, and nitrogen inlet tube. In a typical run, an accurately weighed amount of the pyridine derivative (ca. $5 \times 10^{-2}$ mol) was dissolved in acetic anhydride in a nitrogen-swept 25-mL volumetric flask; a 10-mL aliquot was transferred to the titration cell, diluted with 60 mL of acetic anhydride, and with magnetic stirring titrated with 0.10 N perchloric acid in acetic acid (Fisher No. SO-P-339, ca. 3.5 mL). The end point and half-neutralization potential were determined graphically. All runs were carried out in duplicate, with a precision of ±2 mV.

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**Registry No.**—**1**, 25186-34-9; **4**, 17425-57-9; **5**, 42997-61-5; 2-oxocyclopentanecarboxaldehyde, 1192-54-7; cyclopentanone, 120-92-3; cyclohexanone, 108-94-1; 2-butanone, 78-93-3.

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