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The Friedlander condensation of 2-aminonicotinaldehyde with cyclic ketones leads to the preparation of 2,3-fused 1,8-naphthyridines. The spectral properties and basicities of these molecules are discussed.

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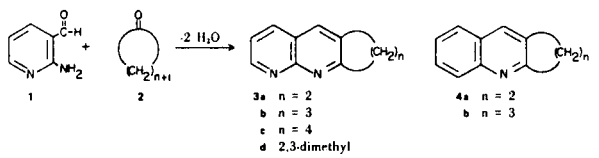
The fusion of a small ring to an aromatic nucleus results in significant changes in the chemical and physical properties of the system. We have recently reported on the results of such fusions to benzene (1) and pyridine (2). In this paper we would like to report on the preparation of a series of 2,3-fused 1,8-naphthyridines and some of the properties exhibited by these molecules.

Friedlander condensation of 2-aminonicotinaldehyde (3) with cyclobutanone under basic conditions (potassium hydroxide in aqueous ethanol at 25°) leads to the formation of **3a**, while **3b** and **3c** could be prepared under acidic conditions (refluxing acetic acid containing a catalytic amount of sulfuric acid). Markgraf and Scott have prepared the corresponding fused quinolines **4a** and



4b by condensation of cyclic ketones with *o*-aminobenzaldehyde (4) while Caluwe and coworkers have prepared more complex mono- and bis-annelated 1,8-naphthyridines by condensations with activated carbonyl compounds (5).

The ^{1}H nmr and uv spectral data for **3a-d** are recorded in Table I. It should be noted that when the size of the fused ring is decreased from five carbons to four (**3b** → **3a**) H4 shifts upfield by 0.17 ppm. A similar upfield shift of 0.23 ppm is observed when one compares the analogous 2,3-fused quinolines **4a** (H_4 = 7.66 ppm) and **4b** (H_4 = 7.89 ppm). This change is in the opposite direction of what one would expect based on arguments involving rehybridization of the bridgehead carbons which would tend to increase electron density at C_4 resulting in polarization of the C-H bond and deshielding of H_4 (2). The observed upfield shift might be explained by a partial disruption of the deshielding anisotropy of the aromatic ring due to the influence of the fused cyclobutene ring. In the ultraviolet spectra a regular hypsochromic shift is observed as the size of the annelated ring is decreased.

Table II records the half-neutralization potentials (HHP) for **3a-d** as determined by titration at 25° in acetic anhydride with 0.10 *N* perchloric acid in acetic acid (2,6). Also recorded are the pK_a's as determined by titration with 0.0908 *N* hydrochloric acid at 25° in 4% ethanol-water. A plot of HNP vs. pK_a affords the expected straight-line relationship (7). Markgraf and Scott found that the fusion of a small ring in the 2,3-position of quinoline significantly decreases the basicity of compound **4a** (pK_a = 4.55) when compared to its dimethyl analog (pK_a = 5.99) (4). For 1,8-naphthyridines, we observe that the fusion of a four-membered ring in the 2,3-position results in a similar decrease in basicity. The nitrogen in the eight-position should be much less influenced by the small fused ring and therefore the overall basicity of the molecule is not affected as dramatically as for the corresponding quinolines.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were obtained on a Varian Associates EM-390 MHz nmr 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. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona.

Cyclobuta[*b*]-1,8-naphthyridine (**3a**).

A solution of 0.5 g. (4 mmoles) of 2-aminonicotinaldehyde (3) and 0.24 g. (3.4 mmoles) of cyclobutanone in 10 ml. of 95% ethanol containing 2 ml. of 33% aqueous potassium hydroxide was allowed to stand at room temperature for three days, brought

Table I

Nmr and Uv Spectral Data for 2,3-Fused 1,8-Naphthyridines

	n	Chemical Shifts (ppm) H_4	H_5	H_6	H_7	λ max (95% Ethanol) (ε)			
3a	2	7.63	8.10	7.37	8.96	260 (5,300)	302 (9,500)	307 (10,200)	315 (10,700)
3b	3	7.80	8.04	7.33	8.96	260 (4,540)	305 (10,500)	310 (10,600)	318 (12,500)
3c	4	7.78	8.14	7.37	9.01	265 (3,800)	307 (8,500)	313 (8,700)	320 (9,900)
3d		7.85	8.08	7.39	9.00		303 (6,710)	308 (6,850)	316 (7,760)

Table II

Basicities of 1,8-Naphthyridines

Compound	HNP	pK_a (a)
Cyclobuta[*b*]-1,8-naphthyridine (**3a**)	312 mv	4.37
Cyclopenta[*b*]-1,8-naphthyridine (**3b**)	296	4.49
Cyclohexa[*b*]-1,8-naphthyridine (**3c**)	275	4.82
2,3-Dimethyl-1,8-naphthyridine (**3d**)	288	4.74

(a) Determined by titration at 25° in 4% ethanol-water with 0.0980 *N* hydrochloric acid.

rapidly to reflux, diluted with 20 ml. of water, treated with charcoal, and filtered. The filtrate was then extracted with four 20 ml. portions of dichloromethane. The extracts were dried over potassium carbonate and evaporated to yield 0.25 g. of a yellow solid. This material was purified in a thermal gradient sublimer (100°/0.005 mm) to give 0.20 g. (39%) of white crystals, m.p. 147-148°; nmr (deuteriochloroform): δ 8.96 (H_7, d of d, $J_{7,6}$ = 4.4 Hz, $J_{7,5}$ = 2.1 Hz), 8.10 (H_5, d of d, $J_{5,6}$ = 8.3 Hz, $J_{5,7}$ = 2.1 Hz), 7.63 (H_4, t, J = 1.2 Hz), 7.37 (H_6, d of d, $J_{6,7}$ = 4.4 Hz, $J_{6,5}$ = 8.3 Hz), 3.63 (m, 2H), and 3.30 ppm (m, 2H); ir (potassium bromide): 3060, 2960, 1620, 1595, 1410, 1370, 800 and 750 cm^{-1}; uv λ max (95% ethanol): 315 (10,700), 307 (10,200), 302 (9,500), and 260 mμ (5,300); mass spectrum: m/e (relative intensity) 156 (100), 155 (72), 149 (27), 144 (23) and 89 (31).

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 77.04; H, 5.31; N, 17.66.

Cyclopenta[*b*]-1,8-naphthyridine (**3b**).

To a mixture of 0.61 g. (5 mmoles) of 2-aminonicotinaldehyde (3) and 0.38 g. (4.5 mmoles) of cyclopentanone was added 5 ml. of glacial acetic acid and two drops of concentrated sulfuric acid. The mixture was refluxed for six hours, cooled, and poured into 8 ml. of ammonium hydroxide and 20 g. of ice. A yellow precipitate was obtained which turned into a gummy solid upon standing. The whole mixture was extracted four times with dichloromethane. The extracts were dried over potassium carbonate and evaporated to give 0.79 g. of **3b**, m.p. 125°. The crude product could be purified by sublimation to give crystals, m.p. 140-141°; nmr (deuteriochloroform): δ 8.96 (H_7, d of d, $J_{7,6}$ = 4.2 Hz, $J_{7,5}$ = 1.9 Hz), 8.04 (H_5, d of d, $J_{5,6}$ = 8.0 Hz, $J_{5,7}$ = 1.9 Hz), 7.80 (H_4, t, J = 1.4 Hz), 7.33 (H_6, d of d, $J_{6,7}$ = 4.2 Hz, $J_{6,5}$ = 8.0 Hz), 3.20 (t, 2H, J = 7.5 Hz), 3.07 (t, 2H, J = 7.5 Hz), and 2.18 ppm (quintet, 2H, J = 7.5 Hz); ir (potassium bromide): 3020, 2990, 1620, 1595, 1560, 1408, 790, and 735 cm^{-1}; uv λ max (95% ethanol): 318 (12,500), 310 (10,600), 305 (10,500), and 260 mμ (4540); mass spectrum: m/e (relative intensity) 170 (91), 169 (100), 158 (55), 149 (14), 142 (28), 115 (27), and 91 (24).

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.34; H, 5.88; N, 16.89.

Cyclohexa[*b*]-1,8-naphthyridine (**3c**).

A mixture of 0.5 g. (4.1 mmoles) of 2-aminonicotinaldehyde (3) and 0.30 g. (3.4 mmoles) of cyclohexanone in 5 ml. of glacial acetic acid containing two drops of concentrated sulfuric acid was refluxed for eight hours and then worked up in the manner described above to yield 0.71 g. of a brown solid, m.p. 103-104°. Purification by sublimation gave 0.44 g. (70%) of white crystals of **3c**, m.p. 110-111°; nmr (deuteriochloroform): δ 9.01 (H_7, d of d, $J_{7,6}$ = 4.2 Hz, $J_{7,5}$ = 2.0 Hz), 8.14 (H_5, d of d, $J_{5,6}$ = 8.1 Hz, $J_{5,7}$ = 2.0 Hz), 7.78 (H_4, broad s), 7.37 (H_6, d of d, $J_{6,7}$ = 4.2 Hz, $J_{6,5}$ = 8.1 Hz), 3.22 (t, 2H, J = 6 Hz), 2.98 (t, 2H, J = 6 Hz) and 1.96 ppm (m, 4H); ir (potassium bromide): 3020, 2920, 1550, 1474, 1446, 1410, and 800 cm^{-1}; uv λ max (95% ethanol): 320 (9,900), 313 (8,700), 307 (8,500), and 265 mμ (3,800).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 78.29; H, 6.62; N, 15.26.

2,3-Dimethyl-1,8-naphthyridine (**3d**).

A mixture of 0.61 g. (5 mmoles) of 2-aminonicotinaldehyde (3), 5 ml. of 2-butanone, and 0.12 g. of piperidine was refluxed for 20 hours. The unreacted 2-butanone was removed under vacuum and the resulting yellow solid (0.63 g.) was chromatographed on silica gel, eluting with ether, to yield 0.27 g (34%) of yellow crystalline solid **3d**, m.p. 135-136°; nmr (deuteriochloroform): δ 9.00 (H_7, d of d, $J_{7,6}$ = 4.2 Hz, $J_{7,5}$ = 2.0 Hz), 8.08 (H_5, d of d, $J_{5,6}$ = 8.0 Hz, $J_{5,7}$ = 2.0 Hz), 7.85 (H_4, broad s), 7.39 (H_6, d of d, $J_{6,7}$ = 4.2 Hz, $J_{6,5}$ = 8.0 Hz), 2.76 (s, 3H, 2-methyl) and 2.48 ppm (s, 3H, 3-methyl); ir (potassium bromide): 3010, 1638, 1603, 1560, 1448, 1423, 1378, 1000, and 795 cm^{-1}; uv λ max (95% ethanol): 316 (7,760), 308 (6,850), and 303 mμ (6,710).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.23; H, 6.52; N, 17.72.

Basicity Measurements.

Basicities were determined according to the method of Markgraf and Katt (6) by potentiometric titration with a Radiometer TRS622 Recording Titration System fitted with a glass indicator electrode and a saturated calomel reference electrode, previously equilibrated with acetic anhydride for 48 hours. Titrations were carried out at 25.00 ± 0.05° under 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, therometer, and nitrogen inlet tube. In a typical run, an accurately weighed amount of the naphthyridine derivative (*ca.* 5 x 10^{-2} mole) 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-399, *ca.* 3.5 ml.). The end point and half-neutralization potential were determined graphically. All runs were carried out in duplicate, with a percision of ± 2 mv.

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