SYNTHESIS OF 7, 12-DIHYDROPYRIDOPYRROLOINDOLES (AZAPYRIDODIINDOLES) *via* THE FISCHER INDOLE CYCLIZATION. A SEARCH FOR WATER SOLUBLE BENZODIAZEPINE RECEPTOR LIGANDS.

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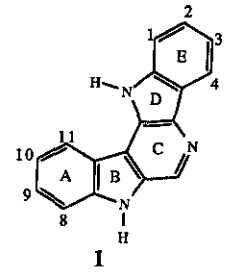
Abstract- The thermally-induced Fischer indole cyclization of the 3-acylindole **7** with various substituted hydrazinopyridines provides a simple route to the 7,12-dihydropyridopyrroloindoles **2, 4** and **5,** respectively. In contrast, the corresponding acid-catalyzed process yielded only 4-amino-β-carboline **15**. Moreover, attempts to prepare the 3-aza-analog **3**, from reaction of **7** and 4-hydrazinopyridine **12** under thermal or acidic conditions, provided only **15**. The difference between the reactivity of the 4-substituted pyridine **12**, in comparison to **11** or **13**, is discussed in terms of pK_a values and intermediates in the Fischer indole cyclization.

During a search for new ligands with which to probe the topography of benzodiazepine receptors (BzR), the rigid planar 7,12-dihydropyrido[3,2-b:5,4-b']diindole **1** was discovered to exhibit high affinity for these receptors.[1] A wide variety of functional groups have been substituted for hydrogen at positions -1, -2, -3, -4 and -10 of the pyridodiindole nucleus to determine the effect on binding affinity.[1,2] During this work it was proposed to increase the water solubility of these pyridodiindoles and to, simultaneously, alter the electron density distribution of these important rigid pyridodiindole probes without perturbing their topography.

A simple means by which to achieve this goal was to replace C-H at positions -1, -2, -3 or -4 of **1** with a nitrogen atom. This provides the new heterocyclic ring system, 7,12-dihydropyridopyrroloindole also referred to as the aza-7,12-dihydropyrido[3,2-b:5,4-b']diindole, in reference to **1**.[3] The dihydrochloride salt of this new heterocycle should demonstrate increased water solubility in comparison to **1**. Replacement of



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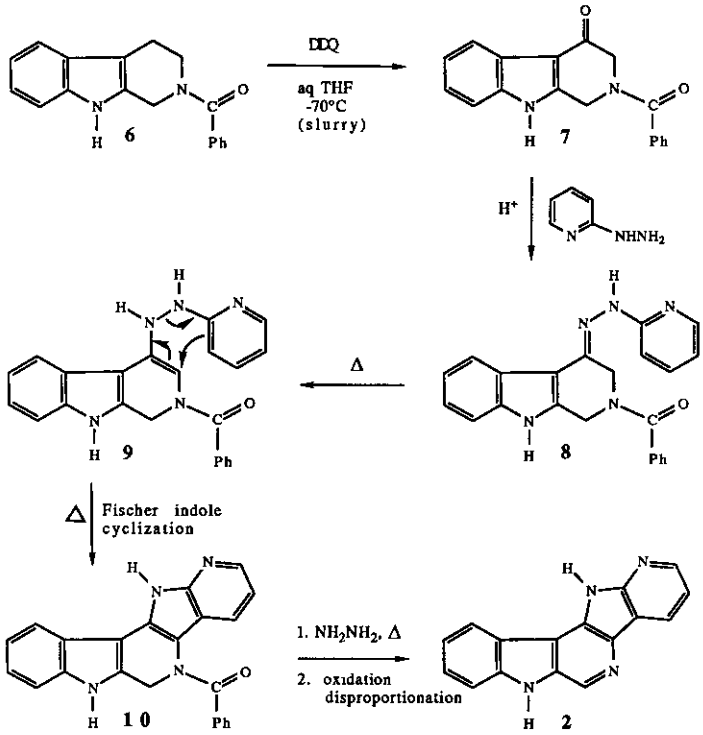
carbon with nitrogen at positions -1 through -4 of **1** would alter the electron density distribution in ring E of the molecule (MNDO calculations).[4] More importantly, in accord with a recent model of the pharmacophore[5] for the inverse agonist site at BzR, an electron rich pyridine nitrogen at position -4 (see **4**) might well enhance the ability of this azapyridodiindole to interact with a hydrogen bond acceptor atom on the benzodiazepine receptor site, thereby enhancing inverse agonist activity.

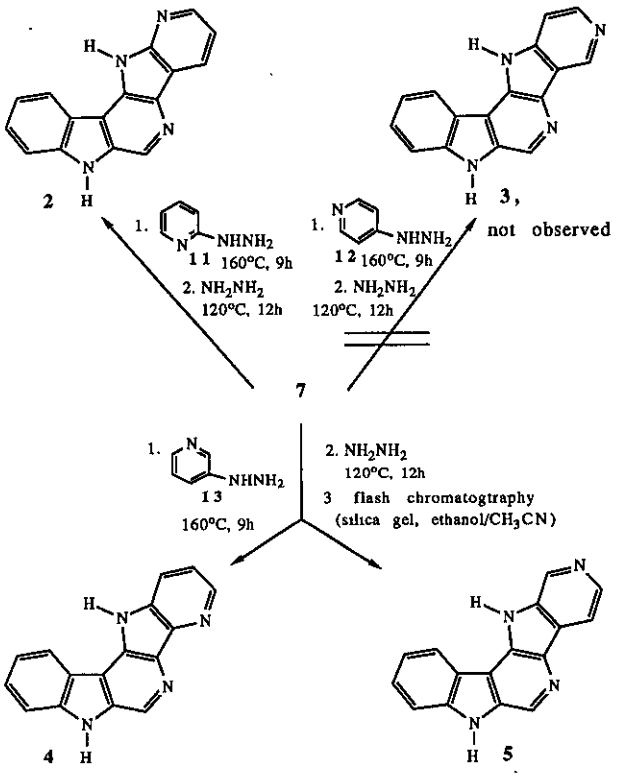
The synthesis of azapyridodiindoles **2, 4** and **5** is based on chemistry previously developed in our laboratory[1] in combination with the Fischer indole cyclization, and is outlined in Scheme I for one of the azapyridodiindoles. The oxidation of 2-benzoyl-1,2,3,4-tetrahydronorharmane **6** with DDQ, according to published procedures,[6,7] provides the 3-acylindole **7** in reasonable yield.[1,7] Treatment of **7** with 2-hydrazinopyridine provides the hydrazone **8**; however, acid-catalyzed Fischer indole cyclization (*via* **9**) was not attempted at this stage. It is known that acid-catalyzed Fischer indolization of pyridylhydrazones either fails or affords low yields of the desired azapyridodiindoles.[8,9] This is due to deactivation of the pyridine ring by the inductive effect of the nitrogen atom and also by protonation of this pyridine nitrogen atom in the acidic media. The Fischer indole cyclization involves a [3,3] sigmatropic rearrangement, therefore the cyclization will take place thermally.[10,11] When the hydrazone **8** was heated at 160°C for 9 h the Fischer indole cyclization took place, *via* intermediate **9**, to provide the azapyridodiindole **10**. In keeping with previous work in the diindole area,[1] hydrazine was added to the reaction mixture to cleave the benzamide group, while permitting the disproportionation of the 5,6-dihydropyridodiindole to take place to provide **2** in 71% overall yield. It is not known whether hydrazine serves as the oxidizing agent during the disproportionation reaction, or whether some other agent (ie. O_2) is responsible for loss of hydrogen across the 5,6-dihydro bond of **2**.

Scheme I



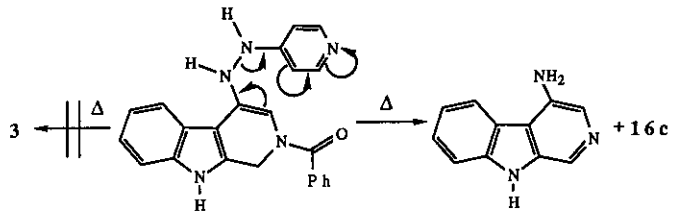
The route outlined in Scheme I serves as a general strategy for synthesis of three of the ring-E substituted azapyridodiindoles (**2, 4, 5**) as illustrated in Scheme II. The 2-hydrazinopyridine **11** is commercially available, while 3-hydrazinopyridine **13** was prepared by the method of Binz and Räth.[12] The required 4-hydrazinopyridine **12** was synthesized from 4-chloropyridine by the method of Mann *et al.*[13] The reaction of **7** with **11**, gave the 1-aza-7,12-dihydropyrido[3,2-b:5,4-b']diindole **2**[3] as illustrated in Scheme I, while heating **7** with 4-hydrazinopyridine **12**, in contrast, provided only 4-amino-β-carboline. On the other hand, treatment of acylindole **7** with the 3-hydrazinopyridine **13** resulted in the formation of both 4-aza-7,12-dihydropyrido-[3,2-b:5,4-b']diindole **4** and 2-aza-7,12-dihydropyrido[3,2-b:5,4-b']diindole **5**, as expected, in view of the mechanism of the Fischer indole cyclization.[8-11,3] The latter regioisomer **5** comprised the majority of the material. As anticipated, when **11** was reacted with **7** in refluxing ethanolic hydrogen chloride, the principal product was 4-amino-β-carboline **15**. This β-carboline derivative was identical to that prepared by an independent route.[14] This result serves to confirm further the need to execute the thermally-induced Fischer indole cyclization in the case of hydrazinopyridines[10,11] rather than the use of the acid-catalyzed process.[14] The reasons for the failure of **14** to

Scheme II



undergo the Fischer-indole cyclization are several-fold. If the aromatic ring of the phenylhydrazine is substituted with deactivating groups, the reaction will yield 4-amino-β-carboline **15**[14] in preference to the product of a Fischer-indole cyclization (Scheme III). The cleavage of the nitrogen-nitrogen bond in **14** must occur in both

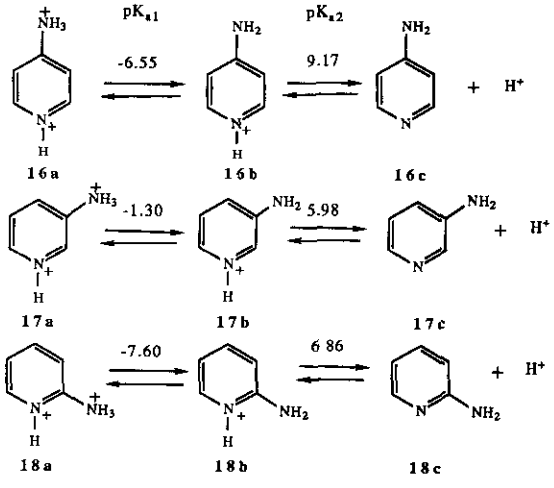
Scheme III



cases to provide either **15** or **3**. In the case of **14**; however, the nitrogen function of the 4-substituted pyridine (from **12**) accepts most of the electron density, rather than permits attack on the β-carboline ring in a Fischer indole cyclization [see **9** (Scheme I)

for an example of a successful cyclization]. In essence, the pyridine nitrogen atom of **14** readily accepts electron density to promote nitrogen-nitrogen bond cleavage of the intermediate **14** to form **15** at the expense of the Fischer indole cyclization. In contrast, both **11** and **13** enter successfully into the Fischer indole cyclization principally because the developing negative charge on the leaving group (**17c** or **18c**) is not delocalized as effectively as it is on 4-aminopyridine **16c**. This is supported by the pK_{a2} values for the three bases **16c** (9.17), **17c** (5.98) and **18c** (6.86).[15] Of the three compounds, 4-aminopyridine **16c** is the stronger base (pyridine nitrogen) because the electron density from the amino group is delocalized more effectively onto the pyridine nitrogen atom. This weakens the nitrogen-nitrogen bond of **14** more than would be expected for **17c** or **18c** (Scheme IV). The situation is more complicated than this, and the pK_{a1}'s of the substituted aminopyridines can be employed to further illustrate this point. Comparison of the pK_{a1} values for **16a** and **17a** clearly indicate that **17a** is a stronger base than **16a** with regard to proton loss from the aniline "like" nitrogen functions. This illustrates that electron density from the 4-amino function is more readily released and delocalized into the pyridine ring of **16a** than into the corresponding ring of **17a**. This would facilitate cleavage of the nitrogen-nitrogen bond in **14** (Scheme III) by stablilization of the developing negative charge in comparison to a hydrazine

Scheme IV



generated from **13**. Moreover, this electron release is supported by the pK_{a2} values for these aminopyridines (Scheme IV). Proton loss from the 4-aminopyridinium species **16b** has a pK_{a2} of 9.17, while the value for **17b** (5.98) is indicative of the higher electron density on the pyridine nitrogen atom of **16c** relative to **17c**.

Comparison of the pK_{a1} values between **16a** and the 2-aminopyridine **18a** cannot be employed here because of charge effects between the two closely disposed cationic functions of **18a**; however, the ratio of the pK_{a2} values for **16b** and **18b** is similar to that for **16b** and **17b**. It is felt, therefore, that the same effect must be operating in the case of **11** (**18c**) as in **13c**(**17c**).

In summary, the pyridine nitrogen atom of 4-aminopyridine **16c** accepts charge density more readily than either **17c** or **18c**, consequently, scission of the nitrogen-nitrogen bond of **14** to expel **16c** is more facile than the analogous process (from **11** or **13**) to furnish **17c** or **18c**. As a result, the desired Fischer indole cyclization occurred between **7** and hydrazinopyridines **11** and **13**, respectively, but not in the case of 4-hydrazinopyridine **12**.

As expected, the three azapyridodiindoles (**2, 4** and **5**) demonstrate enhanced water solubility in comparison to **1**, moreover, azapyridodiindoles **2** and **4** bind to benzodiazepine receptor with potent affinity (see Table). The biological activity of these compounds will be reported elsewhere.

Table *In vitro* Binding Affinity For Benzodiazepine Receptors

	IC_{50}
1	4.0 nM
2	10.6 nM
3	—
4	10.2 nM
5	51.5 nM
diazepam (control)	5.0 nM

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3. Azapyridodiindoles

   2: 7,12-Dihydropyrido[3",2":4',5']pyrrolo[2',3':5,6]pyrido[3,4-b]indole. mp >300°C; ^{1}H NMR (DMSO-d_6, 250 mHz) δ 7.51 (d, 1H, J=5.2 Hz), 7.54 (d, 1H, J=5.2 Hz), 7.80 (t, 1H, J=8.1 Hz), 7.87 (t, 1H, J=8.3 Hz), 8.71 (d, 1H, J=1.6 Hz), 8.73 (d, 1H, J=1.5 Hz), 9.10 (m, 2H), 9.31 (s, 1H).

   4: 7,12-Dihydropyrido[2",3":4',5']pyrrolo[2',3':5,6]pyrido[3,4-b]indole mp >300°C; ^{1}H NMR (DMSO-d_6, 250 mHz) δ 7.52 (t, 1H, J=7.3 Hz), 7.73 (t, 1H, J=6.3 Hz), 7.85 (m, 2H), 8.60 (d, 1H, J=7.95 Hz), 8.76 (d, 1H, J=5.3 Hz), 8.93 (d, 1H, J=7.9 Hz), 9.20 (s, 1H), 12.80 (s, 1H), 13.65 (s, 1H)

   5: 7,12-Dihydro[4",3":4',5']pyrrolo[2',3':5,6]pyrido[3,4-b]indole mp >300°C; ^{1}H NMR (DMSO-d_6, 250 mHz) δ 7.45 (t, 1H, J=7.5 Hz), 7.65 (t, 1H, J=7.5 Hz), 7.80 (d, 1H, J=8.0 Hz), 8.60 (d, 1H, J=7.3 Hz), 8.65 (d, 1H, J=7.2 Hz), 8.85 (d, 1H, J=8.0 Hz), 9.15 (s, 1H), 9.35 (s, 1H), 12.60 (s, 1H), 13.75 (s, 1H).

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