MOLECULAR YARDSTICKS: SYNTHESIS OF HIGHER HOMOLOGS OF 7,12-DIHYDROPYRIDO[3,4-b: 5,4-b']DIINDOLE. PROBING THE DIMENSIONS OF THE BENZODIAZEPINE RECEPTOR INVERSE AGONIST SITE

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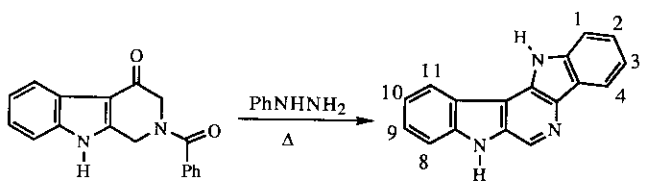
Abstract- The synthesis of some of the higher homologs of 7,12-dihydropyridodiindole **2**, eg. diindoles **3**, **4**, **6**, and **7**, *via* a thermally induced Fischer indole cyclization of **1** with the appropriate naphthylhydrazines and quinolylhydrazines is described. These pyridodiindoles are to be used as molecular yardsticks in defining the spatial dimensions of the benzodiazepine receptor inverse agonist site.

Recently, we reported[1] the synthesis of a novel 7,12-dihydropyrido[3,2-b: 5,4-b']diindole **2** as part of the search for rigid planar ligands with which to study the topography of the benzodiazepine(Bz) binding site. The pyridodiindole **2** was synthesized by reacting phenylhydrazine with 4-oxo-1,2,3,4-tetrahydro-β-carboline **1** (eq. 1). A number of substituted 7,12-dihydropyridodiindoles were prepared as



(1)

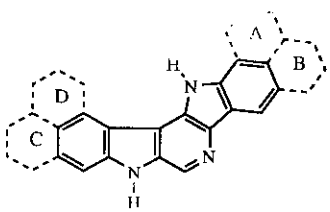
1 **2**

analogs and were found to potently bind *in vitro* (5nM) to benzodiazepine receptor binding sites.[2] Moreover, some of these diindoles behave as inverse agonists at this site. On the basis of the *in vitro* data[2] of a number of substituted pyridodiindoles, it became clear that steric factors were important in determining the binding affinities of these compounds at the Bz receptor site, while electronic factors played a major

role in their *in vivo* activity. For example, diindoles with substituents at positions 1 and 2 of the pyridodiindole system still bound relatively tightly to the receptor site whereas compounds with substituents at positions 3 and 4 showed significantly less affinity.

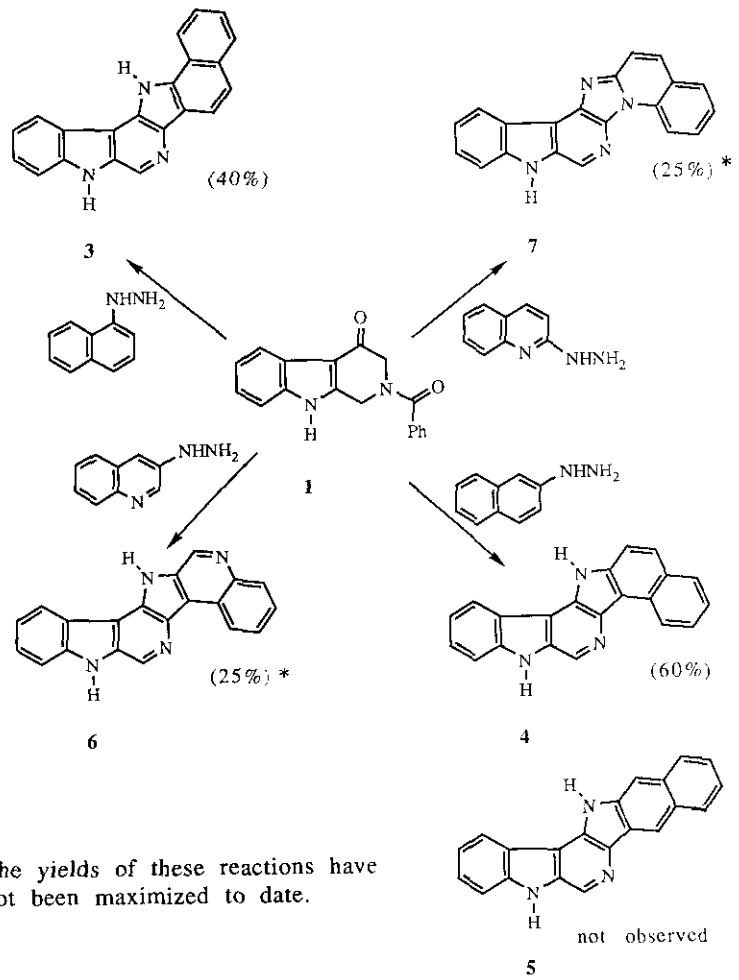
The significance of the *in vitro* data of these pyridodiindoles rests on the rigid, planar nature of these ligands, which have no degrees of conformational freedom, bind with high affinity to Bz receptors and have different pharmacological profiles. Hence, these pyridodiindoles serve as templates or molecular yardsticks with which to probe the structure of the pharmacophore for Bz receptor. Rigid analogs related to these ligands are important to better define the actual dimensions of the receptor binding space in which the ligands interact with the receptor. The goal then is to add on rings A, B, C, D, one or more at a time, to the parent pyridodiindole **2** (Figure 1) to determine the molecular dimensions of the inverse agonist binding site. Communicated here is the initial progress toward this goal.

Figure 1



When 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline **1** was heated with α-naphthylhydrazine at 150-170°C followed by treatment with hydrazine, the pyridodiindole **3** was obtained in 40% yield as the only isolable product (Scheme 1). Similarily, when the ketobenzamide **1** was heated with β-naphthylhydrazine followed by treatment with hydrazine, the pyridodiindole **4** was isolated in 60% yield. Moreover, none of the linear isomer **5** was observed (Scheme 1). It is known[3] that β-naphthylhydrazones and hydrazones of β-tetralone lead only to angularly substituted carbazoles and our results are in agreement with this. When 1-bromo-2-naphthylhydrazine was used in the place of β-naphthylhydrazine in order to obtain the linear isomer,[4] under thermal conditions of the Fischer indole cyclization only decomposition occurred. Furthermore, under acid-catalyzed conditions the angular isomer **4** was obtained, facilitated by the loss of a bromine atom and accompanied by

Scheme 1

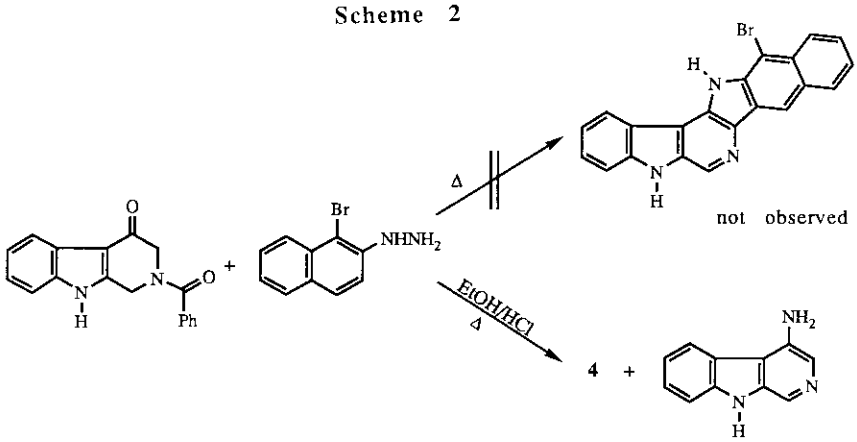


* The yields of these reactions have not been maximized to date.

4-amino-β-carboline (Scheme 2). Clearly under acid catalyzed conditions, Fischer indole cyclization occurs *via* position 1 of the naphthalene ring. At the same time the competing process occurs in which 1-bromo-2-naphthylamine becomes a leaving group and 4-amino-β-carboline is formed.[1]

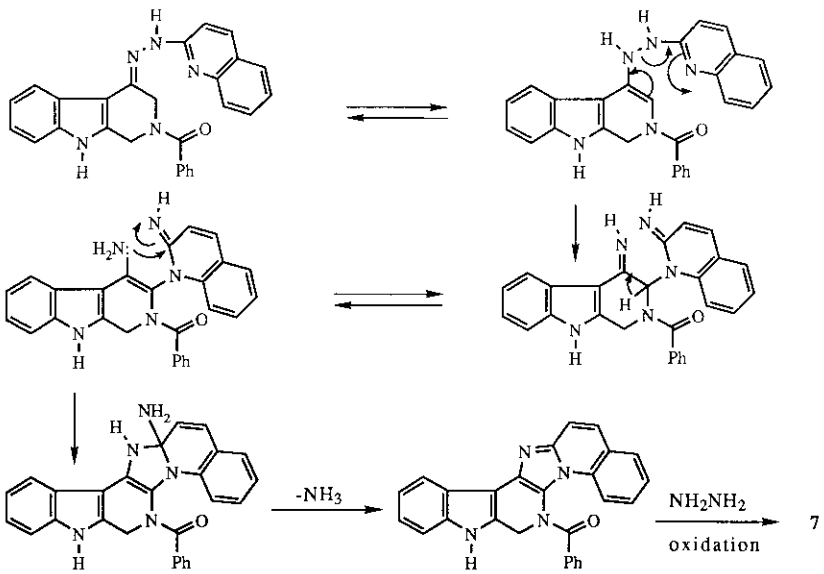
In order to overcome the problem of regiospecificity, as well as to obtain more water soluble analogs,[5] it was decided to react 3-quinolylhydrazine and 2-quinolylhydrazine with the ketobenzamide **1** (Scheme 1). With 3-quinolylhydrazine, the angular isomer **6** was obtained, while in the case of 2-quinolylhydrazine, the reaction took a different course and the rearranged product **7** was obtained. There

Scheme 2



are very few cases[6] in which 2-quinolylhydrazine has been used in the Fischer indole cyclization in contrast to quinolylhydrazines substituted at positions 3, 4, 6, or 7. The azabenzodiindole **7** arises as a result of a [3.3]sigmatropic rearrangement *via* the carbon-nitrogen double bond rather than through the carbon-carbon double bond of the pyridine ring system (Scheme 3). This is in contrast to 2-hydrazinopyridine in which the product of the normal Fischer indole cyclization was observed.[5] The evidence for the structure of diindole **7** comes from the examination of the ^{1}H nmr spectrum[7] in which only one indole proton is observed, accompanied by two doublets which represent the signals for the adjacent protons on the pyridine ring of the

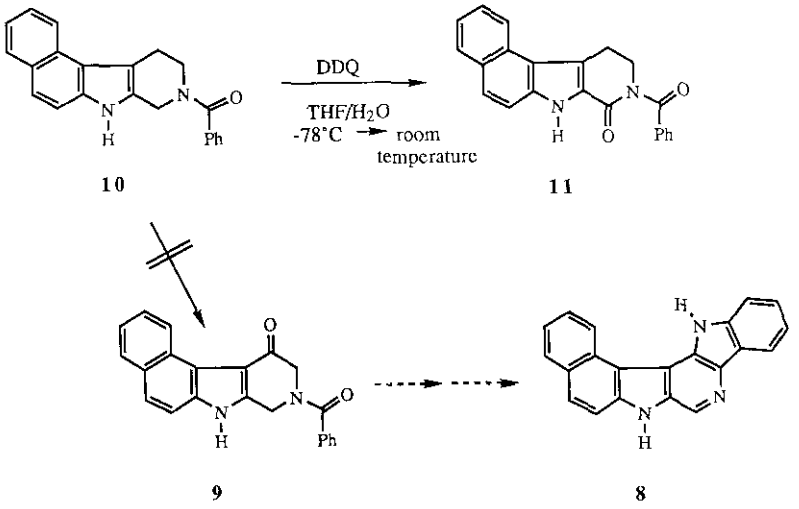
Scheme 3



quinoline system. In the spectrum of pyridodiindoles, the two indole protons are clearly different and both can be observed in the ^1H nmr spectrum[7] (e.g. δ 12.86 and 13.44 for diindole **3**).

Next, attention focused on the synthesis of the pyridodiindole **8**. For this, the corresponding ketobenzamide **9** was required for the Fischer indole cyclization. However, when 2-benzoyl-5,6-benzo-1,2,3,4-tetrahydro-β-carboline[8] **10** was subjected to DDQ oxidation under the standard conditions developed originally by Oikawa and Yonemitsu,[9] only the 1-ketobenzamide **11** was obtained (Scheme 4).

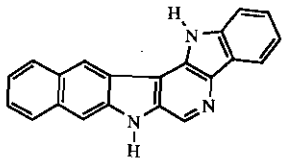
Scheme 4



10 **11**

9 **8**

Currently, efforts continue toward the synthesis of pyridodiindole **8**, as well as **12**, using the corresponding benzindoles whose syntheses were reported recently by Sakamato *et al.*[10]



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As expected, the binding affinities of pyridodiindoles **3**, **4**, **6**, and **7** are in agreement with the model of the pharmacophore for the benzodiazepine inverse agonist site (see Table). Thus, the diindole **3**, which is substituted at the 1,2-positions of the parent pyridodiindole (**2**) ring exhibits a binding affinity at least an order of magnitude tighter than the pyridodiindoles **4**, **6**, and **7** which are substituted at the 3,4-positions of the parent system **2**. Further work in this area is underway and will be reported in due course.

Table. *In vitro* Binding Affinity to Benzodiazepine Receptors.

	(IC_{50})
diazepam(control)	5.0 nM
2	4.0 nM
3	98 nM
4	>>125 nM
6	1030 nM
7	3220 nM

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3. a) B. Cecchetti and E. Ghigi, Gazz. Chim. Ital., 1930, **60**, 185. b) S. A. Bryant and S. G. P. Plant, J. Chem. Soc., 1931, 93. c) H. Plieninger and I. Nogradi, Chem. Ber., 1955, **88**, 1964. d) R. J. Owellen, J. A. Fitzgerald, B. M. Fitzgerald, D. A. Walsh, D. M. Walker, and P. L. Southwick, Tetrahedron Lett., 1967, 1741. e) S. H. Oakeshott and S. G. P. Plant, J. Chem. Soc., 1928, 1940.

4. Y. Murakami and T. Watanabe, J. Chem. Soc., Perkin Trans. I, 1988, 3005. These authors also point out that linear benz[*f*]indoles cannot be prepared by Fischer indolization of 2-naphthylhydrazones which carry a variety of substituents at position C-1.

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6. a) B. Robinson, Chem. Rev., 1963, **63**, 373 and references cited therein. b) B. Robinson, Chem. Rev., 1969, **69**, 227. c) P. A. Crooks and B. Robinson, Chem. Ind., 1967, 547.

7. Physical data for pyridodiindoles **3**, **4**, **6**, and **7** crystallized as hydrochloride salts.

3: mp > 300°C; ^{1}H nmr (DMSO-d_6, 500MHz) δ 7.55 (t, J = 8.0Hz, 1H), 7.70 (t, J = 8.0Hz, 1H), 7.80 (t, J = 8.0Hz, 1H), 7.90 (m, 2H) 8.15 (d, J = 8.0Hz, 1H), 8.60 (d, J = 8.0Hz,1H), 9.15 (d, J = 8.0Hz, 1H), 9.25 (s, 1H), 9.30 (d, J = 8.0Hz, 1H), 12.86 (s, 1H), 13.44 (s, 1H); mass spectrum (CI, CH_4) m/z 308 (M^+ + 1).

4: mp > 300°C; ^{1}H nmr (DMSO-d_6, 500MHz) δ 7.50 (t, J = 8.0Hz, 1H), 7.60 (t, J = 8.0Hz, 1H), 7.75 (t, J = 8.0Hz, 1H), 7.80 (t, J = 8.0Hz, 1H), 8.00 (d, J = 8.0Hz, 1H), 8.10 (d, J = 8.0Hz, 1H), 8.15 (d, J = 8.0Hz, 1H), 9.10 (d, J = 8.0Hz, 1H), 9.15 (s, 1H), 9.45 (d, J = 8.0Hz, 1H), 12.50 (s, 1H), 13.50 (s, 1H); mass spectrum (CI, CH_4), m/z 308 (M^+ + 1).

6: mp > 300°C; ^{1}H nmr (DMSO-d_6, 500MHz) δ 7.45 (t, J = 8.0Hz, 1H), 7.65 (t, J = 8.0Hz, 1H), 7.70 (t, J = 8.0Hz, 1H), 7.80 (m, 2H), 8.20 (d, J = 8.0Hz, 1H), 8.90 (d, J = 8.0Hz, 1H), 9.15 (s, 1H), 9.45 (s, 1H), 9.45 (d, J = 8.0Hz, 1H), 12.40 (s, 1H), 13.20 (s, 1H); mass spectrum (CI, CH_4) m/z 309 (M^+ + 1).

7: mp > 300°C; ^{1}H nmr (DMSO-d_6, 500MHz) δ 7.40 (t, J = 8.0Hz, 1H), 7.65 (t, J = 8.0Hz, 1H), 7.75 (t, J = 8.0Hz, 1H), 7.80 (d, J = 8.0Hz, 1H), 8.00 (d, J = 8.0Hz, 1H), 8.05 (t, J = 8.0Hz, 1H), 8.20 (d, J = 7.0Hz, 1H), 8.30 (d, J = 8.0Hz, 1H), 8.80 (d, J = 8.0Hz, 1H), 9.10 (s, 1H), 10.10 (d, J = 7.0Hz, 1H), 12.25 (s, 1H); mass spectrum m/z 308 (M^+).

8. For the preparation of this compound see T. J. Hagen, K. Narayanan, J. Names, and J. M. Cook, J. Org. Chem., 1989, **54**, 2170.

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