Studies on Synthetic Approaches to 1*H*- and 2*H*-Indazolyl Derivatives

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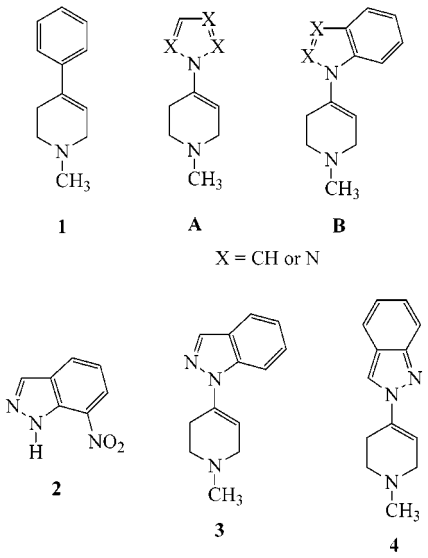
Synthetic approaches designed to provide 1*H*- and 2*H*-indazolyl derivatives of potential biological interest are reported. Special emphasis has been placed on the characterization of indazolylpyridinium products generated from reactions between indazole and 4-chloro-1-methylpyridinium iodide under various conditions. A stable mixture consisting of 3 parts of the 1*H*-isomer **9** to 1 part of the 2*H*-isomer **10** was obtained at room temperature in the presence of the base 2,2,6,6-tetramethylpiperidine (TMP). The same reaction at 60 °C gave only the 1*H*-isomer **9**. At 100 °C in the absence of TMP only the 2*H*-isomer **10** was formed. The isomerization of **10** to **9** was found to proceed quantitatively at 60 °C but only in the presence of TMP. The effects of temperature and base on the course of these reactions are rationalized in terms of kinetic and thermodynamic parameters.

The monoamine oxidases A and B (MAO-A and MAO-B) are outer mitochondrial membrane bound flavoenzymes[1] that catalyze the oxidative deamination primarily of straight chain primary and secondary amines.[2] The Parkinsonian-inducing proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [(MPTP) (**1**)] is one of the rare examples of a cyclic tertiary amine that displays MAO substrate properties.[3] As part of our studies designed to explore the structural features that characterize MAO-A and MAO-B substrates,[4] we have synthesized a series of MPTP analogues in which the 4-substituent is a nitrogen-linked triazolyl, pyrrolyl, imidazolyl, benzotriazolyl, indolyl, and indazolyl group (represented by structures **A** and **B**).[5] The indazolyl analogues have become of greater interest following reports that 7-nitroindazole (**2**) displays neuroprotective properties[6] that may be linked to its inhibition of neuronal nitric oxide synthase[7] and/or MAO-B.[8] These reports and our interests in the design of tetrahydropyridinyl prodrugs that may be bioactivated by MAO[9] have prompted us to examine reaction pathways for the preparation of a variety of 1*H*- and 2*H*-indazolyltetrahydropyridinyl derivatives. In this paper we present the results of our studies to develop regiochemically defined and efficient synthetic methods for the preparation of the indazolyl derivatives **3** and **4**.



1 A B 2 3 4

Results and Discussion

A previously reported synthetic route to **3** proceeded through the pyridinyl intermediate **7** that was prepared by nucleophilic aromatic substitution of 4-fluoropyridine (**5**) with indazole (**6**) in the presence of NaH (Scheme 1).[8] The structure assignment for **7** vs the isomeric 2-(4-pyridinyl)indazole (**8**), however, was not fully defended. Therefore, the present study started with a more detailed examination of this reaction.

Analysis of the reaction mixture by gas chromatography−electron ionization mass spectrometry (GC-EIMS) showed the slow formation of a mixture of **7** and **8** at 100 °C. A detailed study of reaction conditions established that the solvent (DMF, DMSO, THF), base (NaH, LiH,

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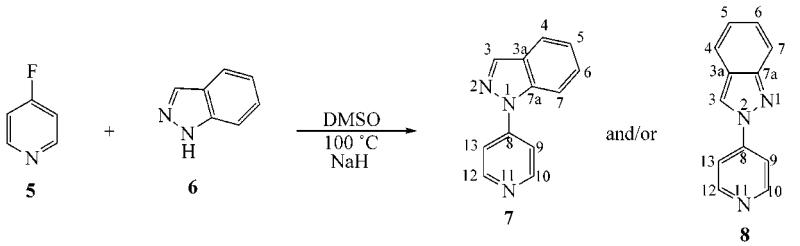
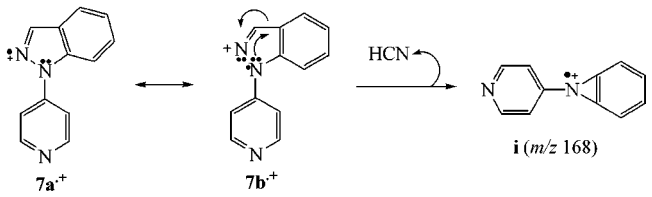
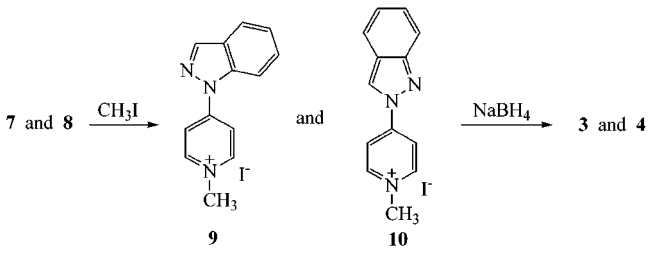
Scheme 1



Scheme 2



Scheme 3



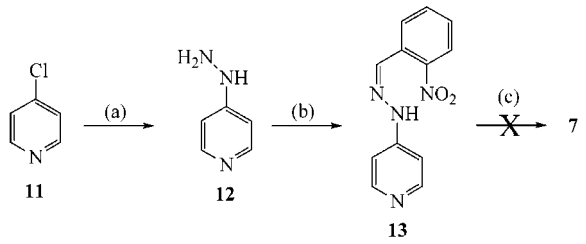
KH), temperature (0 to 100 °C), and time (1 to 24 h) had little effect on the course of the reaction except that the reaction proceeded faster at higher temperatures.

Column chromatography provided both indazolylpyridines in pure form and modest yield. Comparison of their ^{1}H NMR spectra led to tentative structure assignments. On the basis of reported assignments for the corresponding phenyl analogues,[10] the 2*H*-isomer was assigned to the compound displaying the signal for the C-3 proton (8.54 ppm) downfield relative to the chemical shift for the C-3 proton (8.26 ppm) of the 1*H*-isomer. Unambiguous assignments of the structures for **7** and **8** were obtained by a ^{1}H double-pulsed field gradient spin-echo (DPFGSE) 1D NOE experiment.[11] Irradiation of the signal for the C-3 proton of one isomer resulted in an enhancement of the signals for the protons attached to C-4, C-9, and C-13, consistent with the 2*H*-isomer. As required, the corresponding experiment with the 1*H*-isomer led to the enhancement of the signal for the proton attached to C-4 only. On the other hand, irradiation of the signal for the C-7 proton of the 2*H*-isomer lead to the enhancement of the signal for the C-6 proton while the corresponding experiment with the 1*H*-isomer showed enhancements of the signals for the C-6, C9, and C-13 protons.

The GC-EI mass spectral data provided additional evidence for these assignments. Although very similar, the mass spectra can be distinguished by the presence in one isomer of an intense fragment ion (**i**) at *m*/*z* 168 which corresponds to the loss of HCN (27 amu) from the molecular radical cation **7**$^{\bullet+}$. This fragment ion is weak in the spectrum of the 2*H*-isomer. Loss of HCN from 1*H*-isomer can be rationalized as shown in Scheme 2. To cleave HCN from the corresponding radical cation of the 2*H*-isomer, the pyridinyl group first must migrate to an adjacent atom.

Compounds **7** and **8** were converted to the corresponding pyridinium species **9** and **10** which were reduced with $NaBH_4$ to give the desired tetrahydropyridinyl derivatives **3** and **4**, respectively (Scheme 3).

Scheme 4[a]



[a] Reagents and conditions: (a) $NH_2-NH_2\cdot H_2O$, *n*-BuOH, Δ, 55%; (b) *o*-nitrobenzaldehyde, refluxing EtOH, 53%; (c) KOH, EtOH.

The technical difficulties of preparing 4-fluoropyridine (see Experimental Section), and the modest yields led us to explore alternative approaches to the pyridinyl substituted 1*H*- and 2*H*-indazolyl systems. Several ring syntheses, based on older literature reports describing the preparation of the corresponding phenyl analogues, were examined. For example, treatment of 4-hydrazinylpyridine (**12**), obtained from 4-chloropyridine (**11**), with *o*-nitrobenzaldehyde gave hydrazone **13** (Scheme 4). Unlike the corresponding phenylhydrazone,[12] however, treatment of **13** with base failed to yield the desired ring closed product **7**, presumably because of the reduced nucleophilicity of the attacking nitrogen of **13**.

A more recent report describes the successful base-catalyzed displacement of fluorine from *o*-fluorobenzaldehyde (**14**) by various nucleophiles.[13] Since the indazolyl anion was effective in this reaction, the synthesis of **7** was attempted via intramolecular displacement of the fluorine atom in the intermediate pyridinylhydrazone **15** that was obtained from the reaction of **12** with **14** (Scheme 5). Attempts to convert **15** to **7**, however, failed under a variety of reaction conditions.

A final ring closure reaction, based on an early report describing the synthesis of phenylindazolyl derivatives through the reductive cyclization of *o*-nitrobenzylamines,[14]

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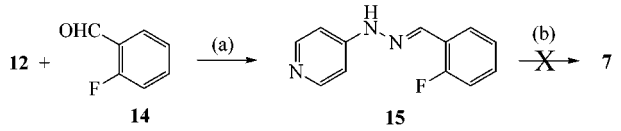
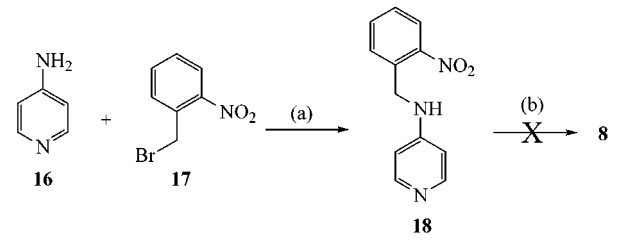
Scheme 5[a]



[a] Reagents and conditions: (a) refluxing EtOH/molecular sieves; (b) DMF/NaH or DMSO/K_2CO_3 or EtOH

Scheme 6[a]



[a] Reagents and conditions: (a) refluxing EtOH; (b) reducing agent.

was examined (Scheme 6). The intermediate 4-(*o*-nitrobenzyl)aminopyridine (**18**), prepared from 4-aminopyridine (**16**) and 2-nitrobenzyl bromide (**17**), however, failed to cyclize to **8** when treated with Sn/HCl, Zn/HCl, or Zn/HOAc.

These failures led us to consider the reaction between 4-chloro-1-methylpyridinium iodide (**19**) and indazole. Initial stability studies with NaH as base showed that **19** underwent hydrolysis to 1-methyl-4-pyridone upon work up of the reaction mixture. Compound **19**, however, proved to be stable in the presence of the sterically hindered and weaker base 2,2,6,6-tetramethylpiperidine (TMP). On the basis of the sluggish reactivity of the indazolyl anion with 4-fluoropyridine, the reaction between **19** and indazole in the presence of 2 equiv of TMP was run first in refluxing DMF. The reaction mixture was examined by GC-EIMS after 24 h by which time the starting materials had been consumed. Unlike the reaction with 4-fluoropyridine, only one product was detected. Comparison of its GC-EI mass spectral features with those of the synthetic standards obtained earlier from the reaction with 4-fluoropyridine (Scheme 1) led to the identification of this compound as 1-(4-pyridinyl)indazole (**7**). One interpretation of these data assumes that **7** was formed by thermal N-demethylation of the *N*-methylpyridinium product **9** in the injection port of the GC. As expected, GC-EI mass spectral analysis of **9** showed only a single peak that corresponded to that of **7**. Upon workup of the above reaction mixture, however, the pyridinyl compound **7**, and not the expected pyridinium species **9**, was obtained. Consequently, **9** must be undergoing thermal N-demethylation in this reaction.

The N-demethylation observed during the course of this high-temperature reaction prompted a follow-up study employing milder reaction conditions. To detect the formation of the anticipated intermediate pyridinium species, the progress of the reaction was monitored both by GC-EIMS and HPLC-diode array (HPLC-DA). At room temperature in the presence of 2 equiv of TMP, the GC-EI mass spectral tracing obtained after 15 min showed a decrease in the intensity of the peak corresponding to indazole and the formation of two isomeric products ($M^{\bullet+}$ 195 Da) in a ratio of 3 (the 1*H*-isomer **7**) to 1 (the 2*H*-isomer **8**). This ratio remained constant throughout the course of the reaction. The HPLC-DA tracing also showed the appearance of two peaks with retention times and UV spectral characteristics corresponding to those of synthetic **9** (three parts) and **10** (one part); no evidence for the pyridinyl products **7** and **8** was observed. Consequently, the elevated temperatures initially used to promote this reaction are not required.

The reaction mixture turned cloudy by 30 min and crystals began to separate. By 48 h, almost all of the starting material had been consumed. The ^{1}H NMR spectrum of the crystalline product that separated during the course of the reaction proved to be identical to the ^{1}H NMR spectrum of **9** obtained from the N-methylation of **7**. The ^{1}H NMR spectrum of the less abundant product, which was isolated in crystalline form from the filtrate, was identical to the spectrum of **10** obtained from the N-methylation of **8**. Consequently, the reaction of **19** with indazole at room temperature in the presence of TMP proceeds smoothly to yield a mixture of the isomeric products **9** and **10** (Scheme 7) both of which undergo thermal N-demethylation when subjected to GC-EIMS.

The production of both isomeric pyridinium products **9** and **10** at room temperature but only the 1*H*-isomer **9** (isolated as **7**) under reflux conditions suggested that the 2*H*-isomer **10** was isomerizing to **9** at elevated temperatures. The possible thermal promoted reversal of the addition−elimination reaction leading to **10** (Scheme 7) with the eventual accumulation of the thermodynamically more stable 1*H*-isomer **9** was evaluated by examining the stability of the pure 1*H*- and 2*H*-isomers **9** and **10** by HPLC-DA. Unexpectedly, both compounds proved to be stable even when heated in DMF at 150 °C. In the presence of 1 equiv of TMP, compound **10** also was stable at room temperature but isomerized quantitatively (48 h) to **9** at 60 °C. As expected, the 1*H*-isomer **9** was stable under these conditions. The irreversible isomerization of **10** to **9** was viewed as evidence for the reversal of the addition−elimination reaction leading to **10** and the subsequent irreversible formation of the thermodynamically more stable 1*H*-isomer **9**. Consistent with this interpretation, energy calculations on indazole indicate that the 1*H*-isomer is more stable than the 2*H*-isomer by 4 kcal/mol.[15]

The irreversible, base-promoted isomerization of **10** to **9** at 60 °C suggested that the reaction of 4-chloro-1-methylpyridinium iodide (**19**) with indazole in the presence of a sufficient excess of TMP to catalyze the isomerization reaction (Scheme 7) should progress at 60 °C to yield, eventually, only the more stable 1*H*-isomer **9**. This proved to be the case. HPLC-DA analysis of this reaction mixture in the presence of 2 equiv of TMP documented the time-dependent increase in the peak ratios of **9** to **10**. By 48 h only the peak corresponding to **9** was present in the tracing. This product was isolated in pure, crystalline form in 76% yield.

The requirement of TMP for the isomerization of **10** to **9** led us to examine the TMP dependence of the reaction of indazole with 4-chloro-1-methylpyridinium iodide. A reaction, in fact, did take place at 100 °C in the absence of TMP. In this case, however, only the 2*H*-isomer was formed. This regiospecificity may be rationalized by the higher energy, charge-localized intermediate **20** leading to **9** compared to the lower energy, resonance-stabilized intermediate **21** leading to **10**. This analysis

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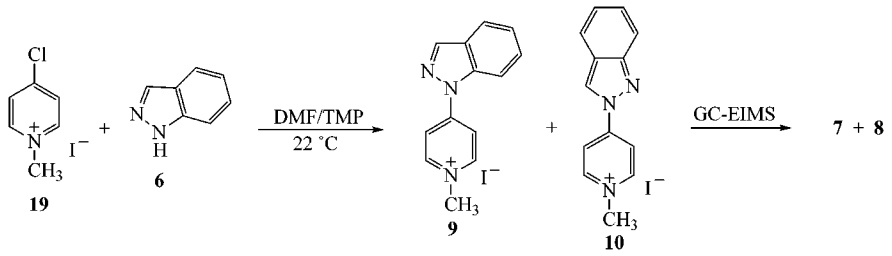
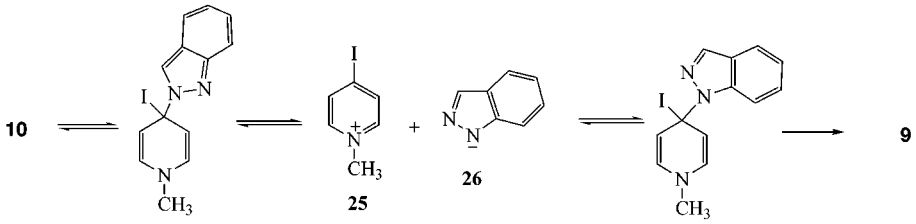
Scheme 7



19 **6** **9** **10**

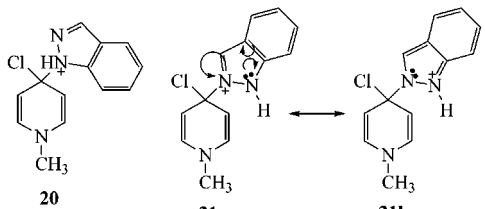
Scheme 8



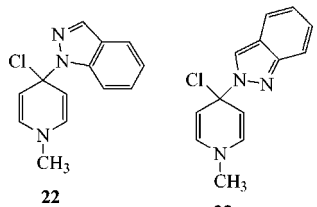
10 **24** **25** **26** **27** **9**

was supported by AM1 semiempirical calculations that predicted that the enthalpy of formation for **20** would be higher than the enthalpy of formation for **21** by 9 kcal/mol. The exclusive formation of the 2*H* isomer **10** in the absence of TMP may be viewed as consistent with the obligatory role of the indazolyl anion for production of the more stable 1*H*-isomer **9**.

It will be recalled that the reaction between indazole and the pyridinium reagent **19** at room temperature in the presence of TMP (Scheme 7) leads to the formation of a stable, 3 to 1 mixture of the 1*H*- and 2*H*-pyridinium isomers **9** and **10**, respectively. This product ratio favoring the 1*H*-isomer may be kinetically determined. Calculations predict that the energy of the tetrahedral intermediate **22** generated by N-1 attack of the indazolyl anion will be favored over the corresponding intermediate **23** generated by N-2 attack by 5 kcal/mol.



20 **21a** **21b**



22 **23**

If the isomerization reaction is a consequence of the reversibility of the addition−elimination reaction shown in Scheme 7, then, upon warming the 2*H*-isomer **10** must be converted to the 4-iodo tetrahedral addition product **24** that collapses to the 4-iodo-1-methylpyridinium species **25** and the indazolyl anion **26**. Reaction of **25** with **26** then gives, irreversibly, the 1*H*-isomer **9** via intermediate **27** (Scheme 8).

We postulated a catalytic role for TMP in this reaction to maintain the indazole reagent in the anionic form following its protonation by a trace amount of water contaminating the reaction mixture. In agreement with this proposal, this reaction was found to go to completion in the presence of only 0.1 equiv of TMP. On the other hand, all efforts to exclude water from the isomerization reaction mixture failed to overcome the requirement for TMP. Consequently, an alternative mechanism for the isomerization reaction in which TMP acts as a nucleophile instead of a base was considered.[16] As shown in Scheme 9, attack of TMP at C-6 (C-3 and C-4 are also possible reaction centers) could increase the nucleophilicity of N-1 and lead to the spirodiazirinyl intermediate **28**. This addition product would be expected to collapse with the preferential formation of the more stable 1*H*-pyridinium species **9**. A distant analogy to the proposed initial step in this sequence is the reported Michael addition reaction between TMP and electron-deficient acetylenes.[17]

According to the above mechanism, replacement of TMP with piperidine, a less hindered amine of comparable basicity,[18] would be expected to increase the rate of the isomerization reaction. In this case, however, the pyridinium system underwent aminolysis to give indazole and the known 1-methyl-4-piperidin-1-yl species **29** (Scheme 10) which was characterized by comparison of its spectral properties with a synthetic standard.[19]

The effects of basicity vs nucleophilicity on the isomerization reaction was examined next with triethylamine. The calculated enthalpies of formation indicate that the TMP-derived intermediate **28** is favored over the corresponding triethylamine-derived intermediate **30** by about 5 kcal/mol. Consistent with these calculations and the pathway presented in Scheme 9, the triethylamine-promoted isomerization reaction proceeded at a compa-

(16) The authors acknowledge with thanks this suggestion made by a reviewer of this manuscript.

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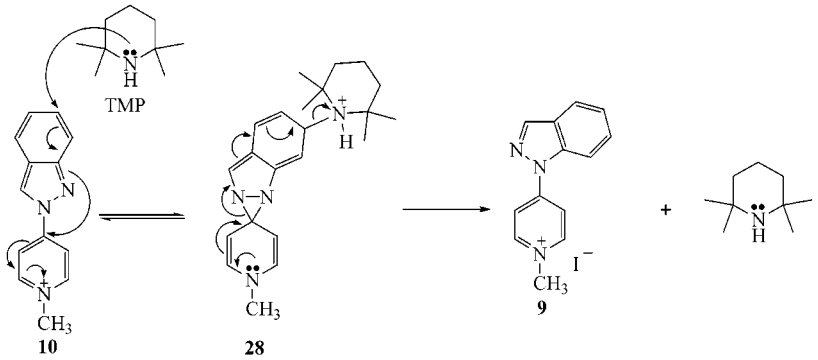
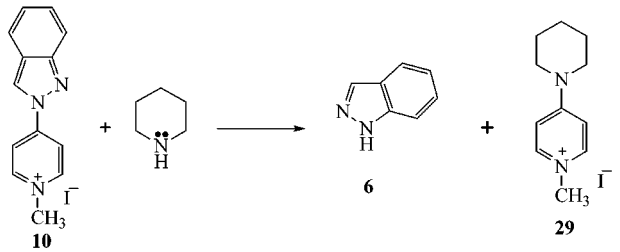
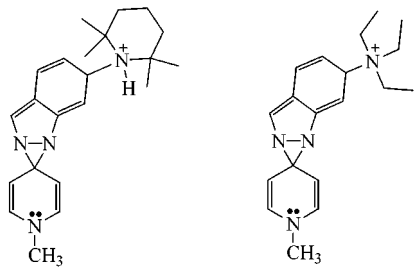
Scheme 9



Scheme 10



rable rate to that observed with TMP at 60 °C but only when the reaction mixture was heated to 90 °C.



Our interpretation of the results of these experiments is summarized in Scheme 11. The reaction between indazole and the pyridinium reagent **19** at room temperature in the presence of an excess of TMP leads irreversibly to the kinetically determined formation of a stable 3 to 1 mixture of the 1*H*- and 2*H*-pyridinium isomers **9** and **10**, respectively. The preference for the 1*H*-isomer may be rationalized by the greater stability of **22** vs **23**, the intermediate that proceeds to give the 2*H*-isomer. At 60 °C, a second reaction takes place in which TMP promotes the isomerization of **10** to **9** most likely via intermediate **28**, i.e., by the same reaction pathway that has been invoked to rationalize the isomerization of pure **10** to **9** in the presence of TMP (Scheme 9). An analogous isomerization of the 2*H*-pyridinylindazole **8** would not be expected and hence both **7** and **8**, formed in the reaction of 4-fluoropyridine with indazole in the presence of TMP (Scheme 1), survive. Finally, the reaction of neutral indazole with 4-chloro-1-methylpyridinium iodide that yields exclusively the less stable 2*H*-isomer **10** may be rationalized in terms of the lower energy barrier that must be mounted to form to the charge-delocalized intermediate **21** leading to **10** relative to the corresponding barrier to reach **20** leading to **9**.

These insights should prove valuable in our future efforts to prepare a variety of tetrahydropyridinylindazoles of biological interest.

Experimental Part

Caution! When working with the very reactive and explosive anhydrous hydrogen fluorine gas, special body protection and other safety precautions must be taken. The reactions must be carried out using polyethylene bottles and tubes.

General. THF and Et_2O were distilled from sodium/benzophenone ketyl. Toluene, dichloromethane, and acetonitrile were distilled over CaH_2. Acetone was distilled over K_2CO_3. DMF was distilled over P_2O_5 and stored over molecular sieves. DMSO was stored over molecular sieves. All reactions were conducted using flame-dried glassware under an atmosphere of dry nitrogen. Melting points are uncorrected. All GC-EI mass spectral data were obtained using an initial oven temperature of 45 °C followed by a ramp of 25 °C/min to a final temperature of 290 °C with a solvent delay of 2 min and an injection port temperature of 220 °C. HPLC-DA analyses were performed using a 250 mm × 4.6 mm Zorbax SB−C8 5 μm column (reverse phase) with an in-line precolumn filter (2 μM, Upchurch Scientific Inc.) using isocratic conditions of 50% acetonitrile and 50% aqueous buffer containing 0.6% acetic acid and 1% triethylamine. Compounds **12**,[20] **19**,[21] and **29**[19] were prepared according to the literature and showed the expected ^{1}H NMR and mp behavior. The reduction of **9** to give **3** was carried out as previously described[5] and showed expected ^{1}H NMR and mp behavior.

HCl Salt of 4-Fluoropyridine (5·HCl). A suspension of 4-aminopyridine (7.06 g, 75.1 mmol) in 40 mL of anhydrous dichloromethane was added with stirring over a period of 15 min at −78 °C to anhydrous HF (31.2 g, 1.6 mol) that had been condensed in a polyethylene bottle at −78 °C. The reaction mixture was allowed to warm to −5 °C, and $NaNO_2$ (6.22 g, 90.1 mmol) was added portionwise over a 10 min period while maintaining the temperature between −5 and 0 °C. The mixture was allowed to warm to room temperature and then was heated to 40−50 °C for 1.5 h. Dichloromethane (50 mL) was added in one portion. After cooling to −10 °C, 30% aqueous NH_4OH was added dropwise over 10 min to adjust the pH to 10. The resulting emulsion was broken by filtration, and the reaction mixture was extracted with dichloromethane. After drying over silica, HCl gas was bubbled through the solution. The solvent was evaporated in vacuo to yield 4.9 g (37.1 mmol, 50%) of a yellowish salt: mp 99 °C (reported[22] mp 100 °C); ^{1}H NMR (CD_3OD, 360 MHz) δ 9.34 (m, 2H), 7.98 (m, 2H); ^{13}C NMR (CD_3OD, 90 MHz) δ 174.8, 147.5, 117.3;[23] UV (MeOH) 206, 240, 288 nm.

4-(1*H*-Indazolyl)pyridine·HCl (7·HCl). NaH (395 mg, 16.5 mmol) was added portionwise with stirring at 0 °C to a

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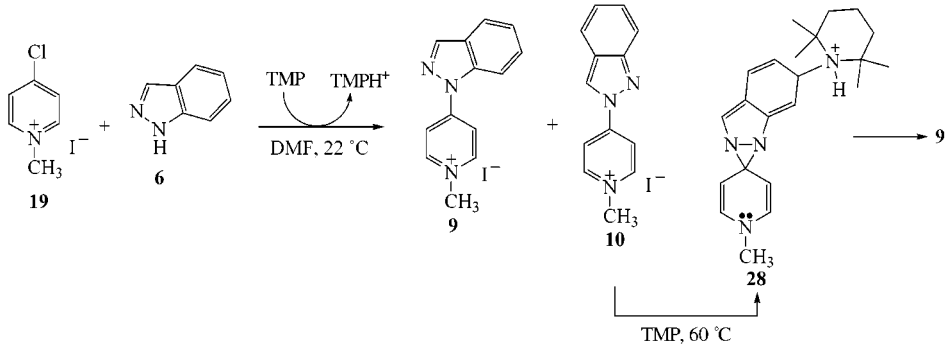
Scheme 11



solution of indazole [**6** (1.6 g, 13.6 mmol)] in 15 mL of DMSO. In another flask, NaH (395 mg, 16.5 mmol) was added portionwise with stirring at 0 °C to a solution of the HCl salt of **5** (1.5 g, 11.3 mmol) in 15 mL of DMSO. After 10 min, both solutions were combined, and the resulting reaction mixture was stirred for 18 h at 100 °C. After cooling, the DMSO was extracted with 50% aqueous ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated in vacuo to yield a crude product that was separated by column chromatography eluting with hexane:ethyl acetate (80:20) to provide 652 mg (3.3 mmol, 30%) of **7** as a yellowish oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.73 (m, 2H), 8.26 (d, J = 0.9 Hz, 1H), 7.90 (dddd, J = 0.9 Hz, J = 0.9 Hz, J = 0.9, J = 8.5 Hz, 1H), 7.83 (ddd, J = 1.1 Hz, J = 1.1 Hz, J = 8.1 Hz, 1H), 7.78 (m, 2H), 7.52 (ddd, J = 1.2 Hz, J = 7.0 Hz, J = 8.4 Hz, 1H), 7.30 (ddd, J = 0.8 Hz, J = 7.0 Hz, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 151.2, 147.0, 137.6, 128.2, 126.4, 122,6, 121.9, 120.9, 115.2, 110.9; GC-EIMS *m*/*z* (rel int) 195 ($M^{\cdot+}$ 100), 168 (40), 153 (2), 140 (13), 114 (6), 105 (6), 78 (9), 51 (47); UV (MeOH) 208, 256, 305 nm. This product was converted to its HCl salt in anhydrous methanolic HCl. The salt was precipitated with Et_2O and was crystallized from MeOH (90% yield): mp 222−224 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 8.92 (m, 2H), 8.76 (d, J = 0.9 Hz, 1H), 8.47 (m, 2H), 8.34 (dddd, J = 0.8 Hz, J = 0.8 Hz, J = 0.8, J = 8.6 Hz, 1H), 8.03 (ddd, J = 1.0 Hz, J = 1.0 Hz, J = 8.0 Hz, 1H), 7.73 (ddd, J = 1.1 Hz, J = 7.1 Hz, J = 8.4 Hz, 1H), 7.49 (ddd, J = 0.7 Hz, J = 7.1 Hz, J = 7.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 152.1, 143.6, 141.6, 138.2, 129.6, 127.1, 124.3, 122.6, 115.1, 112.6; UV (MeOH, nm) 208, 256, 321, 332.

4-(2*H*-Indazolyl)pyridine (8). Continued elution of the column with hexane:ethyl acetate (70:30) gave 589 mg (3.0 mmol, 27%) of **8** as white crystals: mp 120−121 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.76 (m, 2H), 8.54 (d, J = 0.9 Hz, 1H), 7.89 (m, 2H), 7.76 (dddd, J = 0.9 Hz, J = 0.9 Hz, J = 0.9, J = 8.5 Hz, 1H), 7.70 (ddd, J = 1.1 Hz, J = 1.1 Hz, J = 8.5 Hz, 1H), 7.35 (ddd, J = 1.1 Hz, J = 6.6 Hz, J = 8.8 Hz, 1H), 7.13 (ddd, J = 0.9 Hz, J = 6.6 Hz, J = 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 151.5, 150.8, 146.9, 128.0, 123.5, 123.2, 120.6, 120.1, 118.3, 114.3; GC-EIMS *m*/*z* (rel int) 195 ($M^{\cdot+}$ 100), 168 (21), 155 (1), 140 (8), 118 (8), 91 (6), 78 (15), 51 (35); UV (MeOH) 205, 240, 303 nm. Anal. Calcd for $C_{12}N_3H_9$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.32; H, 4.77; N, 21.22.

4-(1*H*-Indazolyl)-1-methylpyridinium Iodide (9). 4-(1*H*-Indazolyl)pyridine [**7** (246 mg, 1.2 mmol)] was dissolved in 20 mL of acetone. Iodomethane (341 mg, 2.4 mmol) was added dropwise while stirring. The resulting reaction mixture was stirred for 18 h at 25 °C. The mixture was filtered to give 404 mg (1.2 mmol, 99%) of **9** as a tan solid: mp 261−263 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): δ 8.94 (m, 2H), 8.77 (d, J = 0.9 Hz, 1H), 8.53 (m, 2H), 8.36 (dddd, J = 0.9 Hz, J = 0.9 Hz, J = 0.9 Hz, J = 8.6 Hz, 1H), 8.02 (ddd, J = 0.9 Hz, J = 0.9 Hz, J = 8.0 Hz, 1H), 7.73 (ddd, J = 0.9 Hz, J = 7.1 Hz, J = 8.5 Hz, 1H), 7.49 (ddd, J = 0.9 Hz, J = 7.2 Hz, J = 8.0 Hz, 1H), 4.3 (s, 3H); ^{13}C NMR (DMSO-d_6, 90 MHz) 150.9, 146.6, 142.1, 138.2, 129.8, 127.2, 124.6, 122.7, 115.2, 112.8, 46.6; UV (MeOH) 209, 224, 266, 335 nm. Anal. Calcd for $C_{13}H_{12}IN_3$: C, 46.31; H, 3.59; N, 12.47. Found: C, 46.41; H, 3.62; N, 12.40.

4-(2*H*-Indazolyl)-1-methylpyridinium Iodide (10). In a similar way 4-(2*H*-indazolyl)pyridine [**8** (589 mg, 3.0 mmol)] and iodomethane (857 mg, 6.0 mmol) gave 930 mg (2.8 mmol, 91%) of **10** as a yellow solid: mp 241−243 °C; ^{1}H NMR (DMSO-d_6, 360 MHz): δ 9.55 (d, J = 1.0 Hz, 1H), 9.13 (m, 2H), 8.77 (m, 2H), 7.83 (ddd, J = 1.1 Hz, J = 1.1 Hz, J = 8.7 Hz, 1H), 7.74 (dddd, J = 1.1 Hz, J = 1.1, J = 1.1 Hz, J = 8.9 Hz, 1H), 7.44 (ddd, J = 1.1 Hz, J = 6.5 Hz, J = 8.9 Hz, 1H), 7.2 (ddd, J = 1.1 Hz, J = 6.5 Hz, J = 8.7 Hz, 1H), 4.4 (s, 3H); ^{13}C NMR (DMSO-d_6, 90 MHz) δ 151.0, 150.2, 147.3, 129.8, 124.7, 124.3, 123.4, 121.5, 117.8, 116.4, 47.1; UV (MeOH) 205, 219, 257, 327 nm. Anal. Calcd for $C_{13}H_{12}IN_3$: C, 46.31; H, 3.59; N, 12.47. Found: C, 46.38; H, 3.62; N, 12.50.

1-Methyl-4-(2*H*-indazolyl)-1,2,3,6-tetrahydropyridine (4). Sodium borohydride (160 mg, 4 mmol) was added in small portions to a suspension of **10** (340 mg, 1 mmol) in 5 mL of methanol at room temperature while stirring. After 2 h methanol was evaporated in vacuo, and the residue was partitioned between dichloromethane and saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo to give 185 mg (0.88 mmol, 88%) of the corresponding tetrahydropyridinyl product **4** free base as a white solid: mp 101−103 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 8.62 (d, J = 0.7 Hz, 1H), 7.69 (ddd, J = 1.1 Hz, J = 1.1 Hz, J = 8.5 Hz, 1H), 7.62 (dddd, J = 1.0 Hz, J = 1.0 Hz, J = 1.0 Hz, J = 8.8 Hz, 1H), 7.26 (ddd, J = 1.1 Hz, J = 6.6 Hz, J = 8.8 Hz, 1H), 7.05 (ddd, J = 0.9 Hz, J = 6.6 Hz, J = 8.4 Hz, 1H), 6.51 (m, 1H), 3.10 (m, 2H), 2.81 (m, 2H), 2.67 (t, J = 5.3 Hz, 2H), 2.32 (s, 3H);^{13}C NMR (DMSO-d_6, 100 MHz) δ 148.0, 134.9, 126.3, 121.5, 121.4, 120.7, 120.4, 117.1, 114.5, 52.8, 51.0, 44.9, 26.2; GC-EIMS *m*/*z* (ret int) 258 ($M^{\cdot+}$, 2), 212 (65), 185 (73), 169 (54), 157 (69), 131 (26), 94 (100), 53 (39); UV (MeOH) 207, 229, 297 nm. Anal. Calcd for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 72.70; H, 7.17; N, 19.55.

2-Nitrobenzaldehyde 4-Pyridinylhydrazone (13). A mixture of 4-hydrazinylpyridine free base **12** (570 mg, 5.2 mmol) and 2-nitrobenzaldehyde (780 mg, 5.2 mmol) in 20 mL of ethanol was heated under reflux for 3 h. The residue obtained after removing the solvent was purified by column chromatography eluting with hexane:ethyl acetate (60:40) followed by ethyl acetate:methanol (95:5). Crystallization from acetone gave 678 mg (2.8 mmol, 53%) of an orange solid: mp 203−205 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 11.31 (s, 1H), 8.35 (s, 1H), 8.26 (m, 2H), 8.15 (dd, J = 1.4 Hz, J = 7.9 Hz, 1H), 7.80 (dd, J = 1.2 Hz, J = 8.2 Hz, 1H), 7.73 (ddd, J = 1.2 Hz, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.56 (ddd, J = 1.4 Hz, J = 7.4 Hz, J = 8.3 Hz, 1H), 7.01 (m, 2H); ^{13}C NMR (DMSO- d_6, 90 MHz) δ 150.1, 149.8, 147.2, 135.2, 133.2, 129.2, 128.9, 127.5, 124.5, 107.2; UV (MeOH) 218, 245, 283, 324 nm. Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.25; H, 4.19; N, 23.06.

2-Fluorobenzaldehyde 4-Pyridinylhydrazone (15). A mixture of 4-hydrazinylpyridine free base **12** (545 mg, 5.0 mmol) and *o*-fluorobenzaldehyde [**14** (620 mg, 5.0 mmol)] in 15 mL of ethanol was heated under reflux for 18 h in the presence of 4 Å molecular sieves. After filtering and removing the solvent, the residue was purified by column chromatography, eluting with hexane:ethyl acetate (9:1) followed by ethyl acetate:methanol (9.5:0.5). The compound was crystallized from ethyl acetate to yield 258 mg (1.2 mmol, 24%) of a yellow solid: mp 204−205 °C; ^{1}H NMR (DMSO-d_6, 360 MHz) δ 11.03

(s, 1H), 8.25 (m, 2H), 8.15 (s, 1H), 7.96 (ddd, J = 1.9 Hz, J = 7.7 Hz, J = 7.7 Hz, 1H), 7.40 (m, 1H), 7.26 (m, 2H), 6.98 (m, 2H); ^{13}C NMR (DMSO- d_6, 90 MHz) δ 161.7, 159.0, 149.9, 132.5, 130.4, 125.9, 124.8, 122.1, 115.9, 107.0; GC-MS (EI) m/z (rel int) 215 ($M^{\cdot+}$ 100), 187 (3), 168 (1), 140 (2), 120 (15), 94 (23), 75 (17), 67 (47); UV (MeOH, nm) 205, 227, 332. HR−CIMS. Calcd. for $C_{12}H_{10}N_3F$: 215.0858756. Found: 215.085907.

4-(2-Nitrophenylamino)pyridine·HBr (18·HBr). A mixture of 2-nitrobenzyl bromide [**17** (1.08 g, 5.0 mmol)] and 4-aminopyridine [**16** (0.47 g, 5.0 mmol)] in 70 mL of ethanol was heated under reflux with stirring for 14 h. Upon cooling, the product crystallized out slowly first at 25 °C and then at −20 °C to give 1.36 g (4.4 mmol, 89%) of pure **18·HBr**: mp 252−253 °C (dec); ^{1}H NMR (CD_3OD), 360 MHz) δ 8.23 (dd, J = 1.4 Hz, J = 8.1 Hz, 1H), 8.10 (m, 2H), 7.78 (ddd, dt like, J = 1.3 Hz, J = 7.5 Hz, J = 7.6 Hz, 1H), 7.69 (ddd, J = 1.4 Hz, J = 7.5 Hz, J = 8.1 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 6.88 (m, 2H), 5.73 (s, 2H); ^{13}C NMR (CD_3OD), 90 MHz) δ 161.2, 149.4, 144.7, 136.0, 132.0, 131.7, 131.3, 127.1, 111.1, 59.3; UV (MeOH) 210, 275 nm. Anal. Calcd for $C_{12}H_{12}BrN_3O_2$: C, 46.47; H, 3.90; N, 13.55. Found: C, 46.57; H, 3.93; N, 13.49.

Reactions between Indazole (6) and 19 in the Presence of TMP. A mixture of TMP (0.68 mL, 4 mmol), indazole [**6** (240 mg, 2 mmol)], and 4-chloro-1-methylpyridinium iodide [**19** (510 mg, 2 mmol)] in 10 mL of DMF was heated under reflux for 18 h. After removing the solvent, the residue was purified by column chromatography eluting with hexane:ethyl acetate (7:3) to yield 245 mg (1.3 mmol, 63%) of 4-(1*H*-indazolyl)pyridine (**7**) as a yellowish oil. The product displayed spectroscopic properties identical to those reported above for **7** obtained from the reaction of indazole with 4-fluoropyridine.

In a second reaction, a mixture of indazole [**6** (240 mg, 2 mmol)], 4-chloro-1-methylpyridinium iodide [**19** (510 mg, 2 mmol)], and TMP (0.37 mL, 2.2 mmol) in 3 mL of DMF was stirred for 48 h at 22 °C. The reaction mixture was cooled to 5 °C, and the resulting solid was collected and recrystallized from methanol to give 365 mg (1.08 mmol, 54%) of 4-(1*H*-indazolyl)-1-methylpyridinium iodide (**9**). The product displayed identical melting point and spectroscopic behavior as reported above for **9** obtained from the methylation of **7**. The mother liquor was cooled to 0 °C, and the resulting crystals were collected to give 50 mg (0.15 mmol, 7%) of 4-(2*H*-indazolyl)-1-methylpyridinium iodide (**10**), identical in every way to the product obtained from the methylation of **8**. In a third a reaction, a mixture of indazole **6** (240 mg, 2 mmol)], 4-chloro-1-methylpyridinium iodide **19** (510 mg, 2 mmol), and TMP (0.68 mL, 4.0 mmol) in 3 mL of DMF was stirred at 60 °C for 36 h. The reaction mixture was cooled to room temperature, and the resulting solid was collected and recrystallized from methanol to give 510 mg (1.51 mmol, 76%) of pure **9**.

Reaction between Indazole (6) and 19 in the Absence of Base. A solution of indazole [**6** (120 mg, 1 mmol)] and 4-chloro-1-methylpyridinium iodide [**19** (260 mg, 1 mmol)] in 3 mL of DMF was stirred for 24 h at 100 °C. The solid which separated upon cooling was recrystallized from methanol to give 180 mg (0.53 mmol and 53%) of 4-(2*H*-indazolyl)-1-methylpyridinium iodide (**10**). The product displayed identical melting point and spectroscopic behavior to those reported above for **10** obtained from the methylation of **8**.

Isomerization of 4-(2*H*-Indazolyl)-1-methylpyridinium Iodide (10) to 4-(1*H*-Indazolyl)-1-methylpyridinium Iodide (9). A mixture of **10** (10 mg, 0.03 mmol) in 0.3 mL of DMF containing TMP (5 μL, 0.03 mmol) was stirred at 60 °C. Aliquots (10 μL) of the reaction mixture in 0.5 mL of acetonitrile were analyzed by HPLC-DA (350 nm). The intensity of the peak (t_R = 3.14 min) corresponding to **10** decreased with time and was replaced with a peak corresponding to **9** (t_R = 3.28 min). By 48 h, the peak corresponding to **10** had disappeared completely and the only peak remaining corresponded to **9**.

In a second reaction, a mixture of **10** (10 mg, 0.03 mmol) in 0.3 mL of DMF containing triethylamine (4 μL, 0.03 mmol) was stirred at 90 °C. Aliquots (10 μL) of the reaction mixture in 0.5 mL of acetonitrile were analyzed by HPLC-DA (350 nm). The intensity of the peak (t_R = 3.14 min) corresponding to **10** decreased with time and was replaced with a peak corresponding to **9** (t_R = 3.28 min). By 48 h, the peak corresponding to **10** had disappeared completely, and the only peak remaining corresponded to **9**.

Aminolysis of 4-(2*H*-Indazolyl)-1-methylpyridinium Iodide (10) To Give Indazole (6) and the 1-Methyl-4-piperidin-1-yl Species 29. A mixture of **10** (10 mg, 0.03 mmol) in 0.3 mL of DMF containing piperidine (3 μL, 0.03 mmol) was stirred at 22 °C. Aliquots (10 μL) of the reaction mixture in 0.5 mL of acetonitrile were analyzed by HPLC-DA (350 nm). The intensity of the peak (t_R = 3.14 min) corresponding to **10** decreased with time and was replaced with two peaks corresponding to **29** (t_R = 3.50 min) and **6** (t_R = 4.37 min). By 30 min, the peak corresponding to **10** had disappeared completely, and the only peaks remaining corresponded to **29** and **6**. Ether addition led to the precipitation of **29**. Its spectral properties were shown to be identical those of synthetic **29**.

Molecular Modeling. AM1 semiempirical calculations were performed using the MacSpartan Plus program (version 1.1.7; Wave function, Irvine, CA) running on a Power Macintosh G3 with a PowerPC G3 processor at 266 MHz.

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