NOVEL PYRIDODIINDOLES, AZADIINDOLES, AND INDOLOPYRIDOIMIDAZOLES VIA THE FISCHER-INDOLE CYCLIZATION

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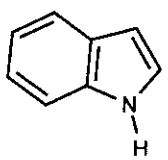
Abstract - The scope of the Fischer-indole cyclization of 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**2**) with various arylhydrazines is reviewed.

INTRODUCTION

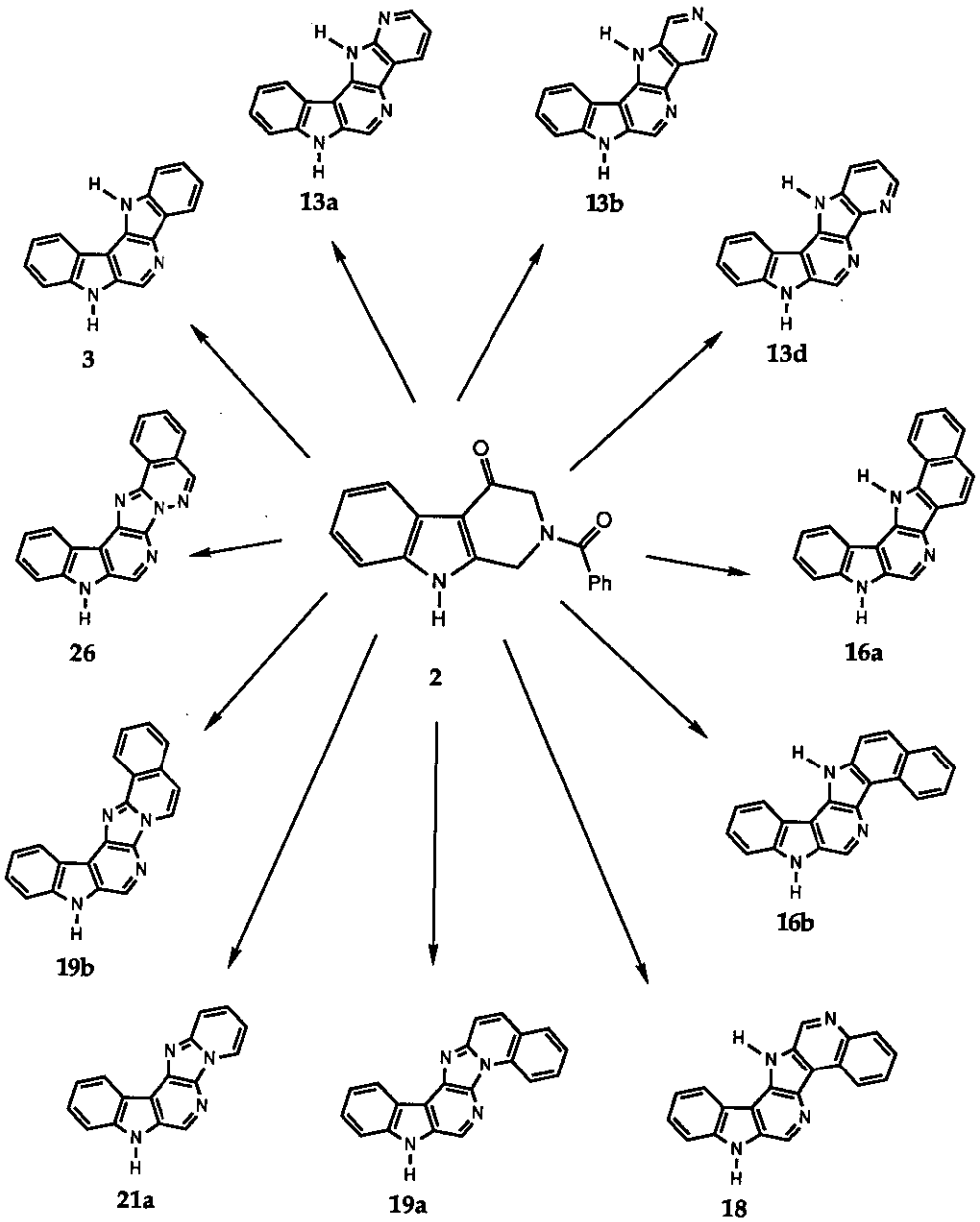
One of the many faces of the genius of Emil Fischer was the discovery in 1883 that the phenylhydrazone of pyruvic acid underwent an acid-catalyzed intramolecular cyclization to form the fully aromatic, 10π electron indole (**1**) nucleus.[1,2] Since that time, the mechanism of formation, scope of substitution reactions, and reactivity of indole (**1**) have been explored thoroughly.[3] With the isolation of approximately 1400 naturally occurring alkaloids that bear an indole moiety,[4] both the formation of indole (**1**) and the substitution at the indole (**1**) nucleus have rendered this heterocycle critical to natural product total synthesis.[5-10]



indole **1**

In 1985, the reaction of the 3-acylindole, 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**2**) with phenylhydrazine via a thermally-induced Fischer-indole cyclization produced the nitrogen

Figure 1. Pyridoindole Ring Systems from Ketobenzamide (2) via the Fischer-Indole Route.

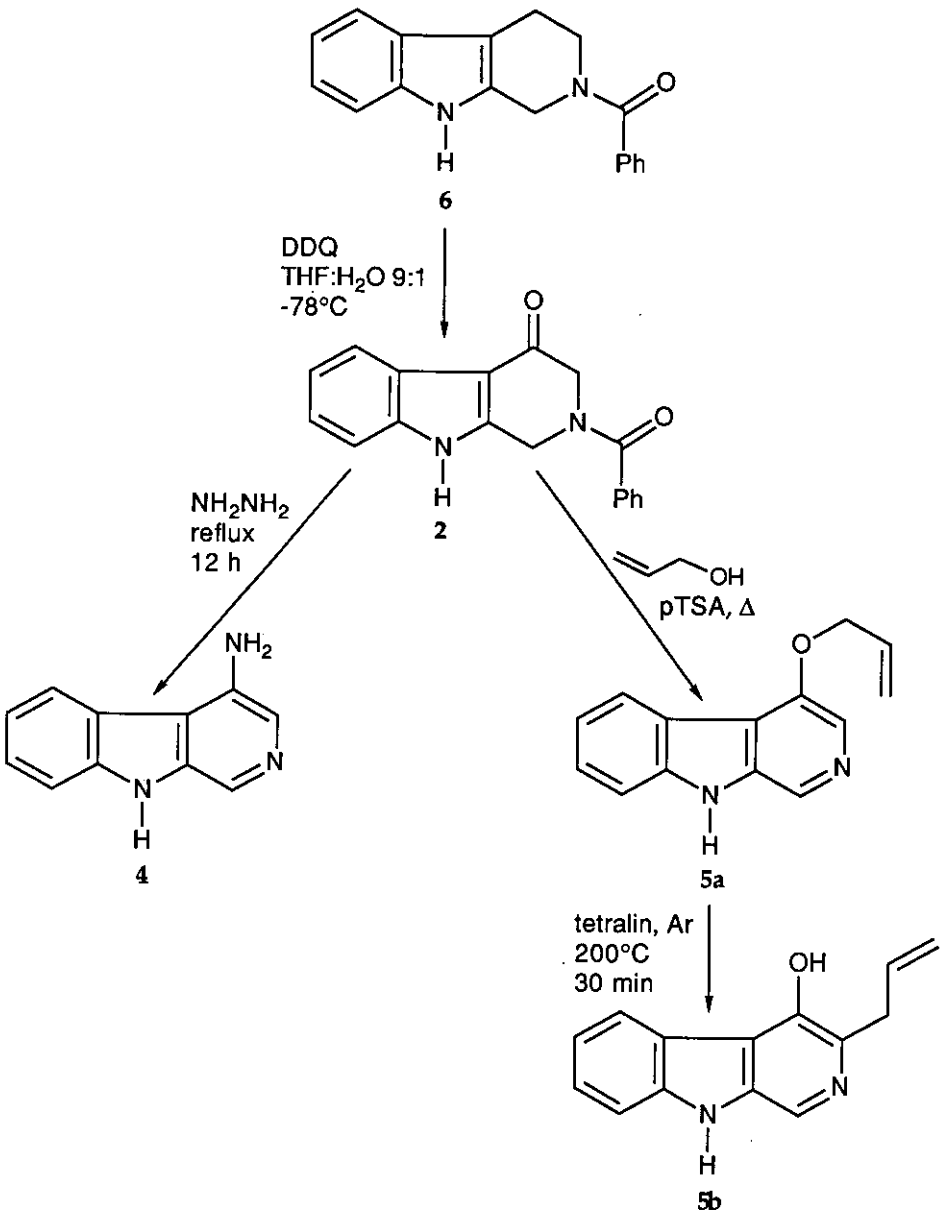


containing heterocycle, 7,12-dihydropyrido[3,2-b:5,4-b']diindole (**3**).[11,12a] This fully aromatic, 22π electron heterocycle consists of two indole moieties fused to a central pyridine ring, and its planar topography has provided an excellent probe through which the topography of the benzodiazepine receptor has been studied via computer-assisted modeling and structure-activity relationships.[13-17] Variation of the initial arylhydrazine has afforded a number of indole systems (see Figure 1),[17-19] and MNDO calculations have been employed to correlate electrophilic substitution of the aromatic system with experimental results.[20a,b] The syntheses and reactivity of these substituted 7,12-dihydropyridodiindole systems form the subject of this review.

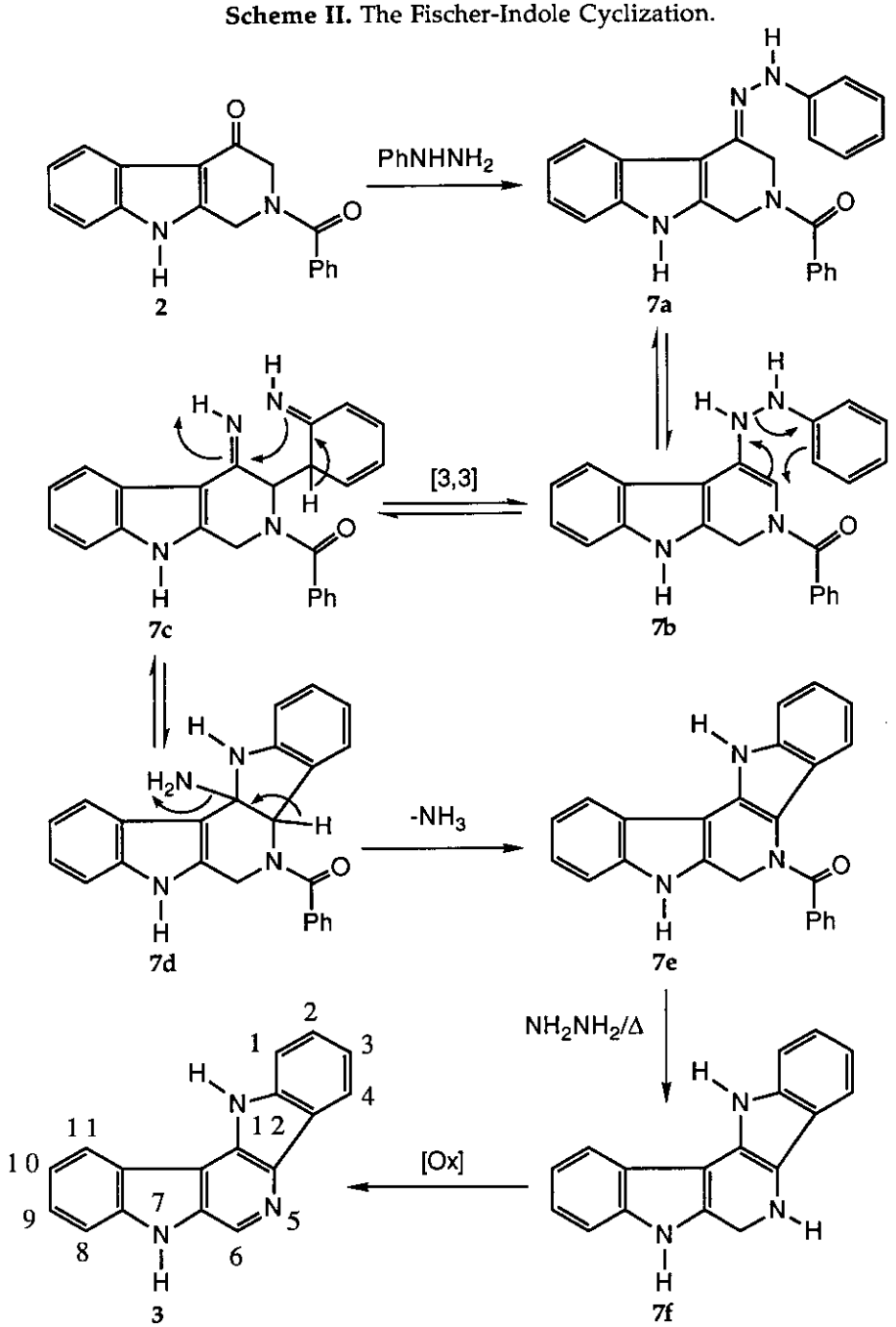
PYRIDODIINDOLES

Entry into the diindole system was gained through an investigation of an amination-oxidation reaction (Scheme I, **2** —> **4**) and the related sigmatropic rearrangement (Scheme I, **5a** —> **5b**) of 2-benzoyl-4-oxo-1,2,3,4-tetrahydro-β-carboline (**2**). The key functionality of this 3-acylindole (**2**) was incorporated (see Scheme I) into the tricyclic skeleton of benzamide (**6**) via oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). This process developed by Yonemitsu[21] has been employed effectively to prepare 3-acylindole systems in our laboratories.[22-24] The piperidylbenzamide (**6**) formed by Pictet-Spengler cyclization of tryptamine and formaldehyde was first admixed with DDQ (2-5 equivalents) to produce a solid mixture. This mixture was subsequently cooled to -78°C, and addition of a solution of THF:water (9:1) at -78°C furnished a slurry with an intense blue color due to the formation of a charge-transfer complex. DDQ mediated 1,4-dehydrogenation across the indole nitrogen-allyl bridge was followed by Michael addition of water to the benzylic position [C(4)] of the tetrahydro-β-carboline nucleus.[21] A second dehydrogenation of the proposed intermediate, secondary alcohol proceeded in a similar 1,4-fashion, and tautomerization of the enol which resulted afforded the 3-acyl-β-carboline (**2**).[22] Further transformations of ketobenzamide (**2**) provided valuable insight into the reactivity of this unique vinylogous amide. Reaction of ketobenzamide (**2**) with excess hydrazine at reflux resulted in the formation of 4-amino-β-carboline (**4**) via the amination-oxidation pathway.[11,12a] This fragmentation of the

Scheme I. Entry into 3- and 4-Substituted β-Carbolines via Ketobenzamide (2).



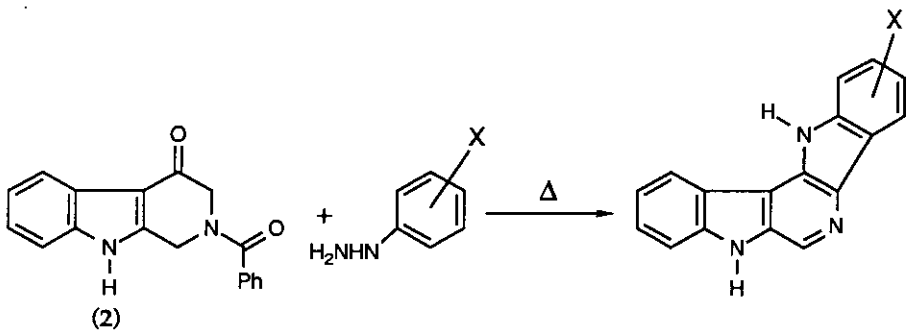
Scheme II. The Fischer-Indole Cyclization.



hydrazine N-N bond, which was accompanied by rearrangement of the hydrazone, has been recently observed in a related system.[12b] As illustrated in Scheme I, the 4-allyl ether (**5a**), formed from ketobenzamide (**2**) and 2-propen-1-ol in the presence of pTSA/Δ and a water scavenger, underwent a Claisen rearrangement in tetralin at 200°C in 84% yield to afford the 3-allyl-4-hydroxy derivative (**5b**).[11] This facile functionalization of position-3 of the β-carboline nucleus accompanied by auto-oxidation to the fully aromatic β-carboline system provided the impetus to explore further this novel method of generating 3-substituted or 3,4-annellated β-carbolines.

Thus, ketobenzamide (**2**) was allowed to react with phenylhydrazine at reflux (25-fold excess, 12 h) to afford diindole (**3**) in 70-90% yield via a thermally-induced Fischer-indole cyclization (see Scheme II).[11,12a,20a] This reversible [3,3] sigmatropic rearrangement of hydrazone (**7a**) to bis-imine (**7c**) becomes irreversible with the elimination of ammonia from **7d**. This resulted in the formation of the aromatic indole ring of **7e**. Hydrazine-mediated cleavage (12 h at reflux) of the benzamide protecting group furnished **7f**, and oxidation (presumably by air) to the 22π electron aromatic system afforded diindole (**3**). The ^{1}H nmr spectrum of this new heterocycle revealed a diindole signal pattern which became characteristic for these systems: two broadened, distinct singlets appeared downfield between δ 10-14 ppm. Inclusion of ortho, meta, and para substituted phenylhydrazines in the thermally-allowed Fischer-indole protocol (**2** plus a 5-10 fold excess of arylhydrazine for 4-6 h at 160-200°C, either neat or in glycol solution, followed by a 25 fold excess of anhydrous hydrazine for 12 h at reflux) resulted in the preparation of appropriately substituted diindoles (see Table I).[12a,13,15] In cases with meta substituted phenylhydrazines, cyclization occurred as expected[3] through two nonequivalent centers, and a mixture of 2- and 4-substituted pyridodiindoles was produced with the 2-isomer as the predominate regioisomer (see Table I, Entries **8e-8q**). These isomeric diindole bases could be separated by flash chromatography in all cases. Consonant with the mechanism of electrophilic aromatic substitution, arylhydrazines bearing activating substituents (i.e. **8v** -OMe) reacted in improved yields, and those bearing deactivating groups (i.e. **8a** -F, **8b** -Cl, **8c** -Br) reacted in lower yields. Arylhydrazines substituted with strongly deactivating substituents (i.e. **8x** 4-NO_2) effectively prevented

Table I. Fischer-Indole Cyclization of Ketobenzamide (**2**) with Substituted Phenylhydrazines.



Diindole	Aryl hydrazine	Substitution 1	2	3	4	Yield* %
3	$PhNHNH_2$	H	H	H	H	88
8a	2-F-$PhNHNH_2$	F	H	H	H	51
8b	2-Cl-$PhNHNH_2$	Cl	H	H	H	51
8c	2-Br-$PhNHNH_2$	Br	H	H	H	25
8d	2-Me-$PhNHNH_2$	Me	H	H	H	71
8e	3-F-$PhNHNH_2$	H	F	H	H	50
8f		H	H	H	F	not observed
8g	3-Cl-$PhNHNH_2$	H	Cl	H	H	64
8h		H	H	H	Cl	11
8i	3-Br-$PhNHNH_2$	H	Br	H	H	33
8j		H	H	H	Br	not observed
8k	3-Me-$PhNHNH_2$	H	Me	H	H	36
8m		H	H	H	Me	4
8n	3-OMe-$PhNHNH_2$	H	OMe	H	H	66
8o		H	H	H	OMe	12
8p	3-OBn-$PhNHNH_2$	H	OBn	H	H	26
8q		H	H	H	OBn	6

Table I. (continued).

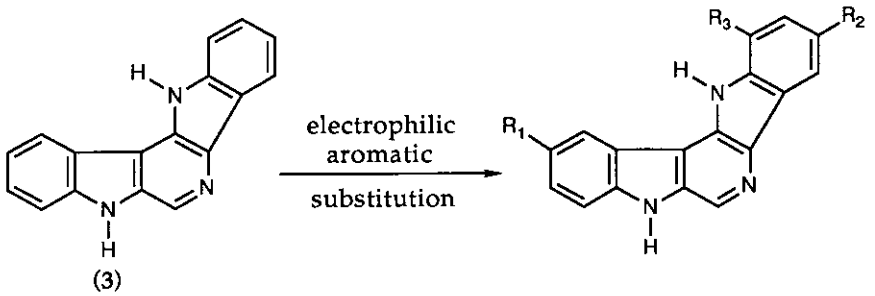
Diindole	Aryl hydrazine	Substitution 1	2	3	4	Yield* %
8r	4-F-PhNHNH$_2$	H	H	F	H	69
8s	4-Cl-PhNHNH$_2$	H	H	Cl	H	68
8t	4-Br-PhNHNH$_2$	H	H	Br	H	40
8u	4-Me-PhNHNH2	H	H	Me	H	58
8v	4-OMe-PhNHNH$_2$	H	H	OMe	H	90
8w	4-OBn-PhNHNH$_2$	H	H	OBn	H	58
8x	4-NO$_2$-PhNHNH$_2$					**

* All diindoles were isolated as the corresponding hydrochloride salts.
** 4-Amino-β-carboline (**4**) was the exclusive product isolated (36% yield).

the Fischer-indole cyclization[11,12a-b] and resulted instead in the formation of 4-amino-β-carboline (**4**).

A casual inspection of diindole (**3**) might suggest comparable reactivites toward electrophilic substitution for the ring-A and ring-E benzene nuclei. In fact, a definite electron withdrawing effect of the β-carboline nitrogen atom [N(5)] in the protonated form upon ring-E exists, such that electrophilic attack occurs regioselectively at position-10 of ring-A. A survey of the reactivity of diindole (**3**) towards electrophiles can be found in Table II.[20a] When **3** was stirred in fuming nitric acid at 0°C, a mixture of polynitrated products resulted; however, treatment of diindole (**3**) with 1.6 equivalents of $NaNO_2$ in TFA at 0°C afforded a 92% yield of 10-nitropyridodiindole (**9a**). Likewise, treatment of diindole (**3**) with one equivalent of NBS in CH_2Cl_2/TFA at room

Table II. Electrophilic Aromatic Substitution on Pyridodiindole (3).



(3)

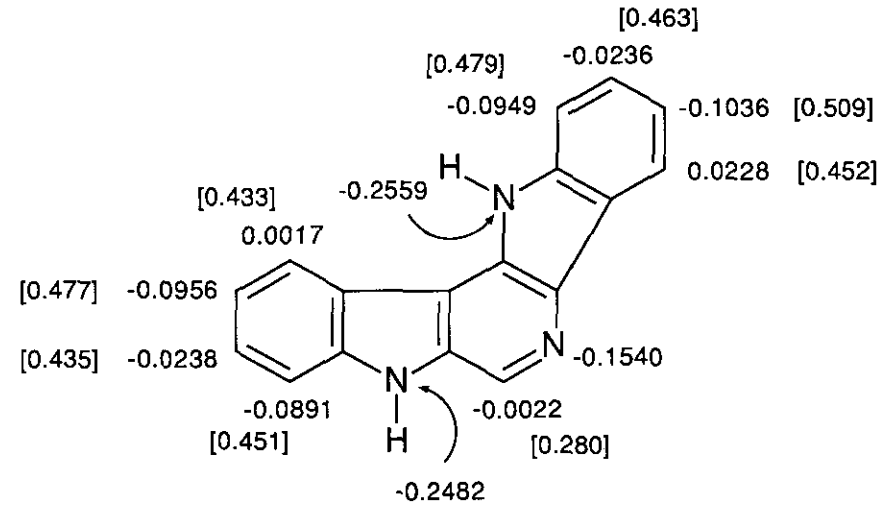
Diindole	Conditions	Substitution			Yield
		R_1	R_2	R_3	%
	fuming HNO_3				complex mixture
	NO_2BF_4/MeOH				no reaction
9a	1.6 eq. $NaNO_2$/TFA	NO_2	H	H	92
9b	1 eq. Br_2/HOAc/NaOAc	Br	H	H	12
9c		H	Br	H	10
9d		Br	Br	H	15
9b	1 eq. NBS/CH_2Cl_2/TFA	Br	H	H	73
9d		Br	Br	H	8
9d	2 eq. NBS	Br	Br	H	96
9b		Br	H	H	4
	excess NBS				complex mixture
9e	1 eq. NCS/CH_2Cl_2/TFA	Cl	H	H	trace
9f	excess NCS	Cl	Cl	H	30
9g		Cl	H	Cl	21
9h	excess conc. H_2SO_4	HSO_3	HSO_3	H	80

temperature furnished 10-bromopyridodiindole (**9b**) in 73% yield, accompanied by a small amount of 3,10-dibromopyridodiindole (**9d**) [8%] and unreacted diindole (**3**) [17%]. Attempted monochlorination with NCS in CH_2Cl_2/TFA provided only a 30% yield of the 3,10-dichloropyridodiindole (**9f**) accompanied by the 1,10-dichloro congener (**9g**) in 21% yield. The apparent lesser reactivity and selectivity of the chlorinating reagent (NCS), in comparison to the brominating reagent (NBS), may be due to the fact that the N-Cl bond is stronger than the N-Br bond in the respective reagents. The reaction conditions employed above may not have been conducive to formation of the necessary electrophile from NCS. However, once Cl^+ has been formed, it is much less selective[25] than Br^+, and complex product mixtures result. Attempts to monosulfonate diindole (**3**) under standard conditions (H_2SO_4, room temperature) were unsuccessful, providing instead the 3,10-disulfonate (**9h**) in 80% yield.

In order to understand this electrophilic reaction pattern, electron densities were calculated for protonated and nonprotonated diindole (**3**) [see Figure 2].[20a] The electron densities computed from net atomic charges and HOMO population densities suggested a substitution order different from that observed. However, since electrophilic aromatic substitution proceeds through attack of the electrophile at the π-cloud of the aromatic system, p_z electron densities were proposed as a better measure of reactivity. The highest amount of electron density was estimated to be present at position-10 of protonated diindole (**3**) [0.495], with only slightly less density at positions-3 [0.490] and -8 [0.490]. This difference is insufficient to account for the selectivity observed. In order to further quantify the difference in reactivity between positions-8 and -10, the relative π-localization energies were calculated for the σ-complex transition state using the Wheland model[20c] for electrophilic aromatic substitution. Calculations indicated that electrophilic attack at position-10 is favored over that at position-8 by 0.44 kcal/mole, in agreement with the experimental results.

MNDO calculations were also employed[20b] to differentiate the reactivity of the N(7)-H and N(12)-H nitrogen nuclei of diindole (**3**) towards electrophilic attack by iodomethane. The

Figure 2. Net Atomic Charges [p_z Population Densities].



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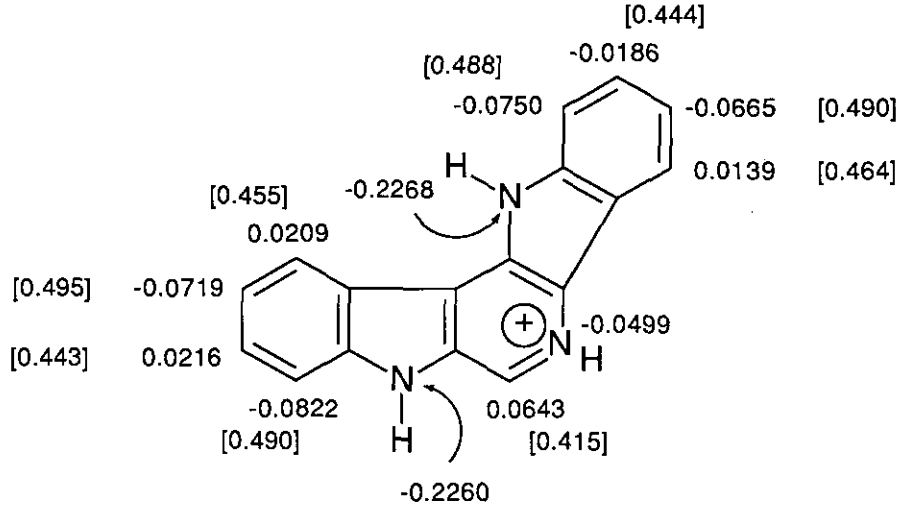
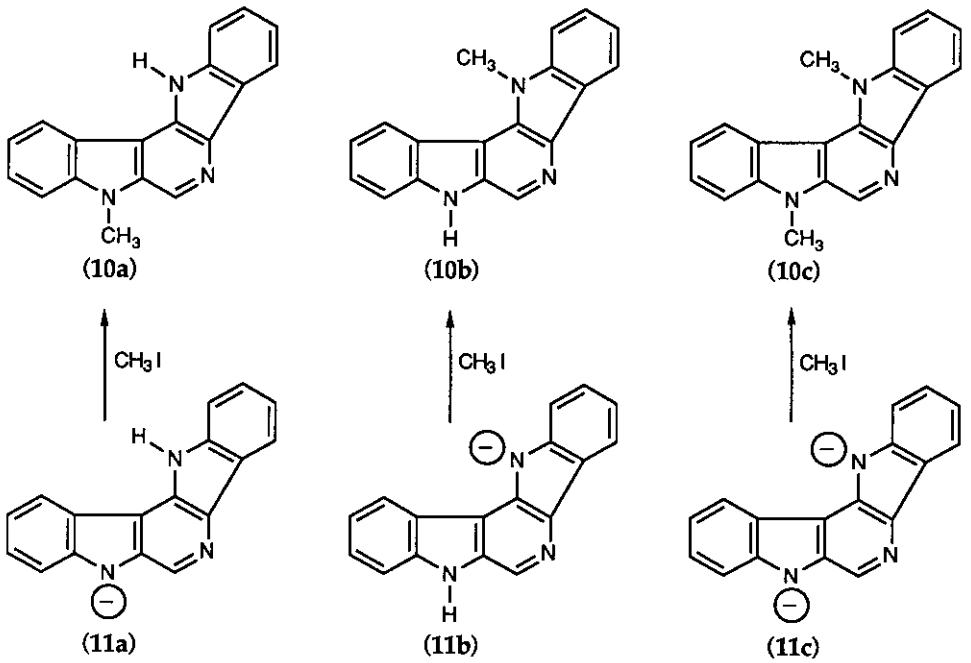


3-H^+

Table III. Selective Methylation of Diindole (3).



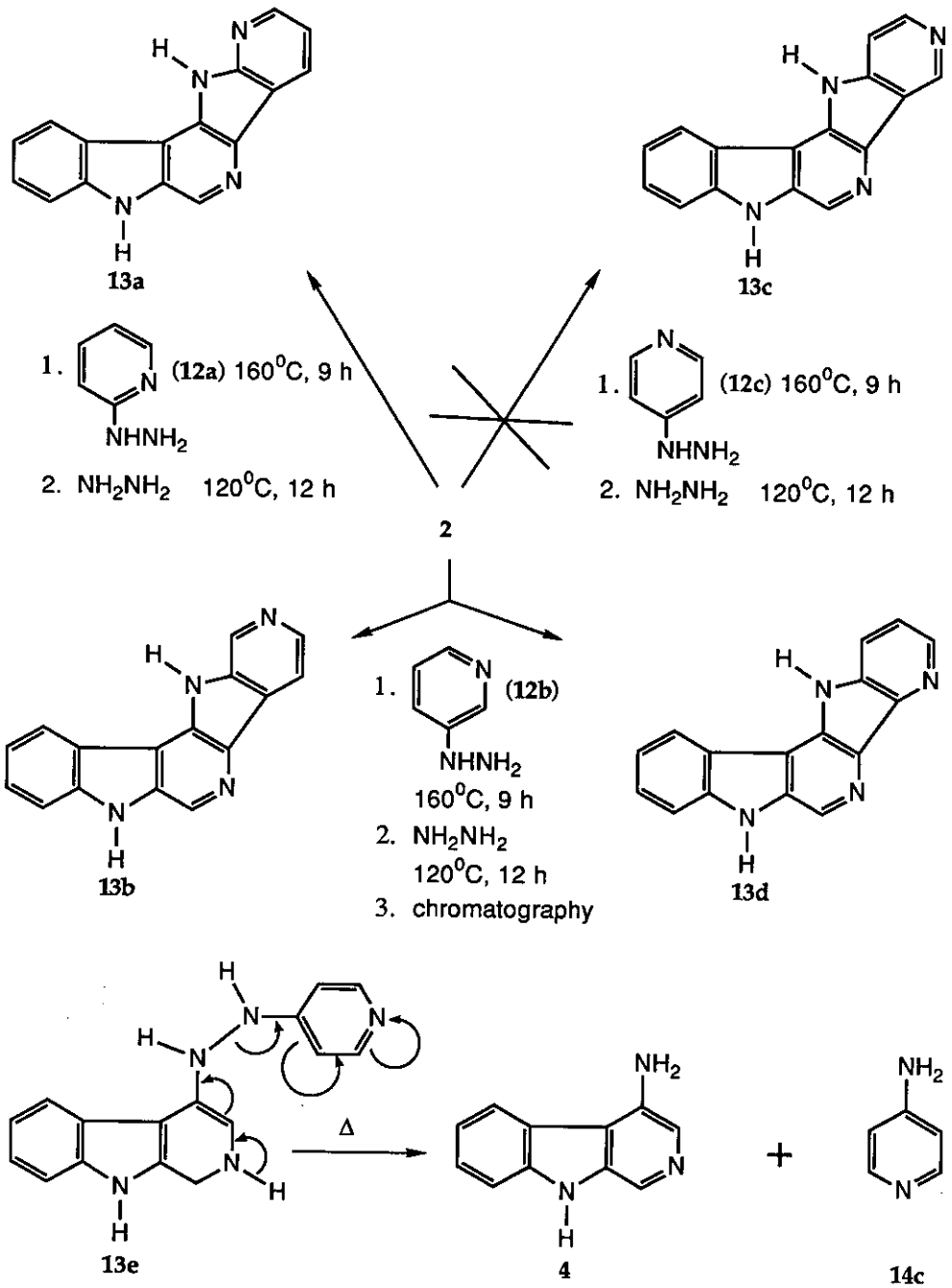
Diindole	N(7)	N(12)	relative stability (kcal/mol)
3	-0.248	-0.252	
11a	-0.337	-0.260	0
11b	-0.263	-0.354	3.33
11c	-0.383	-0.379	37.95

7-methyldiindole isomer (**10a**) could be obtained from the N_a-methyl derivative of ketobenzamide (**2**) and phenylhydrazine through the standard thermal Fischer-indole protocol. Unfortunately, the 12-methyldiindole congener (**10b**) could not be prepared readily via this route.[12a-b] It was initially expected that electrophilic iodomethane would not differentiate between the indolic nitrogen atoms N(7)$^-$ and N(12)$^-$ of dianion (**11c**). However, estimates of net atomic electron densities (see Table III) for diindole (**3**), monoanions (**11a**) and (**11b**), and dianion (**11c**) indicated that the N(7)$^-$ monoanion (**11a**) was more stable than the N(12)$^-$ monoanion (**11b**) by 3.33 kcal/mol. This suggested that monoanion N(7)$^-$ (**11a**) could be generated and methylated regioselectively under conditions of thermodynamic equilibration. In this regard, treatment[20b] of diindole (**3**) with one equivalent of potassium hydride in DMSO at room temperature, followed by addition of iodomethane, furnished 7-methyldiindole (**10a**) in 71% yield. The thermodynamic stability of monoanion N(7)$^-$ (**11a**) was also exploited[20b] to selectively methylate N(12) to furnish 12-methyldiindole (**10b**). Dianion N(7)$^-$/N(12)$^-$ (**11c**) was generated in Na/liquid NH_3, and the less stable anion at N(12)$^-$ was selectively alkylated via kinetic trapping with one equivalent of iodomethane. The more stable anion at N(7)$^-$ which remained was then quenched with water to furnish the desired 12-methyldiindole (**10b**) as the major product (40% yield), accompanied by the dimethyl derivative 7,12-dimethyldiindole (**10c**) (30% yield). These methylated diindole congeners were characterized through ^{1}H nmr and NOE difference spectroscopy. None of the monomethyl derivative (**10a**) was observed under these conditions, in agreement with the predictions of reactivity by MNDO.

AZAPYRIDODIINDOLES

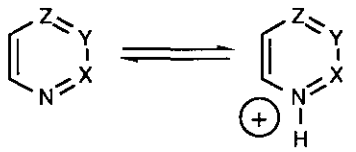
The inclusion of pyridylhydrazines in the classical Fischer-indole cyclization had resulted previously[3] in poor yields of the desired N-fused pyridodiindoles. This is due to the deactivating effect of the pyridine ring towards electrophilic substitution, which is amplified by protonation of the pyridine nitrogen function in acidic media. However, the Fischer-indole cyclization has been shown to arise via a thermally-allowed [3,3] sigmatropic rearrangement.[1-3,11,12a] Thus,

Scheme III. Azadiindoles via the Fischer-Indole Cyclization.



2-hydrazinopyridine (**12a**) was allowed to react with ketobenzamide (**2**) in the standard thermally-allowed protocol to furnish 7,12-dihydropyrido[3",2":4',5']pyrrolo[2',3':5,6]pyrido[3,4-b]indole [1-azapyridodiindole] (**13a**) in 71% yield (see Scheme III).[17,18] The characteristic diindole singlets were observed at δ 12.95 and 13.80 in the ^{1}H nmr spectrum of **13a**. The inclusion of 3-hydrazinopyridine (**12b**) in the thermally-allowed protocol with **2** afforded the expected[3] mixture of 2-aza- (**13b**) and 4-azadiindoles (**13d**) in moderate yield (see Scheme III).[17,18] These isomers were separable by flash chromatography on silica gel. In addition to the characteristic singlets [δ 12.60/13.75 (**13b**) and δ 12.80/13.65 (**13d**)], the spectrum of the 2-azadiindole (**13b**) congener contained a singlet that appeared downfield at δ 9.35, which was attributed to the proton at C(1) adjacent to the nitrogen function.

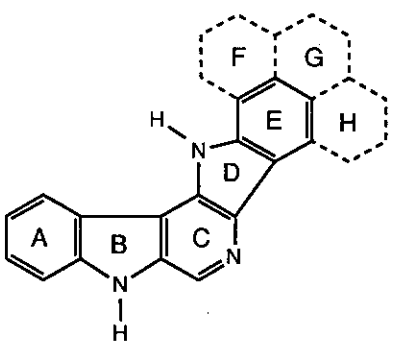
Table IV. Dissociation Constants of Substituted Aminopyridines.



	substituted pyridine	X	Y	Z	pK_a
14a	2-NH_2-Pyr	C–NH_2	CH	CH	6.86
14b	3-NH_2-Pyr	CH	C–NH_2	CH	5.98
14c	4-NH_2-Pyr	CH	CH	C–NH_2	9.17

All attempts to effect the reaction of 4-hydrazinopyridine (**12c**) with ketobenzamide (**2**) to produce the 3-azadiindole (**13c**) failed uniformly and furnished instead 4-amino-β-carboline (**4**) [see Scheme III].[17,18] In essence, the pyridine nitrogen atom readily accepts electron density from the hydrazone fragment of **13e** to promote N-N bond cleavage at the expense of the Fischer-indole cyclization. In contrast, the cyclizations involving the 2-hydrazino (**12a**) and 3-hydrazino (**12b**) congeners occur successfully, principally because the developing negative charge of the leaving group is not comparably delocalized into the pyridine ring. This electronic effect was correlated with the dissociation constants for the protonated pyridine nitrogen atoms of the 2-, 3-, and 4-aminopyridines (see Table IV, Entries **14a-c**). The pK_a values for 2- (**14a**) and 3-amino-pyridine (**14b**) approximate neutrality [6.86 and 5.98, respectively], while the value for 4-amino-pyridine (**14c**) [9.17] reflects the distinct basicity of this isomer. This basicity indicates that electron density is localized on the pyridine nitrogen atom and that withdrawal of electron density from the aniline nitrogen of hydrazone (**13e**) takes place readily. The deactivated nature of 4-substituted pyridine (**12c**) that provides 4-amino-β-carboline (**4**) remains consistent with the mechanism of the Fischer-indole cyclization.[11,12a]

Figure 3. Benzannellated Pyridodiindoles and Indolopyridoimidazoles.



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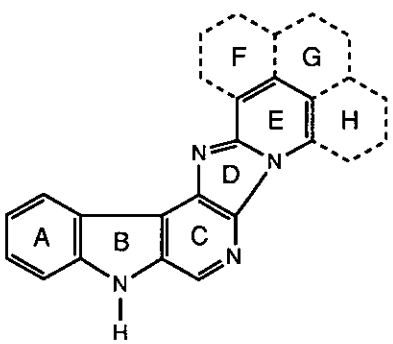


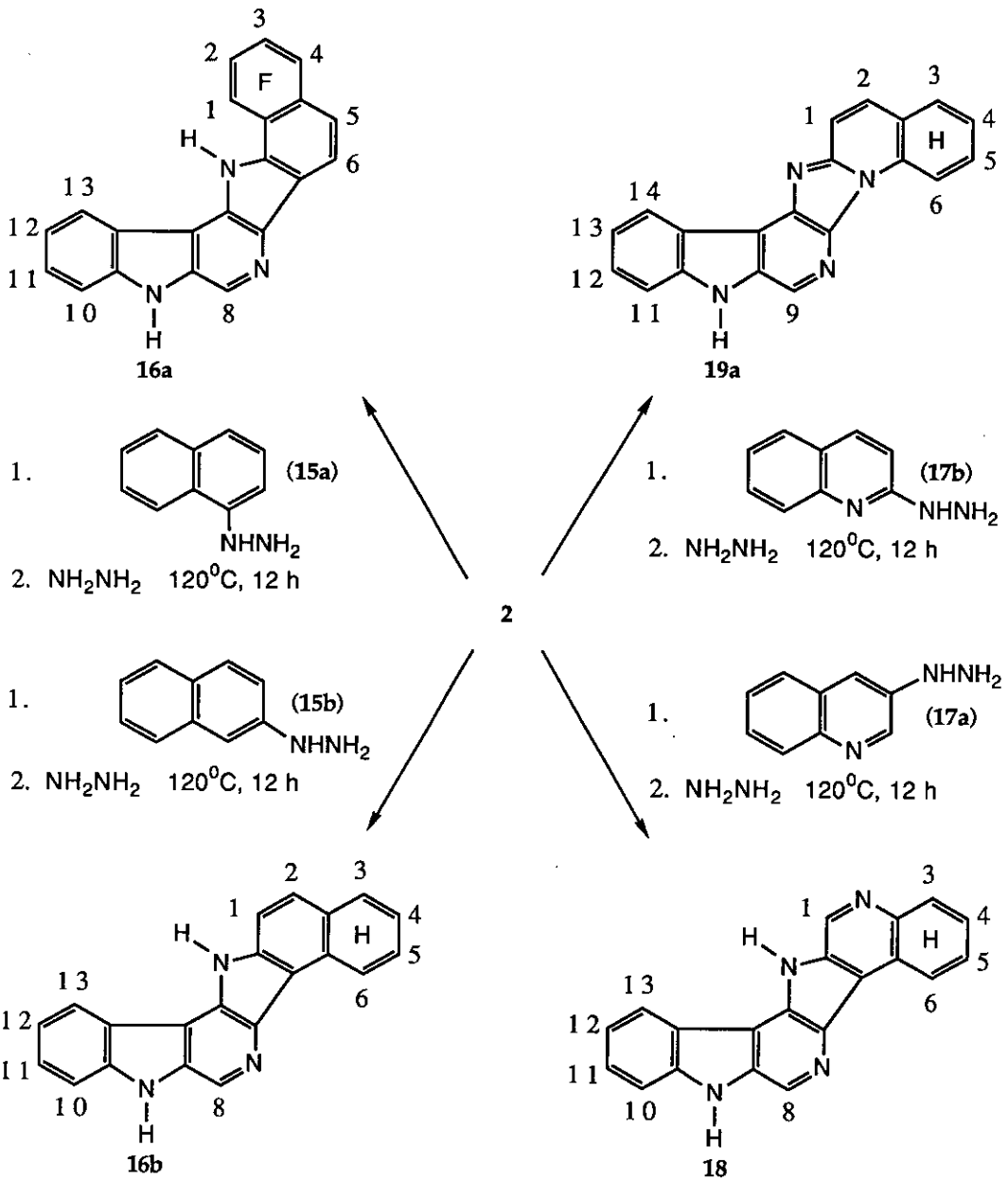
21a

BENZOPYRIDODIINDOLES

The successful synthesis of azadiindoles encouraged further exploration of the condensation of arylhydrazines with ketobenzamide (**2**) in the thermally-allowed reaction. As illustrated in Figure 3, the logical extension of this approach centered on fusion of rings F, G, and H to the diindole nucleus through the substitution of naphthylhydrazines in place of phenylhydrazines, as well as quinolylhydrazines in place of pyridylhydrazines, in the Fischer-indole cyclization. In this fashion (see Scheme IV),[17,19] 1-hydrazinonaphthalene (**15a**) was allowed to react with ketobenzamide (**2**) under standard thermally-allowed conditions to furnish the ring-F annellated 9,14-dihydroindolo[2",3":5',4']pyrido[2',3':4,5]pyrrolo[2,3-a]naphthalene [1,2-benzodiindole] (**16a**) in 40% yield. Analysis of the decoupling data from the ^{1}H nmr spectrum employed in the structure determination of **16a** revealed long-range coupling which was observed as the concurrent interaction of the triplet (2H) at δ 7.80, the multiplet (2H) at δ 7.90, and the doublets (1H each) at δ 8.60 and 9.15. The structure of **16a** was assigned based on coupling patterns, decoupling data and correlation of the ^{1}H nmr spectrum with that of diindole (**3**).

It is possible that reaction of 2-hydrazinonaphthalene (**15b**) could yield a mixture of benzodiindoles,[3] with cyclization occurring through two nonequivalent centers, α/C(1) and β'/C(3), to furnish the 3,4-angular and 2,3-linear isomers, respectively. In reality, only one product was isolated in 60% yield (see Scheme IV).[17,19] Detailed analysis of the ^{1}H nmr spectrum indicated that cyclization had occurred exclusively through the α-position to furnish the 3,4-benzodiindole (**16b**). Although attack at the β'-position of the naphthalene ring would yield the more thermodynamically stable intermediate,[25] the sigmatropic rearrangement followed by concomitant loss of NH_3 is irreversible (see Scheme II), and therefore thermodynamic equilibrium is never attained. Instead, an increased reaction rate for electrophilic substitution at the α-position[25] resulted in attack to yield the kinetically favored angular 3,4-benzodiindole (**16b**). Formation of the linear 2,3-isomer was not observed. It has been reported[26a,b] that the hydrazones of β-hydrazinonaphthalenes and β-tetralones undergo Fischer-indole cyclization to

Scheme IV. Benzodiindoles via the Fischer-Indole Cyclization.



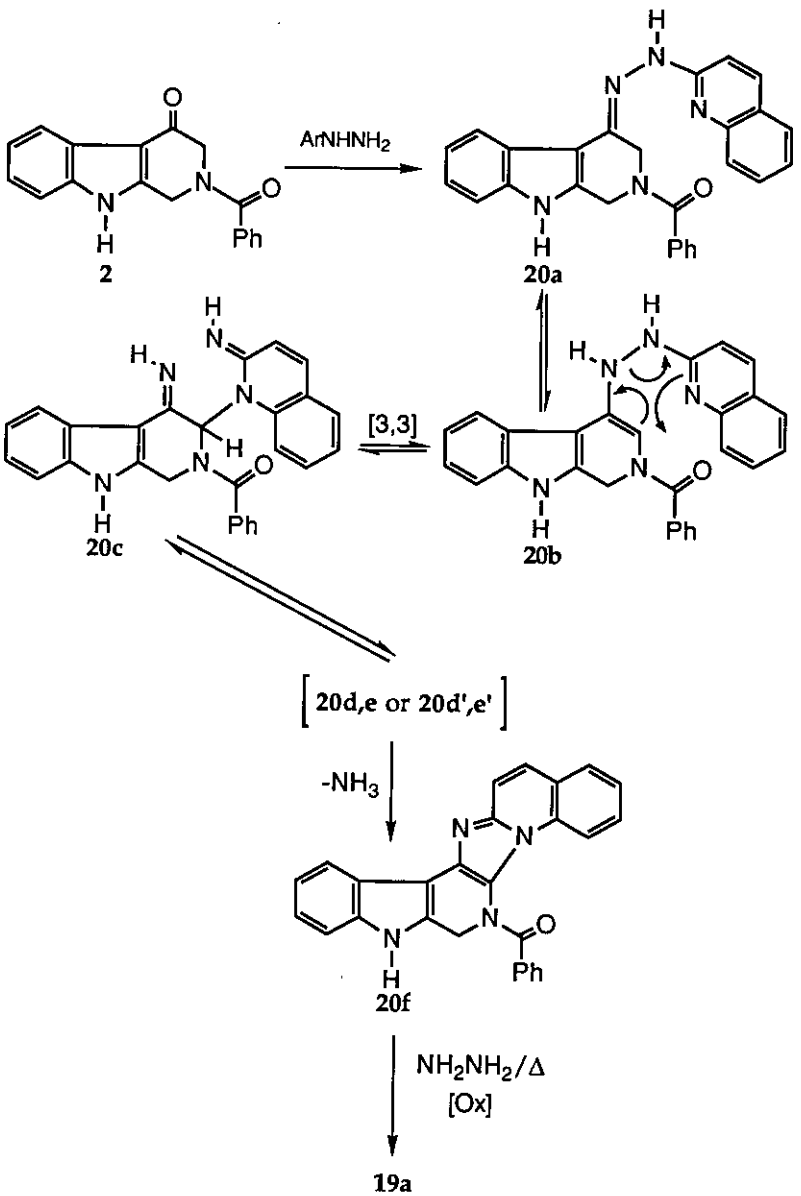
yield angularly substituted indolocarbazoles exclusively. Furthermore, Murakami et al.[27] have recently demonstrated that Fischer-indole cyclizations of β-naphthylhydrazones failed to yield benz[f]indoles (linear benzannellation), even when α-substituted hydrazones were employed. In fact, placement of a blocking group at the α-position (i.e. 1-bromo-2-hydrazinonaphthalene) to force cyclization via the β'-position resulted not in the desired linear diindole congener, but the usual product of ene-hydrazine N-N bond scission,[11,12a-b] 4-amino-β-carboline (**4**). These findings are in agreement with the results described here.

In a similar sense, reaction of 3-quinolylhydrazine (**17a**) with ketobenzamide (**2**) in the thermally-allowed protocol proceeded through the α'-position [C(4)] exclusively to provide the 3,4-benzo-azadiindole (**18**), albeit in low yield (see Scheme IV).[17,19] None of the 2,3-linear isomer was observed.

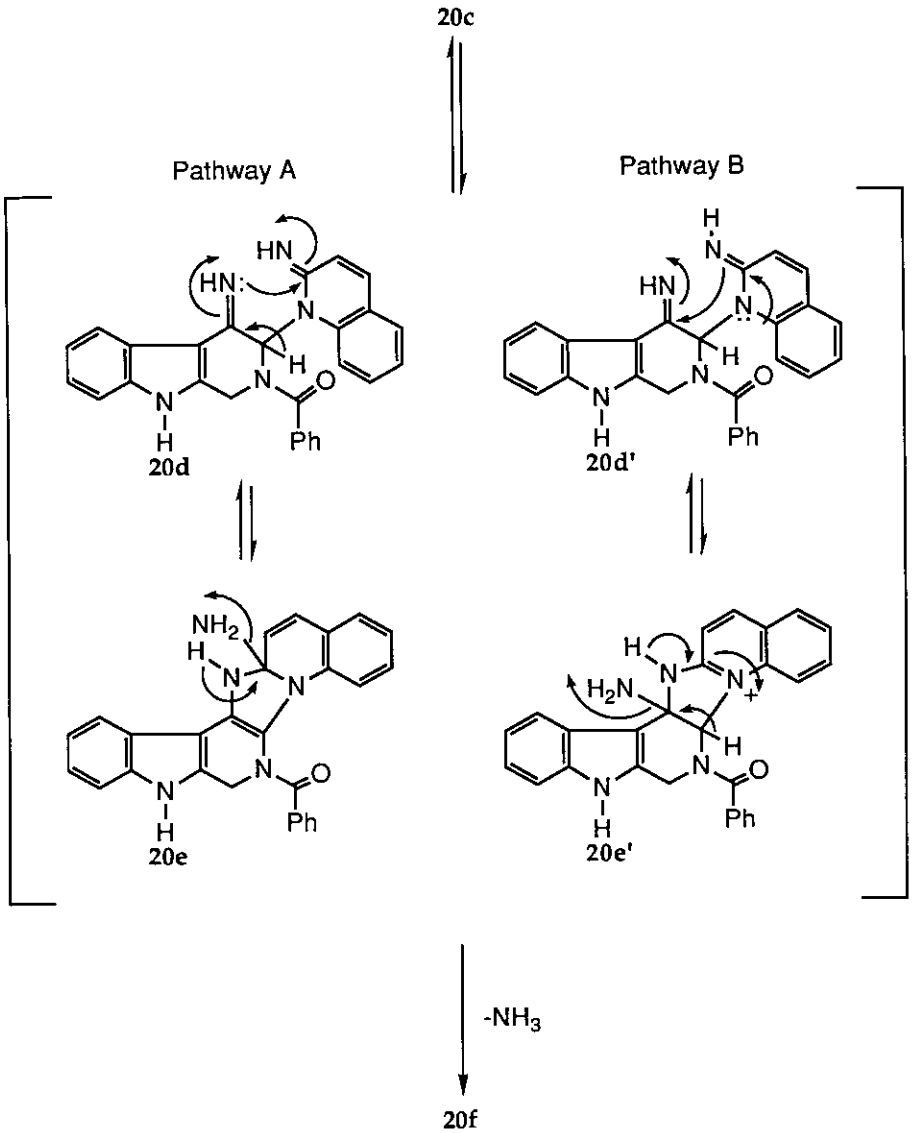
INDOLOPYRIDOIMIDAZOLES

An intriguing modification to the "normal" Fischer-indole cyclization was realized with the inclusion of 2-hydrazinoquinoline (**17b**) in the thermally-allowed protocol (see Scheme IV). As expected, cyclization did not proceed through the β'-position, but occurred instead at the α-position through the quinoline nitrogen via an aza-Fischer-indole cyclization (see Scheme V, pathways A and B) to furnish the 10H-indolo[2",3":5',4']pyrido[2',3':4,5]imidazo[1,2-a]quinoline [indolopyridoimidazole] (**19a**) in 25% yield.[17,19] In contrast to the "normal" Fischer-indole cyclization (see Scheme II), it is possible that the aza-cyclization proceeds via intramolecular attack of the enamine nonbonded pair of electrons at the iminopyridine fragment, as depicted in Scheme V (pathway A, **20d-e**). Loss of ammonia across the newly formed N-C bond would then furnish the imidazole system. It is also possible that the quinoline nonbonded pair of electrons participates in re-establishing the resonance energy of the pyridine ring. Cyclization could then proceed via attack of the "aniline-like" nonbonded pair of electrons at the vinylogous imide moiety as depicted in Scheme V (pathway B, **20d'-e'**), and loss of ammonia would occur as in

Scheme V. The Proposed Aza-Fischer-Indole Cyclization.



Scheme V (continued). Possible Pathways for the Formation of the Pentacyclic System.

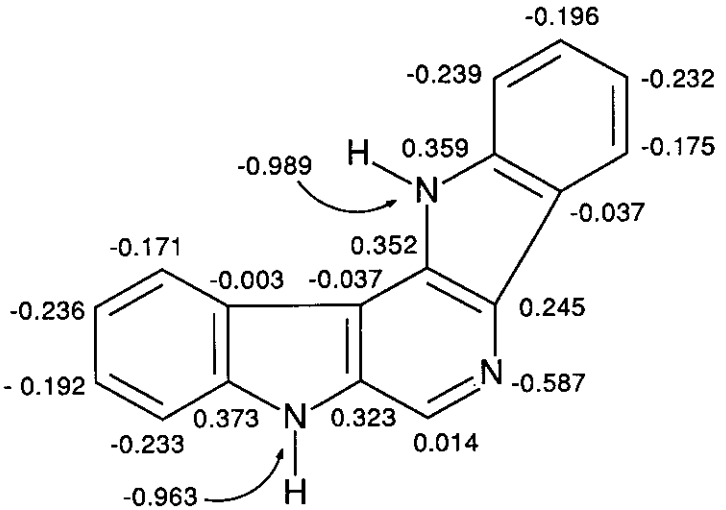


Scheme II. Support for the latter pathway can be found in a comparison of the stabilities of aminopyridine tautomers.[28] Unlike o-hydroxypyridines which exist principally in the pyridone form, o-aminopyridines exist primarily as the aminopyridine tautomers. This favors the "aniline-like" configuration of **20d'-e'**. Conversely, support for the former pathway is evident from an inspection of the two pathways; the uncharged route of **20d-e** would normally be expected to be more energetically favorable. The nature of the thermally-mediated Fischer-indole protocol precludes the isolation of the rearrangement product prior to cyclization, although studies with ^{15}N-labeled arylhydrazines would shed light on the preferred pathway.[3] These experiments remain for future work.

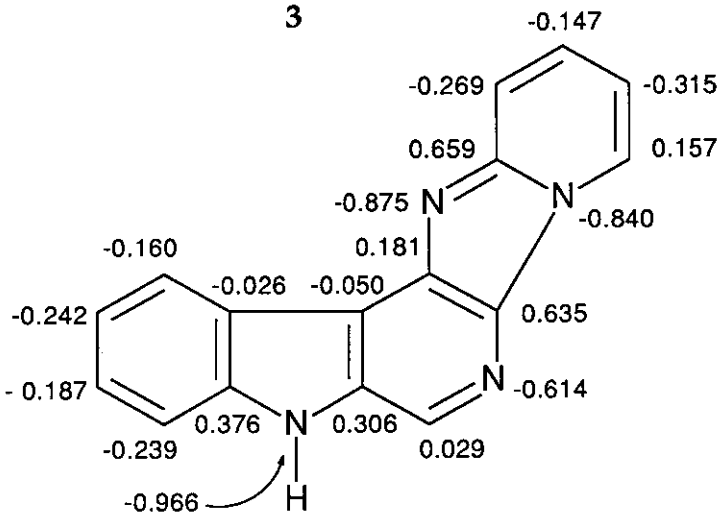
The direction of cyclization of **19a** was ascertained via an examination of the ^1H nmr spectrum of this heterocycle, in which only one indole N-H resonance was observed (δ 12.25). This apparently trivial departure from the usual Fischer-indole pathway furnished a pentacyclic system with distinctly altered electron densities with respect to **3**[29a,b] (see Figure 4), and further investigation into this novel heterocycle was warranted.

The ability to functionalize the pyridine nitrogen atom of heterocyclic arylhydrazines was utilized to prepare the parent indolopyridoimidazole (**21a**) [see Scheme VI]. Thus, 3-chloro-2-hydrazinopyridine (**22a**) was included in the thermally-allowed protocol to afford the 1-chloro-8H-pyrido[1",2":1',2']imidazo[4',5':5,6]pyrido[3,4-b]indole congener (**21b**), accompanied by a number of other products.[29a] The deactivating effect of the chlorine atom on an already deactivated ring system is evident in the depressed yields of the target and the number of other products (see Scheme VI), which included the parent compound[3,29a,30] 8H-pyrido[1",2":1',2']-imidazo[4',5':5,6]pyrido[3,4-b]indole (**21a**) [2% yield], azadiindole (**13b**) [6.5% yield] which resulted from Fischer-indole cyclization followed by oxidative loss of a chlorine atom,[3,29a,30] and the expected 4-amino-β-carboline (**4**)[11,12a-b] [11% yield]. The 1-chloro congener (**21b**) was then subjected to the conditions of catalytic transfer hydrogenation[31] to afford both the tetrahydro derivative (**21c**) [10% yield] and the parent indolopyridoimidazole (**21a**) [50% yield].[29a]

Figure 4. Ab Initio Net Atomic Charges.

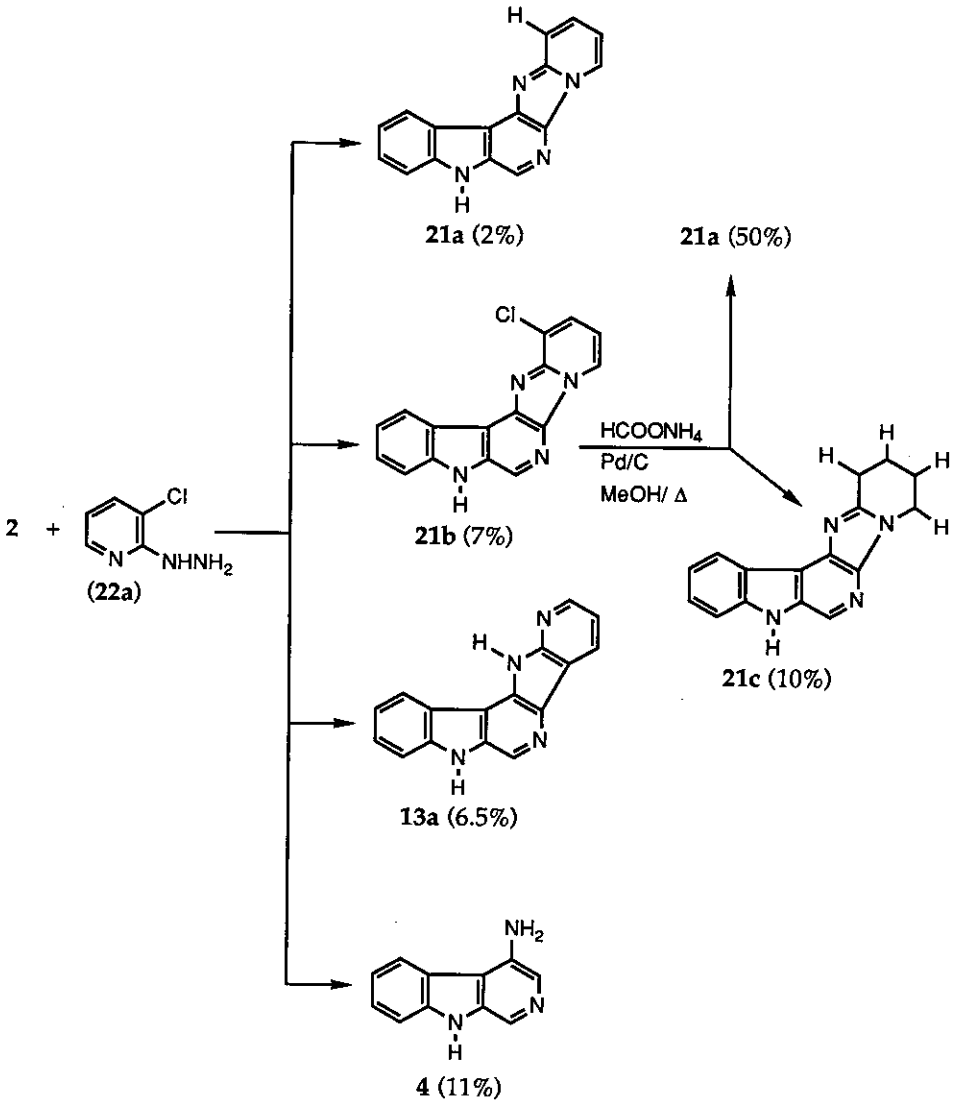


3



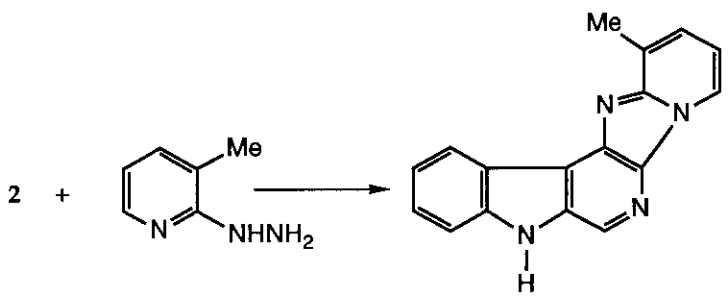
21a

Scheme VI. Synthesis of Indolopyridoimidazole (**21a**) via the Fischer-Indole Cyclization.



In order to avert the sideproducts encountered with a thermally labile blocking group, 2-hydrazino-3-methylpyridine (**22b**) was employed in the thermally-allowed aza-Fischer-indole protocol (see Scheme VII).[29a] Cyclization proceeded as desired through the pyridine nitrogen function to afford 1-methylindolopyridoimidazole (**21d**) in 30% yield. All the indolopyrido-imidazole derivatives [1-chloro (**21b**), parent (**21a**), tetrahydro (**21c**), and 1-methyl (**21d**)] obtained by this route exhibited ^{1}H nmr spectra consistent with that of **19a**.[29a]

Scheme VII. Synthesis of Indolopyridoimidazole (**21d**) via the Fischer-Indole Cyclization.



(**22b**) **21d** (30%)

Attempts to include 2-hydrazinopyrimidine (**23a**) in the thermally-allowed cyclization failed uniformly[29a] (see Scheme VIII), due to the further deactivation of the ring system by the inclusion of an additional nitrogen atom. This effect was examined using calculated gas-phase enthalpies of protonation[29a,b] for selected aminopyridines and aminopyrimidine (see Table V, Entries **24a-d**). The enthalpy of protonation is a measure of the available electron density present at an individual atom, and can therefore be viewed as an indication of the electron density available in systems (**24a-d**). For 3-chloro-2-aminopyridine (**24c**) [3-chloro-2-hydrazinopyridine reacted in 7% yield], protonation requires an additional 12.35 kcal/mol in energy relative to the 1-methyl derivative (**24a**). For the aminopyrimidine analogue (**24d**), an energy difference of

Scheme VIII. Attempted Synthesis of Indolopyridopyrimidine (**23b**) via the Fischer-Indole Cyclization.

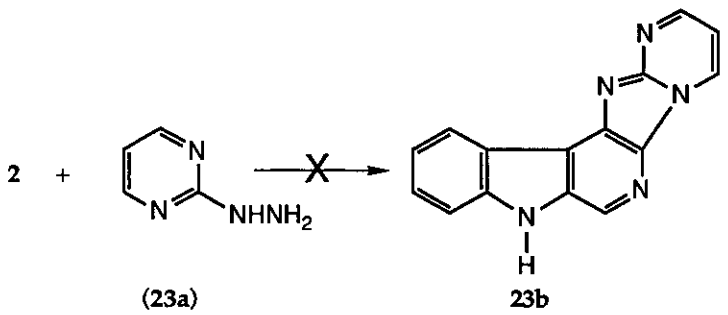
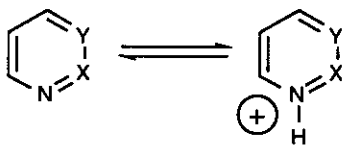


Table V. Calculated Enthalpies of Protonation of Substituted Aminopyridines and Aminopyrimidine.



	nitrogen heterocycle	X	Y	ΔΔH *
24a	2-NH_2-3-Me-Pyr	C–NH_2	C–Me	0.00 **
24b	2-NH_2-Pyr	C–NH_2	C–H	2.16
24c	2-NH_2-3-Cl-Pyr	C–NH_2	C–Cl	12.35
24d	2-NH_2-Pyrim	C–NH_2	N	12.70

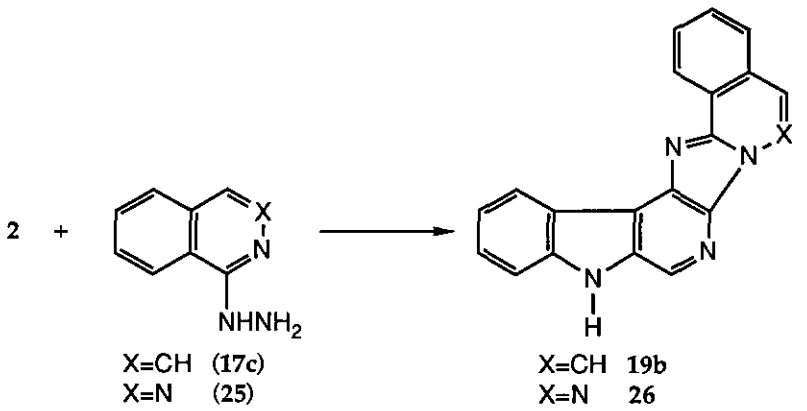
* ΔΔH values were calculated with *Gaussian-90* using STO-3G//STO-3G energies. See reference 17.

** (**24a**) was used as a point of reference.

12.70 kcal/mol was calculated relative to the 1-methyl derivative (**24a**). Since the Fischer-indole cyclization is an example of electrophilic aromatic substitution, this greater energy difference indicated that reaction of the corresponding hydrazine in the thermally-allowed protocol would proceed at a significantly slower rate than either the 1-methyl (**19b**) or the 1-chloro congeners (**19a**), due to decreased available electron density. This significant retardation of reaction rate for the desired product should favor reaction along alternate pathways; i.e. 4-amino-β-carboline (**4**) was expected as the major product. In fact, the reaction of ketobenzamide (**2**) with **23a** under a variety of conditions gave only 4-amino-β-carboline (**4**) as an isolable product.[29a]

With the ring-H annellated 3,4-indolopyridoquinoline (**19a**) in hand and the 2,3-linear isomer unavailable via this approach, the 1,2-angular, ring-F annellated congener could be obtained from inclusion of hydrazinoisoquinoline in the thermally-allowed aza-Fischer-indole protocol. Thus, 1-hydrazinoisoquinoline (**17c**) was prepared[17,32] in several steps from isoquinoline and was allowed to react with ketobenzamide (**2**) under the usual thermally-allowed conditions to

Scheme IX. Ring-F Homologated Indolopyridoimidazoles via the Fischer-Indole Cyclization.



afford the desired ring-F annellated 10H-indolo[3",2":4',5']pyrido[3',2':4,5]imidazo[2,1-a]-isoquinoline (**19b**) in low yield[17,32] (see Scheme IX), accompanied by the expected byproducts of N-N bond scission, 4-amino-β-carboline (**4**) and 1-aminoisoquinoline. In addition to the single indole N-H resonance at δ 11.97, this ring-F congener (**19b**) exhibited long-range coupling of the protons within rings E and F similar to that observed for (**16a**). This resulted in a series of complex, interrelated resonances at δ 7.72 (d, J=8 Hz, 1H), 7.82 (m, J=9 Hz, 2H), 8.04 (m, J=9 Hz, 1H), 8.61 (d, J=8 Hz, 1H), and 8.85 (m, J=9 Hz, 1H).

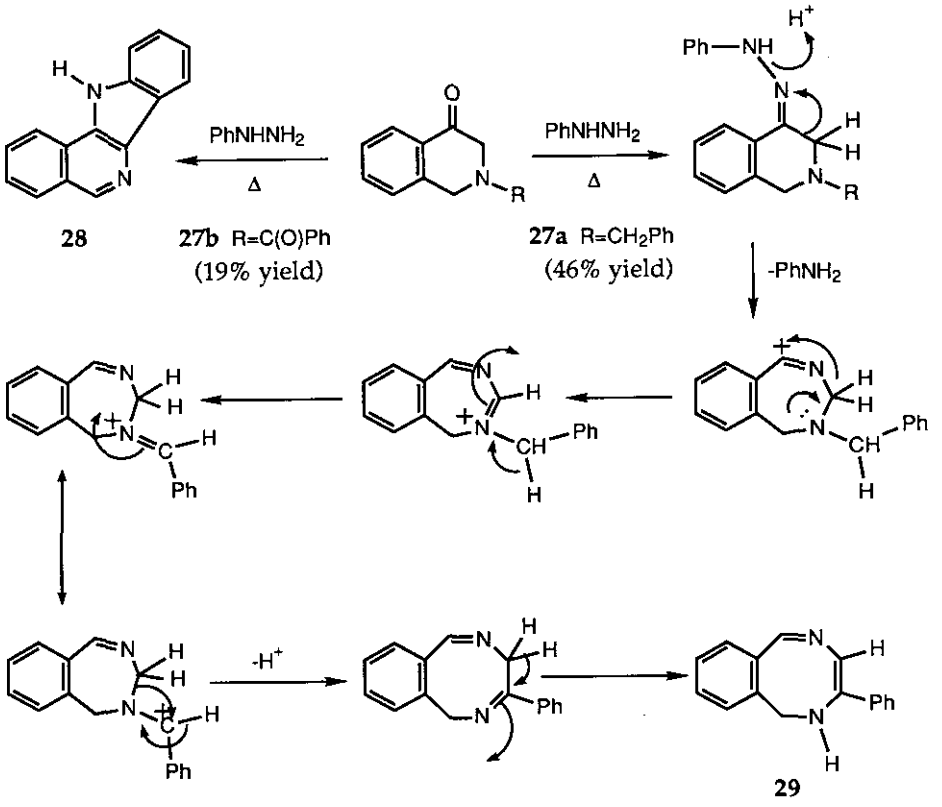
A similar phenomenon was also encountered in the condensation of 1-hydrazinophthalazine (**25**) and ketobenzamide (**2**). The hydrazine (**25**) was obtained[17,29a] from the corresponding hydrazinohydralazine through air-oxidation upon basic workup of the hydrochloride salt. The phthalazinylhydrazone of ketobenzamide (**2**) was allowed to react under the standard thermally-allowed conditions to furnish the ring-F annellated 10H-indolo[3",2":4',5']-pyrido[3',2':4,5]imidazo[2,1-a]phthalazine (**26**) in 33% overall yield (see Scheme IX).[29a] Along with the single indole N-H resonance at δ 12.15, decoupling experiments revealed the interrelationship of the protons of rings E and F. Specifically, the protons H-2 (δ 8.01), H-3 (δ 8.14), and H-5 (δ 8.92) demonstrated the presence of long-range coupling upon double irradiation.

BENZODIAZOCINE AND INDOLOISOQUINOLINE

In an effort to expand the scope of the thermally-induced Fischer-indole cyclization, 2-benzyl- (**27a**) and 2-benzoyl-1,2,3,4-tetrahydro-4-(1H)-isoquinolone (**27b**) were included in the thermally-allowed protocol[33] (see Scheme X). Attempted Fischer-indole cyclization of the N_b-benzyl derivative of ketobenzamide (**2**) had been reported[33] as unsuccessful. The inductive effect of the electron deficient carbonyl carbon of ketobenzamide (**2**) upon the ene-hydrazine intermediate increases the electrophilic character at C(3) of the tetrahydro-β-carboline nucleus and may facilitate cyclization. In comparison, the N_b-benzyl group would increase the electron density at C(3) and inhibit cyclization, therein favoring alternate pathways. This inductive effect

Scheme X. Inclusion of Isoquinolinones (**27a**) and (**27b**) in the Thermally-Allowed Fischer-Indole Cyclization.

One Possible Pathway for the Formation of Benzodiazocine (**29**).



of the amide functionality would also be expected to increase the acidity of the protons at C(3) and subsequently favor isomerization of the hydrazone to the corresponding ene-hydrazine required for cyclization. Additionally, the carbonyl moiety is capable of assuming a coplanar orientation with the double bond which would be expected to reduce the transition-state energy of the incipient [3,3] sigmatropic rearrangement, whereas the benzyl group cannot. In fact, when the

phenylhydrazone of **27a** was allowed to react in either ethanolic hydrogen chloride or ethylene glycol, no cyclization was observed.[33] Pyrolysis of the phenylhydrazone of **27a** (R=CH_2Ph) at 360°C for 15 min (see Scheme X)[33] did not furnish the desired indoloisoquinoline (**28**). Instead, the material from an unexpected ring expansion process, 1,2-dihydro-4-phenyl-2,5-benzodiazocine (**29**)[34] [identified by mass spectral fragmentation patterns and ^1H nmr characterization], was isolated in 46% yield.[33] A possible route for the origin of benzodiazocine (**29**) is illustrated in Scheme X. Rearrangement of the hydrazone C(3)-[C(4)=N-NHPh] bond may occur with simultaneous ring expansion and elimination of aniline, which may proceed either heterolytically[33] or homolytically.[35] A second ring expansion *via* the benzyl-imine tautomer C(3)-[N=CHPh] bond would afford benzodiazocine (**29**). Other pathways are possible but are not illustrated here.

In order to obtain indoloisoquinoline (**28**), the 2-benzoyl derivative (**27b**) was prepared[17,33] from the 2-benzyl compound (**27a**) through catalytic debenzylation of the protecting group (which also reduced the ketone carbonyl moiety), benzamide protection of the free secondary nitrogen function, and oxidation of the secondary alcohol residue to refurnish the ketone carbonyl moiety. This isoquinolinone (**27b**) was then allowed to react with phenylhydrazine in the standard thermally-allowed protocol (see Scheme X) to provide the desired indolo[3,2-*c*]isoquinoline (**28**) in 19% yield.[17,33] The ^1H nmr spectrum of this indoloisoquinoline exhibited only one indole resonance at δ 12.18, which verified the monoindolization. The remaining assignments were based on decoupling data and correlation of the spectral data with that of known systems. These deductions were consistent with the structure of **28**.[17,33]

CONCLUSION

The condensation of several arylhydrazines with the 3-acylindole (**2**) *via* a thermally-induced Fischer-indole cyclization has furnished a number of new heterocyclic ring systems, including pyridodiindoles, azadiindoles, and the corresponding homologated systems. Additionally, the discovery that this versatile electrophilic aromatic substitution proceeded through the nitrogen

atom of pyridyl-, quinolyl-, isoquinolyl- and phthalazinylhydrazines via a thermally-induced aza-Fischer-indole cyclization provided access to the novel new indolopyridoimidazole system and the annellated congeners. Heterocycle (**21a**) possesses distinctly altered electron density versus diindole (**3**) as demonstrated through ab initio calculations, a fact which is being employed in the elucidation of the topography of the benzodiazepine receptor binding site(s).[14-17]

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