Enamine Rearrangement of Pyridinium Salts to Indole Ring: A Combined Experimental and Molecular Modeling Study

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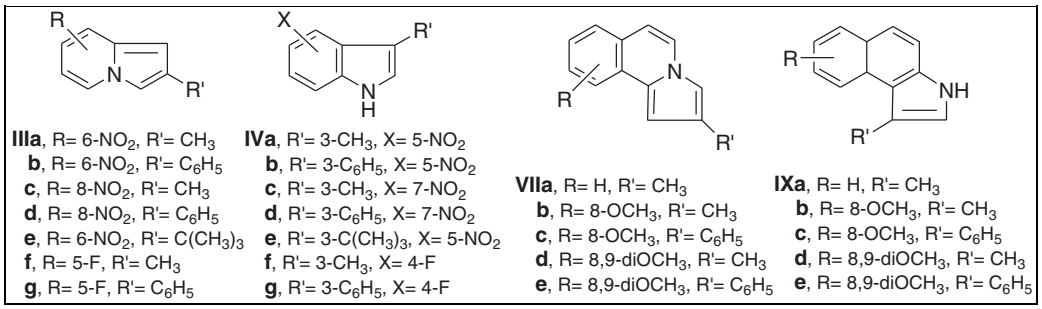
Received November 29, 2011
DOI 10.1002/jhet.1629
Published online in Wiley Online Library (wileyonlinelibrary.com).



N-Alkyl pyridinium (**II**) and *N*-alkyl isoquinolinium salts **V** undergo cyclization reaction when heated with sodium bicarbonate to give the corresponding indolizine derivatives **III** and **VI**, respectively, which undergo ring opening and recyclization reactions when heated with aqueous sodium hydroxide to give the corresponding indole derivatives **IV** and **IX**, respectively. Molecular modeling tools including Molecular Mechanics using Augmented MM3 parameters followed by geometry optimization calculations in MO-G using PM3 parameters were performed to gain better understanding and more insights on the thermodynamic properties of the recyclization reactions of compounds **IIa–g** to the corresponding **IIIa–g** and **IIIa–g** to the corresponding **IVa–g**. The results were in excellent agreement with the experimental data and hence were proven to be a good tool in explaining different yields % because of the steric and electronic effects of electron-withdrawing groups on the reactivity of the pyridine ring for nucleophilic attack.

J. Heterocyclic Chem., **50**, 638 (2013).

INTRODUCTION

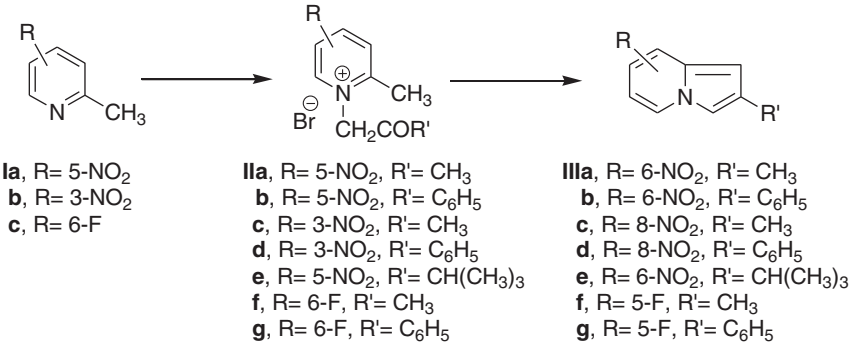
Fadda and coworkers [1–9] have reported the recyclization of *N*-alkyl pyridinium salts in the presence of aqueous alkali, alkyl amine or alkyl ammonium sulphite to give the corresponding aminobiphenyl derivatives. The nature and position of substituents in the pyridine ring have a considerable effect on these types of reactions [10]. It was expected that 2-benzylpyridinium salts that have an alkyl radical in different positions in the pyridine ring would undergo recyclization reaction. The use of pyridinium salts in the organic syntheses is now receiving a considerable interest. As a part of our program directed to develop a new, simple, and efficient methodology for the synthesis of new aromatic compounds using readily available pyridinium salts, the enamine rearrangement [1–10] appears to be a fundamental type of pyridine-into-benzene ring transformation. The important purpose of this original work is to study the reactions of such pyridinium salts, which might be extended to include and develop a new methodology for the synthesis of some new indole derivatives that are expected potential biological activity. In addition, it is planned to evaluate the biological activity of the newly synthesized compounds as antitumor and antischistosomal agents.

RESULTS AND DISCUSSION

In the present study, the action of aqueous sodium bicarbonate on *N*-alkylpyridinium salts **IIa–g** led to the formation of indolizine derivatives **IIIa–g** (Chichibabin reaction) (Scheme 1).

In this reaction, it was noticed that the yield of **IIIe** (31%) was less than half of **IIIa** (70%) probably because of the steric effect of the *t*-butyl group that resists cyclization to the indolizine **IIIe**. The ^{1}H NMR spectrum of 2-methyl-6-nitroindolizine (**IIIa**) showed singlet signal at δ 8.31 ppm because of H-5 of pyridine ring. This signal was observed in all indolizine compounds having free 5-position. This low field signal of H-5 in **IIIa** is attributed to the presence of electron acceptor nitro group in position 6. In addition, signal at δ 6.77 ppm is corresponding to H-3 and not for H-7 or H-8; protons H-7 and H-8 were observed at δ 7.05–7.40 ppm as multiplet signal, whereas signal appeared as singlet at δ 6.2 ppm is due to H-1. The ^{1}H NMR spectrum of 2-methyl-8-nitroindolizine (**IIIc**) showed a triplet at δ 6.95 ppm for 6-H as a result of the interaction with H-5 and H-7. Other signals were observed at δ 6.75 as singlet signal for 3-H, where signals at δ 6.65 is due to H-1, δ 7.83 as

Scheme 1. Synthesis of indolizine derivatives **IIIa–g**.



Ia, R= 5-NO_2
b, R= 3-NO_2
c, R= 6-F

IIa, R= 5-NO_2, R'= CH_3
b, R= 5-NO_2, R'= C_6H_5
c, R= 3-NO_2, R'= CH_3
d, R= 3-NO_2, R'= C_6H_5
e, R= 5-NO_2, R'= $CH(CH_3)_3$
f, R= 6-F, R'= CH_3
g, R= 6-F, R'= C_6H_5

IIIa, R= 6-NO_2, R'= CH_3
b, R= 6-NO_2, R'= C_6H_5
c, R= 8-NO_2, R'= CH_3
d, R= 8-NO_2, R'= C_6H_5
e, R= 6-NO_2, R'= $CH(CH_3)_3$
f, R= 5-F, R'= CH_3
g, R= 5-F, R'= C_6H_5

doublet for 5-H ($J_{5,6}$ = 8 Hz), δ 7.79 for H-7 ($J_{7,6}$ = 8 Hz), and finally at δ 2.22 as singlet signal for CH_3 protons. On the other hand, the ^{1}H NMR spectrum of 2-methyl-5-fluoroindolizine (**IIIf**) showed three singlet signals at δ 2.2, 6.08, and 6.88 ppm attributable to CH_3, 1-H, and 3-H, respectively. Other signals were observed at δ 6.22 as multiplet for H-6, 6.82 as multiplet for H-7, and δ 7.23 as multiplet for H-8. The mass spectrum of nitroindolizine showed the molecular ion peak as base peak and showed fragments because of $(M\text{-}NO)^+$ and $(M\text{-}NO_2)^+$. These results are in agreement with those reported earlier for indolizine having electron acceptor group [11].

To gain better understanding of the reaction thermodynamics of the reaction leading to the formation of compounds **IIIa–g**, the structures of the reactants **IIa–g** and products **IIIa–g** were refined by performing optimize geometry calculations in Molecular Mechanics using Augmented MM3 parameters followed by geometry optimization calculations in MO-G using PM3 parameters. Table 1 shows the total heat of formation for compounds **IIa–g** and **IIIa–g** and the stabilization energy (ΔE) for each cyclization reaction. The data in Table 1 demonstrate clearly that all cyclization reactions of **IIa–g** to **IIIa–g** are exothermically driven. Moreover, the ΔE of the cyclization of compound **IIa** to compound **IIIa** is 1.833 kcal lower than that of compounds **IIe** to **IIIe**, which explains the greater % yield of the former, owing to the steric effect of *t*-butyl group that resists cyclization to the indolizine in the latter (Table 1).

It has been found that the presence of a nitro group in position 6 in the pyridine ring of indolizine will increase the reactivity of position 5 toward nucleophilic attack. Thus, treatment of all the indolizine compounds **IIIa–g** with aqueous alcoholic sodium hydroxide afforded the corresponding indole derivatives **IVa–g**. It is worth noting that 2-methyl-6-nitroindolizines and 2-phenyl-6-nitroindolizines **IIIa**, **b** gave the corresponding nitroindoles in 85 and 90% yields, respectively, whereas 2-methyl-8-nitroindolizines and 2-phenyl-8-nitroindolizines **IIIc**, **d** afforded the corresponding nitroindoles in 40 and 48% yields, respectively. These results show that the nitro group at position 8 in the pyridine ring of indolizine decreases the reactivity at C-5 toward nucleophilic attack and consequently decreases the yield of the recyclization product.

Moreover, the recyclization of the fluoroindolizines **IIIf**, **g** afforded the corresponding indole derivatives **IVf**, **g**, upon treatment with the same aforementioned base, in lower yields 30 and 34%, respectively. These results may be due to the steric effect of the fluorine atom in position 5 that resists the step of hydrolytic solvolysis and consequently the recrystallization reaction to give the corresponding indole derivatives **IVf**, **g**. In addition, treatment of the aforementioned indolizines **IIIa–g** with sodium ethoxide in ethanol or with

Table 1

Calculated (MM3/PM3 parameters) heats of formation and stabilization energies (ΔE) of recyclization reactions of compounds **IIa–g** to the corresponding **IIIa–g**.

Compound	*E* (kcal/mol)	Compound	kcal/mol	$\Delta E_{(kcal/mol)}$
IIa	142.2305	**IIIa**	32.6232	−109.607
IIb	175.7517	**IIIb**	66.3819	−109.3698
IIc	146.7033	**IIIc**	34.9058	−111.7975
IId	176.5561	**IIId**	68.4451	−108.111
IIe	126.1100	**IIIe**	18.3369	−107.7731
IIf	105.4314	**IIIf**	−1.6568	−107.0882
IIg	128.8626	**IIIg**	31.8391	−127.0235

E = total heat of formation; stabilization energy = $\Delta E = E_{product} - E_{reactant}$.

aqueous potassium hydroxide led to the indole derivatives in very poor yields, whereas heating with sodium methoxide failed to effect recrystallization. The rearrangement of indolizines **IIIa–g** to indole derivatives **IVa–g** can be considered as a new route for indoles bearing an alkyl or aryl groups in position 3. Such indoles, especially 7-nitroindole derivatives **IVc**, **d** are difficult to be prepared by any known methods, have been prepared by the aforementioned route. The recyclization of indolizines **IIIa–g** to indole derivatives **IVa–g** may take place following the mechanism as shown in Scheme 2.

To gain insights on the thermodynamics of the recyclization of compounds **IIIa–g** to compounds **IVa–g**, Molecular Mechanics using Augmented MM3 parameters followed by geometry optimization calculations in MO-G using PM3 parameters were performed to calculate the total heat of formation for the equilibrium molecular geometry of compounds **IVa–g**. Table 2 shows the ΔE for the recyclization of **IIIa–g** to the corresponding **IVa–g**, which confirms that all recyclization reactions are thermodynamically favorably driven. The data in Table 2 show clearly that the ΔE for the recyclization of **IIIa**, **b** to the corresponding **IVa**, **g** are less thermodynamically favorable than that of **IIIc**, **d** to the corresponding **IVc**, **d** because the presence of the nitro group at position 6 in the pyridine ring of the indolizines (**IIIa**, **b**) exerts steric effect for the nucleophilic attack to take place effectively at C-5, which explains the lower % yield for compounds **IVa–b** compared with compounds **IVc**, **d**.

Moreover, the data in Table 2 show that the ΔE for the recyclization of **IIIf**, **g** to the corresponding **IVf**, **g** are the lowest thermodynamically favorable compared with compounds **IVa–d**, which explains why they had the lowest % yield owing to the steric effect exerted by the fluorine

Table 2

Calculated (MM3/PM3 parameters) heats of formation and stabilization energies (ΔE) of recyclization reactions of compounds **IIIa–g** to the corresponding **IVa–g**.

Compound	E (kcal/mol)	Compound	kcal/mol	$\Delta E_{t(kcal/mol)}$
IIIa	32.6232	**IVa**	22.0271	−10.596
IIIb	66.3819	**IVb**	55.6721	−10.7098
IIIc	34.9058	**IVc**	22.5452	−12.3606
IIId	68.4451	**IVd**	55.2858	−13.1593
IIIe	18.3369	**IVe**	8.0650	−10.2719
IIIf	−1.6568	**IVf**	−9.9453	−8.2885
IIIg	31.8391	**IVg**	25.8478	−5.9913

E = total heat of formation; ΔE = stabilization energy = $E_{product} - E_{reactant}$.

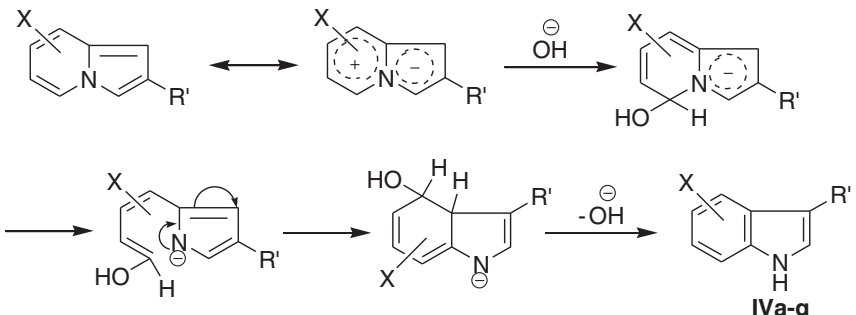
atom at C-5 that resists the step of hydrolytic solvolysis and accordingly the recyclization reaction to furnish the corresponding indole derivatives **IVf**, **g**. Moreover, in compounds **IIIa–d**, the nitro group posses more electron-withdrawing power than the F atom in compounds **IIIg**, **h**, which leads to a more electron-deficient center at C-5 favoring stronger nucleophilic attack and effective recyclization reactions to the corresponding indole derivatives (Table 2).

The structure of the intermediate σ-complex was established on the basis of NMR data. It seems that the NMR spectra of σ-complexes (**A**) and (**B**) are the same in which there are two doublets for H-6 and H-7 in case of (**A**) and for H-5 and H-6 in case of (**B**).

Thus, from the ^{1}H NMR study of both indolizine compounds and σ-complex, we can see that the OH ion is added to C-5 and not C-7 to form the intermediate σ-complex (**A**) (Figure 1).

Moreover, when 1,3-dialkylisoquinolinium salts **VIa–d** when heated in water–alcohol alkali afforded the corresponding

Scheme 2. Mechanism of formation of indole derivatives **IVa–g**.



IVa-g

IVa, R'= 3-CH_3, X= 5-NO_2
b, R'= 3-C_6H_5, X= 5-NO_2
c, R'= 3-CH_3, X= 7-NO_2
d, R'= 3-C_6H_5, X= 7-NO_2
e, R'= 3-$C(CH_3)_3$, X= 5-NO_2
f, R'= 3-CH_3, X= 4-F
g, R'= 3-C_6H_5, X= 4-F

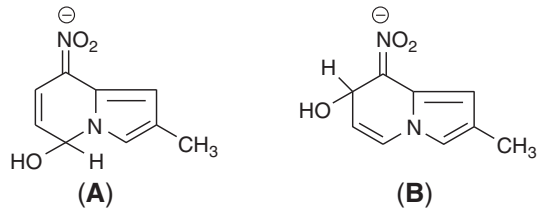


Figure 1. Structure of the intermediate σ-complexes (**A**) and (**B**) of indolizine compounds.

2-methylpyrrolo[2,1-*a*]isoquinoline derivatives **VIIa–d** in 40–80% yields (Scheme 3).

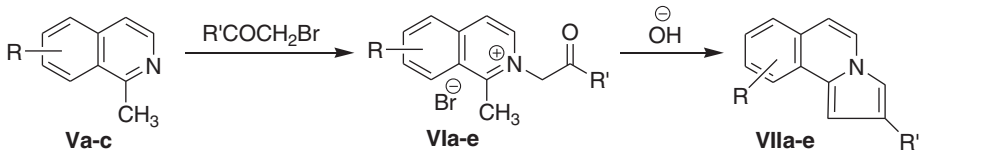
The ^{1}H NMR spectrum of 1-methyl-2-(2-oxopropyl) isoquinolinium bromide **VIa** showed two singlet signals at δ 2.2, 2.93, and 5.95 ppm because of $COCH_3$, CH_3, and CH_2 protons, respectively, and two doublets at δ 8.5 and 8.91 ppm because of H-3 and H-4, respectively, whereas the ^{1}H NMR spectrum of 2-methylpyrrolo[2,1-*a*]isoquinoline **VIIa** showed three singlet signals at δ 2.01, 6.0, and 6.8 ppm attributable to CH_3, H-1, and H-3 (pyrrole ring) and two doublets at δ 7.5 and 8.4 ppm because of H-5 and H-6. This reaction, too, begins with the nucleophilic attack by the hydroxide anion directed at the carbon atom by the aromatic nitrogen. The next stage is the ring opening (probably according to the electrocyclic mechanism) by C-N bond fission. It is then followed by ring closure and the C-C bond formation (such as the mechanism of the rearrangement of indolizines to indoles) (Scheme 4).

The ^{1}H NMR spectrum of 1-methyl-3*H*-benzo[*e*]indole **IXa** showed three singlet signals at δ 2.3, 7.1, and 9.9 ppm attributable to CH_3, H-2, and NH protons, respectively, and two doublets at δ 7.3 and 7.6 ppm because of H-4 and H-5 protons.

CONCLUSION

The evidence on the pyridine ring recyclization available at present concerns primarily the formation of heterocycles and carbocycles, which is quite natural considering the high solvolysability of the N=CH bond in pyridinium salts. Some of these reactions are significant as preparative methods. The enamine rearrangement of pyridinium salts into aromatic amines described by Fadda et al. is a new type of recyclization. The information on the structural factors and reaction conditions obtained so far promises to provide new exciting results. The recyclization of pyridine derivatives not activated by quaternization is relatively scarce. Because of the insufficient polarization of the aromatic ring in this case, the nucleophilic attack is nonselective, and the C-C as well as C-N bond cleavage takes place.

Scheme 3. Synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives **VIIa–e**.

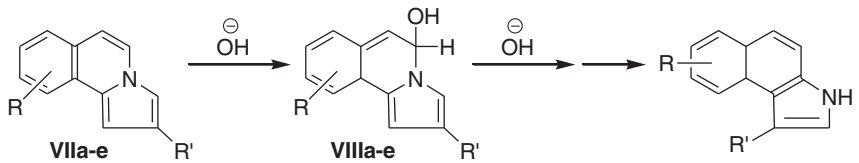


Va, R= H
b, R= 6-OCH_3
c, R= 6,7-diOCH_3

VIa, R= H, R'= CH_3
b, R= 6-OCH_3, R'= CH_3
c, R= 6-OCH_3, R'= C_6H_5
d, R= 6,7-diOCH_3, R'= CH_3
e, R= 6,7-diOCH_3, R'= C_6H_5

VIIa, R= H, R'= CH_3
b, R= 8-OCH_3, R'= CH_3
c, R= 8-OCH_3, R'= C_6H_5
d, R= 8,9-diOCH_3, R'= CH_3
e, R= 8,9-diOCH_3, R'= C_6H_5

Scheme 4. Synthetic route of formation of benzoindole derivatives **IXa–e**.



IXa, R= H, R'= CH_3
b, R= 8-OCH_3, R'= CH_3
c, R= 8-OCH_3, R'= C_6H_5
d, R= 8,9-diOCH_3, R'= CH_3
e, R= 8,9-diOCH_3, R'= C_6H_5

Molecular modeling tools using Molecular Mechanics, MM3 parameters, and Quantum Mechanics, PM3 parameters were proven to be effective tools in understanding the thermodynamics of cyclization/recyclization reactions and explaining the different % yields because of differences in steric effects and/or electronic properties.

EXPERIMENTAL

Molecular modeling. The equilibrium molecular geometry of the compounds **IIa–g**, **IIIa–g**, and **IVa–g** was predicted in Molecular Mechanics using Augmented MM3 parameters followed by geometry optimization calculations in MO-G using PM3 parameters, and the total heat of formation (*E*) for each compound and the stabilization energy (ΔE) of each cyclization/recyclization reaction were calculated. All calculations were run in Scigress Explorer Professional Version 7.7.0.47, on an Intel(R) Core (TM)2 Quad, CPU Q6600 @2.4 GHz with 3.5 G of RAM. MLR was used.

Synthesis. All melting points are (uncorrected) in degree centigrade and were determined on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, London, Great Britain). The reaction products were shown to be single entity by thin layer chromatography (TLC) in benzene. The infrared spectra were recorded in potassium bromide disks on a pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd., Cambridge, England and Shimadzu, Tokyo, Japan, respectively). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (USA) at 300 and 75 MHz, respectively. Chemical shifts were related to that of the solvent. The mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX (Japan) mass spectrometer at 70 eV. Elemental analyses were recorded on PERKIN-ELMER 2400 Elemental analyzer at the Microanalytical Center at Cairo University, Cairo, Egypt.

2-Methyl-5-nitropyridine (Ia). It was prepared according to the procedure reported earlier [12], 63%, mp 110–111°C.

2-Methyl-3-nitropyridine (Ib). It was obtained according to the previously reported work [13], 86%, mp 23–24°C, bp 84–86/5 mm.

2-Fluoro-6-methylpyridine (Ic). It was supplied by Aldrich [407–22–7] code no., bp 140°C.

Formation of *N*-acetonyl pyridinium salts IIa, c, f. ***General procedure.*** A mixture of **Ia**, **c**, **f** (3 mmol) and ω-bromoacetone (3.5 mmol) in acetone (5 mL) was refluxed at 60–80°C on a water bath for 10–15 h. The resultant solid was filtered and recrystallized from ethanol to give **IIa**, **f**. Compound **IIc** did not separate, and therefore, it could not be crystallized.

***N*-Acetonyl-5-nitro-2-methylpyridine (IIa).** 78%; mp 165–166°C; IR: 1710 (CO), 1620 cm^{-1} (C=N); Calcd for $C_9H_{11}BrN_2O_3$: C, 39.3; H, 4.1; N, 10.2. Found C, 39.4; H, 4.1; N, 10.1.

***N*-Acetonyl-6-fluoro-2-methylpyridine (IIf).** 64%; mp 102–104°C; Calcd for $C_9H_{11}BrNOF$: C, 43.8; H, 4.5; N, 5.6. Found C, 43.6; H, 4.3; N, 5.4.

Formation of *N*-phenacyl pyridinium salts IIb, d, g. ***General procedure.*** A mixture of **Ib**, **d**, **g** (3.6 mmol) and phenacyl bromide (5 mmol) in acetone (3 mL) was refluxed at 90°C on a water bath for 9 h. The resultant solid was filtered and recrystallized from ethanol to give **IIb**, **d**, **g**.

***N*-Phenacyl-5-nitro-2-methylpyridine (IIb).** 70%; mp 189–190°C; Calcd for $C_{14}H_{15}BrN_2O_3$: C, 49.8; H, 4.1; N, 8.3. Found C, 49.7; H, 4.0; N, 8.1.

***N*-Phenacyl-3-nitro-2-methylpyridine (IId).** 80%; mp 160–161°C; Calcd for $C_{14}H_{13}BrN_2O_3$: C, 49.87; H, 3.89; N, 8.31. Found C, 49.6; H, 3.7; N, 8.27.

***N*-Phenacyl-6-fluoro-2-methylpyridine (IIg).** 60%; mp 126°C; Calcd for $C_{14}H_{13}BrFNO$: C, 54.21; H, 4.22; N, 4.52. Found C, 54.01; H, 4.03; N, 4.35.

***N*-Pinaconyl-2-methyl-5-nitropyridinium bromide (IIe).**

Formation of 4-bromo-2,2-dimethylbutan-3-one. To pinacolone [14], 0.014 g (0.14 mmol), anhydrous ether (200 mL) at 0°C was added drop by drop bromine 0.022 g (0.14 mmol). After complete addition, the solution turned yellow in color. The reaction mixture was then poured into ice cold water (100 mL) and then extracted with diethyl ether. The ethereal extract was then dried over sodium sulfate and evaporated *in vacuo* to give 63% yield, boiling point 80–82°C/12 mL [14].

Formation of IIe. A mixture of **Ia** 0.21 g (1.5 mmol) and 4-bromo-2,2-dimethylbutan-3-one was dissolved in acetophenone or ethyl methyl ketone (1 mL). The reaction mixture is then heated at 120°C for 20 h (or heated in pressure tube at 70–80°C for 3 h). The obtainable crystals on cooling are washed and crystallized from acetone to give **IIe**. 35%, mp 241°C; Calcd for $C_{12}H_{17}BrN_2O_3$: C, 45.44; H, 5.40; N, 8.83. Found C, 45.35; H, 5.37; N, 8.77.

Formation of indolizine derivatives IIIa–g. ***General procedure.*** A mixture of **II** (5 mmol) and sodium bicarbonate 1.0 g (12 mmol) in absolute ethanol (20 mL) was heated with continuous stirring for 1–3 h. The reaction mixture was filtered, the filtrate evaporated *in vacuo*, and the residue recrystallized from heptanes under cooling to give **IIIa–g**.

2-Methyl-6-nitroindolizine (IIIa). 70%; mp 85–87°C (crystallization from hexane or heptanes); IR: 1560 (C=C), 1530, 1350 cm^{-1} (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.0 (s, 3H, CH_3), 6.2 (s, 1H, H-1), 6.77 (s, 1H, H-3), 7.05–7.40 (m, 2H, H-7, H-8), 8.31 ppm (s, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.8, 130.7, 124.6, 121.3, 121.2, 112.6, 111.8, 103.6, 20.4 ppm; MS: *m/z* (%): 176 (100.0), 131 (7.2), 130 (80), 128 (5.0), 118 (3.0), 103 (35.0), 102 (10.0), 77 (40.0), 63 (5.0), 51 (15.0). Calcd for $C_9H_8N_2O_2$. C, 61.36; H, 4.58; N, 15.90. Found C, 61.2; H, 4.5; N, 15.8.

2-Phenyl-6-nitroindolizine (IIIb). 80%; mp 203–204°C (crystallization from ethanol); IR: 1562 (C=C), 1530–1350 cm^{-1} (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.8 (s, 1H, H-1), 7.1 (s, 1H, H-3), 7.37 (d, 1H, H-8), 7.4–7.52 (m, 5H, Ar-H), 7.8 (d, 1H, H-7), 8.37 ppm (s, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.6, 136.6, 130.5, 130.3, 129.8, 129.3, 129.1, 128.0, 127.4, 121.3, 121.2, 112.8, 109.4, 98.1 ppm; MS: *m/z* (%): 238 (100.0), 193 (20), 192 (70), 191 (30), 190 (10), 180 (15.5), 165 (30.1), 164 (12.2), 163 (10.5), 115 (10.5). Calcd for $C_{14}H_{10}N_2O_2$. C, 70.58; H, 4.23; N, 11.76. Found C, 70.63; H, 4.26; N, 11.83.

2-Methyl-8-nitroindolizine (IIIc). A mixture of 2-methyl-3-nitropyridine 0.5 g (3.6 mmol) and bromoacetone 2 g (14.4 mmol) was heated at 90°C for 6 h. The resultant mass was acidified with dil. HCl to pH 2–3, heated again, and filtered while hot. Sodium bicarbonate was added to the hot filtrate and heated to boiling. The reaction mixture was extracted with chloroform. The chloroform extract was dried on magnesium sulfate and matographed over silica gel column by using chloroform as eluent to give **IIIc**. 36%; mp 101–103°C (crystallization from hexane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.22 (s, 3H, CH_3), 6.65 (s, 1H, H-1), 6.75 (s, 1H, H-3), 6.95 (t, 1H, H-6), 7.79 (d, 1H, H-7, $J_{7,6}$ = 8 Hz), 7.83 ppm

(d, 1H, H-5, $J_{5,6}$ = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 139.8, 130.1, 129.7, 124.1, 113.7, 112.5, 111.9, 103.7, 20.3 ppm; MS: *m/z* (%): 176 (100.0), 131 (8.5), 130 (90.5), 129 (15.2), 128 (14.3), 110 (10.5), 109 (12.2), 103 (10.2), 91 (40.5), 77 (30.2), 69 (10.2). Calcd for $C_9H_8N_2O_2$. C, 61.36; H, 4.58; N, 15.90. Found C, 61.1; H, 4.4; N, 15.8.

2-Phenyl-8-nitroindolizine (IIId). 86%; mp 172–173°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (m, 1H, H-6), 7.4–7.58 (m, 5H, C_6H_5), 7.61 (s, 1H, H-3), 7.81 (s, 1H, H-1), 8.28, 8.58 ppm (d, d, 2H, H-7, $J_{7,6}$ = 8 Hz, H-5, $J_{5,6}$ = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 141.3, 137.4, 130.9, 130.8, 129.6, 129.4, 129.3, 128.9, 114.1, 113.4, 97.5 ppm; MS: *m/z* (%): 238 (100.0), 192 (60.5), 191 (55), 190 (12.2), 165 (20.5), 128 (20), 91 (15), 78 (38), 69 (15), 63 (15). Calcd for $C_{14}H_{10}N_2O_2$. C, 70.58; H, 4.23; N, 11.76. Found C, 70.45; H, 4.15; N, 11.66.

2-t-Butyl-6-nitroindolizine (IIIe). 31%; mp 92–94°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.38 (s, 9H, 3CH_3), 6.1 (s, 1H, H-1), 6.8 (s, 1H, H-3), 6.98 (m, 1H, H-6), 7.43 (d, 1H, H-7), 7.83 ppm (d, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.8, 130.7, 124.5, 120.5, 120.3, 112.4, 111.9, 105.2, 39.1, 24.3 ppm; MS: *m/z* (%): 218 (90.5), 204 (15), 203 (100.0), 176 (5.5), 157 (15), 156 (10), 130 (10), 128 (15), 115 (10), 90 (10). Calcd for $C_{12}H_{14}N_2O_2$. C, 66.04; H, 6.47; N, 12.84. Found C, 66.0; H, 6.3; N, 12.7.

2-Methyl-5-fluoroindolizine (IIIf). 30%; mp 126°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), 6.08 (s, 1H, H-1), 6.22 (m, 1H, H-6), 6.82 (m, 1H, H-7), 6.88 (s, 1H, H-3), 7.23 ppm (m, 1H, H-8); ^{13}C NMR (75 MHz, DMSO-d_6): δ 140.7, 132.8, 124.6, 123.5, 118.6, 11.6, 105.2, 98.6, 19.6 ppm; MS: *m/z* (%): 149 (M^+, 100.0), 150 (M^+ + 1, 10). Calcd for C_9H_8FN. C, 72.47; H, 5.41; N, 9.39. Found C, 72.35; H, 5.33; N, 9.25.

2-Phenyl-5-fluoroindolizine (IIIg). 34%; mp 163–161°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 141.2, 137.5, 131.6, 131.2, 130.7, 130.2, 129.8, 129.1, 127.4, 123.4, 120.2, 109.3, 97.8, 97.7 ppm; MS: *m/z* (%): 211 (M^+, 100.0), 212 (M^+ + 1, 15.5), 213 (M^+ + 2, 2.1). Calcd for $C_{14}H_{10}FN$. C, 79.60; H, 4.77; N, 6.63. Found C, 79.51; H, 4.63; N, 6.49.

Rearrangement of IIIa–g to indole derivatives IVa–g. ***General procedure.*** Compound **IIIa** 0.2 g (1.15 mmol), **IIIb** 0.27 g (1.15 mmol), **IIIc** 0.2 g (1.15 mmol), **IIId** 0.27 g (1.15 mmol), **IIIe** 0.23 g (1.15 mmol), **IIIf** 0.17 g (1.15 mmol), or **IIIg** 0.24 g (1.15 mmol) was refluxed with alcoholic potassium hydroxide (10 mL ethanol, 10% H_2O, 2 g KOH) in atmospheric argon for 5–15 h. The reaction mixture was then poured into 100 mL of water. The obtainable precipitate was filtered off and washed with water to give **IV** as a yellow material.

3-Methyl-5-nitroindole (IVa). 85%; mp 125–127°C (crystallization from xylene); IR: 3325 (NH), 1530 (Antisymm. NO_2), 1350 cm^{-1} (Symm. NO_2); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3), 7.18 (s, 1H, H-2), 7.37 (d, 1H, H-7, $J_{7,6}$ = 9 Hz), 7.9 (q, 1H, H-6, $J_{6,4}$ = 2 Hz, $J_{6,7}$ = 9 Hz), 8.46 (d, 1H, H-4, $J_{4,6}$ = 2 Hz), 10.1 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.6, 132.5, 129.4, 128.9, 123.1, 114.6, 112.3, 111.4, 17.4 ppm; MS: *m/z* (%): 176 (100.0), 175 (16), 130 (75), 129 (25), 103 (35), 102 (12.4), 77 (30), 69 (15), 57 (16), 55 (10). Calcd for $C_9H_8N_2O_2$. C, 61.36; H, 4.58; N, 15.9. Found C, 61.21; H, 4.53; N, 15.8.

3-Phenyl-5-nitroindole (IVb). 90%; mp 190–192°C; Lit., mp 187°C [15] (crystallization from benzene); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.2–7.7 (m, 7H, C_6H_5, H-2, H-7), 8.02 (q, 1H, H-6, $J_{6,4}$ = 2 Hz, $J_{6,7}$ = 9 Hz), 8.66 (d, 1H, H-4, $J_{4,6}$ = 2 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.6, 136.7, 132.8, 130.3, 129.6, 129.5, 128.1, 127.7, 127.4, 124.9, 114.3, 112.6, 111.4 ppm; MS: *m/z* (%): 238 (100.0), 192 (35), 165 (70), 164 (15), 97 (10.2), 83 (20), 71 (20), 69 (30), 57 (50), 55 (40).

3-Methyl-7-nitroindole (IVc). 40%; mp 139–141°C (crystallization from benzene); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.07 (t, 1H, H-5, H-7, $J_{5,6}$ = $J_{5,4}$ = 8 Hz), 7.13 (s, 1H, H-2), 7.93 (t, 2H, H-4, H-6, $J_{6,5}$ = $J_{4,6}$ = 8 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 136.4, 130.8, 128.4, 125.6, 123.4, 122.8, 114.7, 111.1, 17.2 ppm; MS: *m/z* (%): 176 (100.0), 175 (50), 130 (64.5), 129 (30), 128 (10), 103 (35), 102 (15), 76 (10), 75 (5), 51 (10). Calcd for $C_9H_8N_2O_2$. C, 61.36; H, 4.58; N, 15.9. Found C, 61.29; H, 4.49; N, 15.84.

3-Phenyl-7-nitroindole (IVd). 48%; mp 156–158°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 137.1, 136.8, 130.7, 130.1, 130.0, 129.8, 129.5, 127.8, 127.3, 125.7, 125.1, 123.3, 114.2, 110.9 ppm; MS: *m/z* (%): 238 (M^+, 100.0), 192 (40), 191 (20), 190 (20), 165 (31), 164 (10), 163 (10), 128 (10), 91 (10). Calcd for $C_{14}H_{10}N_2O_2$. C, 70.58; H, 4.23; N, 11.76. Found C, 70.36; H, 4.18; N, 11.66.

3-t-Butyl-7-nitroindole (IVe). 27%; mp 210°C (crystallization from benzene); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.4 (s, 9H, 3CH_3), 7.2 (s, 1H, H-2), 7.57 (t, 1H, H-6, $J_{6,5}$ = $J_{6,4}$ = 8 Hz), 7.99 (d, 1H, H-4, $J_{4,6}$ = 8 Hz), 8.11 (d, 1H, H-5, $J_{5,6}$ = 8 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.6, 132.5, 128.5, 127.3, 124.8, 123.5, 114.0, 112.4, 42.6, 32.7 ppm; MS: *m/z* (%): 218 (M^+, 100.0), 219 (M^+ + 1, 15), 220 (M^+ + 2, 5). Calcd for $C_{12}H_{14}N_2O_2$. C, 66.04; H, 6.47; N, 12.84. Found C, 66.0; H, 6.26; N, 12.73.

3-Methyl-4-fluoroindole (IVf). 30%; mp 127129°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.01 (d, 1H, H-5, $J_{5,6}$ = 8 Hz), 7.09 (m, 2H, H-6, $J_{6,5}$ = $J_{6,7}$ = 8 Hz, H-7, $J_{7,6}$ = 8 Hz), 7.21 (s, 1H, H-2), 10.21 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.7, 138.4, 123.6, 122.0, 121.2, 119.4, 116.8, 111.3, 107.5, 21.6 ppm; MS: *m/z* (%): 149 (M^+, 100.0), 150 (M^+ + 1, 10.5). Calcd for C_9H_8FN. C, 77.47; H, 5.41; N, 9.39. Found C, 77.39; H, 5.33; N, 9.28.

3-Phenyl-4-fluoroindole (IVg). 34%; mp 213°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ H-5, H-6 and H-7 gave signals like that of **IVf**; on the other hand, H-2 appeared at δ 8.4 ppm (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 155.0, 137.9, 136.8, 129.6, 129.2, 128.3, 124.9, 122.4, 115.8, 113.7, 110.4, 106.8 ppm; MS: *m/z* (%): 211 (M^+, 100.0), 212 (M^+ + 1, 20), 213 (M^+ + 2, 5). Calcd for $C_{14}H_{10}FN$. C, 79.60; H, 4.77; N, 6.63. Found C, 79.49; H, 4.63; N, 6.49.

The *σ*-complex (**A**) could be isolated after adding sodium hydroxide to indolizine; it precipitated out on cold.

Formation of *N*-acetonyl and *N*-phenacyl isoquinolinium salts (VIa–e). It has been prepared according to the general method for preparing salts **IIa**, **c**, **f**.

N-Acetonyl-1-methylisoquinolinium bromide (VIa). 80%; mp 9294°C (washed by ether); IR: 1725 (CO), 1620 cm^{-1} (C=N); Calcd for $C_{13}H_{14}BrNO$. C, 55.73; H, 5.04; N, 5.0. Found C, 55.62; H, 4.88; N, 5.0.

N-Acetonyl-1-methyl-6-methoxyisoquinolinium bromide (VIb). 76%; mp 162164°C (crystallization from heptane). Calcd for $C_{14}H_{16}BrNO_2$. C, 54.21; H, 5.20; N, 4.52. Found C, 54.16; H, 5.13; N, 4.48.

N-Phenacyl-1-methyl-6-methoxyisoquinolinium bromide (VIc). 82%; mp 180–182°C (crystallization from heptane);

Calcd for $C_{19}H_{18}BrNO_2$. C, 61.30; H, 4.87; N, 3.76. Found C, 61.25; H, 4.80; N, 3.65.

N-Acetonyl-1-methyl-6,7-dimethoxyisoquinolinium bromide (VId). 63%; mp 210212°C (crystallization from heptane). Calcd for $C_{15}H_{18}BrNO_3$. C, 52.96; H, 5.33; N, 4.12. Found C, 52.77; H, 5.25; N, 4.10.

N-Phenacyl-1-methyl-6,7-dimethoxyisoquinolinium bromide (VIe). 72%; mp 189–191°C (crystallization from heptane). Calcd for $C_{20}H_{20}BrNO_3$. C, 59.71; H, 5.01; N, 3.48. Found C, 59.65; H, 4.89; N, 3.35.

Formation of pyrrolo[2,1-*a*]isoquinolines VIIa–e. It has been prepared according to the general procedure for indolizine formation.

2-Methylpyrrolo[2,1-a]isoquinoline (VIIa). 64%; mp 186–188°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 3H, CH_3), 6.03 (s, 1H, H-1), 6.8 (s, 1H, H-3), 7.51 (d, 1H, H-6, $J_{6,5}$ = 8 Hz), 7.54–7.88 (m, 4H, Ar-H), 8.52 ppm (d, 1H, H-5, $J_{5,6}$ = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 136.9, 131.7, 129.0, 127.8, 127.3, 127.0, 126.5, 125.1, 124.2, 121.4, 111.7, 105.2, 21.4 ppm. Calcd for $C_{13}H_{11}N$. C, 86.15; H, 6.12; N, 7.73. Found C, 86.10; H, 6.09; N, 7.56.

2-Methoxy-2-methylpyrrolo[2,1-a]isoquinoline (VIIb). 78%; mp 210–212°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.04 (s, 1H, H-1), 6.9 (s, 1H, H-3), 7.01 (s, 1H, H-5), 7.25 (d, 1H, H-7, $J_{7,8}$ = 8 Hz), 7.45 (d, 1H, H-6, $J_{6,5}$ = 8 Hz), 7.91 (d, 1H, H-8, $J_{8,7}$ = 8 Hz), 8.61 ppm (d, 1H, H-5, $J_{5,6}$ = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.7, 137.8, 130.3, 125.1, 124.7, 120.6, 120.1, 120.0, 112.2, 108.7, 104.1, 56.4, 19.3 ppm; MS: *m/z* (%): 211 (M^+, 100.0), 212 (M^+ + 1, 20). Calcd for $C_{14}H_{13}NO$. C, 79.59; H, 6.20; N, 6.63. Found C, 79.33; H, 6.15; N, 6.49.

8-Methoxy-2-phenylpyrrolo[2,1-a]isoquinoline (VIIc). 56%; mp 132–135°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.4, 138.2, 136.4, 131.0, 130.6, 130.1, 130.0, 129.5, 127.8, 127.7, 127.6, 126.3, 125.9, 124.3, 123.9, 124.7, 120.3, 120.2, 110.1, 109.7, 108.2, 98.1, 56.3 ppm; MS: *m/z* (%): 173 (M^+, 100.0), 274 (M^+ + 1, 20). Calcd for $C_{19}H_{15}NO$. C, 83.49; H, 5.53; N, 5.12. Found C, 83.35; H, 5.38; N, 5.10.

8,9-Dimethoxy-2-methylpyrrolo[2,1-a]isoquinoline (VIId). 45%; mp 213–215°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.06 (s, 3H, CH_3), 3.91 (s, 6H, $2OCH_3$), 6.84 (s, 1H, H-3), 6.91 (s, 1H, H-7), 7.10 (s, 1H, H-10), 7.4 (d, 1H, H-6, $J_{6,5}$ = 8 Hz), 8.52 ppm (d, 1H, H-5, $J_{5,6}$ = 8 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.5, 146.5, 137.1, 130.3, 125.4, 125.1, 121.2, 120.8, 120.5, 120.4, 112.6, 108.8, 104.9, 57.6, 57.1, 13.6 ppm; MS: *m/z* (%): 241 (M^+, 100.0). Calcd for $C_{15}H_{15}NO_2$. C, 74.67; H, 6.27; N, 5.81. Found C, 74.59; H, 6.21; N, 5.73.

8,9-Dimethoxy-2-phenylpyrrolo[2,1-a]isoquinoline (VIIe). 41%; mp 261–263°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 154.6, 146.4, 137.8, 136.7, 130.8, 130.7, 129.6, 129.4, 129.1, 128.3, 125.4, 120.6, 120.5, 119.3, 109.6, 57.3, 56.9 ppm; MS: *m/z* (%303 :((M^+, 100.0). Calcd for $C_{20}H_{17}NO_2$. C, 79.19; H, 5.65; N, 4.62. Found C, 79.09; H, 5.55; N, 4.46.

Rearrangement of IXa–e to benzoindole derivatives **IXa–e**. These compounds were obtained according to the general procedure for the synthesis of indole from indolizine.

***1-Methyl-3H*-benzo[*e*]indole (IXa).** 81%; mp 181183°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 7.21 (s, 1H, H-2), 7.33 (d, 1H, H-4, $J_{4,5}$ = 8 Hz), 7.61 (d, 1H, H-5, $J_{5,4}$ = 8 Hz), 7.67 (m, 2H, H-7, H-8), 8.16 (t, 1H, H-6, $J_{6,5}$ = 8 Hz), 8.54 (t, 1H, H-9, $J_{9,8}$ = 8 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 134.9, 130.6, 127.6, 127.5, 124.7, 124.6, 122.3, 118.9, 118.5, 117.8, 39.4, 38.7, 17.4 ppm; MS: *m/z* (%): 181 (M^+, 100.0). Calcd for $C_{13}H_{11}N$. C, 86.15; H, 6.12; N, 7.73. Found C, 86.10; H, 6.11; N, 7.65.

8-Methoxy-1-methyl-3H-benzo[e]indole (IXb). 82%; mp 262–264°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.3 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 7.1 (s, 1H, H-2), 7.24 (d, 1H, H-7, $J_{7,6}$ = 8 Hz), 7.32 (d, 1H, H-4, $J_{4,5}$ = 8 Hz), 7.39 (s, 1H, H-9), 7.60 (d, 1H, H-5, $J_{5,4}$ = 8 Hz), 8.10 (d, 1H, H-6, $J_{6,7}$ = 8 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.4, 134.8, 127.8, 1275, 123.5, 123.2, 118.7, 118.3, 117.9, 117.2, 99.7, 53.6, 40.5, 17.4 ppm; MS: *m/z* (%): 211 (M^+, 100.0), 212 (M^+ + 1, 25). Calcd for $C_{14}H_{13}NO$. C, 79.59; H, 6.2; N, 6.63. Found C, 79.39; H, 6.10; N, 6.48.

8-Methoxy-1-phenyl-3H-benzo[e]indole (IXc). 63%; mp 232–233°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 137.1, 136.9, 134.7, 130.1, 130.3, 129.5, 129.2, 128.8, 127.7, 127.3, 127.4, 123.5, 119.6, 116.4, 116.5, 98.6, 54.6, 54.5, 37.3, 31.9 ppm; MS: *m/z* (%): 273 (M^+, 100.0). Calcd for $C_{19}H_{15}NO$. C, 83.49; H, 5.53; N, 5.12. Found C, 83.33; H, 5.49; N, 5.02.

8,9-Dimethoxy-1-methyl-3H-benzo[e]indole (IXd). 66%; mp 172–174°C (crystallization from heptane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 3.83, 3.84 (s, s, 6H, $2OCH_3$), 6.96 (d, 1H, H-6, $J_{6,7}$ = 8 Hz), 7.21 (s, 1H, H-2), 7.34 (d, 1H, H-4, $J_{4,5}$ = 8 Hz), 7.43 (d, 1H, H-6, $J_{6,7}$ = 8 Hz), 7.61 (d, 1H, H-5, $J_{5,4}$ = 8 Hz), 10.2 ppm (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 150.1, 134.8, 127.8, 127.7, 123.5, 123.1, 121.4, 118.7, 118.5, 117.854.1, 53.8, 33.6, 17.4 ppm. Calcd for $C_{15}H_{15}NO_2$. C, 74.67; H, 6.27; N, 5.81. Found C, 74.55; H, 6.14; N, 5.69.

8,9-Dimethoxy-1-phenyl-3H-benzo[e]indole (IXe). 56%; mp 210–212°C (crystallization from heptane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 136.7, 136.4, 134.5, 130.4, 130.1, 129.2, 128.9, 128.6, 127.4, 127.1, 127.0, 123.7, 121.2, 119.3, 116.7, 116.3, 54.1, 54.6, 37.1, 31.5 ppm; MS: *m/z* (%): 303 (M^+, 100.0), 304 (M^+ + 1, 15). Calcd for $C_{20}H_{17}NO_2$. C, 79.19; H, 5.65; N, 4.62. Found C, 79.10; H, 5.56; N, 4.55.

Acknowledgment. Dr. Ahmed El-Shafei, Polymer and Color Chemistry Program, North Carolina State University, Raleigh, USA, is greatly acknowledged for molecular modeling calculations.

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