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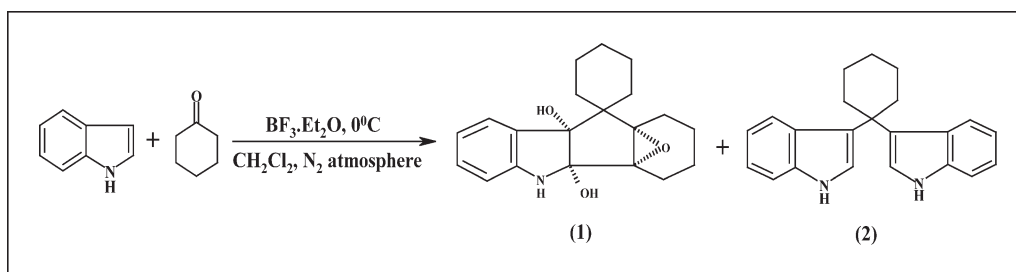
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The reaction of indole with cyclohexanone in the presence of the Lewis acid, boron trifluoride diethyl etherate, resulted in the synthesis of a novel and interesting product (**1**) in addition to the bis(indolyl)methane system (**2**). The structure of this novel compound has been determined by NMR (¹H and ¹³C) and X-ray crystal structure analysis. Compound **1** is a (1:2) addition reaction product of indole with cyclohexanone. The spiro six-membered ring is in the classic chair conformation. An epoxide bridge at C-4a/C-10b and the two hydroxyl groups at C-5a, C-10a are all on the same side of the central five membered ring.

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INTRODUCTION

Bis(indolyl)methanes have come into prominence since the discovery that they effectively inhibit prostate cancer cells. Moreover, in the human system bis(indolyl)methanes promote the metabolism of estrone and estradiol, respectively, to their 2-hydroxy derivatives. Nowadays, supplementation of bis(indolyl)methanes in human diets has become important [1]. In continuation of our studies on the synthesis of bis(indolyl)methanes [2,3] we have also synthesized mechanistically interesting and novel compounds [4] involving the electrophilic substitution reactions of indoles using Lewis acids. In this article, we report the result of our investigation using indole and cyclohexanone in the presence of boron trifluoride diethyl etherate. A unique and novel epoxy compound has been synthesized and characterized by elemental analysis, UV, FTIR, ¹H NMR, ¹³C NMR, and EIMS. The X-ray diffraction structure of compound **1** was determined. An epoxide bridge is present at C_{4a}/C_{10b} and the two hydroxyl groups at C-5a, C-10a are all on the same side of the central five membered ring.

RESULTS AND DISCUSSION

To a solution of indole (1.2 g) in dry methylene chloride (40 mL) and cyclohexanone (1 mL), boron trifluoride

diethyl etherate (1 mL) in dry methylene chloride (5 mL) was added dropwise with continuous stirring at 0°C under nitrogen atmosphere. The reaction mixture was kept at 0°C for 5 h. A dark resinous mass was obtained. The reaction was quenched over ice. The product was extracted with methylene chloride (3 × 50 mL), washed with 2% NaHCO₃ solution and finally with water. The methylene chloride layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate on column chromatography over neutral grade Brockmann alumina afforded a new compound (**1**) together with the known bis(indolyl)methane (**2**).

Compound **1**, C₂₀H₂₅O₃N, M⁺ 327, m.p. 130–131°C (petrol: benzene, 4:1) was obtained in 10% yield. It showed the ultraviolet absorption maxima λ_{max}^(EtOH) at 256 and 209 nm (log ε: 4.38 and 4.90, respectively), which shifted in 50% perchloric acid exhibiting λ_{max}^(EtOH+50% HClO₄) at 292, 241, 217, and 204 nm (logε: 4.32, 4.78, 4.78, and 4.75, respectively) indicating the presence of an indole moiety. In the infrared spectrum of compound **1**, using KBr pellet, significant peaks at 3420 (>NH), 3300 (—OH) and 1610, 1470 (aromatic nucleus) and 750 cm⁻¹ (*o*-disubstituted benzene ring) were discernible.

To get an idea of the proton environment in compound **1**, the 300 MHz ¹H NMR spectrum was studied

in CDCl_3 . One singlet at δ 7.35 (which disappeared on deuteration) confirmed the presence of an >NH . Two triplets (one proton each) appeared at δ 7.11 (1H, t, $J = 7.6$ Hz) for H-7 and δ 6.81 (1H, t, $J = 7.6$ Hz) for H-8. H-6 and H-9 resonated as doublets (one proton each) at δ 7.26 (1H, d, $J = 7.8$ Hz) and δ 6.62 (1H, d, $J = 7.8$ Hz). Two singlets at δ 4.22 and δ 3.92 indicated the presence of two —OH groups (C-10a-OH and C-5a-OH, respectively), which disappeared on deuteration. Eighteen methylene protons resonated in the region δ 1.17–2.07.

The 75.5 MHz ^{13}C NMR spectra including APT experiment of compound **1** showed the presence of twenty carbon atoms. The compound contained only two aromatic sp^2 quaternary carbons (C-9a, C-5b), which appeared at 149.4 and 129.5 ppm, respectively. Four aromatic sp^2 tertiary carbons (C-6, C-7, C-8, C-9) resonated at 126.9, 119.6, 129.3, and 111.0 ppm, respectively. Five sp^3 quaternary carbon atoms (C-10a, C-10b, C-5a, C-5, C-4a) appeared at 101.4, 75.2, 89.1, 50.0, and 69.7 ppm, respectively. Nine sp^3 secondary methylene carbons (C-1, C-2, C-2', C-3, C-3', C-4, C-4', C-5' and C-6') were discernible at 28.6, 25.6, 22.6, 23.7, 21.0, 27.3, 19.9, 20.5, 21.8 ppm, respectively.

The mass spectral analysis by EIMS showed the molecular ion (M^+) 327 for compound **1**. One of the characteristic peaks appeared at 179, which is the most abundant peak. Some other characteristic peaks were observed at 149, 111, and 309. This result is in agreement with the X-ray crystal structure of compound 10H-5,1'-spirocyclohexyl-(4aS*, 5aR*, 10aR*, 10bS*)-5a, 10a-dihydroxy-4a, 10b-epoxy-1, 2, 3, 4, 4a, 5a, 10a, 10b-octahydroindano [1, 2-b] indole (**1**).

On the basis of the UV, FTIR, ^1H , ^{13}C NMR, EIMS, and X-ray crystallographic analysis, the structure of the compound was established as **1**.

Compound **2**, $\text{C}_{22}\text{H}_{22}\text{N}_2$, M^+ 314, was isolated as white prismatic crystals, m.p. 146°C in 20% yield. It exhibited ultraviolet absorption maxima at λ_{max} (EtOH): 290, 288, 287, and 225 nm (log ϵ : 3.22, 3.27, 3.24, and 3.93, respectively) which shifted in 50% HClO_4 to λ_{max} (50% HClO_4 + EtOH) 350, 270, 264, 234, 220 and 204 nm (log ϵ : 3.50, 3.75, 3.74, 3.58, 3.56, and 3.58, respectively) indicating the presence of a bis(indolyl)methane system. In the infrared spectrum in KBr pellet peaks at 3420 (>NH), 1615, 1460, 1420 (aromatic nucleus), and 740 cm^{-1} (*o*-disubstituted benzene ring) were discernible.

The 300 MHz ^1H NMR spectrum accounted for half the number of aromatic protons as the molecule was symmetrical. This was evident from the M^+ ion. Two indole >NH protons appeared as a broad singlet at δ 7.86, (which disappeared on deuteration), due to coupling with the H-2 and H-2'. Three doublets at δ 7.58

(2H, d, $J = 8.0$ Hz), 7.29 (2H, d, $J = 8.0$ Hz), and 7.06 (2H, d, $J = 2.4$ Hz) were attributed to the H-4/H-4', H-7/H-7', and H-2/H-2' protons, respectively. The signal at δ 7.06 sharpened to a singlet on deuteration. Two triplets at δ 6.92 (2H, t, $J = 7.8$ Hz) and 7.09 (2H, t, $J = 7.8$) appeared for H-6/H-6' and H-5/H-5' protons. Ten methylene protons resonated as a multiplet in the region δ 2.55–2.58 (4H, m) and δ 1.62–1.68 (6H, m).

The structure of compound **2** was confirmed from its 75.5 MHz ^{13}C NMR spectra including APT experiments in CDCl_3 .

Six aromatic sp^2 quaternary carbon atoms C-7a/C-7'a, C-3a/C-3'a, and C-3/C-3' appeared at 137.1, 126.5, and 123.6 ppm, respectively. Ten aromatic sp^2 tertiary carbon atoms C-2/C-2', C-4/C-4', C-5/C-5', C-6/C-6', and C-7/C-7' resonated at 122.0, 118.6, 121.5, 121.3, and 110.0 ppm, respectively. One sp^3 quaternary carbon atom C-8 appeared at 39.7 ppm. Five sp^3 secondary methylene carbons C-9/C-13, C-10/C-12, and C-11 resonated at 37.0, 23.0, and 26.8 ppm, respectively. From the above spectral analysis the structure of this product could be definitely established as bis(indolyl) system as **2**.

The mass spectrometrical analysis by EIMS showed the molecular ion (M^+) 314 for compound **2**. One of the characteristic peaks appeared at 117 for the indole moiety, which is the most abundant peak. Other characteristic peaks were observed at 143, 156, and 196.

On the basis of the UV, FTIR, ^1H NMR, ^{13}C NMR, and EIMS spectral analysis, the structure of the compound could be definitely established as 3,3'-cyclohexylidenebis[1H-indole] (**2**).

X-ray crystallography. Compound **1** was obtained as a white powder. Crystals of the compound were very difficult to grow. The only way to get correct monocrystals was to prepare a charge transfer complex by crystallizing by slow evaporation in anisole [5].

A crystal plate with approximate size $0.5 \times 0.5 \times 0.02$ mm was mounted on a PHILIPS PW 1100 four-circle diffractometer, operating the $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). The space group was $\text{P}2_1/\text{n}$, monoclinic, cell parameters were $a = 16.423$ (5); $b = 9.898$ (2); $c = 14.736$ (7) Å , and $\beta = 104.71$ (4) $^\circ$. The volume was 2316.9 (2) Å^3 , thereby accounting for one anisole/compound **1** complex in the asymmetric unit ($Z = 4$). The structure was refined with SHELX93 program using the F^{*2} terms to $\text{R}2 = 16.9$ (observed F^{*2}), the conventional R -factors being: $\text{R} = 0.067$ for 2774 Fobs (with $\text{F} > 2\sigma\text{F}$) and $\text{R} = 0.081$ for all data (3301 Fobs). The structure was solved by direct methods.

The X-ray studies showed that an anisole molecule was solvated in the packing. The role of anisole is very important as it stabilized the packing structure by π/π interactions (staggering effect). Compound **1** is a (1:2)

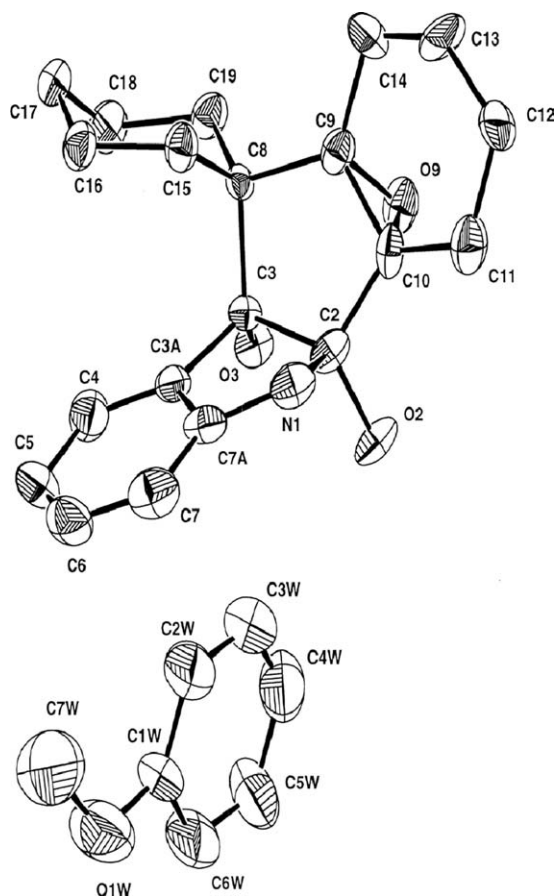


Figure 1. ORTEP diagram of compound **1**. The ellipsoids are drawn at the 50% probability level, hydrogens are omitted for clarity.

adduct of indole with cyclohexanone. The spiro six-membered ring is in the classic chair conformation. The epoxide bridge at C-4a/C-10b and the two hydroxyl groups at C-5a, C-10a are all on the same side of the central five membered ring. The two hydroxyl hydrogens, not visible in the electron density, were not imposed in the final refinements. The ORTEP drawing of the molecules has been shown in Figure 1 with thermal ellipsoids drawn at the 50% probability level.

The packing view of the complete cell is seen in Figure 2. The orientation matrix and cell parameters were obtained from the angular settings of 25 reflections randomly distributed between 18 and 25 degrees in theta and refined by least-squares procedures. Diffraction data were recorded within the 3°–65° theta range.

The positional parameters and mean recalculated isotropic factors for nonhydrogen atoms are given in Table 1.

A plausible mechanism involving the formation of this new system is discussed in Scheme 1.

Indole initially underwent electrophilic substitution at C-3 with one molecule of cyclohexanone followed by dehydration to produce **6**. Nucleophilic attack by a second molecule of cyclohexanone at C-2 of the intermediate followed by cyclisation and simultaneous aerial oxidation yielded compound **1**.

EXPERIMENTAL

General. The melting points were recorded in an electrically heated bath and are uncorrected. Elemental analysis (C, H, N) was obtained using a Perkin-Elmer 2400 elemental

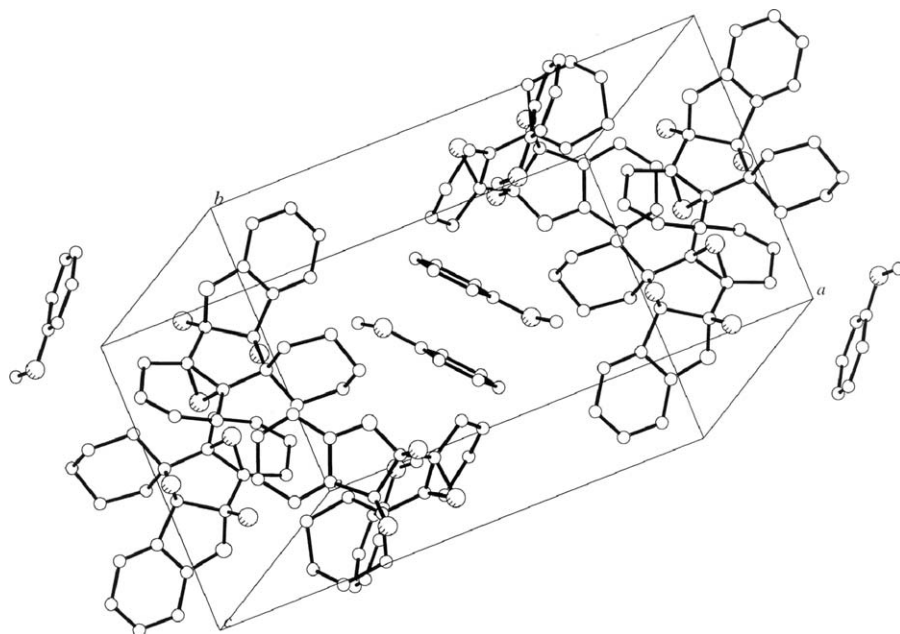


Figure 2. Packing view of the complete cell of compound **1**.

Table 1

Positional parameters ($\times 10^4$) and mean recalculated isotropic factors ($\times 10^3$) for nonhydrogen atoms.

Atom	X	Y	Z	\bar{U}
N1	-1041 (3)	728 (5)	4243 (4)	34 (1)
C2	-624 (3)	1978 (5)	4590 (4)	27 (1)
C3	-1366 (3)	2910 (5)	4718 (4)	20 (1)
C3A	-1985 (3)	1856 (5)	4888 (4)	27 (1)
C4	-2649 (4)	1932 (6)	5279 (5)	40 (2)
C5	-3098 (4)	766 (7)	5364 (5)	52 (2)
C6	-2879 (4)	-446 (7)	5055 (5)	50 (2)
C7	-2204 (4)	-572 (6)	4676 (5)	45 (2)
C7A	-1753 (4)	608 (5)	4604 (4)	33 (1)
O2	-11 (2)	1777 (4)	5468 (3)	37 (1)
O3	-1101 (2)	3717 (3)	5542 (3)	29 (1)
C8	-1626 (3)	3767 (5)	3781 (4)	19 (1)
C9	-816 (3)	3749 (5)	3437 (4)	28 (1)
O9	-76 (2)	4060 (4)	4207 (3)	35 (1)
C10	-243 (3)	2665 (5)	3895 (4)	30 (1)
C11	255 (4)	1813 (7)	3399 (6)	44 (2)
C12	155 (6)	2267 (9)	2417 (7)	57 (6)
C13	-67 (9)	2934 (9)	1916 (7)	53 (5)
C14	-803 (4)	4245 (7)	2489 (5)	42 (2)
C15	-2333 (3)	3093 (6)	3010 (5)	30 (1)
C16	-3227 (3)	3292 (6)	3113 (5)	34 (1)
C17	-3418 (4)	4764 (6)	3282 (5)	41 (2)
C18	-2744 (4)	5353 (6)	4108 (5)	41 (2)
C19	-1874 (3)	5236 (5)	3914 (5)	31 (1)
Solvent				
O1W	1790 (4)	311 (7)	1467 (5)	48 (7)
C1W	1253 (5)	-750 (8)	1442 (6)	51 (8)
C2W	1172 (5)	-1438 (10)	2209 (7)	49 (8)
C3W	593 (6)	-2482 (11)	2097 (8)	59 (8)
C4W	104 (5)	-2816 (9)	1229 (8)	57 (8)
C5W	184 (5)	-2127 (9)	456 (7)	58 (8)
C6W	768 (5)	-1089 (10)	567 (7)	57 (8)
C7W	2442 (8)	520 (15)	2283 (11)	79 (9)

analyzer. The UV absorption spectra were measured in a Hitachi U-2000 spectrophotometer in 95% aldehyde free ethanol, the infrared spectra in reflection mode using KBr pellet with a Perkin-Elmer 782 spectrophotometer, the ^1H and ^{13}C NMR spectra using Bruker AM-300L spectrometer using CDCl_3 as solvent. The mass spectra were recorded on a Finnigan MAT-H-SQ-30 mass spectrometer.

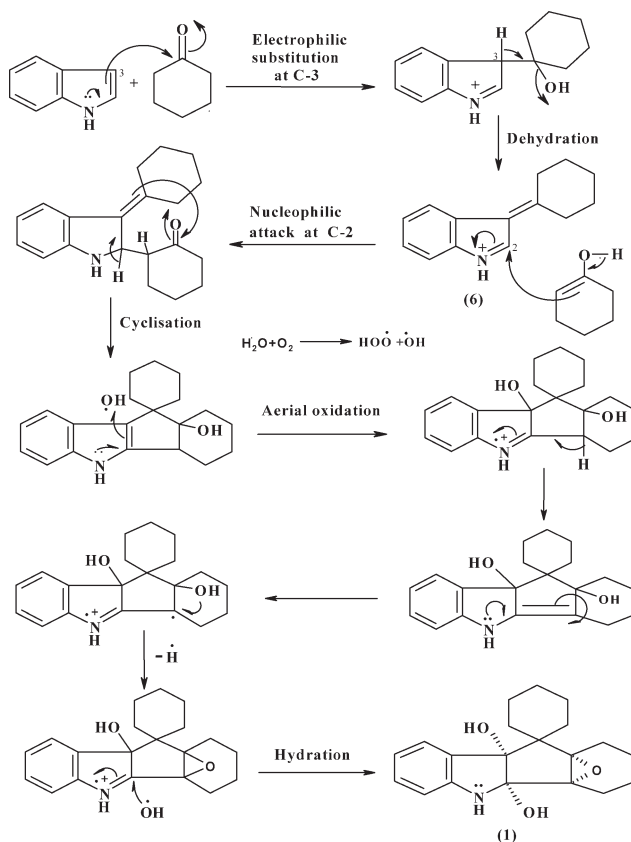
Column chromatographic analysis was carried out with neutral grade alumina standardized according to Brockmann (BDH) and silica gel G (Spectrochem, India) for thin layer chromatography. The spots were detected in an iodine chamber. The analytical samples were routinely dried *in vacuo* over P_2O_5 for 24 h. Anhydrous sodium sulfate was used to dry the organic solvents. Petrol refers to petroleum ether (bp $60^\circ\text{--}80^\circ$). The fractions 11–19 of the petrol-benzene (4:1) eluate afforded compound **1** and the fractions 20–30 of the petrol-benzene (1:1) eluate afforded compound **2**.

General method. To a solution of indole (1.2 g) in dry methylene chloride (40 mL) and cyclohexanone (1 mL), boron trifluoride diethyl etherate (1 mL) in dry methylene chloride (5 mL) was added dropwise with continuous stirring at 0°C under nitrogen atmosphere. The reaction mixture was kept at 0°C for 5 h. A dark resinous mass was obtained. The reaction was quenched over ice. The product was extracted with methylene

chloride (3×50 mL), washed with 2% NaHCO_3 solution and finally with water. The methylene chloride layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The concentrate on column chromatography over neutral grade Brockmann alumina afforded compounds (**1**) and (**2**). The products were characterized by elemental analysis, UV, FTIR, ^1H NMR, ^{13}C NMR, and EIMS.

10H-5,1'-Spirocyclohexyl-(4aS*,5aR*,10aR*,10bS*)-5a, 10a-dihydroxy-4a, 10b-epoxy-1,2,3,4,4a,5a,10a,10b-octahydroindano[1, 2-b]indole (1). White solid, yield 10%, m.p.: $130\text{--}131^\circ\text{C}$; UV: $\lambda_{\text{max}}^{\text{(EtOH)}}$ at 256 and 209 nm (log ϵ : 4.38 and 4.90, respectively), which shifted in 50% perchloric acid exhibiting $\lambda_{\text{max}}^{\text{(EtOH+50\% HClO}_4)}$ at 292, 241, 217, and 204 nm (log ϵ : 4.32, 4.78, 4.78, and 4.75, respectively); IR (KBr, cm^{-1}): 3420 ($>\text{NH}$), 3300 ($-\text{OH}$), 1610, 1470 (aromatic nucleus) and 750 cm^{-1} (*o*-disubstituted benzene ring); ^1H NMR (CDCl_3 , 300 MHz): $\delta = 2.07\text{--}1.17$ (m, 18H), 3.92 (s, 1H, $-\text{OH}$), 4.22 (s, 1H, $-\text{OH}$), 6.62 (d, 1H, $J = 7.8$ Hz), 6.81 (t, 1H, $J = 7.6$ Hz), 7.11 (t, 1H, $J = 7.6$ Hz), 7.26 (d, 1H, $J = 7.8$ Hz), 7.35 (s, 1H, $>\text{NH}$) ppm; ^{13}C NMR (CDCl_3 , 75.5 MHz): $\delta = 149.4$ (C-9a), 129.5 (C-5b), 129.3 (C-8), 126.9 (C-6), 119.6 (C-7), 111.0 (C-9), 101.4 (C-10a), 89.1 (C-5a), 75.2 (C-10b), 69.7 (C-4a), 50.0 (C-5), 28.6 (C-1), 27.3 (C-4), 25.6 (C-2), 23.7 (C-3), 22.6 (C-2'), 21.8 (C-6'), 21.0 (C-3'), 20.5 (C-5'), 19.9 (C-4') ppm; EIMS: m/z 327 $[\text{M}]^+$; Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{O}_3\text{N}$ (M^+ 327): C, 73.39; H, 7.64; N, 4.28%. Found: C, 73.30; 7.57; 4.18%.

3,3'-Cyclohexylidenebis[1H-indole] (2) White solid, yield 20%, mp 146°C ; UV: $\lambda_{\text{max}}^{\text{(EtOH)}}$: 290, 288, 287, and 225 nm (log ϵ : 3.22, 3.27, 3.24, and 3.93, respectively), which shifted

Scheme 1. Probable mechanism of the formation of compound **1**.

in 50% HClO₄ to $\lambda_{\max}^{(50\% \text{ HClO}_4 + \text{EtOH})}$ 350, 270, 264, 234, 220, and 204 nm (log ϵ : 3.50, 3.75, 3.74, 3.58, 3.56, and 3.58, respectively); IR (KBr, cm⁻¹): 3420 (>NH), 1615, 1460, 1420, (aromatic nucleus), and 740 cm⁻¹ (*o*-disubstituted benzene ring); ¹H NMR (CDCl₃, 300 MHz): δ = 1.62–1.68 (m, 6H), 2.55–2.58 (m, 4H), 6.92 (t, 2H, *J* = 7.8 Hz), 7.06 (d, 2H, *J* = 2.4 Hz), 7.09 (t, 2H, *J* = 7.8 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 8.0 Hz), 7.86 (s, 1H, >NH) ppm; ¹³C NMR (CDCl₃, 75.5 MHz): δ = 137.1 (C-7a/C-7'a), 126.5 (C-3a/C-3'a), 123.6 (C-3/C-3'), 122.0 (C-2/C-2'), 121.5 (C-5/C-5'), 121.3 (C-6/C-6'), 118.6 (C-4/C-4'), 110.0 (C-7/C-7'), 39.7 (C-8), 37.0 (C-9/C-13), 26.8 (C-11), 23.0 (C-10/C-12) ppm; EIMS: *m/z* 314 [M]⁺; Anal Calcd for C₂₂H₂₂N₂ (2) (M⁺ 314): C, 84.08; H, 7.00; N, 8.92%. Found: C, 83.91; 6.89; 8.79%.

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- [5] CCDC 757906 contains the supplementary crystallographic data for **1**. This can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+ 44) 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk.