

THE IDENTIFICATION, MECHANISM, AND IMPROVED SYNTHESIS OF A NEW AND UNIQUE HETEROCYCLIC SYSTEM WITH A FUSED IMIDAZOLE RING

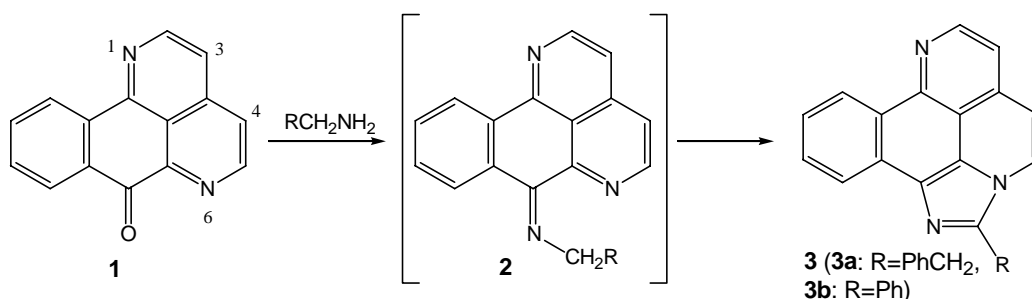
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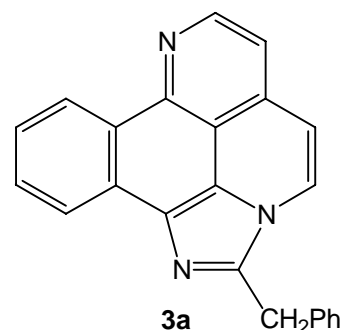
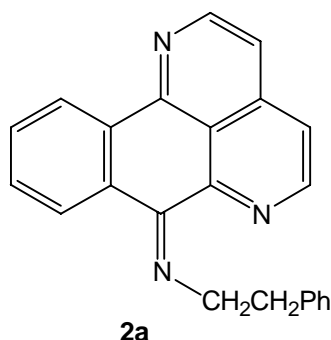
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Abstract- The reaction of sampangine (**1**) with arylalkylamines resulted in unexpected formation of a new and unique sampangine derivative with a fused imidazole ring (**3**). The identification and formation mechanism of **3**, as well as its improved synthesis, are described.

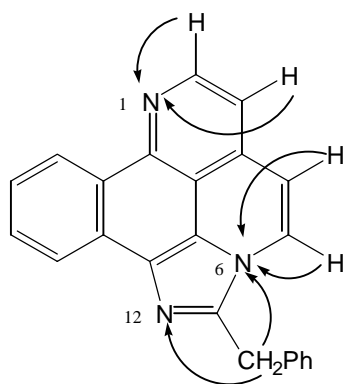
A natural antifungal alkaloid sampangine (**1**) (7*H*-naphtho[1,2,3-*i,j*]naphthyridin-7-one) and its analogs are known to exhibit potent *in vitro* activity against *Candida albicans* and *Cryptococcus neoformans*.¹ These compounds, however, have been reported to be inactive *in vivo* in mice.² In order to improve the *in vivo* activity, our laboratory has been working on the structural modification of **1**. Treatment of **1** with phenethyl- or benzylamine was attempted for the preparation of the corresponding Schiff base (**2**). The carbonyl group in **1** was not affected in refluxing ethanol,³ while it underwent a nucleophilic attack in toluene at reflux temperature. Contrary to expectation, the product arising from the attack has been found to be not the desired **2** but a sampangine derivative with a fused imidazole ring (**3**). This paper describes the identification and formation mechanism of this new and unique heterocyclic system (**3**), as well as its improved synthesis.



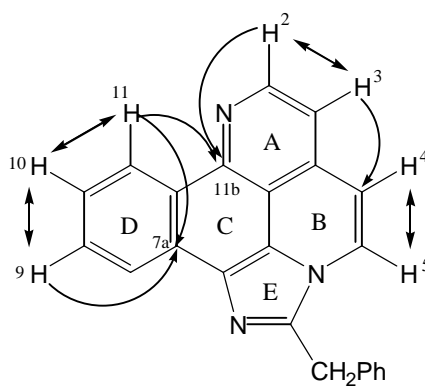
The reaction of sampangine (**1**) with phenethylamine in refluxing anhydrous toluene for 36 h gave several kinds of products. One of these products was shown to have no carbonyl group, as shown by ^{13}C -NMR and IR spectra. The ^1H -NMR spectrum indicated the presence of eight sampangine protons along with five additional signals in the aromatic region, suggesting that **1** underwent the addition of the amine at the carbonyl group. The ^1H - and ^{13}C -NMR spectra, however, showed only one methylene signal in the aliphatic region (4.62 ppm, 34.1 ppm). In addition, the HRFAB MS spectrum revealed the exact molecular weight $[\text{M}+\text{H}]^+$ 334.1408 (molecular formula $\text{C}_{23}\text{H}_{15}\text{N}_3+\text{H}^+$). These spectral data are not consistent with the structure of the expected Schiff base (**2a**) with two methylene signals and a molecular formula $\text{C}_{23}\text{H}_{17}\text{N}_3+\text{H}^+$. In order to determine the structure, this product was subjected to ^1H , ^{15}N -HMBC experiments. The protons of the methylene group showed the HMBC correlations with two nitrogen signals at 176.6 and 254.1 ppm. This result suggests that this methylene group should be maximally two bonds away from both of these nitrogen atoms. Consequently, a new structure with a fused imidazole (**3a**), is now proposed.



The structure of **3a** was confirmed using COSY, and ^1H , ^{13}C -HMQC and -HMBC experiments. On the basis of the COSY spectrum, three protons in the aromatic region were assigned as H-9, 10, and 11 on the D-ring. The H-11 (9.28 ppm) had 3J - ^1H , ^{13}C -HMBC correlation with two carbon singlet at 128.6 and 144.8 ppm. Because the H-9 (7.86 ppm) was also coupled to one of these carbons (C-7a, 128.6 ppm), the other carbon (144.8 ppm) was assigned as C-11b on the A- and C-ring. The ^1H , ^{13}C -HMBC spectrum showed that C-11b has another 3J -correlation with a proton at 8.95 ppm. This proton must therefore be H-2 on the A- ring. The application of COSY determined H-3 (7.34 ppm),⁴ which showed 3J - ^1H , ^{13}C -HMBC correlation with C-4 (111.8 ppm) on the B-ring. The HMQC correlation showed that the proton signal for the H-4 appeared at 6.83 ppm.⁴ Finally, the COSY indicated that the proton signal for the H-5 appeared at 7.52 ppm.⁴ The three ^{15}N signals at 176.6, 254.1, and 296.4 ppm were assigned as N-6, N-12, and N-1, respectively, on the basis of ^1H , ^{15}N -HMBC correlations. The structure of **3b** was also confirmed in a similar manner.

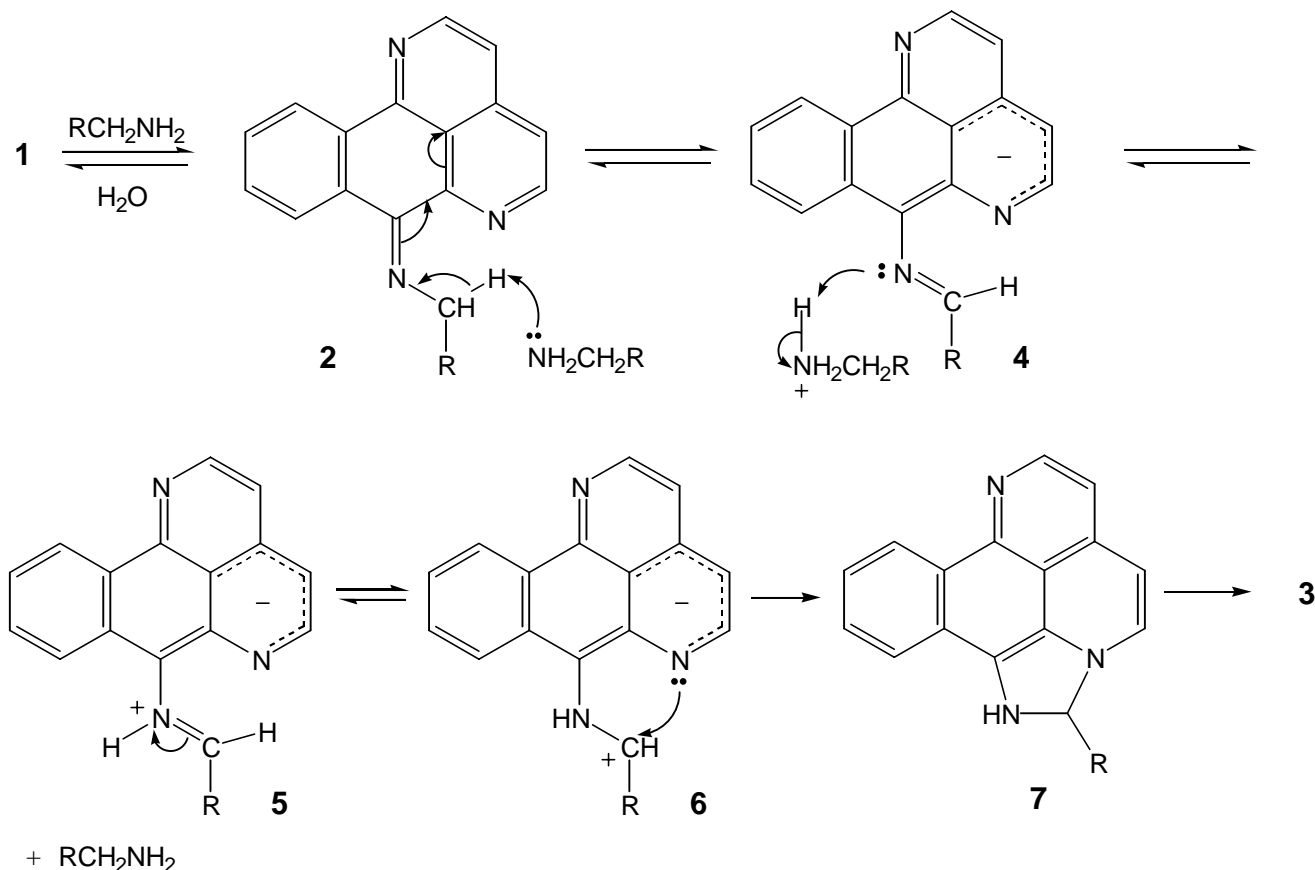


^1H - ^{15}N HMBC correlations



COSY and ^1H - ^{13}C HMBC correlations

Scheme 1 shows a possible mechanism for the formation of fused imidazole (**3**). The first step involves the formation of Schiff base (**2**)⁵ on the reaction of sampangine (**1**) with arylalkylamines. The Schiff base (**2**) might undergo the abstraction of a methylene proton by the attack of amines to yield delocalized anion (**4**)⁶ and amino cation. The imino nitrogen atom in **4** can be protonated by the formed amino cation, providing iminocation (**5**) and the amines. The transformation of **5** to carbocation (**6**), followed by intramolecular cyclization of **6**, gave dihydroimidazole (**7**). Finally, the aerial oxidation of **7** yielded **3**.



Scheme 1

Although the fused imidazole (**3**) has a unique structure and hence can be expected to possess interesting properties, the reaction required a long time (36 h) and gave the product (**3**) in poor yield (**3a**: 12 %, **3b**: 10 %) along with several kinds of by-products, including tar, which is difficult to handle. Therefore, we first attempted to improve the reaction time and yield by changing temperature. Refluxing in *m*-xylene instead of in toluene slightly improved the reaction time and yield (24 h, **3a**: 30 %); this condition also afforded low yield of **3** and a large amount of tar. As mentioned previously, refluxing in ethanol resulted in no formation of **3** and provided 4-amine adduct³ as a major product. In short, the change of temperature hardly induced an improvement in this reaction. Several improved methods have been published for the preparation of Schiff bases in the presence of Lewis acids such as TiCl₄ and ZnCl₂.⁷ These methods, however, seem to be not suitable for the synthesis of **3** because they are usually performed at low to moderate temperature.³ Of another method studied, the addition of silica gel was found to be very effective for the synthesis of **3**. This method led to a significant decrease in the reaction time (3 h) and a remarkable increase in the yield of **3** (**3a**: 79 %, **3b**: 73 %). Although the role of silica gel in this reaction is not clear, it seems to include at least the following two factors: a) removal of water liberated in the formation of the Schiff base (**2**), and b) activation of carbonyl group in sampangine (**1**) and that of imino group in anion (**4**). In summary, we obtained unexpected product (**3**) on the reaction of sampangine (**1**) with arylalkylamines. The product (**3**) was identified as a sampangine derivative with a fused imidazole ring by means of 2D-NMR spectroscopy. In addition, an improved method for the synthesis of **3** has been established by use of silica gel.

ACKNOWLEDGMENT

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EXPERIMENTAL

Anhydrous solvents were purchased from Aldrich Chemical Co. in Sure SealTM bottles. Phenethyl- and benzylamine were also from Aldrich. Melting points (uncorrected) were determined in open capillary tubes on a Thomas Hoover capillary melting point apparatus. IR spectra were recorded using ATI Mattson Genesis Series FTIR spectrophotometer. The NMR spectra were obtained on Bruker DRX-400 spectrometer operating at 400 MHz for ¹H and 100 MHz for ¹³C NMR and chemical shifts were reported in ppm relative to internal CHCl₃ (7.26 ppm for ¹H, 77 ppm for ¹³C). The ¹⁵N NMR spectra were recorded with the same apparatus using nitromethane as an external standard and the ¹⁵N chemical shifts were recalculated relative to NH₃, taken at +380.2 ppm from nitromethane. High-resolution fast atom bombardment mass (HRFABMS) spectra were conducted at the University of Kansas. Analytical TLC

was performed on precoated silica gel G-25 UV₂₅₄ plates (0.25 mm), visualized with short- and longwave UV light and/or iodine. Column chromatography was carried out on Merk or EM Science 230-400 mesh silica gel 60. Starting material (**1**) was prepared according to the literature procedure.^{1b}

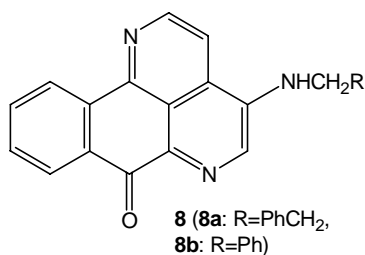
General Procedure for the Synthesis of 3 (Improved Method): To anhydrous or regular toluene (10mL) solution of phenethyl- or benzylamine (0.66 mmol) were added sampangine (**1**) (50 mg, 0.22 mmol) and silica gel (Merk or EM Science for column chromatography, 0.25 g), and the mixture was refluxed while being stirred for 3 h. After removal of the solvent, the residue was purified by column chromatography on silica gel with CH₂Cl₂/AcOEt (10/1). Spectral data of **3** are shown below.

(3a): mp 164 °C (MeOH) (decomp.); IR (KBr) 3023 cm⁻¹; ¹H NMR (CDCl₃) δ = 4.62 (s, 2H), 6.83 (d, *J* = 7.5 Hz, 1H), ⁴ 7.25-7.35 (m, 5H), 7.34 (d, *J* = 5.0 Hz, 1H), ⁴ 7.52 (d, *J* = 7.5 Hz, 1H), ⁴ 7.72 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 7.86 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H), 8.68 (d, *J* = 7.9 Hz, 1H), 8.95 (d, *J* = 5.0 Hz, 1H), 9.28 (d, *J* = 8.2 Hz, 1H); ¹³C NMR (CDCl₃) δ = 34.1, 111.8, 113.8, 114.6, 121.8, 123.9, 124.8, 124.9, 125.3, 127.6, 128.1, 128.4, 128.6, 128.9, 129.0, 131.5, 136.0, 143.5, 144.8, 147.6; HRFABMS *m/z* calcd for C₂₃H₁₆N₃ (M + H)⁺ 334.1344, found 334.1408.

(3b): mp 152 °C (MeOH) (decomp.); IR (CHCl₃) 3023 cm⁻¹; ¹H NMR (CDCl₃) δ = 7.04 (d, *J* = 7.6 Hz, 1H), ⁴ 7.54 (d, *J* = 5.1 Hz, 1H), ⁴ 7.56 (ddd, *J* = 7.6, 7.3, 1.0 Hz, 1H), 7.57 (m, 1H), 7.64 (dd, *J* = 7.4, 7.2 Hz, 1H), 7.88 (ddd, *J* = 7.6, 7.3, 1.0 Hz, 1H), 8.04 (dd, *J* = 7.2, 1.4 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), ⁴ 8.80 (d, *J* = 7.9 Hz, 1H), 9.08 (d, *J* = 5.1 Hz, 1H); ¹³C NMR (CDCl₃) δ = 112.7, 114.3, 114.7, 122.2, 124.5, 125.3, 125.4, 128.0, 128.5, 128.9, 129.0, 129.1, 129.3, 130.3, 132.0, 144.1, 145.2, 147.9; HRFABMS *m/z* calcd for C₂₂H₁₄N₃ (M + H)⁺ 320.1188, found 320.1153.

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2. A. M. Clark, C. D. Hufford, J. K. Zjawiony, S. Liu, and L. A. Walker, Antifungal Copyrine Alkaloids: *In Vitro* and *In Vivo* Antifungal Activities of Sampangines, in Abstracts, The 31st. *Interscience Conference on Antimicrobial Agents and Chemotherapy*, Chicago, IL, 1991.
3. The reaction of sampangine (**1**) with arylalkylamines in ethanol at room or reflux temperature provided sampangine-4-amines (**8**) as a major product without the formation of **3** (Yields of **8a**, **8b** are 62 %, 55 %, respectively). These results suggest that the amines do not attack carbonyl carbon but attack the C-4 position in **1** at low to moderate temperature.



4. The concentration-dependent variation has been recently observed in the chemical shift of the three protons (H-3, -4, and -5) in **3**; the variation in concentration of **3** has been found to shift these proton peaks to a lower or higher field although they are non-exchangeable protons. Detailed results of this phenomenon will be reported as a separate subject.
5. The reaction of pyridyl ketones with benzylamine in the presence of boron trifluoride etherate is reported to yield pyridines with fused imidazole ring as the major product (39-46 %) along with a small amount of the precursor Schiff bases (10 %). Moreover, the treatment of the Schiff bases with LDA at $-78\text{ }^{\circ}\text{C}$ in THF, followed by oxidation, also gave pyridines with fused imidazole ring. See A. P. Krapcho and J. R. Powell, *Tetrahedron Lett.*, 1986, **27**, 3713.
6. It is proposed that Schiff bases containing pyridyl group can be deprotonated with LDA in THF to give the 2-azaallyl anion because the pyridyl group can help stabilize the anion. See J. M. Hornback and B. Murugaverl, *Tetrahedron Lett.*, 1989, **30**, 5853. The fused pyridine system such as sampangine (**1**) must strongly help stabilize this type of anion as shown in scheme 1.
7. For recent examples, see: a) N. D. Kimpe and M. Keppens, *Tetrahedron*, 1996, **52**, 3705. b) S. Franco, F. L. Merchán, P. Merino, and T. Tejero, *Synth. Commun.*, 1995, **25**, 2275. c) G. Martín, E. Guitián, L. Castedo, and J. M. Saá, *J. Org. Chem.*, 1992, **57**, 5907. d) D. Armesto, S. Esteban, W. M. Horspool, J. A. F. Martin, P. M. Alcazar, and R. P. Ossorio, *J. Chem. Soc., Perkin Trans. 1*, 1989, 751. e) H. Ishii, I. S. Chen, and T. Ishikawa, *J. Chem. Soc., Perkin Trans. 1*, 1987, 671.