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Synthesis of diastereomeric 2,4-disubstituted pyrano[2,3-*b*]quinolines from 3-formyl-2-quinolones through O–C bond formation via intramolecular electrophilic cyclization

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Abstract—A number of 3-homoallyl-2-quinolones have been synthesized from 3-formyl-2-quinolones by reaction with allylindium bromide in aqueous DMF. Intramolecular electrophilic cyclization of these quinolones with iodine afforded either exclusively, or predominantly, racemic cis-diastereoisomers. Nucleophilic substitution reactions at the iodomethyl group afforded a mixture of tetracyclic products and unreacted racemic trans-diastereoisomer.

Quinolines and their annelated derivatives are important compounds due to their presence in numerous natural products along with their wide-ranging applications as drugs, pharmaceuticals and agrochemicals.[1] Pyranoquinolines are an important class of compounds that are found in a number of alkaloids such as flindersine, oricine, geibalasine and verprisine, and derivatives of these alkaloids show biological activity including anti-allergic, anti-inflammatory, psychotropic and estrogenic.[2]

Consequently, numerous syntheses have been developed for pyrano-annelated quinolines.[3] Cycloaddition and cyclization reactions are amongst the most useful routes for the synthesis of these compounds. Cycloaddition reactions, particularly Lewis acid catalyzed hetero Diels–Alder reactions, have been recently explored for the synthesis of pyrano[3,2-*c*]quinolines.[4] Bhuyan et al. have reported a one-pot synthesis of tetracyclic pyrano[2,3-*b*]quinolines via intramolecular 1,3-dipolar cycloaddition reactions using 1,3-dipoles such as nitrones, nitrile oxides and nitrile imines.[5] Examples of cyclization reactions for the synthesis of pyrano[2,3-*b*]-quinolines include the use of DDQ,[6] the Prevost reaction[7] and polyphosphoric acid.[2e] These have been less explored due to drawbacks such as difficulties in obtaining starting materials and poor yields of both starting materials and final products. Thus there is a need to develop new and efficient synthetic routes for the preparation of this class of compounds.

The 2-chloro-3-formylquinolines **1**,[8] easily accessible from simple acetanilides via a Vilsmeier–Haack approach, and their 3-cyano and 3-methoxycarbonyl derivatives have been used by us to prepare annelated carbocycles[9] and sulfur- and nitrogen-containing heterocycles[10] with diverse functionalities. In continuation of these studies, we report the stereocontrolled synthesis of racemic cis-disubstituted pyrano[2,3-*b*]quinolines from 3-formyl-2-quinolones **2**, (which are themselves easily prepared from 3-formyl-2-quinolines **1**), through O–C bond formation via intramolecular electrophilic cyclization (Scheme 2, Table 1). Reports on analogous compounds have been published via different routes from 2-chloro-3-formylquinolines.[5,11]

The starting 3-formyl-2-quinolones **2** were easily prepared in good yields (80–98%) by refluxing 2-chloro-3-formylquinolines **1** in aqueous acetic acid.[12] Allylation of **2** to give 3-homoallyl-2-quinolones **3** was achieved by reaction with in situ generated allylindium bromide in aqueous DMF at room temperature (Scheme 1) in excellent yields (89–94%). The structure of compound **3a** was ascertained from spectroscopic data.[13] Intramolecular electrophilic cyclization of compound **3a** with I_2 in THF in the presence of sodium bicarbonate at room

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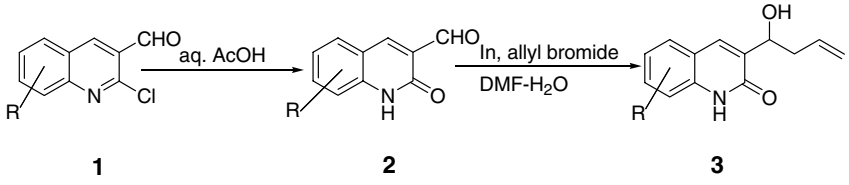
Table 1. Synthesis of diastereomeric *cis*/*trans*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinolines from 3-homoallyl-2-quinolones **3**

Entry	Substrate	R	Time (h)	Product	Ratio (cis/trans)	Yield (%)
1	**3a**	H	4.0	**4a/5a**	77:23	88
2	**3b**	6-Me	2.5	**4b/5b**	90:10	81
3	**3c**	7-Me	4.0	**4c/5c**	79:21	84
4	**3d**	7-OMe	3.0	**4d/5d**	84:16	83
5	**3e**	8-Me	3.5	**4e/5e**	100:0	85
6	**3f**	8-Et	2.5	**4f/5f**	100:0	88

temperature gave an 88% yield of a mixture of **4a/5a**,[14] (Scheme 2) which consisted predominantly of the cis-diastereoisomer, 4-hydroxy-2-iodomethylpyrano[2,3-*b*]-quinoline **4a** (as determined from ^{1}H NMR spectroscopy). The diastereoisomers **4a/5a** were chromatographically inseparable. The stereochemical assignments in *cis*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinoline **4a** were initially determined from NMR spectral data and were supported by chemical transformations. The ^{1}H NMR spectrum of *cis*-**4a** showed a downfield chemical shift for the C-5 proton ($\delta = 8.32$) in comparison to that of the corresponding *trans*-isomer **5a**, which appeared at $\delta = 8.12$.[14,15] The downfield chemical shift of the C-5 proton in the cis-isomers may result from an eclipsed arrangement of the 4-hydroxy group with the C-5 H bond, that is, the hydroxy group occupies an equatorial position in the cis-conformation. Similar observations were also made in the ^{13}C NMR data relating to the chemical shifts of C-2 and C-4 in the cis-isomers, which appeared downfield in comparison to the trans-isomers.[14,15] The magnetically non-equivalent CH_2I group protons were well resolved and showed the expected AB quartet system in cis-compounds, but were considerably less well resolved for the trans-compounds as a result of slow interconversion of the conformers by ring flipping. Dreiding molecular models further suggested that the most stable conformation of the cis-isomers have the hydroxy group at C-4 and the iodomethyl group at C-2 in equatorial positions.

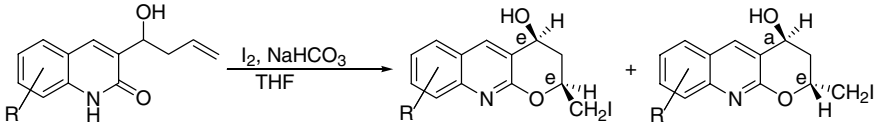
Although the cis and trans isomers in Table 1, entries 1–4 were chromatographically inseparable, nucleophilic substitution at the iodomethyl carbon in cis and trans **4a/5a** with sodium hydroxide in acetonitrile led to two separable compounds on TLC. The products were characterized as tetracyclic quinoline **6a** (63% yield), presumably formed by internal S_N2 attack of the 4-hydroxy group at the 2-iodomethyl group of the pyran ring, which favoured the 1,3-diaxial conformation of *cis*-isomer **4a**. Unreacted *trans*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinoline **5a** (30% yield) was also recovered. Similar results were obtained, when the reaction was carried out with either NaOH or NaCN at reflux in aqueous acetonitrile (Scheme 3).

Finally, we explored the scope of the iodomethyl group in these pyrano-annelated quinolines by performing an elimination reaction on **4a/5a** with DBU or *t*BuOK in dry benzene at room temperature. A mixture of two products was obtained which was characterized as tetracyclic quinoline **6a** (42% yield) along with the desired elimination product **7a**[16] (38% yield). Similarly, *cis* **4e**



1 **2** **3**

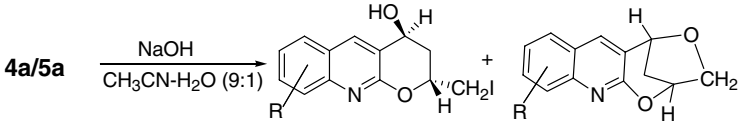
Scheme 1.



3 **4** **5**

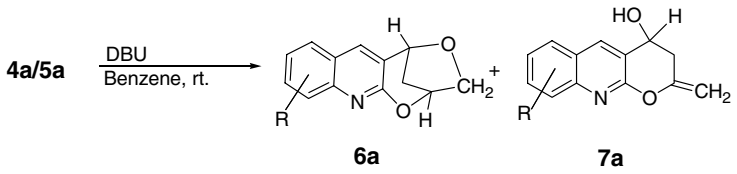
R = H, 6-Me, 7-Me, 7-OMe, 8-Me, 8-Et.

Scheme 2.



5a **6a**

Scheme 3.



Scheme 4.

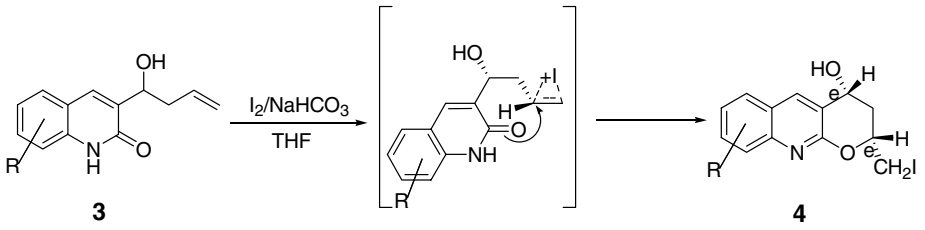


Figure 1.

(Table 1, entry 5) yielded a mixture of tetracyclic **6e** (53% yield) and elimination product **7e** (33% yield) (Scheme 4).

Observations showed that pre-existing chirality in the alkenyl side chain significantly influenced the stereochemistry during this reaction. Thus, in the transition state in which the 4-hydroxy group adopted an equatorial position, an eclipsed arrangement of the carbon–carbon double bond activated by coordination to I^+ with the lactam C═O bond is favoured. In the cyclization step the C═O bond coordinates via oxygen to the activated alkene leading to the cis-diastereoisomer **4** predominantly (Fig. 1).

In conclusion, we have described the synthesis of 4-hydroxy-2-iodomethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]-quinolines. Inexpensive and readily available starting materials and reagents, easy work-up and high yields are advantages of this method.

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References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605–618; (b) Balsubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, Chapter 5.06, p 245; (c) Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Gokcek, Y.; Kendrick, H.; Phillips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187–3194; (d) Sahu, N. S.; Pal, C.; Mandal, N. B.; Banerjee, S.; Raha, M.; Kundu, A. P.; Basu, A.; Ghosh, M.; Roy, K.; Bandyopadhyay, S. *Bioorg. Med. Chem.* **2002**, *10*, 1687–1693; (e) Kournetsov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141–161.
2. (a) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213; (b) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177–1181; (c) Johnson, J. V.; Rauckmann, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949; (d) Nesterova, I.; Alekseeva, L. M.; Andreeva, L. M.; Golovira, S. M.; Granic, V. G. *Khim. Farm. Zh.* **1995**, *29*, 31–34; (e) Rajendra Prasad, K. J.; Sekar, M. *J. Nat. Prod.* **1998**, *61*, 294–296.
3. (a) Desai, M. C.; Thadeio, P. F. *Tetrahedron Lett.* **1989**, *30*, 5223–5226; (b) Ashrof, M. A.; Raman, P. S. *J. Indian Chem. Soc.* **1992**, *69*, 690–691; (c) Cziaky, Z.; Sebok, P. *J. Heterocycl. Chem.* **1994**, *31*, 701–705.
4. (a) Mahesh, C. J.; Makesh, S. V.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2035–2040; (b) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron* **2002**, *58*, 7891–7896; (c) Mahesh, M.; Reddy, Ch. V.; Reddy, K. S.; Raju, P. V. K.; Reddy, V. V. N. *Synth. Commun.* **2004**, *34*, 4089–4104.
5. Bhuyan, P. J.; Baruah, B.; Kalita, P. K. *Tetrahedron Lett.* **2006**, *47*, 7779–7782.
6. Plozzi, F.; Venturella, P.; Bellino, A. *Gazz. Chim. Ital.* **1969**, *99*, 711–714.
7. Subramanian, M.; Mohan, P. S.; Shanmugam, P.; Rajendra Prasad, K. J. *Z. Naturforsch.* **1992**, *47b*, 1016–1020.
8. Singh, R. M.; Srivastava, A. *Indian J. Chem.* **2005**, *44B*, 1868–1875.
9. Singh, R. M.; Chandra, A.; Singh, M. K. *Synth. Commun.* **2007**, *37*, 1689–1695.
10. (a) Singh, R. M.; Chandra, A.; Srivastava, A. *Indian J. Chem.* **2005**, *44B*, 2077–2084; (b) Singh, R. M.; Singh, M. K.; Srivastava, A. *Indian J. Chem.* **2006**, *45B*, 292–296; (c) Singh, R. M.; Chandra, A.; Srivastava, A. *Indian J. Chem.* **2007**, *46B*, 303–307.
11. Szabo, Z.; Cziaky, Z. *J. Heterocycl. Chem.* **1995**, *32*, 755–760.
12. A suspension of aldehyde **1** (1 mmol) in 70% acetic acid (10 ml) was heated under reflux for 4–6 h. The progress of the reaction was checked by TLC. Upon cooling the reaction mixture, a solid product precipitated, which was filtered, washed well with water and dried. The crude product was characterized and used without further purification.

3-Formyl-2(1H)-quinolone **2a**: Yield: 93%; solid; mp 303–304 °C. IR (KBr): 1620, 1684, 3323 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): $\delta = 7.25$ (t, 1H, $J = 7.2$ Hz, H-7), 7.35 (d, 1H, $J = 6.0$ Hz, H-8), 7.66 (t, 1H, $J = 6.6$ Hz, H-6), 7.92 (d, 1H, $J = 6.0$ Hz, H-5), 8.51 (s, 1H, H-4), 10.24 (s, 1H, CHO), 12.24 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.14; H, 3.92; N, 7.93.

13. To a suspension of formyl quinolone **2** (1 mmol) in DMF–water (8–10 ml) was added indium powder (2 mmol) and allyl bromide (3 mmol), and the mixture stirred at room temperature for a time ranging between 4 and 12 h. After completion (checked by TLC), the reaction was quenched with a few drops of 2 N HCl, diluted with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuum. The crude product was characterized and used without further purification.
3-(1-Hydroxy-but-3-en-1-yl)-2-quinolone **3a**: White solid; Yield: 90%; mp 188 °C. IR (KBr): 1664 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): $\delta = 2.23$–2.33 (m, 2H, CH_2), 4.80 (br s, 1H, $=CH_2$), 4.96 (s, 1H, $=CH_2$), 5.05 (d, 1H, $J = 7.5$ Hz, CHOH), 5.25 (d, 1H, $J = 4.5$, 7.5 Hz, OH, D_2O exchangeable), 5.85 (m, 1H, $CH{=}CH_2$), 7.20 (t, 1H, $J = 7.5$ Hz, 6-H), 7.35 (d, 1H, $J = 8.1$ Hz, 5-H), 7.50 (t, 1H, $J = 7.5$ Hz, 7-H), 7.70 (d, 1H, $J = 7.8$ Hz, 8-H), 7.80 (s, 1H, 4-H), 11.75 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (75 MHz; DMSO-d_6): $\delta = 40.8$, 67.2, 115.3, 117.6, 119.7, 122.8, 128.3, 130.4, 135.2, 135.7, 136.6, 137.8, 161.7. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.23; H, 5.91; N, 6.43.

14. To a stirred solution of **3** (0.44 mmol) in THF (15 ml) were added I_2 (0.93 mmol) and $NaHCO_3$ (1.014 mmol) under a nitrogen atmosphere at room temperature and the reaction stirred for 4 h. After the reaction had finished (monitored by TLC), a saturated aq solution of Na_2SO_3 (10 ml) was added. The solution was diluted with water (15 ml), and extracted with EtOAc (3×20 ml). The organic layers were pooled and washed with brine (15 ml) and dried over anhydrous $MgSO_4$ and evaporated to yield a residue, which was purified via silica gel chromatography employing hexane–EtOAc (70:30, v/v) as eluent to afford inseparable products **4/5** as a solid.
cis-2-Iodomethyl-4-hydroxy-4H-2,3-dihydropyrano[2,3-b]-quinoline **4a**: White solid; Yield: 88%; mp 133–134 °C. IR (KBr): 1626, 1259, 1192 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): $\delta = 1.90$ (q, 1H, $J = 12.0$ Hz, CH_2 axial), 2.20 (d, 1H, $J = 7.5$ Hz, OH), 2.70 (ddd, 1H, $J = 1.8$, 5.4, 12.0 Hz, CH_2 equatorial), 3.51 (dd, 1H, $J = 6.9$, 10.5, CH_2I), 3.60 (dd, 1H, $J = 4.2$, 10.5, CH_2I), 4.40 (m, 1H, $CHCH_2$), 5.20 (m, 1H, CHOH), 7.40 (t, 1H, $J = 7.2$ Hz, 6-H), 7.70 (t, 1H, $J = 7.2$ Hz, 7-H), 7.75 (d, 1H, $J = 6.6$ Hz, 5-H), 7.87 (d, 1H, $J = 8.4$ Hz, 8-H), 8.32 (s, 1H, 5-H). ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 7.1$, 37.4, 65.2, 74.3, 122.2, 124.7, 125.5, 127.3, 127.4, 130.2, 136.6, 146.6, 158.5. MS: $m/z =$ 342 (M+1). Anal. Calcd for $C_{13}H_{12}NO_2I$: C, 45.77; H, 3.55; N, 4.11. Found: C, 45.81; H, 3.23; N, 3.98.

15. To a stirred solution of **4a/5a** (0.42 mmol) in CH_3CN–H_2O (9:1 ml) was added a 1 M solution of aq NaOH (0.82 mmol) at room temperature and the reaction was stirred for 45 min. The reaction mixture was extracted with EtOAc and the combined organics washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent under vacuum and purification of the products using silica gel column chromatography employing hexane–EtOAc (75:25, v/v) as eluent gave pure **5a** and **6a**.
trans-2-Iodomethyl-4-hydroxy-4H-2,3-dihydropyrano[2,3-b]-quinoline **5a**: White solid; Yield: 30%; mp 138–139 °C. IR (KBr): 1626, 1235, 1161 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): $\delta = 2.05$ (br s, 1H, OH), 2.08 (ddd, 1H, $J = 3.0$, 11.5, 14.2 Hz, CH_2 axial), 2.40 (ddd, 1H, $J = 3.0$, 3.0, 14.2 Hz, CH_2 equatorial), 3.60 (m, 2H, CH_2I), 4.61 (m, 1H, $CHCH_2I$), 5.10 (dd, 1H, $J = 3.0$, 6.3 Hz, CHOH), 7.41 (t, 1H, $J = 7.4$ Hz, 6-H), 7.66 (t, 1H, $J = 7.6$ Hz, 7-H), 7.74 (d, 1H, $J = 7.8$ Hz, 5-H), 7.90 (d, 1H, $J = 7.8$ Hz, 8-H), 8.12 (s, 1H, 5-H). ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 8.0$, 35.8, 63.5, 71.4, 119.7, 124.6, 125.2, 127.2, 127.4, 130.5, 139.7, 147.0, 158.8. Anal. Calcd for $C_{13}H_{12}NO_2I$: C, 45.77; H, 3.55; N, 4.11. Found: C, 45.65; H, 3.20; N, 4.33.
10-Aza-12,15-dioxa-tetracyclo(11,2,1,$0^{2,11}$,$0^{4,9}$)hexdeca-2,4,6,8,10-pentene **6a**: White solid; Yield: 63%; mp 96 °C. IR (KBr): 1626, 1416, 1200 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): $\delta = 2.27$ (ddd, 1H, $J = 3.0$, 4.8, 12.3 Hz, 16-CH_2 axial), 2.43 (d, 1H, $J = 12.3$ Hz, 16-CH_2 eq), 4.12 (dd, 1H, $J = 3.6$, 10.5 Hz, 14-CH_2), 4.33 (d, 1H, $J = 10.5$ Hz, 14-CH_2), 5.16 (d, 1H, $J = 4.8$ Hz, 1-CH), 5.22 (br s, 1H, 13-CH), 7.38 (t, 1H, $J = 7.5$ Hz, 6-H), 7.63 (t, 1H, $J = 7.5$ Hz, 7-H), 7.70 (d, 1H, $J = 7.8$ Hz, 5-H), 7.82 (s, 2H, 3-H, 8-H). ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 32.8$, 74.3, 75.1, 77.5, 122.4, 124.5, 124.8, 127.2, 127.4, 129.9, 135.1, 147.2, 158.9. MS: $m/z = 214$ (M+1). Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.89; H, 5.09; N, 6.45. See also Yadav, J. S.; Reddy, B. V. S.; Meraj, S.; Vishnumurthy, P.; Narsimulu, K.; Kunwar, A. C. *Synthesis* **2006**, 2923–2926.

16. A mixture of **4a/5a** (0.44 mmol) and DBU (0.88 mmol) in 20 ml of benzene was stirred for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered and the filtrate was washed with dil HCl, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent under vacuum and purification of the products using silica gel column chromatography employing hexane–EtOAc (60:40, v/v) as eluent gave pure **6a** and **7a**.
2-Methylene-3,4-dihydro-2H-1-oxa-9-aza-anthracen-4-ol **7a**: White solid; Yield: 38%; mp 98 °C. IR (KBr): 3201, 1424, 1253 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): $\delta = 2.08$ (d, 1H, $J = 6.9$ Hz, OH), 2.78 (dd, 1H, $J = 7.2$, 13.8 Hz, CH_2), 2.91 (dd, 1H, $J = 3.9$, 13.8 Hz, CH_2), 4.50 (s, 1H, $=CH_2$), 4.98 (s, 1H, $=CH_2$), 5.04 (d, 1H, $J = 5.1$ Hz, CHOH), 7.44 (t, 1H, $J = 7.5$ Hz, 6-H), 7.68 (t, 1H, $J = 6.9$ Hz, 7-H), 7.78 (d, 1H, $J = 8.1$ Hz, 5-H), 7.91 (d, 1H, $J = 8.4$ Hz, 8-H), 8.21 (s, 1H, 10-H). ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 35.6$, 64.5, 95.7, 121.3, 125.1, 125.6, 127.5, 130.4, 137.3, 146.8, 148.8, 151.3, 156.9. Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.93; H, 5.05; N, 6.49.