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REACTIONS OF A 5-HYDROXYMETHYL-1*H*-INDOLE-4,7-DIONE WITH ENAMINES FOR THE FIRST CONSTRUCTION OF 1*H*,5*H*-PYRANO[3,4-*f*]INDOLE-4,9-DIONE DERIVATIVES

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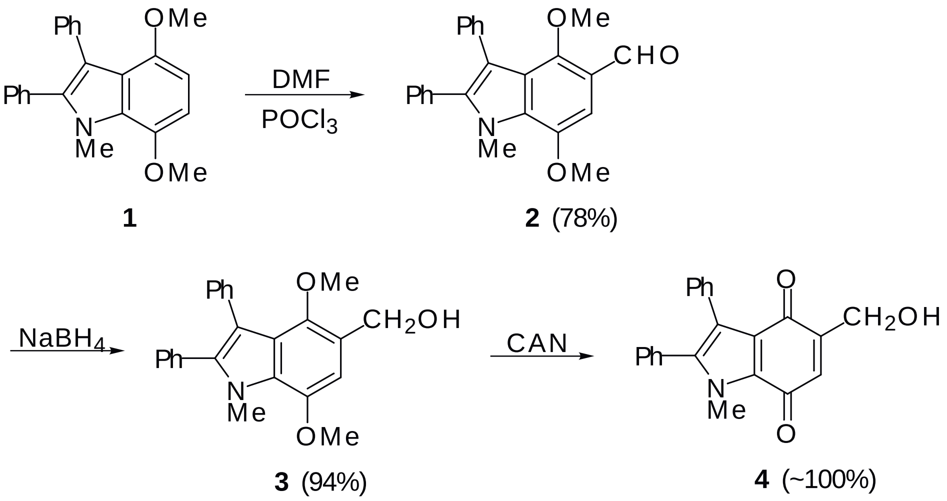
Abstract- 5-Hydroxymethyl-1-methyl-2,3-diphenyl-1*H*-indole-4,7-dione (**4**) was synthesized and the tandem Michael addition/cyclization sequence between this indolequinone and enamines has been used to construct title pyranoindolequinone derivatives (**6**), (**7**), and (**9**).

Previous studies in this laboratory have resulted in the development of an efficient method for the synthesis of 1*H*-naphtho[2,3-*c*]pyran-5,10-dione[1] and 1*H*-benzo[2]pyran-5,8-dione derivatives[2] by the reaction of 2-(1-hydroxyalkyl)-1,4-naphthoquinones and 2-(1-hydroxyalkyl)-1,4-benzoquinones, respectively, with enamines or imines. Herein, we wish to describe an extension of this pyranoquinone synthesis to a 5-hydroxymethyl-1*H*-indole-4,7-dione system (**4**), which offers access to the construction of a novel heterocycle-fused quinone skeleton, 1*H*,5*H*-pyrano[3,4-*f*]indole-4,9-dione.

5-Hydroxymethyl-1-methyl-2,3-diphenyl-1*H*-indole-4,7-dione (**4**) could be easily prepared starting from the known 4,7-dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole (**1**)[1] as illustrated in Scheme 1. Thus, treatment of the indole (**1**) with *N*,*N*-dimethylformamide/phosphoryl chloride gave 4,7-dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole-5-carbaldehyde (**2**) in good yield along with a small quantity of the corresponding 6-carbaldehyde. The structure of this 5-carbaldehyde (**2**) was confirmed by NOE experiments. Thus, irradiation of the signal due to the formyl proton (δ 10.39) resulted in enhancements of the signals due to the 4-methoxy protons (δ 3.21) (15%) and the 6-proton (δ 7.11) (3%). Enhancements of the signals due to the formyl proton (17%) and *ortho*-proton(s) of 3-phenyl (δ 7.21) (6%) were observed on irradiation of the signal due to 4-methoxy protons. Reduction of this aldehyde (**2**) with $NaBH_4$ followed by the cerium(IV) ammonium nitrate (CAN) oxidation of the resulting alcohol (**3**) gave the desired hydroxymethylindolequinone derivative (**4**) in excellent yield.

We began our investigation by first examining the reaction between the indolequinone (**4**) and 1-

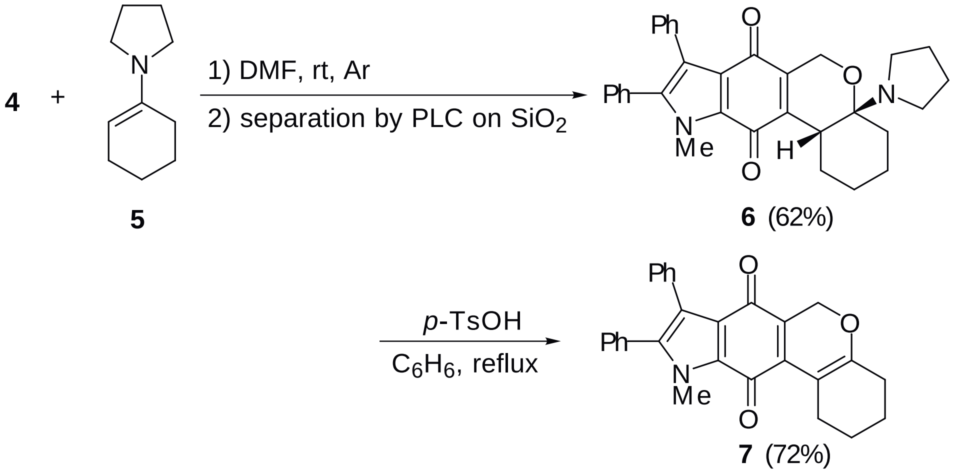


Scheme 1.

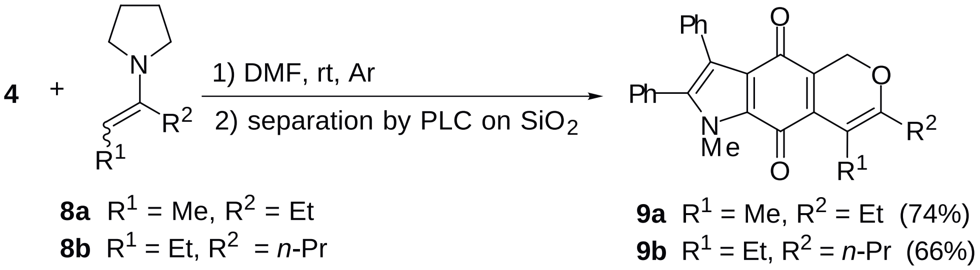
pyrrolidinocyclohexene (**5**) under the conditions for the preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-dione (in toluene at room temperature).[1] However, TLC analysis of the reaction mixture after 1 h did not show any progress of reaction. The reaction proved to proceed in appropriate extent at 70 ˚C to afford *cis*-10-methyl-8,9-diphenyl-4a-pyrrolidino-1,2,3,4,4a,11b-hexahydro-6*H*,10*H*-benzo[1]pyrano[3,4-*f*]indole-7,11-dione (**6**) as the sole isolated product in 49% yield, after usual workup followed by purification using preparative TLC on silica gel. Later, the reaction was found to proceed more smoothly in DMF at room temperature to give the desired product (**6**) in much improved yield. The stereochemistry of this product was confirmed by NOE experiments. Thus, a 10% enhancement of the signal due to the 11b-proton (δ 2.85–2.9) was observed on irradiation of the signal due to the 2-pyrrolidinyl protons (δ 2.6–2.65). The pyrrolidinodihydropyranoindoledione (**6**) could be converted into 10-methyl-8,9-diphenyl-1,2,3,4-tetrahydro-6*H*,10*H*-benzo[1]pyrano[3,4-*f*]indole-7,11-dione (**7**) in fair yield through elimination of pyrrolidine on treatment with *p*-toluenesulfonic acid in refluxing benzene for 5 h. The results of these reactions are shown in Scheme 2.

Reactions between the indolequinone (**4**) and enamines derived from acyclic ketones (**8**) were then carried out. These enamines underwent the Michael addition/cyclization sequence in toluene at room temperature overnight to give the corresponding 1*H*,5*H*-pyrano[3,4-*f*]indole-4,9-dione derivatives (**9a**) and (**9b**) in 41 and 34% yields, respectively, after usual workup followed by purification using preparative TLC on silica gel. Later, these reactions were also found to proceed more smoothly in DMF to give the desired products (**9**) in fair yields, as depicted in Scheme 3.

The foregoing results indicate that preparation of 1*H*,5*H*-pyrano[3,4-*f*]indole-4,9-dione derivatives can be achieved by the reactions of a 6-hydroxymethyl-1*H*-indole-4,7-dione derivative (**4**) with enamines. To the best of our knowledge, no work has been reported on the construction of this pyranoindolequinone skeleton.



Scheme 2.



Scheme 3.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 Series FT IR spectrophotometer as KBr disk. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz. *J* values are given in Hz. TLC was carried out on a Merck Kieselgel 60 PF_{254}. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 4,7-Dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole (**1**),[3] (*E*)- and (*Z*)-3-pyrrolidino-2-pentenes (**8a**),[4] (*E*)-and (*Z*)-4-pyrrolidino-3-heptene (**8b**)[4] were prepared by the appropriate reported methods. All of the other chemicals used in this study were commercially available.

4,7-Dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole-5-carbaldehyde (2). A solution of 4,7-dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole (**1**) (3.9 g, 12 mmol) in toluene (10 mL), containing DMF (1.26 g, 13 mmol) and $POCl_3$ (2.1 g, 14 mmol), was heated at reflux temperature for 50 min. The resulting mixture was diluted with CH_2Cl_2 (50 mL), washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was subjected to column chromatography on silica gel (3:1 hexane–EtOAc) to give **2** (3.5 g, 78%) as a white solid: mp 207–210 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1666; δ_H 3.21 (3H, s), 3.92 (3H, s), 3.99 (3H, s), 7.11 (1H, s), 7.2–7.35 (10H, m), 10.39 (1H, s).

Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.39; H, 5.91; N, 3.67. 4,7-Dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole-6-carbaldehyde was also isolated (0.40 g, 9%) as a pale yellowish-brown solid: mp 195–196 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1668; δ_H 3.72 (3H, s), 3.92 (3H, s), 4.07 (3H, s), 6.94 (1H, s), 7.15–7.35 (10H, m), 10.47 (1H, s). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.43; H, 5.90; N, 3.71.

5-Hydroxymethyl-4,7-dimethoxy-1-methyl-2,3-diphenyl-1*H*-indole (3). To a stirred solution of the indolecarbaldehyde (**2**) (1.5 g, 4.0 mmol) in THF (50 mL) at rt was added $NaBH_4$ (0.45 g, 12 mmol). After 30 min the mixture was diluted with EtOAc (50 mL), washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residual solid was recrystallized from hexane–CH_2Cl_2 to give **3** (1.4 g, 94%) as a white solid; mp 202–205 ˚C; ν_{max}/cm^{-1} 3514; δ_H 2.00 (1H, s), 3.08 (3H, s), 3.88 (3H, s), 3.96 (3H, s), 4.77 (2H, s), 6.66 (1H, s), 7.15–7.35 (10H, m). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.22; H, 6.24; N, 3.54.

5-Hydroxymethyl-1-methyl-2,3-diphenyl-1*H*-indole-4,7-dione (4). To a stirred solution of the indolylmethanol (**3**) (1.2 g, 3.3 mmol) in MeCN (60 mL) at rt was added a solution of CAN (3.6 g, 6.6 mmol) in water (20 mL). After 70 min the mixture was diluted with EtOAc (50 mL), washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residual solid was recrystallized from hexane–CH_2Cl_2 to give **4** (1.1 g, almost quantitative) as a red solid; mp 174–178 ˚C; ν_{max}/cm^{-1} 3521, 1659 (sh), 1633, 1611 (sh); δ_H 2.27 (1H, t, *J* 6.4), 3.87 (3H, s), 4.53 (2H, dd, *J* 6.4, 1.7), 6.57 (1H, d, *J* 1.7), 7.1–7.25 (7H, m), 7.3–7.4 (3H, m). Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.77; H, 5.14; N, 4.25.

***cis*-10-Methyl-8,9-diphenyl-4a-pyrrolidino-1,2,3,4,4a,11b-hexahydro-6*H*,10*H*-benzo[1]pyrano[3,4-*f*]indole-7,11-dione (6).** A mixture of the indolequinone (**4**) (0.27 g, 0.80 mmol) and 1-pyrrolidinocyclohexene (**5**) (0.24 g, 1.6 mmol) in DMF (8 mL) was stirred at rt overnight. The resulting mixture was diluted with Et_2O (30 mL), washed with saturated aqueous NH_4Cl and then brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was purified by preparative TLC on silica gel (3:1 hexane–EtOAc) to give **6** (0.25 g, 62%) as a red solid: mp 160–163 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1641, 1625; δ_H 1.25–2.05 (14H, m), 2.6–2.65 (4H, m), 2.85–2.9 (1H, m), 3.87 (3H, s), 4.44 (1H, dd, *J* 19.0, 1.6), 4.53 (1H, d, *J* 19.0), 7.1–7.2 (7H, m), 7.3–7.4 (3H, m). Anal. Calcd for $C_{32}H_{32}N_2O_3$: C, 78.02; H, 6.55; N, 5.69. Found: C, 78.05; H, 6.79; N, 5.51.

10-Methyl-8,9-diphenyl-1,2,3,4-tetrahydro-6*H*,10*H*-benzo[1]pyrano[3,4-*f*]indole-7,11-dione (7). A solution of the pyrrolidinopyranoindolequinone (**6**) (89 mg, 0.18 mmol) in benzene (3 mL) containing *p*-TsOH monohydrate (34 mg, 0.18 mmol) was heated at reflux temperature for 5 h. The cooled mixture was then diluted with Et_2O (30 mL), washed successively with saturated aqueous NH_4Cl, 1%

aqueous NaOH, and then brine. The ether solution was dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by preparative TLC on silica gel (5:1 hexane–EtOAc) to give **7** (54 mg, 72%) as a red solid; mp 173–176 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1638; δ_H 1.6–1.8 (4H, m), 2.2–2.3 (2H, m), 2.75–2.8 (2H, m), 3.85 (3H, s), 4.85 (2H, s), 7.1–7.2 (7H, m), 7.3–7.4 (3H, m). Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.78; H, 5.59; N, 3.28.

7-Ethyl-1,8-dimethyl-2,3-diphenyl-1*H*,5*H*-pyrano[3,4-*f*]indole-4,9-dione (9a). A mixture of the indolequinone (**4**) (0.25 g, 0.73 mmol) and 3-pyrrolidino-2-pentene (**8a**) (0.28 g, 2.0 mmol) in DMF (8 mL) was stirred at rt for 6 h. The resulting mixture was worked up in a manner similar to that described above for the preparation of **6**. Purification by preparative TLC on silica gel (3:1 hexane-Et_2O) to give **9a** (0.22 g, 74%) as a dark-red solid: mp 156–159 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1639; δ_H 1.11 (3H, t, *J* 7.4), 2.18 (3H, s), 2.36 (2H, q, *J* 7.4), 3.85 (3H, s), 4.79 (2H, s), 7.1–7.2 (7H, m), 7.3–7.35 (3H, m). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found: C, 79.20; H, 5.44; N, 3.40.

8-Ethyl-1-methyl-2,3-diphenyl-7-propyl-1*H*,5*H*-pyrano[3,4-*f*]indole-4,9-dione (9b). The reaction of the indolequinone (**4**) (0.11 g, 0.30 mmol) and 4-pyrrolidino-2-heptene (**8b**) (0.13 g, 0.78 mmol) in DMF (4 mL) at room temperature for 6 h gave **9b** (86 mg, 66%) as a dark-red solid: mp 164–167 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 1639; δ_H 0.98 (3H, t, *J* 7.4), 1.11 (3H, t, *J* 7.4), 1.29 (2H, sept, *J* 7.4), 2.33 (2H, t, *J* 7.4), 2.74 (2H, q, *J* 7.4), 3.85 (3H, s), 4.77 (2H, s), 7.1–7.2 (7H, m), 7.3–7.4 (3H, m). Anal. Calcd for $C_{29}H_{27}NO_3$: C, 79.61; H, 6.22; N, 3.20. Found: C, 79.52; H, 6.20; N, 3.19.

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